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Protocol for Study M15-994

IMMprint: Risankizumab in Moderate to Severe Plaque Psoriasis Patients with Palmoplantar Involvement

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FULL TITLE: IMMprint: A Phase 3b Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating Safety and Efficacy of Risankizumab Compared to Placebo in Adult Subjects with Moderate to Severe Plaque Psoriasis with Palmoplantar (Non-Pustular) Involvement (PPPsO)

Incorporating Version 1.0 and 2.0 and Administrative Change 1

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1 SYNOPSIS

Title: IMMprint: A Phase 3b Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating Safety and Efficacy of Risankizumab Compared to Placebo in Adult Subjects with Moderate to Severe Plaque Psoriasis with Palmoplantar (Non-Pustular) Involvement (PPPsO)	
Background and Rationale:	Psoriasis (PsO) is a chronic debilitating immunologic disease characterized by marked inflammation and thickening of the epidermis resulting in thick, scaly skin plaques. Palmoplantar (non-pustular) plaque psoriasis (PPPsO) represents a localized form of plaque psoriasis where patients present well-defined plaques on palms and soles of feet that can occur in isolation or in combination with generalized plaque PsO. Palmoplantar (non-pustular) plaque psoriasis is considered by healthcare professionals as a difficult-to-treat disease manifestation of plaque PsO, as the thicker stratum corneum of the palms and soles represents a barrier to topical treatment agents. Typically, less than 5% of the body surface area (BSA) is affected by PsO in patients with palmoplantar involvement, precluding these patients from entering clinical research studies with biologics, which usually require a BSA involvement of ≥ 10%. This creates challenges in understanding if results of PsO clinical trials are applicable to patients with palmoplantar disease. Assessing treatment options to address the unmet needs of patients with PPPsO is important, since palmoplantar involvement has a significantly greater impact on patients' quality of life compared to that of patients who have moderate to severe PsO without palmoplantar involvement. This study will provide essential data for risankizumab as treatment for patients with moderate to severe PPPsO, where an unmet need exists for new efficacious treatment options. The primary hypothesis for the trial is that risankizumab will provide superior efficacy compared to placebo with respect to Palmoplantar Investigator's Global Assessment (ppIGA) of "clear" or "almost clear" (0 or 1) with at least a 2-point reduction from Baseline at Week 16, and will be well tolerated in adult subjects with PPPsO.
Objective and Endpoints:	The primary objective of this study is to assess the safety and efficacy of risankizumab (150 mg) versus placebo for the treatment of signs and symptoms of moderate to severe plaque PsO in patients with palmoplantar (non-pustular) involvement. The primary endpoint is the achievement of ppIGA of "clear" or "almost clear" (0 or 1) with at least a 2-point reduction from Baseline at Week 16. The following ranked secondary endpoints will be tested in a hierarchical order, only if the null hypothesis for the primary endpoint has been rejected:

	1. Achievement of ≥ 75% improvement from Baseline in Palmoplantar Psoriasis Area and Severity Index (PPASI 75) response at Week 16 2. Achievement of ≥ 90% improvement from Baseline in Palmoplantar Psoriasis Area and Severity Index (PPASI 90) response at Week 16 3. Achievement of static Physician's Global Assessment (sPGA) of "clear" or "almost clear" (0 or 1) with at least a 2-point reduction from Baseline at Week 16 4. Achievement of 100% improvement from Baseline in Palmoplantar Psoriasis Area and Severity Index (PPASI 100) response at Week 16 All primary and ranked secondary endpoints will be analyzed at all other visits collected.
Investigator(s):	Multicenter
Study Site(s):	Approximately 55 sites in Spain, Canada, and the United States (including Puerto Rico).
Study Population and Number of Subjects to be Enrolled:	The study is designed to enroll 168 subjects with chronic PPPsO with or without psoriatic arthritis for at least 6 months prior to Baseline (Day 1) and a ppIGA of "moderate" or "severe" (≥ 3, at Screening and Baseline) and who are candidates for systemic therapy. Eligible subjects must also have ≥ 1% BSA PsO involvement, sPGA score of "moderate" or "severe" (≥ 3), PPASI ≥ 8 (moderate or severe disease), and at least 1 additional PsO plaque outside of the palms and soles at Screening and the Baseline visit. At least 50% of the overall study population will be comprised of subjects with Baseline BSA ≥ 10%.
Investigational Plan:	This is a Phase 3b multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the safety and efficacy of risankizumab (150 mg) compared to placebo in adult subjects with moderate to severe plaque PsO with palmoplantar involvement. The study is comprised of a Screening period of up to 35 days, a 52-week treatment period, and a follow-up phone call for safety. The 52-week treatment duration includes Period A and Period B. • Period A, Double-Blind Period (Baseline to Week 16): Eligible subjects will be centrally randomized at the Baseline visit in a 1:1 ratio to receive either risankizumab 150 mg as a single subcutaneous (SC) injection, or matching placebo. Study drug administration will occur at Baseline and Week 4. Randomization will be stratified by Baseline ppIGA ("moderate" [3] versus "severe" [4]) and Baseline BSA (< 10% versus ≥ 10%). The final efficacy evaluation of Period A will be at Week 16. • Period B, Open-Label Period (Week 16 to Week 52): Starting at Week 16, all subjects will receive open-label risankizumab

	150 mg once every 12 weeks at Weeks 16, 28, and 40. The final efficacy evaluation will take place at Week 52. A follow-up phone call for safety will be conducted approximately 20 weeks after administration of the last dose of risankizumab.
Key Eligibility Criteria:	Female or male adults with chronic PPPsO with or without psoriatic arthritis for at least 6 months prior to Baseline and a ppIGA of "moderate" or "severe" (≥ 3, at Screening and Baseline) and who are candidates for systemic therapy are eligible for this study. Eligible subjects must also have ≥ 1% BSA PsO involvement, sPGA score of "moderate" or "severe" (≥ 3), PPASI ≥ 8 (moderate or severe disease), and at least 1 additional PsO plaque outside of the palms and soles at Screening and the Baseline visit. At least 50% of the overall study population will be comprised of subjects with Baseline BSA ≥ 10%.
Study Drug and Duration of Treatment:	Subjects will be centrally randomized at the Baseline visit in a 1:1 ratio to receive either SC risankizumab 150 mg or matching placebo during Treatment Period A (at Baseline and Week 4), and all subjects will receive open-label risankizumab 150 mg once every 12 weeks during Treatment Period B (at Weeks 16, 28, and 40).
Date of Protocol Synopsis:	10 June 2021

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2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

This study will provide essential data for risankizumab in the treatment of adult patients with moderate to severe plaque psoriasis (PsO) with palmoplantar (non-pustular) involvement.

Psoriasis is a chronic debilitating immunologic disease characterized by marked inflammation and thickening of the epidermis that result in thick, scaly skin plaques. In most developed countries, the prevalence in adults is between approximately 1.5 and 5%.[1] About 20% of patients have moderate to severe disease with a considerable negative impact on psychosocial and economic status.[2,3] It is increasingly recognized that PsO is more than a superficial disease, with 30% of patients having joint involvement and a high correlation between PsO and obesity, diabetes, depression, metabolic syndrome, and cardiovascular risk exits.[4,5]

Palmoplantar (non-pustular) plaque psoriasis (PPPsO) represents a localized form of PsO. Approximately 3 to 17% of all patients with PsO have palmoplantar involvement,[6-8] presenting with well-defined erythematous, hyperkeratotic desquamative plaques (often with fissures) located on the palms and soles that can occur in isolation or in combination with generalized PsO.[9] Palmoplantar (non-pustular) plaque psoriasis is considered by healthcare professionals as a difficult-to-treat disease manifestation of PsO.[9] The thicker stratum corneum of the palms and soles represents a barrier to topical treatment agents. Systemic treatments, such as methotrexate, cyclosporine, and some biologics, have shown limited efficacy in dedicated studies, compared with the results seen in patients who have PsO without palmoplantar involvement, indicating a medical need for increased treatment efficacy in the palmoplantar patient population.[9-11]

Typically, less than 5% of the body surface area (BSA) is affected by PsO in patients with palmoplantar involvement, precluding these patients from entering clinical research studies with biologics, which usually require a BSA involvement of ≥ 10%.[11] This creates challenges in understanding if results of PsO clinical trials are applicable to patients with palmoplantar disease. Assessing treatment options to address the unmet needs of patients with PPPsO is important, since palmoplantar involvement has a significantly greater impact on patients' quality of life compared to that of patients who have moderate to severe PsO without palmoplantar involvement.[12] One reason for this is because PsO lesions of the dominant hand and/or feet impair patients' ability to work or perform daily activities.[6,13] Therefore, in addition to the BSA involved, other factors such as location of the lesions and impact of PsO on patients' quality of life, have been proposed to more accurately assess PsO severity in PPPsO patients.[14]

Positive results in PsO patients treated with risankizumab were reported in 4 pivotal Phase 3 clinical trials that evaluated risankizumab compared with ustekinumab, placebo, and adalimumab for the treatment of adult patients with moderate to severe PsO. Results from these pivotal studies demonstrated that risankizumab is highly effective for the treatment of PsO, meeting co-primary endpoints of achieving PASI 90 (defined as at least a 90% improvement from Baseline in the Psoriasis Area and Severity Index [PASI]) and static Physician's Global Assessment (sPGA) score of "clear" or "almost clear" (0 or 1) versus comparator or placebo at Week 16 across all 4 studies.[15-17] These Phase 3

PsO studies (M15-995 [Study 1311.28]; M16-008 [Study 1311.3]; and M15-992 [Study 1311.4]) enrolled moderate to severe psoriatic subjects with an affected BSA ≥ 10%, an sPGA of "moderate" or "severe" (≥ 3). A subset of subjects in these trials had documented palmoplantar involvement of their PsO, defined as a Palmoplantar Psoriasis Area and Severity Index (PPASI) > 0. Efficacy data from this subject subgroup showed significant improvement from Baseline PPASI in the risankizumab treatment group compared to subjects who received placebo ($P < 0.01$ in all 3 trials) at Week 16. The response was sustained in the risankizumab-treated subjects until Week 52.[18]

Risankizumab (Skyrizi™) has been approved for the treatment of moderate to severe PsO and is currently being developed for Crohn's disease, ulcerative colitis, psoriatic arthritis (Phase 3 studies), and the treatment of atopic dermatitis and hidradentitis suppurativa (in Phase 2 studies). Risankizumab is a humanized monoclonal antibody (mAb) of the immunoglobin (Ig)G1 subclass directed towards the p19 subunit of interleukin-23 (IL-23). 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.

The current study compares the safety and efficacy of risankizumab versus placebo in adult subjects with moderate to severe PPPsO. For a more detailed description of the risankizumab drug profile, refer to the latest version of the Investigator's Brochure (IB).[17]

Clinical Hypothesis

Risankizumab will provide superior efficacy compared to placebo with respect to Palmoplantar Investigator's Global Assessment (ppIGA) of "clear" or "almost clear" (0 or 1) with at least a 2-point reduction from Baseline at Week 16, and will be well tolerated in adult subjects with PPPsO.

2.2 Benefits and Risks to Subjects

In Phase 1, Phase 2, and Phase 3 studies of risankizumab in patients with PsO, the majority of subjects receiving risankizumab achieved 90% improvement of their disease and risankizumab was well tolerated. As with many immune-modulating agents, risankizumab may impair immune function, resulting in a risk of infection. This will be monitored by collection of all adverse events (AEs) during the treatment and observation periods. In addition, subjects with active systemic infection or clinically important infection will not be included in the study.

Subjects with a positive QuantiFERON®-TB (or interferon gamma release assay [IGRA] equivalent)/tuberculosis (TB) skin test result for TB must fulfill entry criteria as specified in Section 5.1 of this protocol. Interleukin-23 inhibition is not known to increase the risk of TB infection or impair the response to TB infection in animal models.[19,20] Subjects with positive QuantiFERON-TB 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 TB prophylaxis prior to receiving risankizumab, but should be carefully monitored for any sign of TB reactivation.

Published literature indicates that inhibition of IL-23 is unlikely to increase the risk for cancer. Expression of IL-23 is increased in human tumors.[21-23] Moreover, preclinical data have demonstrated a beneficial effect of IL-23 p19 inhibition in animal models, both for pre-existing and tumor-induction

models.[24] 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 events (MACE), including myocardial infarction, cerebrovascular accident, and cardiovascular death, reported initially with anti-IL-12/23 agents such as ustekinumab, have not been observed in longer-term studies with risankizumab. While the likelihood of increased MACE is small, all suspected cardiovascular or cerebrovascular events (serious or nonserious) observed in this study will be adjudicated by an independent 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 while at the site and be given instructions regarding management of signs and symptoms of anaphylaxis to be followed during home dosing visits. 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).

In conclusion, the benefit-risk profile of risankizumab is considered appropriate for this stage of clinical development.[25] Based on data from the integrated safety analyses, risankizumab is safe and well tolerated and demonstrates a favorable benefit-risk profile.

For further details, please see findings from completed studies, including safety data, in the current risankizumab Investigator Brochure.[17]

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

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The primary objective of this study is to assess the safety and efficacy of risankizumab (150 mg) versus placebo for the treatment of signs and symptoms of moderate to severe plaque PsO in patients with palmoplantar (non-pustular) involvement.

The primary efficacy objective is to demonstrate a higher rate of ppIGA of "clear" or "almost clear" (0 or 1) with at least a 2-point reduction from Baseline at Week 16 with risankizumab treatment compared to placebo in the Intent-to-Treat (ITT) Population, which consists of all randomized subjects (Section 7.2).

The hypothesis corresponding to the primary endpoint (Section 3.2) is:

- The proportion of subjects achieving ppIGA of 0 or 1 with at least a 2-point reduction from Baseline with risankizumab is greater than that with placebo at Week 16.

The estimand corresponding to the primary endpoint is defined using composite variable strategy:

- Difference in the proportion of subjects achieving ppIGA of 0 or 1 with at least a 2-point reduction from Baseline at Week 16 without premature discontinuation of study drug due to lack of efficacy prior to Week 16, in the risankizumab group in comparison with the placebo group in the ITT population.

Secondary

The secondary efficacy objectives are based on the ranked secondary endpoints as defined in Section 3.3. The hypotheses and estimands corresponding to these ranked secondary endpoints are summarized in Table 1.

Table 1. Hypotheses and Estimands Corresponding to the Ranked Secondary Endpoints

Hypothesis	Estimand
1. The proportion of subjects achieving PPASI 75 with risankizumab is greater than that with placebo at Week 16.	Difference in the proportion of subjects achieving PPASI 75 at Week 16 without premature discontinuation of study drug due to lack of efficacy prior to Week 16 in the risankizumab group in comparison with the placebo group in the ITT population.
2. The proportion of subjects achieving PPASI 90 with risankizumab is greater than that with placebo at Week 16.	Difference in the proportion of subjects achieving PPASI 90 at Week 16 without premature discontinuation of study drug due to lack of efficacy prior to Week 16 in the risankizumab group in comparison with the placebo group in the ITT population.
3. The proportion of subjects achieving sPGA of 0 or 1 with at least a 2-point reduction from Baseline with risankizumab is greater than that with placebo at Week 16.	Difference in proportion of subjects achieving sPGA of 0 or 1 with at least a 2-point reduction from Baseline at Week 16 without premature discontinuation of study drug due to lack of efficacy prior to Week 16 in the risankizumab group in comparison with the placebo group in the ITT population.
4. The proportion of subjects achieving PPASI 100 with risankizumab is greater than that with placebo at Week 16.	Difference in the proportion of subjects achieving PPASI 100 at Week 16 without premature discontinuation of study drug due to lack of efficacy prior to Week 16 in the risankizumab group in comparison with the placebo group in the ITT population.

ITT = intent-to-treat; PPASI = Palmoplantar Psoriasis Area and Severity Index; sPGA = static Physician's Global Assessment

3.2 Primary Endpoint

The primary endpoint is the achievement of ppIGA of "clear" or "almost clear" (0 or 1) with at least a 2-point reduction from Baseline at Week 16.

3.3 Secondary Endpoints

Secondary Endpoints (Ranked)

The following ranked secondary endpoints will be tested in a hierarchical order, only if the null hypothesis for the primary endpoint has been rejected:

1. Achievement of ≥ 75% improvement from Baseline in Palmoplantar Psoriasis Area and Severity Index (PPASI 75) response at Week 16
2. Achievement of ≥ 90% improvement from Baseline in Palmoplantar Psoriasis Area and Severity Index (PPASI 90) response at Week 16

3. Achievement of sPGA of "clear" or "almost clear" (0 or 1) with at least a 2-point reduction from Baseline at Week 16
4. Achievement of 100% improvement from Baseline in Palmoplantar Psoriasis Area and Severity Index (PPASI 100) response at Week 16

3.4 Additional Efficacy Endpoints

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

- Achievement of ppIGA of "clear" (0)
- Achievement of sPGA of "clear" (0)
- Change from Baseline in PPASI
- Percent change from Baseline in PPASI
- Change from Baseline in PASI
- Percent change from Baseline in PASI among subjects with Baseline PASI ≥ 12
- Change from Baseline in Patient Global Assessment of Skin Pain (PGA-SP), among subjects with Baseline Numerical Rating Scale (NRS) ≥ 4
- Percentage change from Baseline in PGA-SP, among subjects with Baseline NRS ≥ 4
- Change from Baseline in Psoriasis Symptom Scale (PSS)
- Achievement of PSS 0 or 1
- Change from Baseline in Dermatology Life Quality Index (DLQI)
- Achievement of DLQI 0 or 1
- Achievement of DLQI improvement (reduction) of ≥ 4 points, among subjects with Baseline DLQI ≥ 4

In addition, the achievement of ppIGA of "clear" (0), ppIGA of "clear" or "almost clear" (0 or 1) with at least a 2-point reduction from Baseline, and PPASI 75/90/100 response will also be summarized at later visits in Period B, among subjects who are randomized to risankizumab in Period A and have achieved the corresponding response status at the entry of Period B.

3.5 Safety Endpoints

The following safety evaluations will be performed throughout the study as measures of safety and tolerability:

- Adverse event (AE) monitoring
- Vital sign measurements

- Physical examinations
- Clinical laboratory testing

3.6 Pharmacokinetic Evaluation

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

3.7 Biomarker Research

For subjects who consent, optional blood samples (whole blood, serum, and plasma) will be collected as described in the Activity Schedule (Appendix D) to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites. The objective of this research is to analyze samples for biomarkers that will help to understand PsO, related conditions, or response to treatment with risankizumab or similar compounds. Research may also include changes in epigenetics, gene expression, and proteomics that may associate with PsO, related conditions, or the subject's response to treatment. This research is exploratory in nature and the results may not be included with the clinical study report.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3b multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the safety and efficacy of risankizumab (150 mg) compared to placebo in adult subjects with moderate to severe plaque PsO with palmoplantar involvement.

The study is designed to enroll 168 subjects. See Section 5 for information regarding eligibility criteria.

The study duration will be up to approximately 65 weeks. The study is comprised of a Screening period of up to 35 days, a 52-week treatment period, and a follow-up phone call for safety.

The 52-week treatment duration includes Period A and Period B.

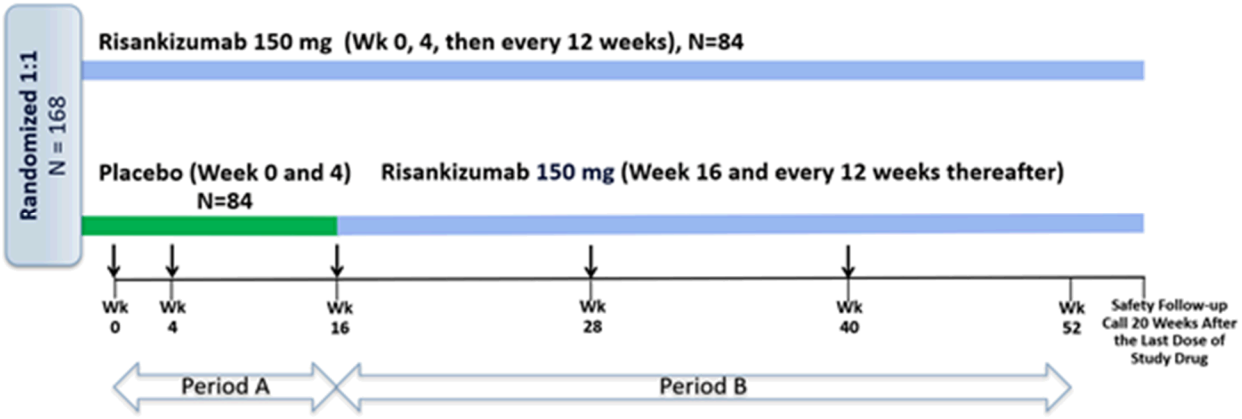
- Period A, Double-Blind Period (Baseline [Day 1] to Week 16): Eligible subjects will be centrally randomized at the Baseline visit in a 1:1 ratio to receive either risankizumab 150 mg as a single SC injection, or matching placebo. Study drug administration will occur at Baseline and Week 4. Randomization will be stratified by Baseline ppIGA ("moderate" [3] versus "severe" [4]) and Baseline BSA (< 10% versus ≥ 10%). The final efficacy evaluation of Period A will be at Week 16.
- Period B, Open-label Period (Week 16 to Week 52): Starting at Week 16, all subjects will receive open-label risankizumab 150 mg once every 12 weeks (q12w) at Weeks 16, 28, and 40. The final efficacy evaluation will take place at Week 52.

A follow-up phone call for safety will be conducted approximately 20 weeks after administration of the last dose of risankizumab.

A subgroup of approximately 15 subjects at prospectively selected sites will be asked to have skin photographs taken of their palms and soles to document disease response during the study. Subjects who consent will have photographs taken at Baseline and Weeks 4, 16, 28, 40, and 52. No efficacy analysis will be made from the obtained material.

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

Figure 1. Study Schematic



N = number of subjects; Wk = week

Solid arrows indicate administration of study drug at study visits.

4.2 Discussion of Study Design

Choice of Control Group

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

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study for assessing disease activity in adult subjects with moderate to severe PPPsO have been used in other studies assessing this subset of patients.[11,15,16,26,27] All clinical and laboratory procedures in this study are standard and generally accepted. Patient-reported outcome (PRO) measures in this study were included to assess patient symptoms and quality of life.

Suitability of Subject Population

Female or male adults with chronic PPPsO with or without psoriatic arthritis for at least 6 months prior to Baseline and a ppIGA of "moderate" or "severe" (≥ 3, at Screening and Baseline) and who are

candidates for systemic therapy are eligible for this study. Eligible subjects must also have ≥ 1% BSA PsO involvement, sPGA score of "moderate" or "severe" (≥ 3), PPASI ≥ 8 (moderate or severe disease),[28] and at least 1 additional PsO plaque outside of the palms and soles at Screening and the Baseline visit. At least 50% of the overall study population will be comprised of subjects with Baseline BSA ≥ 10%. The selection criteria relating to safety ensure that enrolled subjects can safely be treated with risankizumab based on the current knowledge of this drug.

Selection of Doses in the Study

The risankizumab dosing regimen selected for the current study (i.e., 150 mg SC at Weeks 0, 4, and q12w thereafter up to Week 40) is the same as used in the risankizumab pivotal Phase 3 studies in subjects with moderate to severe chronic plaque PsO. The risankizumab 150 mg SC dose has been shown to be efficacious with an acceptable safety profile and is considered appropriate for the treatment of subjects with plaque PsO.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

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

Consent

- 1. Subjects or their legally authorized representative must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.
- 2. Employees of the Sponsor and/or study sites and their family members may not be enrolled in this study.
- 3. Subjects must be willing and able to comply with procedures required in this protocol.

Demographic and Laboratory Assessments

- 4. Adult **male or female**, at least 18 years old (subjects must also meet the legal age of majority per local law).
- 5. **Laboratory values** meeting the following criteria within the Screening period prior to the first dose of study drug:
  - Serum aspartate aminotransaminase (AST) ≤ 2 × upper limit of normal (ULN);
  - Serum alanine aminotransaminase (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 g/dL (100 g/L).

Disease Activity

- 6. Female or male adults with chronic PPPsO (with or without psoriatic arthritis) for at least 6 months prior to Baseline and a ppIGA of "moderate" or "severe" (≥ 3), at Screening and Baseline.
- 7. Subjects must have at Screening and Baseline:
  - Plaque PsO BSA involvement of ≥ 1%,
  - sPGA score of "moderate" or "severe" (≥ 3),
  - PPASI ≥ 8 (moderate or severe disease), and
  - At least 1 additional PsO plaque outside of the palms and soles.

    At least 50% of the overall study population will be comprised of subjects with Baseline BSA ≥ 10%.
- 8. Previously inadequately controlled disease by topicals, phototherapy, and/or systemic treatments.
- 9. Subject must be a candidate for systemic therapy as assessed by the investigator.

Subject History

- 10. 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.
- 11. No forms of PsO other than chronic plaque-type PsO (e.g., pustular PsO, palmoplantar pustulosis, acrodermatitis of Hallopeau, erythrodermic, or guttate PsO).
- 12. No current drug-induced PsO or a drug-induced exacerbation of pre-existing psoriasis.
- 13. No active ongoing inflammatory skin diseases other than PsO and psoriatic arthritis that could interfere with the assessment of PsO (e.g., hyperkeratotic eczema).
- 14. Subjects must not have a history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 6 months.
- 15. Subjects must not have a history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 16. Subjects must not have had **major surgery** performed within 12 weeks prior to randomization or planned during the conduct of the study (e.g., hip replacement, aneurysm removal, stomach ligation).
- 17. Subjects must not have evidence of:
  - Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, defined as:

- HBV: Hepatitis B surface antigen (HBs Ag) positive (+) test or detected sensitivity on the HBV DNA polymerase chain reaction (PCR) qualitative test for subjects who are hepatitis B core antibody (HBc Ab) positive (+) (and for hepatitis B surface antibody [HBs Ab] positive [+] subjects where mandated by local requirements).
- HCV: HCV RNA detectable in any subject with anti-HCV antibody (HCV Ab).

- **Human immunodeficiency virus (HIV)**, defined as confirmed positive anti-HIV Ab test. Note: In case a screened subject has a confirmed positive HIV Ab test, Eligibility Criterion 10 (Subject is judged to be in good general health criteria…) should be selected in electronic case report form (eCRF) for documentation of screening failure.
- **Active TB**. For subjects with latent TB, please see Section 3.16 of the Operations Manual.
- **Active systemic infection/Clinically important infection** during the last 2 weeks prior to Baseline visit as assessed by the investigator.

18. 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.

19. Subject must not have concurrent clinically significant medical conditions 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.

20. No known active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, they should undergo molecular (e.g., 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.

Contraception

21. For all females of child-bearing potential; a **negative serum pregnancy test** at the Screening visit and a **negative urine pregnancy** test at Baseline prior to the first dose of study drug is required.

- 22. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is effective from Study Day 1 through at least 140 days (20 weeks or as guided by the local risankizumab label [if approved], whichever is longer) after the last dose of study drug (local practices may require 2 methods of birth control). Female subjects of non-childbearing potential do not need to use birth control.
- 23. 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)

- 24. No prior exposure to risankizumab.
- 25. Subject must not have received **any live viral or bacterial vaccine** within 4 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 140 days (20 weeks or as guided by the local risankizumab label [if approved], whichever is longer) after the last dose of study drug.
- 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 is currently enrolled in another clinical study or was previously enrolled in this study.
- 27. Subject did not receive any systemic biologics to treat PsO for the following timeframes prior to the Baseline visit:
  - Etanercept (Enbrel®) and biosimilar versions within 3 weeks;
  - Certolizumab (Cimzia®), adalimumab (Humira®), ixekizumab (Taltz®), brodalumab (Siliq®/Kyntheum®), infliximab (Remicade®), and biosimilar versions within 10 weeks;
  - Ustekinumab (Stelara®) and guselkumab (Tremfya®) within 15 weeks;
  - Tildrakizumab (Ilumya™) and secukinumab (Cosentyx®) within 20 weeks.
- 28. Subject did not receive for at least 30 days prior to randomization any:
  - Other systemic immunomodulating treatments (including, but not limited to: e.g., methotrexate, cyclosporine A, corticosteroids, cyclophosphamide, tofacitinib [Xeljanz®], apremilast [Otezla®]);
  - Other systemic PsO treatments (e.g., retinoids, fumarates, any other drug known to possibly benefit PsO);
  - Photochemotherapy (e.g., psoralen and ultraviolet A radiation [PUVA]), phototherapy (e.g., ultraviolet B rays [UVB]).
- 29. Subject did not receive for at least 14 days prior to randomization any topical treatment for PsO or any other skin condition (including, but not limited to: e.g., corticosteroids, vitamin D analogues, vitamin A analogues, pimecrolimus, retinoids, salicyl vaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, or anthralin).

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

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

  - Premenopausal female with permanent sterility or permanent infertility due to one of the following:
    - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy.
    - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
  - Postmenopausal, female:
    - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
    - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulation hormone (FSH) level > 30 IU/L.

- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 140 days (20 weeks or as guided by the local risankizumab label [if approved], whichever is longer) after the last dose of study drug.
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen- and progestogen- containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS).
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence

[e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

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

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

5.3 Prohibited Medications and Therapy

1. During the study, no biologic treatment is allowed. Exception: Treatment with commercially available risankizumab after the Week 52/Premature Discontinuation (PD) assessments if this has been determined as an appropriate subsequent treatment by the investigator in discussion with the subject.
2. Systemic (including oral or injectable administrations) non-biologic therapy that can be used to treat PsO, including but not limited to cyclosporine, corticosteroids, methotrexate, retinoids, apremilast, and fumaric acid derivatives.
3. Phototherapy treatment (UVB or ultraviolet A [UVA] phototherapy, including PUVA), laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments.
4. Topical PsO treatments, including but not limited to corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, urea, α- or β-hydroxyl acids, and medicated shampoos (for example those that contain corticosteroids, coal tar, or vitamin D3 analogues).
5. All other investigational drugs and enrollment in another clinical study are prohibited.
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
- Dengue (Dengvaxia®)

5.4 Prior and Concomitant Therapy

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

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject has received from 4 weeks prior to Screening or receives during the study must be recorded along with the reason for use; date(s) of administration, including start and end dates; and dosage information including dose, route, and frequency on the appropriate eCRF.

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

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with risankizumab can be located in the risankizumab Investigator's Brochure.[17]

Subjects must be able to safely discontinue any prohibited medications (including biologics) 5 half-lives or 4 weeks, whichever is longer, prior to initial study drug administration. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

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

When possible, first dose of study drug should be given at least ± 7 days from non-live SARS-CoV-2 vaccine administration. The potential impact of risankizumab on SARS-CoV-2 vaccination is unknown. The decision to receive a locally available non-live vaccine should be based on local guidance and an individual discussion between the treating physician and the subject and/or guardian.

Allowed Concomitant Medications/Therapy

Allowed concomitant medications and therapies include the following:

- Moisturizers: Provided that moisturizers (without active ingredients) have been used for at least 2 weeks prior to Baseline and are anticipated to be continuously used at least until the Week 16 visit. Subjects should not apply emollients within 8 hours prior to study assessments.
- Only inhaled, topical ophthalmic, or intranasal corticosteroids are permitted during the study.

COVID-19 Pandemic-Related Vaccination Guidance

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual (Appendix F)for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw from the study drug and/or study at any time. Subjects must be withdrawn from the study drug and/or study 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 Therapeutic Area (TA) Medical Director (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 and 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 at least 48 hours apart):
  - ALT or AST > 8 × ULN;
  - ALT or AST > 5 × ULN for more than 2 weeks;
  - ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5;
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
  - Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented (in the eCRF if reported as an AE). If ALT or AST values return to the normal reference range or its Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is

expected to be safe. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug.

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

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

COVID-19 Pandemic-Related Acceptable Protocol Modification

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

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

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

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

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

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

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

If a subject prematurely discontinues study participation, the procedures outlined for the 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 AEs/serious adverse events (SAEs) have been resolved. The 140-day follow-up phone call following the last dose administration of risankizumab study drug during the trial will not be required for any subject who initiates commercially available risankizumab after completion of the Week 52 visit or premature discontinuation visit.

If a subject withdraws from study follow-up or withdraws permission for the collection of their personal data, the study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations.

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 the subject has withdrawn and no longer wishes biomarker sample research to continue, samples will not be analyzed, and no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s). A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from clinical study and/or optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

AbbVie will provide study drug for risankizumab or matching placebo. AbbVie-provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie. Information about the study drug and placebo used in this study is presented in Table 2.

During Period A (Double-Blind Period), study site staff will administer study drug subcutaneously (risankizumab 150 mg or matching placebo in a pre-filled syringe [PFS]) at Baseline and Week 4 visits. Subjects will be trained by site staff on self-injection at the Baseline visit to proactively be prepared for at-home dosing by the subject or caregiver at Weeks 4, 28, and 40, should the need for a virtual visit arise due to COVID-19-related restrictions. Subjects may be retrained on self-injection at the Week 16 visit.

During Period B (Open-Label Period), study site staff will administer risankizumab as a 150 mg SC dose (1 × 150 mg PFS) at Week 16, Week 28, and Week 40 visits.

Only subjects who self-administer study drug at home due to COVID-related visit modifications (e.g., virtual visit) will record the self-administered dosing in a subject dosing diary.

Table 2. Description of Study Drug and Placebo

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Risankizumab (ABBV-066)	Solution for injection in PFS	150 mg Active, 150 mg/mL	SC injection	AbbVie Biotechnology Ltd., Barceloneta, Puerto Rico
Placebo for Risankizumab (ABBV-066)	Solution for injection in PFS	Not applicable	SC injection	AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany

PFS = pre-filled syringe; SC = subcutaneous

Blinded risankizumab or placebo and open-label risankizumab will be packaged in quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug must be kept protected from light in the original packaging,

in a refrigerator between 2°C to 8°C (36°F to 46°F). A temperature log must be maintained for documentation. Study drug must be kept in a secure location and must not be frozen at any time. 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. Upon receipt of the study drugs, the site will acknowledge receipt within the IRT system. All blank spaces on the label will be completed by the site staff prior to dispensing to subjects.

AbbVie will not supply drug other than risankizumab and matching placebo, and study drug will only be used for the conduct of this study. AbbVie-provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie. If a subject is unable to come to the study site to pick up their study drug due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to the Operations Manual in Appendix F for details on DTP shipment of study drug.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the Screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial Screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by Data and Statistical Sciences (DSS) at AbbVie.

Eligible subjects will be centrally randomized in a 1:1 ratio to risankizumab 150 mg or placebo groups during Treatment Period A. The randomization will be stratified by Baseline ppIGA ("moderate" [3] versus "severe" [4]) and Baseline BSA (< 10% versus ≥ 10%). All subjects will receive risankizumab 150 mg during Treatment Period B.

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

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

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

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

Product Complaint

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

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

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

Medical Complaints/Adverse Events and Serious Adverse Events

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory

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abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

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

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

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

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event, along with any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the time of study drug administration until 140 days (20 weeks) after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reaction (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

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

AbbVie will be responsible for SUSAR reporting for the 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/Safety Topics of Interest

Infections, especially opportunistic infections, are a potential risk with immunomodulators. Subjects will be screened and monitored throughout the study for Areas of Safety Interest (ASI)/Safety Topics of Interest. 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 3).

Table 3. Supplemental Adverse Events eCRFs

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** • **ALT/AST > 8 × ULN or ALT/AST > 3 × ULN with a total bilirubin > 2 × ULN**	• Hepatic AE eCRF
Suspected anaphylactic/systemic hypersensitivity reactions	• Hypersensitivity Reaction Signs and Symptoms eCRF
TB Subjects with events of latent TB or suspected 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.[29]

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

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

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

If no specific criteria per CTCAE Version 5 guidelines are available for the reported event, the event should be graded per the investigator's judgment according to the definitions outlined above.

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

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

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

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

6.2 Cardiovascular Adjudication Committee

An independent adjudication committee will adjudicate all observed cardio- and cerebro-vascular events and will remain blinded to treatment allocation. The events that are adjudicated and the adjudication process will be detailed in the CAC Charter. Dedicated eCRFs will be used as outlined in Table 3.

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 prespecified definitions. This independent external AAC will adjudicate suspected anaphylactic reactions and will remain blinded to each subject's initial treatment allocation. The event terms to be adjudicated and the adjudication process are detailed in the AAC Charter. A supplemental Hypersensitivity Reactions Signs and Symptoms eCRF will be used to collect information pertinent to the events. In addition, the site may be contacted for additional source documentation.

If a suspected systemic hypersensitivity reaction occurs at the investigative site, in addition to testing tryptase and histamine levels, drug (serum risankizumab concentration) and antidrug antibody (ADA)/neutralizing antibody (Nab) samples should also be collected. If a systemic hypersensitivity reaction such as anaphylaxis is observed or reported while the subject is not at the investigative site, every effort should be made to obtain tryptase and histamine levels from the treating facility to help better characterize the diagnosis.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

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

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

7.2 Definition for Analysis Populations

The Intent-to-Treat (ITT) Population includes all randomized subjects. The ITT Population will be used for all efficacy analyses. Subjects who are randomized to placebo in Period A and do not continue into Period B will not be included in the analysis in Period B.

The following populations will be used for the safety analysis:

- The Safety Population in Period A (Safety_A) is defined as all subjects who are randomized and received at least 1 dose of study drug in Period A.
- The Safety Population in Period B (Safety_B) is defined as all subjects who received at least 1 dose of study drug in Period B.
- The All Risankizumab Treated (ALL_RZB) Population is defined as subjects who received at least 1 dose of risankizumab as the study drug. This population will be used to provide a comprehensive summary of safety.

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

The primary endpoint (Section 3.2) and the ranked secondary endpoints (Section 3.3) will be analyzed in the ITT Population and the following method will be used to address potential intercurrent events:

- Subjects discontinuing study drug due to lack of efficacy before Week 16 are considered as not achieving the response.

7.4 Statistical Analyses for Efficacy

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

All statistical tests will be performed at a 2-sided alpha level of 0.05 in Period A. The 95% confidence interval (CI) of the treatment effect will be provided.

- For categorical variables, comparison will be made between risankizumab and placebo using the Cochran-Mantel-Haenszel (CMH) test, adjusting for the actual values of stratification factors (Baseline ppIGA and Baseline BSA). Non-Responder Imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C) will be the primary approach to handle missing values.
- For continuous variables, comparison will be made between risankizumab and placebo based on the fixed term of treatment from a Mixed-effect Model Repeat Measurement (MMRM), adjusting for treatment, actual values of stratification factors (Baseline ppIGA and Baseline BSA), and baseline value if applicable (if not duplicating the stratification factors). The MMRM will be the primary approach to handle missing values.

Summary statistics will be provided in Period B by treatment groups. Categorical endpoints will be summarized by the number and proportion of subjects who achieved the endpoint, as well as the 95% confidence interval of that proportion. Continuous endpoints will be summarized by descriptive statistics including the mean, standard error, and the 95% confidence interval of the mean.

Analysis of the Primary Endpoints

Analysis of the primary endpoint, as described in Section 3.2, will be conducted on the ITT population based on treatment as randomized.

Comparison of the primary endpoint will be made between risankizumab and placebo using the CMH test adjusting for the actual values of stratification factors (Baseline ppIGA and Baseline BSA) with a 2-sided significance level of 0.05.

NRI-C will be the primary approach to handle missing values. A sensitivity analysis will also be performed for the primary efficacy endpoint, using multiple imputation (MI) to handle missing values. Analysis details for NRI-C, MI, and other sensitivity analyses (if applicable) will be provided in the SAP.

Analysis of the Secondary Endpoints

Analysis of all ranked secondary efficacy endpoints will be conducted on the ITT population based on treatment as randomized.

To control the overall type I error rate, the null hypotheses for all ranked secondary endpoints will be tested in a hierarchical order as described in Section 3.3, with a 2-sided significance level of 0.05, only if the null hypothesis for the primary endpoint has been rejected.

Analysis of Additional Efficacy Endpoints

Additional endpoints, as described in Section 3.4, will also be analyzed. Analysis details about additional efficacy endpoints will be provided in the SAP.

Subgroup Analysis for Efficacy

To evaluate the consistency of the efficacy across demographic and other baseline characteristics, summaries and analyses will be performed for selected subgroups for the primary efficacy endpoint.

Subgroup analysis will be performed on the primary endpoint using the following subgroups:

- Age group (< 40 years, ≥ 40);
- Sex (male, female);
- Race (white, non-white);
- Smoking (current, ex-, or never);
- Body mass index (BMI) (normal: < 25, overweight: ≥ 25 to < 30, obese: ≥ 30);
- Baseline ppIGA ("moderate" [3], "severe" [4]);
- Baseline BSA (< 10% versus ≥ 10%);
- Psoriatic arthritis (yes, no); and
- Body weight (≤ 100 kg, > 100 kg).

7.5 Statistical Analyses for Safety

All safety analyses will be performed on the Safety Population in each period. Subjects will be analyzed based on the actual treatment received, defined as the first dose of treatment received after randomization. Treatment-emergent adverse events (TEAEs), laboratory assessments, and vital signs will be summarized. Key safety variables will also be summarized on the ALL_RZB Population. Details will be described in the SAP.

A TEAE for the Safety Population is defined as an AE newly occurred or worsened after the first dose of study drug and within 20 weeks (140 days) after the last dose of study drug. The number and percentage of subjects experiencing TEAEs will be tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (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 [PY]) of SAEs, deaths, and AEs leading to discontinuation will be provided as well. Pre-treatment AEs will be summarized separately.

For selected laboratory parameters, a listing of all subjects with any laboratory value that is above Grade 3 of Common Toxicity Criteria will be provided. Mean change in laboratory and vital signs variables will be summarized.

Additional details for the safety analysis are provided in the SAP.

Interim Analysis

No interim analysis is planned for this study.

7.7 Overall Type I Error Control

Overall type I error rate will be controlled at a 2-sided significance level of 0.05 by testing the primary endpoint, followed by the ranked secondary endpoints, in a hierarchical order as described in Section 3.2 and Section 3.3.

7.8 Sample Size Determination

The ppIGA is an endpoint that has been used in another clinical trial in the palmoplantar psoriasis population and which is based on the modified Investigator's Global Assessment version of 2011.[11,30] Given the lack of historical ppIGA data from risankizumab trials, the assumption of response rates in the current study are based on the relevant endpoints of PPASI 75 and PPASI 90 from risankizumab PsO Studies M15-992 (NCT02672852, Study 1311.4), M15-995 (NCT02684357, Study 1311.28), and M16-008 (NCT02684370, Study 1311.3), among subjects who had Baseline PPASI of at least 8. Among these subjects, approximately 80% and 75% of subjects from the risankizumab (RZB) group achieved PPASI 75 and PPASI 90, respectively; compared to 50% and 40% in the placebo (PBO) group.

Assuming that 75% of subjects from the RZB group and 45% of subjects from the PBO group would achieve the primary endpoint of ppIGA of "clear" or "almost clear" (0 or 1) with at least a 2-point reduction from Baseline at Week 16, the sample size of 168 subjects (84 subjects per group) will provide more than 90% power to detect the treatment difference between RZB and PBO, under a 2-sided significance level of 0.05.

7.9 Statistical Analysis of Optional Biomarker Data

Analysis may be conducted on optional biomarker data for the purpose of identification of prognostic, predictive, surrogate, and pharmacodynamic biomarkers associated with safety or efficacy. The association of biomarkers to the efficacy or safety endpoints may be explored for each biomarker one at a time, and also for combinations of biomarkers via some multivariate predictive modeling approaches.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

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 for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. Refer to the Operations Manual in Appendix F for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

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

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

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

10 DATA QUALITY ASSURANCE

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

11 COMPLETION OF THE STUDY

The 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 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 for safety approximately 20 weeks after administration of the last dose of study drug (risankizumab).

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AAC	Anaphylaxis Adjudication Committee
Ab	Antibody
ADA	Antidrug antibody
AE	Adverse event
ALT	Alanine aminotransaminase/aminotransferase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
ASI	Areas of safety interest
AST	Aspartate aminotransaminase/aminotransferase
BCG	Bacille Calmette-Guérin
BMI	Body-mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CAC	Cardiovascular Adjudication Committee
CBC	Complete blood count
CI	Confidence interval
CK	Creatine kinase
CKD-EPI	Creatinine with eGFR
CMH	Cochran-Mantel-Haenszel
CS	Clinically significant
COVID-19	Coronavirus disease of 2019
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
D	Desquamation
DFP	Direct-from-patient
DLQI	Dermatology Life Quality Index
DSS	Data and Statistical Sciences
DSUR	Development safety update report
DTP	Direct-to-patient
E	Erythema
ECG	Electrocardiogram

eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GGT/γ-GT	Gamma-glutamyl transferase
h	Head
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
hsCRP	High-sensitivity C-reactive protein
I	Induration
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
Ig	Immunoglobin
IGRA	interferon gamma release assay
IL	Interleukin
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system

l	Lower extremities
LDL-C	Low-density lipoprotein cholesterol
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular events
MCV	Mean corpuscular volume
MD	Medical Director
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed-effect Model Repeat Measurement
NAb	Neutralizing antibody
NCI	National Cancer Institute
NCS	Not clinically significant
NMSC	Non-melanoma skin cancer
NRI	Non-responder imputation
NRI-C	Non-Responder Imputation incorporating multiple imputation to handle missing data due to COVID-19
NRS	Numerical Rating Scale
PASI	Psoriasis Area and Severity Index
PASI 90	Achievement of ≥ 90% improvement from Baseline in Psoriasis Area and Severity Index
PBO	Placebo
PCR	Polymerase chain reaction
PD	Premature Discontinuation
PFS	Pre-filled syringe
PGA-SP	Patient Global Assessment of Skin Pain
PK	Pharmacokinetics
PPASI	Palmoplantar Psoriasis Area and Severity Index
PPASI 75	Achievement of ≥ 75% improvement from Baseline in Palmoplantar Psoriasis Area and Severity Index
PPASI 90	Achievement of ≥ 90% improvement from Baseline in Palmoplantar Psoriasis Area and Severity Index
PPASI 100	Achievement of ≥ 100% improvement from Baseline in Palmoplantar Psoriasis Area and Severity Index
PPD	Purified protein derivative
ppIGA	Palmoplantar Investigator's Global Assessment
PPPsO	Palmoplantar plaque psoriasis

PRO	Patient-reported outcome
PSD	Psoriasis Symptom Diary
PSI	Psoriasis Symptom Inventory
PsO	Psoriasis
PSS	Psoriasis Symptom Scale
PT	Preferred term
PUVA	Psoralen and ultraviolet A radiation
PY	Patient years
q12w	Once every 12 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell
RSI	Reference Safety Information
RZB	Risankizumab
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SOC	System organ class
sPGA	Static Physician's Global Assessment
SUSAR	Suspected unexpected serious adverse reactions
t	Trunk
TA	Therapeutic Area
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
u	Upper extremities
UACR	Urine albumin-to-creatinine ratio
ULN	Upper limit of normal
UVA	Ultraviolet A rays
UVB	Ultraviolet B rays
WBC	White blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M15-994: IMMprint: A Phase 3b Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating Safety and Efficacy of Risankizumab Compared to Placebo in Adult Subjects with Moderate to Severe Plaque Psoriasis with Palmoplantar (Non-Pustular) Involvement (PPPsO)

Protocol Date: 10 June 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]	Medical Monitor/Medical Director	Medical Affairs, Immunology
[redacted]	Associate Director	Clinical Program Development
[redacted]	Associate Director, Statistics	Data and Statistical Sciences
[redacted]	Director, Statistics	Data and Statistical Sciences
[redacted]	Senior Director/Statistics Therapeutic Area Head	Data and Statistical Sciences
[redacted]	Associate Director	Medical Writing (Protocol Author)

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the subject encounters. The individual activities and allowed modifications due to COVID-19 are described in detail in the **Operations Manual** (Appendix F).

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Study Activities Table

Activity	Screening	Baseline	Week 4	Week 16	Week 28	Week 40	Week 52/Premature Discontinuation	
			Day 29	Day 113	Day 197	Day 281	Day 365	20 Week Safety F/U Call
Visit window	Day –35 to –1	Day 1	± 3 days		± 7 days			
INTERVIEWS & QUESTIONNAIRES								
Informed consent	✓							
Eligibility criteria	✓	✓						
Medical (including psoriasis)/surgical history	✓	✓						
Demographics	✓							
Alcohol, nicotine, and e-cigarette use	✓							
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓
Patient-reported outcomes • Patient Global Assessment of Skin Pain (PGA-SP) • Psoriasis Symptom Scale (PSS) • Dermatology Life Quality Index (DLQI)		✓	✓	✓	✓	✓	✓	
SARS-CoV-2/COVID-19 Risk Assessment Form or comparable tool	✓							
Latent TB risk assessment form	✓							
LOCAL LABS & EXAMS								
12-Lead ECG	✓							
Height (at Screening only) and weight	✓						✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓	
Physical examination	✓	✓					✓	
BSA	✓	✓						
sPGA/PASI	✓	✓		✓			✓	

Activity	Screening	Baseline	Week 4	Week 16	Week 28	Week 40	Week 52/Premature Discontinuation	
			Day 29	Day 113	Day 197	Day 281	Day 365	20 Week Safety F/U Call
Visit window	Day –35 to –1	Day 1	± 3 days		± 7 days			
Efficacy assessments (ppIGA/PPASI)	✓	✓	✓	✓	✓	✓	✓	
Urine pregnancy test (prior to dose administration and for females of childbearing potential only)		✓	✓	✓	✓	✓		
Photography (for a subset of sites; not performed at the PD visit)		✓	✓	✓	✓	✓	✓	
CENTRAL LABS								
HIV/HBV/HCV screening (HBV testing approximately every 12 weeks per local requirements)	✓							
FSH (if applicable, per Operations Manual)	✓							
Serum pregnancy test (for females of childbearing potential only)	✓							
TB test (QuantiFERON-TB Gold test [or IGRA equivalent] and/or local PPD skin test)	✓							
Clinical chemistry, hematology (CBC)	✓	✓		✓			✓	
Urinalysis	✓							
Optional biomarker sample - Whole blood RNA		✓	✓	✓			✓	
Optional biomarker sample - Whole blood serum		✓	✓	✓			✓	
Optional biomarker sample - Whole blood plasma		✓	✓	✓			✓	
Optional biomarker sample - Whole blood DNA		✓						
TREATMENT								
Randomization/drug assignment		✓						
Study drug administration		✓	✓	✓	✓	✓		
Dispense urine pregnancy tests for women of child-bearing potential (for potential virtual visits due to COVID-19)		✓						

Activity	Screening	Baseline	Week 4	Week 16	Week 28	Week 40	Week 52/Premature Discontinuation	
			Day 29	Day 113	Day 197	Day 281	Day 365	20 Week Safety F/U Call
Visit window	Day –35 to –1	Day 1	± 3 days		± 7 days			
Dispense Subject Dosing Diary (for potential virtual visits due to COVID-19)		✓						
Self-Injection Training		✓		✓				
Hypersensitivity Training		✓		✓				
Hypersensitivity monitoring		✓	✓	✓	✓	✓		

BL = Baseline; BSA = Body surface area; CBC = Complete blood count; COVID-19 = coronavirus disease – 2019; DLQI = Dermatology Life Quality Index; ECG = Electrocardiogram; FSH = Follicle-stimulating hormone; F/U = Follow-up; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; IGRA = Interferon gamma release assay; PASI = Psoriasis Area and Severity Index; PD = Premature Discontinuation; PGA-SP = Patient Global Assessment of Skin Pain; PPD = Purified protein derivative; PPASI = Palmoplantar Psoriasis Area and Severity Index; ppIGA = Palmoplantar Investigator's Global Assessment; PSS = Psoriatic Symptom Scale; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; sPGA = static Physician's Global Assessment; TB = Tuberculosis

APPENDIX E. SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	11 December 2020
Administrative Change 1	24 March 2021

The purpose of this version is to update the following sections and incorporate necessary protocol modifications due to the COVID-19 pandemic and changes due to new safety information available as follows:

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

- Vaccine language was updated. A COVID-19 vaccine eCRF is being implemented in the study.
  - Sections affected include: Protocol Section 5.4, Operations Manual Section 4.3

  Rationale: *To ensure subject safety during state-of-emergency or pandemic situations.*
- In Section 2.1 of the Operations Manual, the activities list was updated to indicate that Week 16 labs may be processed at a local lab, if needed.

  Rationale: *Vendor kit shortages due to the COVID-19 pandemic may necessitate the use of local labs.*
- In Section 3.12 of the Operations Manual, language was provided regarding acceptable modifications to ECG collection.

  Rationale: *Due to protocol modifications in state of emergency or pandemic situations, acceptable alternatives may need to be employed.*

Protocol

- Text was updated throughout the Protocol to align with revisions in the protocol template and changes due to new safety information available.
  - Sections include: Section 5.1, Section 5.2, Section 5.4, Section 5.5, Section 6.1 (Table 3), Appendix D (Activity Schedule)

  Rationale: *Updated language to provide align with new safety information available and provide additional clarity.*
- Throughout the Protocol, made typographical, stylistic, and administrative updates.

  Rationale: *To correct known typographical, stylistic, and administrative inconsistencies.*

Operations Manual

- Text was updated throughout the Operations Manual to align with revisions in the Operations Manual template and changes due to new safety information available.
  - Sections include: Section 3.12, Section 3.16, Section 4.1

  Rationale: *Updated language to provide align with new safety information available and provide additional clarity.*

- Protocol Section 2.1 was updated to clarify that vital signs, height, weight, and PASI would not be collected at virtual visits, if utilized (Week 4, Week 28, Week 40, and Week 52). Hematology and clinical chemistry labs at Week 16 were updated with a "+" to indicate that these labs could be performed locally, if needed.

  Rationale: *To provide clarity and correct the discrepancy between the text and visit activities lists. Vendor kit shortages may result in the need to use local laboratories.*

- Throughout the Operations manual, made typographical, stylistic, and administrative updates.

  Rationale: *To correct known typographical, stylistic, and administrative inconsistencies.*