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Protocol for Study M20-326

Plaque Psoriasis: A Phase 4 Multicenter, Randomized, Open-label, Efficacy Assessor-blinded-Study of Risankizumab Compared to Apremilast for the Treatment of Adult Subjects with Moderate Plaque Psoriasis who are Candidates for Systemic Therapy

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FULL TITLE: A Phase 4 Multicenter, Randomized, Open-label, Efficacy Assessor-blinded Study of Risankizumab Compared to Apremilast for the Treatment of Adult Subjects with Moderate Plaque Psoriasis who are Candidates for Systemic Therapy

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

SPONSOR/
EMERGENCY MEDICAL CONTACT:*

[redacted]
Therapeutic Area Medical Director
AbbVie
26525 North Riverwoods Boulevard,
Mettawa IL 60045
USA
Mobile: [redacted]
Email: [redacted]
EMERGENCY 24 hour Number: +1 (973) 784-6402

*For European Union countries: the sponsor is AbbVie Deutschland GmbH & Co. KG. The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority. Additional study contact information can be found in the Operations Manual (Appendix F).

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1 SYNOPSIS

Title: A Phase 4 Multicenter, Randomized, Open-label, Efficacy Assessor-blinded-Study of Risankizumab Compared to Apremilast for the Treatment of Adult Subjects with Moderate Plaque Psoriasis who are Candidates for Systemic Therapy	
Background and Rationale:	Psoriasis (PsO) is a chronic debilitating immunologic disease characterized by marked inflammation and thickening of the epidermis that result in thick, scaly skin plaques. Evidence generated to date has demonstrated the benefits of risankizumab compared to common treatments for PsO, such as adalimumab, ustekinumab, and secukinumab. However, no head-to-head data currently exist between risankizumab and apremilast. This study is designed to evaluate the efficacy and safety of risankizumab versus apremilast for the treatment of adult subjects with moderate plaque PsO who are candidates for systemic therapy.
Objective(s) and Endpoint(s):	The primary objective of the study is to evaluate the efficacy and safety of risankizumab versus apremilast for the treatment of adult subjects with moderate plaque PsO who are candidates for systemic therapy. In addition, the study aims to evaluate the efficacy and safety of switching to risankizumab versus continuing on apremilast for subjects with moderate plaque PsO who do not achieve ≥ 75% reduction from Baseline in Psoriasis Area Severity Index (PASI 75) after 16 weeks of treatment with apremilast. The co-primary endpoints in Period A will be evaluated as: • Achievement of ≥ 90% reduction from Baseline in PASI (PASI 90) at Week 16, among subjects in the Intent to Treat Population in Period A (ITT_A; defined as all subjects who are randomized at Baseline). • Achievement of static Physicians Global Assessment (sPGA) 0 or 1 with at least 2-grade improvement from Baseline at Week 16, among subjects in the ITT_A Population. The primary endpoint in Period B will be evaluated as: • Achievement of PASI 90 at Week 52, among subjects in the Intent to Treat Population in Period B among the Week 16 apremilast (APR)-PASI75NRs (ITT_B_NR; defined as subjects who are randomized to APR at Baseline, fail to achieve PASI 75 at Week 16, and are re-randomized). The following ranked secondary endpoints in Period A and Period B will be evaluated: <u>Period A</u> • Achievement of PASI 75 at Week 16, among subjects in the ITT_A Population. <u>Period B</u> • Achievement of PASI 75 at Week 52, among subjects in the ITT_B_NR Population.

	• Achievement of sPGA 0 or 1 with at least 2-grade improvement from Baseline at Week 52, among subjects in the ITT_B_NR Population.
Investigator(s):	Multicenter
Study Site(s):	Approximately 55 sites (globally)
Study Population and Number of Subjects to be Enrolled:	The study is designed to enroll 330 subjects (diagnosed) with moderate chronic plaque PsO with or without psoriatic arthritis (PsA) for at least 6 months prior to Baseline (Day 1). Eligible subjects must have a body surface area (BSA) of PsO involvement of ≥ 10% and ≤ 15%, PASI ≥ 12 and an sPGA score of "moderate" (3) based on a 5-point scale (0 to 4) at Screening and Baseline.
Investigational Plan:	This is a Phase 4, global, multicenter, randomized, open-label, efficacy assessor-blinded, active comparator study examining the effect of risankizumab compared to apremilast in adult subjects with moderate plaque PsO who are candidates for systemic therapy. 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 (Baseline to Week 16): Eligible subjects will be centrally randomized at the Baseline (Day 1) visit in a 1:2 ratio to receive either risankizumab 150 mg as a single subcutaneous (SC) injection (Arm 1) or apremilast 30 mg orally twice daily (BID) (Arm 2). The randomization will be stratified by Baseline body weight (≤ 100 kg, > 100 kg) and prior exposure to any systemic and/or biologic treatment for PsO (0, ≥ 1). Study drug administration for apremilast will occur beginning at Baseline (Day 1) based on the dose titration schedule from Day 1 to Day 5 and will continue with 30 mg BID until the day prior to the Week 16 visit where re-randomization will occur. Study drug administration for risankizumab will occur at Baseline (Day 1) and Week 4. The final efficacy evaluation for Period A will take place at Week 16. • Period B (Week 16 to Week 52): Subjects initially randomized to risankizumab (Arm 1) will continue to receive risankizumab 150 mg as a single SC injection at Weeks 16, 28, and 40. Subjects initially randomized to apremilast (Arm 2) will be rerandomized at the Week 16 visit in a 1:1 ratio to receive either risankizumab 150 mg as a single SC injection at Weeks 16, 20, 32, and 44 (Arm 2a) or apremilast 30 mg orally BID up to Week 52 (Arm 2b). Rerandomization will be stratified by PASI 75 response (responder, non-responder) at Week 16. Rescue risankizumab will be offered to subjects who are re-randomized to apremilast (Arm 2b) and are PASI 50 non-responders at Week 28 (Arm 3a; rescue risankizumab will be administered at Weeks 28, 32, and 44) or Week 40 (Arm 3b; rescue risankizumab will be administered at

	Weeks 40 and 44). The final efficacy evaluation will take place at Week 52. A follow up phone call for safety will be conducted approximately 20 weeks (140 days) after administration of the last dose of risankizumab or approximately 4 weeks (28 days) after the last dose of apremilast depending on the treatment at the end of the study.
Key Eligibility Criteria:	Male or female adults who are candidates for systemic therapy with a diagnosis of moderate chronic plaque PsO (with or without PsA) at Screening and Baseline for at least 6 months prior to Baseline defined as: • BSA ≥ 10% and ≤ 15%; • PASI ≥ 12; and • sPGA = 3 (moderate) based on a 5-point scale (0 to 4)
Study Drug and Duration of Treatment:	Subjects will be centrally randomized at the Baseline visit in a 1:2 ratio to receive either SC risankizumab 150 mg at Baseline and Week 4 or apremilast orally with a dose titration from Day 1 to Day 5 and continuing with 30 mg BID until the day prior to Week 16. At the Week 16 visit, subjects initially randomized to apremilast will be re-randomized in a 1:1 ratio to receive either SC risankizumab 150 mg dose at Weeks 16, 20, 32 and 44 or apremilast 30 mg dose orally BID up to Week 52. Subjects initially randomized to risankizumab will continue to receive SC risankizumab 150 mg at Weeks 16, 28, and 40. Rescue risankizumab will be offered for apremilast non-responders at Week 28 or Week 40.
Date of Protocol Synopsis:	10 November 2022

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

Psoriasis (PsO) 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 exists.[4,5]

This study seeks to demonstrate that a significantly higher proportion of patients with moderate PsO treated with risankizumab can achieve a high level of skin clearance (≥ Psoriasis Area and Severity Index [PASI] 90) compared to patients treated with apremilast providing a significant improvement in patient outcomes.

Evidence generated to date has demonstrated the benefits of risankizumab compared to other advanced therapies for PsO, such as adalimumab, ustekinumab, and secukinumab in moderate to severe PsO.[6-9] However, no head-to-head data currently exist between risankizumab and apremilast.

Risankizumab (Skyrizi™) has been approved for the treatment of moderate to severe PsO and is currently being developed for Crohn's disease, ulcerative colitis, and psoriatic arthritis (PsA) (Phase 3 studies). Risankizumab is a humanized monoclonal antibody 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.

This study is designed to evaluate the efficacy and safety of risankizumab versus apremilast for the treatment of adult subjects with moderate plaque PsO who are candidates for systemic therapy. In addition, the study aims to evaluate the efficacy and safety of switching to risankizumab versus continuing on apremilast for subjects with moderate plaque PsO who do not achieve ≥ 75% reduction from Baseline in Psoriasis Area Severity Index (PASI 75) after 16 weeks of treatment with apremilast.

For a more detailed description of the risankizumab drug profile, refer to the latest version of the Investigator's Brochure (IB).[8]

2.2 Benefits and Risks to Subjects

In risankizumab studies 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.

This study is designed to learn more about the treatment effect of risankizumab compared with apremilast in adult subjects with moderate plaque PsO who are candidates for systemic therapy as well as to learn more about the potential treatment effect of switching to risankizumab in a subset of apremilast-treated subjects considered as non-responders after 16 weeks of treatment as compared with continuing with apremilast.

Subjects with a positive QuantiFERON®-TB (or interferon gamma release assay [IGRA] equivalent)/tuberculosis (TB) skin test result for TB must fulfill entry criteria as specified in Section 5.1 of this protocol. IL-23 inhibition is not known to increase the risk of TB infection or impair the response to TB infection in animal models.[10,11] 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.[12-14] Moreover, preclinical data have demonstrated a beneficial effect of IL-23 p19 inhibition in animal models, both for pre-existing and tumor-induction models.[15] While there is not enough clinical information at this time to rule out a risk of cancer with risankizumab, this risk is considered small.

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

Increases in major adverse cardiovascular (MACE) events, including myocardial infarction, cerebrovascular accident, and cardiovascular death, 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 administered biologic therapies are usually limited to redness, swelling, or induration at the injection site. Manifestations of systemic hypersensitivity reactions may include anaphylaxis, generalized urticaria, hypotension, and respiratory distress. Both local and systemic hypersensitivity reactions are readily detectable, transient in nature, and manageable with standard medical treatment. Subjects will be closely monitored during study drug administration. An independent Anaphylaxis Adjudication Committee (AAC) will adjudicate observed systemic hypersensitivity and anaphylactic events. The AAC will remain blinded to treatment allocation (Section 6.3).

In conclusion, the benefit-risk profile of risankizumab is considered appropriate for this stage of clinical development.[16] 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 IB.[8]

Apremilast (Otezla®) was first approved as a safe and efficacious product for the treatment of plaque PsO by the United States Food and Drug Administration in 2014 and by the European Medicines Agency in 2015; since then, it has been approved in a number of additional countries. Please refer to the local label available to you for information regarding the efficacy and safety of this product.[17,18]

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

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

The objective of the study is to evaluate the efficacy and safety of risankizumab versus apremilast for the treatment of adult subjects with moderate plaque PsO who are candidates for systemic therapy.

In addition, the study aims to evaluate the efficacy and safety of switching to risankizumab versus continuing on apremilast for subjects with moderate plaque PsO who do not achieve PASI 75 after 16 weeks of treatment with apremilast.

Primary Efficacy Objective

The primary efficacy objective in Period A is to demonstrate a higher rate of a) PASI 90 (defined as ≥ 90% reduction from Baseline in PASI) and b) sPGA 0 or 1 with at least 2-grade improvement from Baseline after 16 weeks of treatment with risankizumab when compared to apremilast based on Intent to Treat (ITT) Population in Period A (ITT_A), which consists of all randomized subjects.

The hypotheses corresponding to the co-primary endpoints in Period A are:

- The proportion of subjects achieving PASI 90 in the risankizumab (RZB) group is greater than that in the APR group at Week 16, among the ITT_A Population.
- The proportion of subjects achieving sPGA 0 or 1 with at least 2-grade improvement from Baseline in the RZB group is greater than that in the apremilast (APR) group at Week 16, among the ITT_A Population.

The primary efficacy objective in Period B is to demonstrate a higher rate of PASI 90 after switching the treatment at Week 16 from APR to RZB for 36 weeks (APR/RZB) when compared to continuing with APR (APR/APR) based on the Intent to Treat Population in Period B for Week 16 APR-PASI75NRs (ITT_B_NR), which consists of subjects who are randomized to APR at Baseline, fail to achieve PASI 75 at Week 16, and are re-randomized.

The hypothesis corresponding to the primary endpoint in Period B is:

- The proportion of APR-PASI75NR subjects achieving PASI 90 in the APR/RZB group is greater than that in the APR/APR group at Week 52, among the ITT_B_NR Population.

Key Secondary Efficacy Objectives

The key secondary efficacy objective in Period A is to demonstrate higher efficacy of treatment with RZB when compared to APR with respect to the ranked and only secondary endpoint in Period A, as specified in Section 3.3 below.

The hypothesis corresponding to the ranked and only secondary endpoint in Period A is:

- The proportion of subjects achieving PASI 75 in the RZB group is greater than that in the APR group at Week 16, among the ITT_A Population.

The key secondary efficacy objectives in Period B are to demonstrate higher efficacy of treatment with APR/RZB when compared to APR/APR among APR-PASI75NRs, with respect to the key secondary endpoints in a ranked order in Period B, as specified in Section 3.3 below.

The hypotheses corresponding to the ranked secondary endpoints in Period B are:

- The proportion of APR-PASI75NR subjects achieving PASI 75 in the APR/RZB group is greater than that in the APR/APR group at Week 52, among the ITT_B_NR Population.
- The proportion of APR-PASI75NR subjects achieving sPGA 0 or 1 with at least 2-grade improvement from Baseline in the APR/RZB group is greater than that in the APR/APR group at Week 52, among the ITT_B_NR Population.

Estimands Corresponding to the Primary and Ranked Secondary Endpoints

The estimand corresponding to each of the primary and ranked secondary endpoints in Period A is defined using composite variable strategy as follows:

- Difference in the proportion of subjects achieving the corresponding endpoint at Week 16, without receiving alternative PsO treatment, regardless of premature discontinuation of study drug, in the RZB group in comparison with the APR group among the ITT_A population.

The estimand corresponding to each of the primary and ranked secondary endpoints in Period B is defined using composite variable strategy:

- Difference in the proportion of subjects achieving the corresponding endpoint at Week 52 without satisfying the rescue criteria or receiving the rescue medication, and without receiving alternative PsO treatment, regardless of premature discontinuation of study drug in the APR/RZB group in comparison with the APR/APR group among the ITT_B_NR population.

3.2 Primary Endpoints

Co-Primary Endpoints in Period A:

- Achievement of PASI 90 at Week 16, among subjects in the ITT_A Population.

- Achievement of sPGA 0 or 1 with at least 2-grade improvement from Baseline at Week 16, among subjects in the ITT_A Population.

Primary Endpoint in Period B:

- Achievement of PASI 90 at Week 52, among subjects in the ITT_B_NR Population.

3.3 Secondary Endpoints

Ranked Secondary Endpoint in Period A:

- Achievement of PASI 75 at Week 16, among subjects in the ITT_A Population.

Ranked Secondary Endpoints in Period B:

- Achievement of PASI 75 at Week 52, among subjects in the ITT_B_NR Population.
- Achievement of sPGA 0 or 1 with at least 2-grade improvement from Baseline at Week 52, among subjects in the ITT_B_NR Population.

3.4 Additional Efficacy Endpoints

All variables listed above as primary or ranked secondary endpoints will also be analyzed at all other visits collected. Additionally, the following endpoints will be evaluated at all visits collected:

- Achievement of 100% reduction from Baseline in PASI (PASI 100)
- Achievement of sPGA 0
- Change from Baseline in PASI
- Percent change from Baseline in PASI
- Change from Baseline in body surface area (BSA)
- Achievement of Palmoplantar Investigator's Global Assessment (ppIGA) 0 or 1, among subjects with Baseline ppIGA of at least 3
- Change from Baseline in Psoriasis Scalp Severity Index (PSSI), among subjects with Baseline scores > 0
- Change from Baseline in Nail Psoriasis Severity Index (NAPSI), among subjects with Baseline scores > 0
- 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

- Change from Baseline in Work Productivity and Activity Impairment (WPAI) scores
- Treatment Satisfaction Questionnaire for Medication version 9 (TSQM-9) scores (at each post-Baseline visit in Period A)
- Change from Entry of Period B in TSQM-9 scores, among subjects who are re-randomized at Week 16
- Change from Baseline in Psoriasis Symptoms Scale (PSS) scores
- Percentage change from Baseline in PSS, among subjects with Baseline scores > 0
- Achievement of PSS 0
- Achievement of PSS 0 or 1

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 (hematology and chemistry)

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.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 4, global, multicenter, randomized, open-label, efficacy assessor-blinded, active comparator study examining the effect of risankizumab compared to apremilast in adult subjects with moderate plaque PsO who are candidates for systemic therapy.

The study is designed to enroll 330 subjects. See Section 5.1 for information regarding enrollment criteria.

The study duration for subjects administered risankizumab or provided apremilast will be up to approximately 69 weeks or 61 weeks, respectively. The study is comprised of a Screening period of up to 35 days, a 52week treatment period, and a follow-up phone call for safety. Depending on the

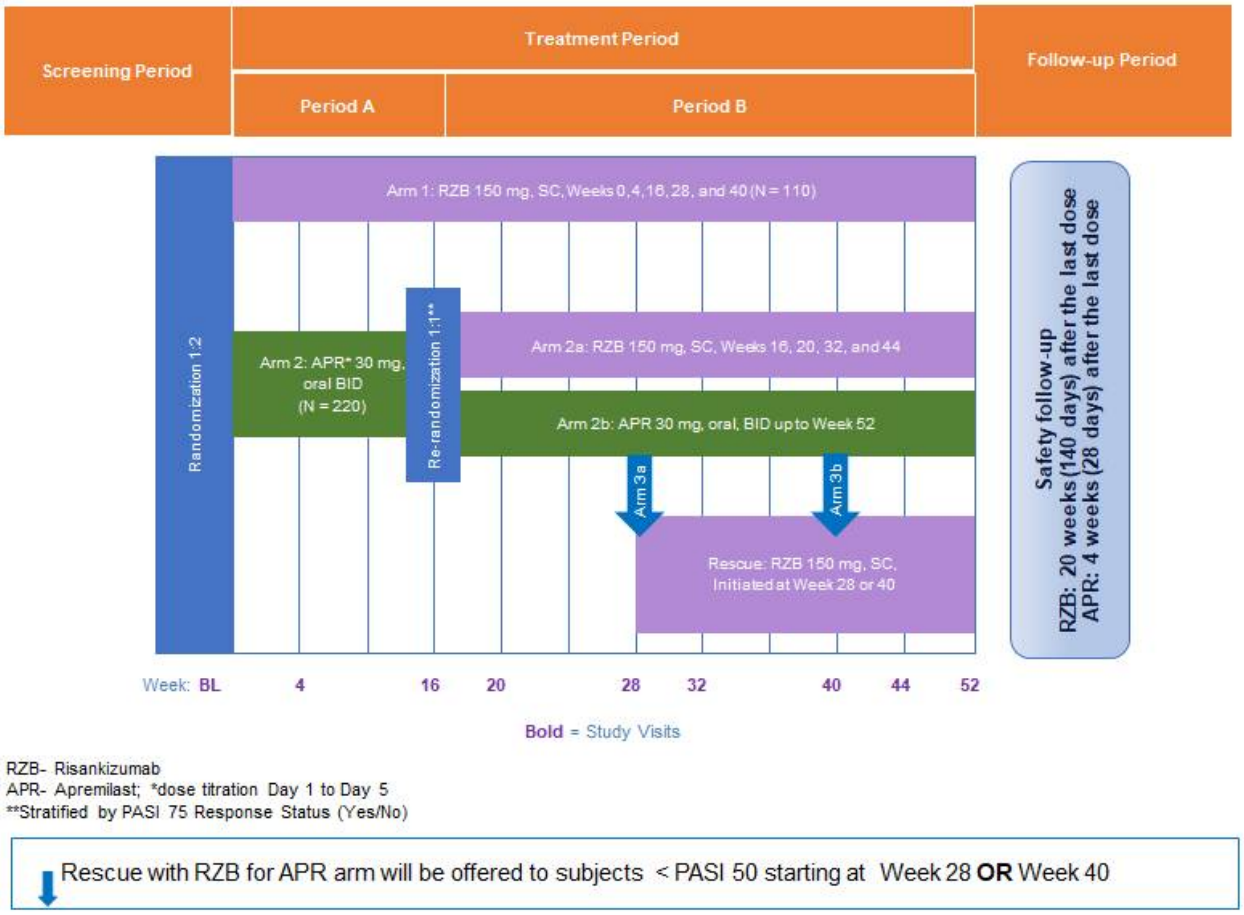
treatment at the end of the study, the follow-up phone call for safety will be conducted approximately 20 weeks (140 days) after administration of the last dose of risankizumab (i.e., Week 40 for subjects originally randomized to risankizumab and Week 44 for subjects switched from apremilast to risankizumab) or approximately 4 weeks (28 days) after the last dose of apremilast (for subjects who remain on the APR arm after re-randomization).

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

- Period A (Baseline to Week 16): Eligible subjects will be centrally randomized at the Baseline (Day 1) visit in a 1:2 ratio to receive either risankizumab 150 mg as a single subcutaneous (SC) injection (Arm 1) or apremilast 30 mg orally twice daily (BID) (Arm 2). The randomization will be stratified by Baseline body weight (≤ 100 kg, > 100 kg) and prior exposure to any systemic and/or biologic treatment for PsO (0, ≥ 1). Study drug administration for apremilast will occur beginning at Baseline (Day 1) based on the dose titration schedule from Day 1 to Day 5 and will continue with 30 mg BID until the day prior to the Week 16 visit where re-randomization will occur. Study drug administration for risankizumab will occur at Baseline (Day 1) and Week 4. The final efficacy evaluation for Period A will take place at Week 16.
- Period B (Week 16 to Week 52): Subjects initially randomized to risankizumab (Arm 1) will continue to receive risankizumab 150 mg as a single SC injection at Weeks 16, 28, and 40. Subjects initially randomized to apremilast (Arm 2) will be re-randomized at the Week 16 visit in a 1:1 ratio to receive either risankizumab 150 mg as a single SC injection at Weeks 16, 20, 32, and 44 (Arm 2a) or apremilast 30 mg orally BID up to Week 52 (Arm 2b). Rerandomization will be stratified by PASI 75 response (responder, non-responder) at Week 16. Rescue risankizumab will be offered to subjects who are re-randomized to apremilast (Arm 2b) and are PASI 50 non-responders at Week 28 (Arm 3a; rescue risankizumab will be administered at Weeks 28, 32, and 44) or Week 40 (Arm 3b; rescue risankizumab will be administered at Weeks 40 and 44). The final efficacy evaluation will take place at Week 52.

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



BID = twice daily; PASI = Psoriasis Area Severity Index; SC = subcutaneous

4.2 Discussion of Study Design

Choice of Control Group

An active comparator group randomized to receive apremilast will be used in this study to examine the effect of 150 mg risankizumab every 12 weeks versus 30 mg apremilast BID in subjects with moderate plaque PsO who are candidates for systemic therapy.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are standard for assessing disease activity in subjects with moderate plaque PsO. All clinical and laboratory procedures in this study are standard and generally accepted. All patient-reported outcomes (PRO) measures in this study were adequately developed and validated to measure specific concepts of interest relevant to this study.

Suitability of Subject Population

Male or female subjects with a diagnosis of moderate chronic plaque PsO (with or without PsA) for at least 6 months prior to Baseline and who are candidates for systemic therapy are eligible for this study. Eligible subjects must also have moderate chronic plaque PsO as defined by BSA ≥ 10% and ≤ 15%, PASI ≥ 12, and sPGA = 3 (moderate) based on a 5-point scale (0 to 4) at Screening and the Baseline Visit. The selection criteria relating to safety guarantee that subjects enrolled can safely be treated with risankizumab or apremilast based on the current knowledge of these drugs.

Selection of Doses in the Study

The selected dose of 150 mg SC for risankizumab is the same as the approved labeled dose in the treatment of moderate to severe plaque PsO tested in Phase 3 global studies in subjects with moderate to severe plaque PsO. The risankizumab 150 mg SC dose has been shown to be efficacious with an acceptable safety profile and considered appropriate for the treatment of patients with moderate plaque PsO. For apremilast, the selected dose is as recommended in the approved product labeling for the treatment of plaque PsO.

Blinded Efficacy Assessor

A qualified physician (may be a non-dermatologist) or designee (may be a non-physician) from the site will be responsible for performing the efficacy assessments, including PASI, BSA, and sPGA at all appropriate study visits (Table 1). The site will make every attempt to have the same qualified physician or designee perform these assessments throughout the study for each subject. The efficacy assessor must remain blinded to patient's treatment, clinical laboratory results, and all subject safety data during the course of the study. The efficacy assessor will not view or discuss any subject specific safety data with the investigators or any other site personnel, with the exception of the dermatologic safety findings requiring urgent medical attention. The efficacy assessor therefore cannot be the Principal Investigator. The efficacy assessor will not access patient's electronic case report form (eCRF) and will document the dermatologic assessments and potential dermatologic safety findings on paper worksheets that will be filed as source in the patient's record. It is recommended that each study site has a designated back-up for the efficacy assessor.

Table 1. Tasks of the Efficacy Assessor and Investigators

Activities	Responsible Party
Assesses PASI, sPGA, BSA, ppIGA, NAPSI, and PSSI	Efficacy Assessor[a]
Looks for any potential dermatologic safety finding	Efficacy Assessor
Documents the efficacy assessments and any potential dermatologic safety findings on worksheets	Efficacy Assessor
Assesses safety	Investigator
Knows treatment allocation	Investigator
Reviews laboratory data	Investigator
Conduct the complete and any targeted physical examinations[b]	Investigator
Completes the CRF	Investigator, unblinded study team
Documents findings in the eCRF	Investigator, unblinded study team
Reports information about safety findings[c]	Investigator

BSA = body surface area; CRF = case report form; eCRF = electronic case report form; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; ppIGA = Palmoplantar Investigator's Global Assessment; PSSI = Psoriasis Scalp Severity Index; sPGA = Static Physician Global Assessment

a. The efficacy assessor is a physician or a designee that is blinded to all aspects of the study other than the efficacy assessments.

b. The investigator will also look for potential dermatologic safety findings.

c. If the efficacy assessor identifies a safety issue this will be transmitted to the investigator over the worksheet via paper collection. Dermatologic safety findings requiring urgent medical attention will be the only safety issues that the efficacy assessor may discuss with the investigator.

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 transaminase (AST) ≤ 2 × upper limit of normal (ULN);
  - Serum alanine transaminase (ALT) ≤ 2 × ULN;
  - Serum total bilirubin ≤ 2.0 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
  - Total white blood cell (WBC) count ≥ 3,000/µL;
  - Absolute neutrophil count ≥ 1,500/µL;
  - Platelet count ≥ 100,000/µL;
  - Hemoglobin ≥ 10 g/dL (100 g/L);
  - Estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR [CKD-EPI]) ≥ 30 mL/min/1.73 m^2.

Disease/Condition Activity

- 6. Male or female subject with a diagnosis of chronic plaque PsO with or without PsA, for at least 6 months prior to Baseline.
- 7. Stable moderate chronic plaque PsO at both Screening and Baseline as defined as:
  - BSA ≥ 10% and ≤ 15%,
  - PASI ≥ 12, and
  - sPGA = 3 (moderate) based on a 5-point scale (0 to 4).
- 8. PsO 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. Subject must not have any form of PsO other than chronic plaque PsO (e.g., pustular PsO, palmoplantar pustulosis, acrodermatitis of Hallopeau, erythrodermic, or guttate PsO).
- 12. Subject must not have a history of current drug-induced PsO or a drug-induced exacerbation of pre-existing PsO.
- 13. Subject must not have a history of active ongoing inflammatory skin diseases other than PsO and PsA that could interfere with the assessment of PsO (e.g., hyperkeratotic eczema).

- 14. Subject must not have a history of severe renal insufficiency defined as creatinine clearance < 30 mL/min and/or requiring hemodialysis or peritoneal dialysis.
- 15. Subject must not have a history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 6 months.
- 16. Subject must not have a history of an **allergic reaction** or significant sensitivity to constituents of the study drugs (and its excipients) and/or other products in the same class.
- 17. Subject must not have had **major surgery** performed within 12 weeks prior to randomization or planned during the conduct of the study (e.g., hip replacement, aneurysm removal, stomach ligation).
- 18. 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., polymerase chain reaction [PCR]) testing to rule out SARS-CoV-2 infection. In addition, if based on the answers to the SARS-CoV-2 Infection Risk Assessment Tool the site considers the subject currently at risk for developing SARS-CoV-2 infection, then the subject should either be tested or advised to come back for study screening after 14 days.

  Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:

  - At least 14 days since first PCR test result have passed in asymptomatic patients or 14 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.
- 19. 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 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 3.13 of the Operations Manual.

  Active systemic infection/Clinically important infection during the last 2 weeks prior to Baseline visit as assessed by the investigator.
- 20. Subjects 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.
- Prior history of suicide attempt at any time in the subject's lifetime prior to signing the informed consent and randomization, or major depression or suicidal ideation or attempt requiring hospitalization within the last 3 years prior to signing the informed consent.
- Hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption.

21. 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.

Contraception

22. 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.

23. Risankizumab:

- 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.
- Female subjects may not be **pregnant, breastfeeding, or considering becoming pregnant or donating eggs** 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.

Apremilast:

- 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 28 days (or as guided by the local apremilast label, 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.
- Female subjects may not be **pregnant, breastfeeding, or considering becoming pregnant or donating eggs** during the study or for approximately 28 days (or as guided by the local apremilast label, whichever is longer) after the last dose of study drug.

Concomitant Medications (Prior Medication Restrictions)

24. Subject must not have had any prior exposure to risankizumab or apremilast.

- 25. Subject must not have received **any live viral or bacterial vaccine** within 4 weeks prior to the first dose of study drug, or expect the need for live vaccination during study participation including at least 140 days (20 weeks or as guided by the local risankizumab label [if approved], whichever is longer) after the last dose of risankizumab or at least 28 days after the last dose of apremilast.
- 26. 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.
- 27. Subject did not receive for at least 30 days prior to Baseline any:
  - Other systemic immunomodulating treatments (including, but not limited to: e.g., methotrexate, cyclosporine A, corticosteroids, cyclophosphamide, tofacitinib [Xeljanz®]);
  - 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]) or prolonged exposure or use of tanning booths or ultraviolet light sources.
- 28. Subject must not have been treated with **any investigational drug** within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or be currently enrolled in another interventional clinical study.
- 29. Subject did not receive for at least 14 days prior to Baseline 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).
- 30. Subject must not be treated with any strong cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin, St. John's Wort) within 30 days or 5 half-lives of start of treatment with apremilast.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

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

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

- Females, of Childbearing Potential

    Females of childbearing potential must avoid pregnancy while taking study drug 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 risankizumab or 28 days (or as guided by the local apremilast label, whichever is longer) after the last dose of apremilast. Females must commit to one of the following methods of birth control:

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

For those subjects who are re-randomized to risankizumab or are rescued with risankizumab, contraception guidelines for risankizumab apply.

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 (including any biosimilar thereof) to treat moderate plaque PsO 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, and fumaric acid derivatives. Exception: Treatment with commercially available apremilast after the Week 52/PD assessments if this has been determined as an appropriate subsequent treatment by the investigator in discussion with the subject.
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. For subjects on apremilast: strong cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin, and St. John's Wort).
7. Live attenuated vaccines (except non-replicating live vaccines, e.g., JYNNEOS monkeypox vaccine) 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 risankizumab or up to 28 days after the last dose of apremilast.

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

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

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

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with risankizumab and/or apremilast can be located in the risankizumab Investigator's Brochure[8] or apremilast label.[17,18]

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.

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 (Day 1) 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, ophthalmic, otic, or intranasal corticosteroids are permitted during the study.

5.5 Withdrawal of Subjects and Discontinuation of Study

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

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

- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix where discontinuation is at the discretion of the Investigator.
- The subject becomes pregnant while on study drug.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk.
- The investigator determines the subject is significantly noncompliant with study procedures.
- Post-Baseline occurrence of new or worsening psychiatric symptoms, including suicidal ideation or a suicidal attempt.
- Post-Baseline occurrence of one or more of the following hepatic abnormalities (confirmed on a second separate sample as 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 source documents. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug.

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

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at their site if they have safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modification

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

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

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

During the study drug dosing period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- At least 14 days since first positive test result have passed in asymptomatic patients or at least 14 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Follow 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 efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the subject has the option to continue in the study and complete the remaining visits as scheduled. If remaining visits will be completed, a PD visit is not required. If the subject does not continue in the study, the procedures outlined for the PD visit must be completed, ideally within 2 weeks of the decision and preferably prior to the initiation of another therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition.

Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a follow-up phone call approximately 140 days (20 weeks) after the last dose of risankizumab or approximately 28 days after the last dose of apremilast may be completed to ensure all treatment-emergent AEs/serious adverse events (SAEs) have been resolved. The 140-day (20-week) or 28-day follow-up phone calls following the last dose of risankizumab or apremilast, respectively, during the trial will not be required for any subject

who initiates commercially available risankizumab or apremilast upon or after the study Completion Visit (i.e., Week 52 or during the follow-up period) or PD 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.

5.7 Study Drug

Study site staff will administer risankizumab (150 mg [1 × 1 mL 150 mg/mL pre-filled syringe]) subcutaneously or study staff will provide apremilast (30 mg [10 mg, 20 mg, 30 mg, film-coated tablets]) beginning at Baseline (Day 1) (Table 2).

Apremilast subject dosing (orally) will be recorded on a subject dosing diary. The subject will be instructed to return all apremilast packaging (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

Table 2. Identity of Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Risankizumab (ABBV-066)	Solution for injection in pre-filled syringe (PFS)	150 mg (1x 1 mL 150 mg/mL PFS)	Subcutaneous injection	AbbVie
Apremilast	Tablets	10 mg, 20 mg, 30 mg film-coated tablets	Oral	Amgen

AbbVie will not supply drug other than risankizumab and apremilast. AbbVie provided study drugs should not be substituted or alternately sourced unless otherwise directed by AbbVie.

Open-label risankizumab and apremilast will be packaged in quantities sufficient to accommodate study design. Each risankizumab kit or apremilast package will be labeled per local requirements and this label must remain affixed to the respective packaging. Upon receipt, study drug should be stored as specified on the label in their original packaging and kept in a secure location. A temperature log must be maintained for documentation. Each kit or package will contain a unique kit or package number. This number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff prior to dispensing to subjects. Study drugs will only be used for the conduct of this study.

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.

Study treatment duration includes Period A and Period B:

- Period A (Baseline to Week 16): Eligible subjects will be centrally randomized at the Baseline (Day 1) visit in a 1:2 ratio to receive either risankizumab 150 mg as a single SC injection (Arm 1) or apremilast orally with a dose titration from Day 1 to Day 5 and continuing with 30 mg BID until the day prior to Week 16 (Arm 2). The randomization will be stratified by Baseline body weight (≤ 100 kg, > 100 kg) and prior exposure to any systemic and/or biologic treatment for PsO (0, ≥ 1).
- Period B (Week 16 to Week 52): Subjects initially randomized to apremilast (Arm 2) will be rerandomized at the Week 16 visit in a 1:1 ratio to receive either risankizumab 150 mg as a single SC injection (Arm 2a) or apremilast 30 mg orally BID (Arm 2b). Rerandomization will be stratified by PASI 75 response (responder, non-responder) at Week 16. Rescue risankizumab will be offered for subjects who are re-randomized to the apremilast arm and are PASI 50 non-responders at Week 28 (Arm 3a) or Week 40 (Arm 3b).

This is an open-label study; however, the efficacy assessor will remain blinded to each subject's treatment, clinical laboratory results, and all subject safety data during the course of the study.

In the event of a medical emergency in which the Investigator believes that knowledge of study drug treatment is required for the efficacy assessor, reasonable efforts must be made to contact the AbbVie Emergency Contact.

The date and reason that the efficacy assessor's 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 the investigational products must be reported to AbbVie.

Product Complaint

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

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

Product complaints concerning the investigational products and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

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

Medical Complaints/Adverse Events and Serious Adverse Events: Study Drug

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

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

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

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly

during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

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

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event 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 risankizumab or apremilast administration until 140 days (20 weeks) after discontinuation of risankizumab administration or 28 days after discontinuation of apremilast administration will be collected, whether solicited or spontaneously reported by the subject. After 140 days (20 weeks) following the last dose of study drug or completion of study treatment only

spontaneously reported SAEs will be collected (nonserious AEs will not be collected.) In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent. If a subject prematurely discontinues study participation and begins commercially available risankizumab (Skyrizi) or apremilast (Otezla) all adverse events reported by healthcare professionals or the patient, will be captured as postmarketing reports. The follow-up phone call following the last dose of risankizumab during the study will not occur for subjects who begin commercially available risankizumab or apremilast.

The following definitions will be used for Serious Adverse Reactions (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 unexpected (not listed in the applicable Reference Safety Information [RSI]), and meets one of the above serious criteria.

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

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 eCRF(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 eCRF
Cardiac events: • **Myocardial infarction or unstable angina** • **Cerebral vascular accident** • **Cardiovascular death**	• Cardiovascular History and CV Risk Factors eCRF • Cardiovascular (Cardiac) AE eCRF • Myocardial Infarction and Unstable Angina AE eCRF • Heart Failure AE eCRF • Cerebral Vascular Accident and Transient Ischemic Attack AE eCRF • Combination Thrombotic Event AE eCRF • Arrhythmia AE eCRF
In the case of any of the following AEs, the appropriate supplemental eCRFs should be completed: • **Discontinuation or interruption of study drug due to any hepatic-related AE** • **Any Hepatic-related SAE** • **A subject experiencing an ALT/AST > 8 × ULN** • **A subject experiencing an 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; ALT = alanine aminotransferase; AST = alanine aminotransferase; CV = cardiovascular; eCRF = electronic case report form; SAE = serious adverse event; TB = tuberculosis; ULN = upper limit of normal

Apremilast

At any time during the study, the PI may deem it appropriate to withhold the dosage of apremilast administered to a study subject. The PI may choose to withhold the apremilast dosage as a result of subject reported symptoms, physical examination, AEs, and/or changes in clinical laboratory profiles. If apremilast is withheld due to physical exam or subject reported AEs, the PI should determine the risk/benefit of continuing a subject in the study.

Additionally, apremilast administration should be evaluated at any time during the study in the following circumstances:

- Psychiatric disorders: If subjects suffered from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt is identified, it is recommended to discontinue treatment with apremilast.
- Diarrhea, nausea, and vomiting: If patients develop severe diarrhea, nausea, or vomiting, discontinuation of treatment with apremilast may be considered.
- Weight decrease: If unexplained or clinically significant weight loss occurs, evaluate weight loss and according to outcomes of the assessment, consider discontinuation of apremilast.

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.[19]

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

- **Grade 1 (Mild);** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2 (Moderate);** minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- **Grade 3 (Severe);** medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4 (Severe);** Life-threatening consequences; urgent intervention indicated.
- **Grade 5 (Severe);** Death related to AE

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

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

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be

discontinued (Section 5.5). If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered 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 pre-specified definitions. This independent external Anaphylaxis Adjudication Committee (AAC) will adjudicate suspected anaphylactic reactions and will remain blinded to treatment allocation. The event terms to be adjudicated and the adjudication process are detailed in the AAC Charter. A supplemental Hypersensitivity Reactions Signs and Symptoms eCRF will be used to collect information pertinent to the events. In addition, the site may be contacted for additional source documentation.

If a suspected systemic hypersensitivity reaction occurs at the investigative site, in addition to testing tryptase and histamine levels, PK, 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 for Period A will be conducted after all continuing subjects have completed Week 16 visit and the database is locked. This will be the only and final analysis for the primary and secondary efficacy endpoints for Period A.

The Primary Analysis for Period B will be conducted after all continuing subjects have completed Week 52 visit and the database is locked. This will be the only and final analysis for the primary and secondary efficacy endpoints for Period B.

The final analysis will be conducted upon study completion. The statistical analysis will be described and fully documented in the SAP. All statistical tests will be performed at a two-sided alpha level of 0.05. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Intent to Treat Population in Period A (ITT_A) includes all randomized subjects. The ITT_A Population will be used for all efficacy analyses in Period A.

The Intent to Treat Population for APRPASI75NRs in Period B (ITT_B_NR) includes subjects who are randomized at Baseline (Day 1), fail to achieve PASI 75 at Week 16, and are re-randomized. The ITT_B_NR Population will be used for the analysis comparing switch-to-RZB (APR/RZB) versus continue-with-APR (APR/APR) among APR-PASINRs in Period B.

The Intent to Treat Population for APR-PASI75 responders in Period B (ITT_B_R) includes subjects who are randomized to APR at Baseline, achieve PASI 75 at Week 16, and are re-randomized (APR-PASI75Rs). The ITT_B_R Population will be used for the summary of efficacy for APR/RZB and APR/APR among APR-PASI75Rs in Period B.

The Intent to Treat Population for Period B combined Population (ITT_B_Combined) includes subjects who are randomized to APR at Baseline and are re-randomized at Week 16. The ITT_B_Combined Population will be used for combined analysis (APR-PASI75NRs and APR-PASI75Rs) between subjects re-randomized to APR/RZB and APR/APR in Period B.

The Intent to Treat Population for Long Term Efficacy (ITT_LT) includes subjects who are randomized to receive continuous RZB (i.e., all subjects randomized to RZB at Baseline) and subjects who are randomized and re-randomized to receive continuous APR, including half of the subjects randomized to APR at Baseline and prematurely discontinued from study before entering Period B. The ITT_LT Population will be used for the analysis comparing long term efficacy between continuous treatment of RZB/RZB and APR/APR in Period B.

The Intent to Treat Population for Rescued Population (ITT_Res) includes subjects who are re-randomized to APR at Week 16, fail to achieve PASI 50 at Week 28 and Week 40, and receive RZB as the rescue medication. The ITT_Res Population will be used for the summary of efficacy after being rescued with RZB.

Each ITT Population will have a corresponding Safety Population. In addition, an all risankizumab treated (ALL_RZB) Population will be utilized for a comprehensive safety summary of RZB. The ALL_RZB Population is defined as all subjects who receive at least one dose of RZB as the study drug.

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

The co-primary endpoints (Section 3.2) and the ranked secondary endpoint (Section 3.3) in Period A will be analyzed in the ITT_A Population and subjects with the following intercurrent event will be considered as non-responders:

- Subjects who receive alternative PsO treatment regardless of premature discontinuation of study drug before Week 16.

The primary endpoints (Section 3.2) and the ranked secondary endpoints (Section 3.3) in Period B will be analyzed in the ITT_B_NR Population and subjects with the following intercurrent event will be considered as non-responders:

- Subjects who receive alternative PsO treatment regardless of premature discontinuation of study drug before Week 52.
- Subjects who satisfy rescue criteria or receive the rescue medication at Week 28 or Week 40.

7.4 Statistical Analyses for Efficacy

Summary and Analysis of the Primary Endpoints

All statistical tests will be performed at a 2-sided alpha level of 0.05.

Analysis of the co-primary endpoints in Period A will be conducted among the ITT_A Population based on treatment as randomized. The number and proportion (n, %) of subjects achieving the endpoints will be summarized within each treatment group. Comparison of the proportion of responders for each co-primary endpoint will be made between the RZB and APR groups (i.e., adjusted difference, 95% CI, p-value) using the Cochran-Mantel-Haenszel (CMH) test adjusting for the actual values of stratification factors in the initial randomization at Baseline.

Analysis of the primary endpoint in Period B will be conducted among the ITT_B_NR Population based on treatment as re-randomized. The number and proportion (n, %) of subjects achieving the endpoint will be summarized within each treatment group. Comparison of the proportion of responders will be made between the APR/RZB and APR/APR groups (i.e., difference, 95% CI, p-value) using the Chi-square test. Subjects who satisfy the rescue criteria at Week 28 or Week 40 or receive rescue medication in Period B will be counted as non-responders for the primary endpoint in Period B.

Non-Responder Imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-MI) will be used to handle missing data.

Summary and Analysis of Ranked Secondary Endpoints

Analysis of the ranked secondary endpoint in Period A will be conducted among the ITT_A Population based on treatment as randomized. The number and proportion (n, %) of subjects achieving the endpoint will be summarized within each treatment group. Comparison of the proportion of responders

will be made between RZB and APR groups (i.e., adjusted difference, 95% CI, p-value) using the CMH test adjusting for the actual values of stratification factors in the initial randomization at Baseline.

Analysis of the ranked secondary endpoints in Period B will be conducted among the ITT_B_NR Population based on treatment as rerandomized. The number and proportion (n, %) of subjects achieving the endpoint will be summarized within each treatment group. Comparison of the proportion of responders will be made between APR/RZB and APR/APR groups (i.e., difference, 95% CI, p-value) using the Chi-square test. Subjects who satisfy the rescue criteria at Week 28 or Week 40 or receive rescue medication will be counted as non-responders for the ranked secondary endpoints in Period B.

NRI-MI will be used to handle missing data.

Summary and Analysis of Additional Efficacy Endpoints

Additional binary endpoints will be analyzed among each Population as follows:

- Comparison of additional endpoints among the ITT_A and ITT_LT Populations will be made using CMH test adjusting for the actual values of stratification factors in the initial randomization at Baseline. NRI-MI will be used to handle missing data.
- Comparison of additional endpoints among the ITT_B_NR Population will be made using Chi-square test. NRI-MI will be used to handle missing data.
- Comparison of additional endpoints among the ITT_B_Combined Population will be made using CMH test adjusting for the actual value of the stratification factor in the re-randomization at Week 16. NRI-MI will be used to handle missing data.
- Summary statistics will be provided for additional endpoints among the ITT_B_R Population. NRI-MI will be used to handle missing data.
- Summary statistics will be provided for additional endpoints among the ITT_Res Population, based on Observed Cases (OC).

Additional continuous endpoints will be analyzed among each Population as follows:

- Comparison of additional endpoints on ITT_A and ITT_LT Population will be made based on the fixed term of treatment from a Mixed-effect Model Repeat Measurement (MMRM), adjusting for treatment, actual values of stratification factors and Baseline value if applicable (if not duplicating the stratification factors).
- Comparison of additional endpoints on ITT_B_NR Population will be made based on the fixed term of treatment from a MMRM, adjusting for treatment and Baseline value.
- Comparison of additional endpoints among the ITT_B_Combined Population will be made based on the fixed term of treatment from a MMRM, adjusting for treatment, actual values of stratification factors in the re-randomization at Week 16 and Baseline value.
- Summary statistics will be provided for additional endpoints among the ITT_B_R Population, based on the fixed term of treatment from a MMRM, adjusting for treatment and Baseline value.

- Summary statistics will be provided for additional endpoints among the ITT_Res Population, based on OCs.

Subgroup Analysis for Efficacy

Subgroup analysis will be performed on co-primary endpoints in Period A using the following subgroups:

- Age group: < 40, ≥ 40 to < 65, ≥ 65
- 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 PASI score (by median)
- Psoriatic arthritis (yes, no)
- Prior systemic treatment (0, ≥ 1)

Age ≥ 65 years or BMI ≥ 30 subgroups will be combined with their adjacent subgroup when having fewer than 10% subjects.

7.5 Statistical Analyses for Safety

All safety analyses will be performed among the Safety Populations. Subjects will be analyzed based on the first dose of treatment received after randomization or re-randomization. A treatment-emergent adverse event (TEAE) in each analysis period is defined as follows:

A TEAE in Period A is defined as any AE with an onset date on or after the first dose of study drug in Period A and

1. within the minimum of 140 days after the last dose of RZB in Period A and first dose of study drug in Period B for subjects who receive RZB at Baseline and
2. within the minimum of 28 days after the last dose of APR in Period A and first dose of study drug in Period B for subjects who receive APR at Baseline.

A TEAE in Period B is defined as any AE with an onset date on or after the first dose of study drug in Period B and

1. within 140 days after the last dose of RZB in Period B for subjects who receive RZB in Period B and
2. within the minimum of 28 days after the last dose of APR in Period B, first dose of rescue risankizumab (if any) for subjects who receive APR in Period B.

A TEAE during the administration of rescue risankizumab is defined as any AE with an onset date on or after the first dose of rescue risankizumab and within 140 days after the last dose of rescue risankizumab.

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

The number and percentage of subjects experiencing TEAEs will be tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, by severity, and by relationship to the study drug as assessed by the investigator. Summaries (including percentages and events per 100 PYs) of SAEs, deaths, and AEs leading to discontinuation of study drug will be provided as well. Pre-treatment SAEs will be summarized separately.

For selected lab parameters, a listing of all subjects with any laboratory value that is above Grade 3 of Common Toxicity Criteria will be provided. Mean change in laboratory and vital signs variables will be summarized. Additional details for the safety analysis are provided in the SAP.

7.6 Interim Analysis

No interim analysis is planned for this study.

7.7 Overall Type I Error Control

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

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

7.8 Sample Size Determination

This study plans to enroll a total of N = 330 subjects, to be sufficiently powered to detect the treatment difference between RZB and APR with respect to the co-primary endpoints in Period A, as well as between APR/RZB and APR/APR with respect to the primary endpoint in Period B:

- Assuming that 50% of APR-PASI75NR subjects in the APR/RZB group and 20% of APR-PASI75NR subjects in the APR/APR group will achieve PASI 90 at Week 52 in Period B, the sample size of 120 re-randomized APR-PASI75NR subjects (60 subjects per group) will have more than 90% power to detect the treatment difference between APR/RZB and APR/APR, using a Chi-square test with a 2-sided significance level of 0.05.
- Assuming 55% of subjects initially randomized to APR will be re-randomized at Week 16 under the APR-PASI75NR (as defined by the PASI 75 response at Week 16) stratum, the total sample size for the initial APR group is 120/55% = 220. Assuming the treatment difference is at least 40% with respect to the co-primary endpoints of PASI 90 and sPGA of 0 or 1 at Week 16 in Period A, the total sample size of N = 330 subjects (RZB: 110, APR: 220) will also provide more

than 90% power to detect the treatment difference between RZB and APR, using a Chi-square test with a 2-sided significance level of 0.05.

8 ETHICS

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

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

8.2 Ethical Conduct of the Study

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

8.3 Subject Confidentiality

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

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

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

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

10 DATA QUALITY ASSURANCE

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

11 START AND COMPLETION OF THE STUDY

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

The end-of-study is defined as the date of end of study participation by the last subject in the last country where the study was conducted.

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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
ALL_RZB	All risankizumab treated population
ALT	Alanine aminotransferase/transaminase
APR	Apremilast
APR-PASI75NR	Apremilast PASI75 non-responders
APR-PASI75R	Apremilast PASI75 responders
ASI	Areas of safety interest/adverse events of safety interest
AST	Aspartate aminotransferase/transaminase
BCG	Bacille Calmette-Guérin
BID	Twice daily
BMI	Body mass index
BSA	Body surface area
CAC	Cardiovascular Adjudication Committee
CBC	Complete blood count
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease of 2019
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
HB	Hepatitis B
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HIV	Human immunodeficiency virus
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-23	Interleukin-23
IMP	Investigational Medicinal Product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent to treat
ITT_A	Intent to Treat Population in Period A
ITT_B_Combined	Intent to Treat Population for Period B combined Population
ITT_LT	Intent to Treat Population for Long-term Efficacy
ITT_Res	Intent to Treat Population for Rescued Population
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model Repeat Measurement
nAb	Neutralizing antibody
NAPSI	Nail Psoriasis Severity Index
NCI	National Cancer Institute
NMSC	Non-melanoma skin cancer
NRI-MI	Non-Responder Imputation incorporating multiple imputation
OC	Observed case
PASI	Psoriasis Area and Severity Index
PCR	Polymerase chain reaction
PD	Premature Discontinuation
PFS	Pre-filled syringe
PK	Pharmacokinetic(s)
PPD	Purified protein derivative (tuberculin)
ppIGA	Palmoplantar Investigator's Global Assessment
PRO	Patient-reported outcome

PsA	Psoriatic arthritis
PsO	Psoriasis
PSS	Psoriasis Symptoms Scale
PSSI	Psoriasis Scalp Severity Index
PT	Preferred term
PY	Patient year
q12w	Every 12 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
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 Global Assessment
SUSAR	Suspected unexpected serious adverse reactions
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
TEAE	Treatment emergent adverse event
TSQM-9	Treatment Satisfaction Questionnaire for Medication version 9
ULN	Upper limit of normal
US	United States
WPAI	Work Productivity and Activity Impairment

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M20-326: A Phase 4 Multicenter, Randomized, Open-label, Efficacy Assessor-blinded Study of Risankizumab Compared to Apremilast for the Treatment of Adult Subjects with Moderate Plaque Psoriasis who are Candidates for Systemic Therapy

Protocol Date: 10 November 2022

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

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

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Therapeutic Area Medical Director	Medical Affairs, Immunology
[redacted]	Director, Statistics	Data and Statistical Sciences

APPENDIX D. ACTIVITY SCHEDULE

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

Study Activities Table

Activity	Screening	Baseline	Week 4	Week 16	Week 20	Week 28	Week 32	Week 40	Week 44	Week 52 Premature Discontinuation	Safety Follow-up Call
	Day –35 to Day –1	Day 1	Day 29	Day 113	Day 141	Day 197	Day 225	Day 281	Day 309	Day 365	
Visit Window			± 3 Days								
INTERVIEWS & QUESTIONNAIRES											
Informed consent	✓										
Eligibility criteria	✓	✓									
Medical (including psoriasis)/surgical history	✓	✓									
Demographics	✓										
Alcohol, nicotine, and e-cigarette use	✓										
Token information (US only)	✓										
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient Reported Outcomes: • Psoriasis Symptom Scale (PSS) • Dermatology Life Quality Index (DLQI) • Work Productivity and Activity Impairment (WPAI)		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Patient Reported Outcomes: • Treatment Satisfaction Questionnaire for Medication (TSQM-9)			✓	✓	✓	✓	✓	✓	✓	✓	
SARS-CoV-2 Infection Risk Assessment Tool	✓										

Activity	Screening	Baseline	Week 4	Week 16	Week 20	Week 28	Week 32	Week 40	Week 44	Week 52 Premature Discontinuation	Safety Follow-up Call
	Day –35 to Day –1	Day 1	Day 29	Day 113	Day 141	Day 197	Day 225	Day 281	Day 309	Day 365	
Visit Window			± 3 Days								
Latent TB risk assessment form	✓										
LOCAL LABS & EXAMS											
12-Lead ECG	✓										
Height (at Screening only) and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination	✓	✓								✓	
BSA	✓	✓		✓						✓	
sPGA/PASI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
ppIGA/NAPSI/PSSI		✓	✓	✓		✓		✓		✓	
Urine pregnancy test (prior to dose administration and for females of childbearing potential only)		✓	✓	✓	✓	✓	✓	✓	✓	✓	
CENTRAL LABS											
HIV/HBV/HCV screening (HBV testing 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)	✓										

Activity	Screening	Baseline	Week 4	Week 16	Week 20	Week 28	Week 32	Week 40	Week 44	Week 52 Premature Discontinuation	Safety Follow-up Call
	Day –35 to Day –1	Day 1	Day 29	Day 113	Day 141	Day 197	Day 225	Day 281	Day 309	Day 365	
Visit Window			± 3 Days								
Hematology (CBC)	✓	✓		✓			✓			✓	
Clinical chemistry (electrolytes and lipids not applicable for Weeks 4, 20, 32 and 44)	✓	✓	✓	✓	✓		✓		✓	✓	
Urinalysis	✓										
℞ TREATMENT											
Randomization/drug assignment in IRT		✓									
Arm 1: Study drug administration for subjects initially randomized to risankizumab		✓	✓	✓		✓		✓			
Arm 2: Study drug dispensation initially randomized to apremilast		✓	✓								
Re-randomization in IRT for subjects initially randomized to apremilast (Arm 2)				✓							
Arm 2a: Study drug administration for subjects re-randomized to switch-to-risankizumab				✓	✓		✓		✓		
Arm 2b: Continuation of apremilast (study drug administration/dispensation)				✓	✓	✓	✓	✓	✓		
Arm 3a: Study drug administration of risankizumab for subjects rescued at Week 28						✓	✓		✓		
Arm 3b: Study drug administration of risankizumab for subjects rescued at Week 40								✓	✓		
Hypersensitivity monitoring (Risankizumab arms only)		✓	✓	✓	✓	✓	✓	✓	✓		

BSA = body surface area; CBC= complete blood count; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IGRA = interferon gamma release assay; IRT = interactive response technology; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PPD = purified protein derivative (tuberculin); ppIGA = Palmoplantar Investigator's Global Assessment; PSSI = Psoriasis Scalp Severity Index; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; sPGA = static Physician Global Assessment; TB = tuberculosis; US = United States

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	29 March 2021
Administrative Change 1	15 April 2021
Administrative Change 2	17 February 2022

The purpose of Protocol Version 2.0 is to capture Administrative Changes 1 and 2, and update text for Primary Analysis for Period B. Administrative Change 1, which changed the study phase from Phase 4 to Phase 3b, was not incorporated into Protocol Version 2.0. The study drug, risankizumab 150 mg/ml, has now been approved in all study countries, and the study phase is re-confirmed as Phase 4.

Protocol Version 2.0 also incorporates necessary protocol modifications in the protocol template and new safety information as follows:

Protocol

- Text was updated throughout the Protocol to align with revisions in the protocol template and changes due to new safety information available.
  - Protocol sections include: Section 2.2, Section 4.1, Section 5.1, Section 5.4, Section 5.5, Section 5.6, Section 6.1, Section 9, Section 11, Appendix B, Appendix C, Appendix D, and Appendix E.
- Protocol Section 7.1: added the interim lock for primary analysis for Period B.
- Administrative Change 2: Update the Sponsor/Emergency Medical Contact information to [redacted] as Sponsor/Emergency Medical Contact.
  - Rationale: Reflects a change in the Sponsor/Emergency Medical Contact for the study.

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.
  - Operations Manual sections include: Section 1, Section 2.1, Section 3.1, Section 3.12, Section 3.13, Section 4.1, Section 4.3, Section 6.3, and Section 8.7.
- Administrative Change 2: Update the Sponsor/Emergency Medical Contact information to [redacted] as Sponsor/Emergency Medical Contact.
  - Rationale: Reflects a change in the Sponsor/Emergency Medical Contact for the study.