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Protocol for Study M15-998

Psoriatic Arthritis: Risankizumab Therapy Vs Placebo in Bio-IR Subjects

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SPONSOR:	For Non-EU Countries:* AbbVie 1 North Waukegan Road Bldg. AP31 North Chicago, IL 60064 USA	For EU Countries:* AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 50 67061 Ludwigshafen Germany	
NUMBER OF SITES:	Approximately 170 sites		
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FULL TITLE: A Phase 3, Randomized, Double-Blind Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis Including Those Who Have a History of Inadequate Response or Intolerance to Biologic Therapy(ies) (KEEPsAKE 2)

Incorporating Versions 1.0, 2.0, 3.0, and 4.0

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

SPONSOR/EMERGENCY MEDICAL CONTACT:* [redacted]

AbbVie
Avenida De Burgos 91,
Madrid, Spain 28050
Office/Mobile: [redacted]
Email:

*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 3, Randomized, Double-Blind Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis Including Those Who Have a History of Inadequate Response or Intolerance to Biologic Therapy(ies) (KEEPsAKE 2)	
Background and Rationale:	Patients with psoriatic arthritis (PsA) require treatment of the entire spectrum of disease manifestations. The primary goal of treating patients with PsA is to maximize long-term health-related quality of life, through control of symptoms, prevention of structural damage, normalization of function and social participation and abrogation of inflammation. Initial treatment of musculoskeletal symptoms consists of nonsteroidal anti-inflammatory drugs (NSAIDs) and local corticosteroid injections, while topical therapies are used for the initial treatment of psoriasis. For patients who experience lack of efficacy or toxicity with these measures, for the treatment of peripheral arthritis, both the European League Against Rheumatism (EULAR) and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommend systemic therapy with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) (methotrexate [MTX], leflunomide [LEF], sulfasalazine [SSZ], or ciclosporin A), followed by anti-tumor necrosis factor (TNF) therapy in patients who do not respond adequately to csDMARDs. Other biologic therapies (e.g., Interleukin[IL]-12/23 or IL-17 inhibitors) are also recommended as alternatives to anti-TNF agents in selected patients with PsA. JAK inhibitors are also now available to treat PsA. Additional specific recommendations differ slightly between EULAR and GRAPPA, however recommendations for therapeutic choice are made based on a patient's clinical presentation, as some manifestations of PsA, such as enthesitis, dactylitis, and axial disease are either not responsive or poorly responsive to csDMARDs. Specific therapeutic options are also recommended for treatment of skin disease. Despite the beneficial results achieved with currently available biologic agents, approximately 40% of patients do not achieve at least 20% improvement in American College of Rheumatology (ACR) scores and only 58% to 61% of patients with PsA are able to achieve clinical remission after 1 year of treatment. Only approximately 43% achieve sustained remission for at least 1 year as measured by minimum disease activity (MDA). Thus, there remains a clear medical need for additional therapeutic options in PsA for patients with inadequate response to or intolerance to currently available therapies. Risankizumab is a humanized immunoglobulin (Ig) G1 antagonistic monoclonal antibody (mAb) directed against the p19 subunit of the human cytokine IL-23. IL-23 plays a critical role in the differentiation and function of T helper (Th) 17 cells, which have emerged as an important T-cell subpopulation involved in the pathogenesis of immune mediated disorders.

Background and Rationale (Continued):	This study is being conducted to evaluate subjects with moderately to severely active PsA who have had an inadequate response or were intolerant to csDMARDs or biologic therapies. A previous clinical study suggested that risankizumab dosed at 150 mg at Weeks 0, 4 and every 12 weeks (q12w) thereafter is effective in the treatment of PsA.
Primary Objective and Endpoint:	Primary Objective: **Period 1 Double-blind** To compare the efficacy of risankizumab 150 mg versus placebo for the treatment of signs and symptoms of PsA in the study population (see Study Population section below). Primary Endpoint: The primary endpoint is the proportion of subjects achieving American College of Rheumatology (ACR) 20 response at Week 24.
Investigator(s):	Investigator information on file at AbbVie.
Study Site(s):	Approximately 170 sites
Study Population and Number of Subjects to be Enrolled:	Approximately 420 (210/arm) adult subjects with moderately to severely active PsA in a study population that will consist of no more than 50% of enrolled subjects with a demonstrated inadequate response (lack of efficacy after a minimum 12 week duration of therapy) or intolerance to 1 or 2 biologic therapies (Bio-IR). The remaining study population will be subjects who have a demonstrated inadequate response (lack of efficacy after a minimum 12 week duration of therapy) or intolerance to at least 1 csDMARD.
Investigational Plan:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study
Key Eligibility Criteria:	• Subjects must be able to read, understand, and 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. • Adult **male or female**, at least 18 years old (subjects must also meet the legal age of majority per local law). Disease Activity • Clinical diagnosis of PsA with symptom onset at least 6 months prior to the Screening Visit and fulfillment of the Classification Criteria for PsA (CASPAR) at Screening Visit. • Subject has active disease defined as ≥ 5 tender joints (based on 68 joint counts) and ≥ 5 swollen joints (based on 66 joint counts) at both the Screening Visit and Baseline. • Diagnosis of active plaque psoriasis with at least one psoriatic plaque of ≥ 2 cm diameter or nail changes consistent with psoriasis at Screening Visit.

Key Eligibility Criteria (Continued):	Subject History
	• Subject must have demonstrated:
	  • Bio-IR population: Inadequate response (lack of efficacy after minimum 12 week duration of therapy) or intolerance to treatment with 1 or 2 biologic therapies intended to treat PsA OR
	  • csDMARD-IR population: Inadequate response (lack of efficacy after minimum 12 week duration of therapy) to previous or current treatment with at least 1 csDMARD at maximally tolerated dose:
	  • sulfasalazine (SSZ)
	  • leflunomide (LEF)
	  • apremilast
	  • bucillamine
	  • iguratimod
	  • ciclosporin A
	  • methotrexate (MTX)
	  • MTX-IR is defined as an inadequate response (lack of efficacy after minimum 12 weeks duration of therapy) at the following doses ranges: ≥ 15 mg/week, or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week after complete titration (for subjects in some countries, such as China, Korea, Malaysia, Singapore, Hong Kong, Taiwan, and Japan inadequate response to MTX is defined as ≥ 7.5 mg/week or as required per local authorities).
	• Alternatively, subject may have an intolerance to csDMARDs as determined by the investigator.

Study Drug and Duration of Treatment:	Subjects randomized to risankizumab: 150 mg (2 × 75 mg pre-filled syringe [PFS]) subcutaneous (SC) at Week 0 (Baseline/Study Day 1), 4, and q12w thereafter to Week 208. At Week 24, subjects will receive a single dose of blinded placebo to maintain the blind. At Week 28 and q12w thereafter, subjects will receive open-label risankizumab. Subjects randomized to placebo: Placebo injection at Weeks 0, 4, and 16. At Week 24, subjects will receive blinded risankizumab. At Week 28 and q12w thereafter to Week 208, subjects will receive open-label risankizumab.
Date of Protocol Synopsis:	10 September 2020

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Psoriatic arthritis (PsA) is a chronic systemic inflammatory disease classified as a sub-type of spondyloarthritis (SpA) and characterized by the association of arthritis and psoriasis. The course of PsA is usually characterized by flares and remissions.[1] Left untreated, patients with PsA can have persistent inflammation, progressive joint damage, disability, and a reduced life expectancy.[1,2] Patients with PsA experience varying combinations of disease manifestations affecting the synovium, tendons, entheses, skin, and bone. These manifestations of disease range in prevalence, with peripheral arthritis and variable degrees of psoriasis observed in all patients at some point during their disease course, axial disease in 40% to 74% depending on the criteria used for diagnosis,[3] enthesitis in 25% to 51%, dactylitis in 8% to 59%[4-6] and anterior uveitis in 2% to 25%.[7] Additionally, patients with PsA are more likely to experience the co-morbid conditions of cardiovascular disease, metabolic syndrome, obesity, diabetes, fatty liver disease, inflammatory bowel disease, kidney disease, osteoporosis, fibromyalgia,[8] depression, and anxiety than healthy subjects,[9] and have decreased quality of life and functional impairment.[10,11]

Patients with PsA require treatment of the entire spectrum of disease manifestations. The primary goal of treating patients with PsA is to maximize long-term health-related quality of life, through control of symptoms, prevention of structural damage, normalization of function and social participation, and abrogation of inflammation. Initial treatment of musculoskeletal symptoms consists of nonsteroidal anti-inflammatory drugs (NSAIDs) and local corticosteroid injections, while topical therapies are used for the initial treatment of psoriasis. For patients who experience lack of efficacy or toxicity with these measures, for the treatment of peripheral arthritis, both the European League Against Rheumatism (EULAR)[12] and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)[13] recommend systemic therapy with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) (methotrexate [MTX], leflunomide [LEF], sulfasalazine [SSZ], or ciclosporin A), followed by anti-tumor necrosis factor (TNF) therapy in patients who do not respond adequately to csDMARDs. Other biologic therapies (e.g., Interleukin[IL]-12/23 or IL-17 inhibitors) are also recommended as alternatives to anti-TNF inhibitors in selected patients with PsA. Janus kinase (JAK) inhibitors are also now available to treat PsA. Additional specific recommendations differ slightly between EULAR and GRAPPA, however recommendations for therapeutic choice are made based on a patient's clinical presentation as some manifestations of PsA, such as enthesitis, dactylitis, and axial disease are either not responsive or poorly responsive to csDMARDs. Specific therapeutic options are also recommended for treatment of skin disease.[12,13]

Despite the beneficial results achieved with currently available biologic agents, approximately 40% of patients do not achieve at least 20% improvement in American College of Rheumatology (ACR) scores,[12,14-20] and only 58%[21] to 61%[22] of patients with PsA are able to achieve clinical remission after 1 year of treatment. Only approximately 43% achieve sustained remission for at least 1 year as measured by minimal disease activity (MDA).[23] Thus, there remains a clear medical need for additional therapeutic options in PsA for patients with inadequate response to or intolerance to currently available therapies.

Risankizumab is a humanized immunoglobulin (Ig) G1 antagonistic monoclonal antibody (mAb) directed against the p19 subunit of the human cytokine IL-23. IL-23 plays a critical role in the differentiation and function of T helper (Th) 17 cells, which have emerged as an important T-cell subpopulation involved in the pathogenesis of immune mediated disorders.[24]

The therapeutic rationale for an IL-23 antagonist in inflammatory diseases such as psoriasis (PsO), Crohn's disease (CD), ulcerative colitis (UC), and PsA is supported by several lines of evidence. IL-23 knockout mice are resistant to experimental arthritis, experimental autoimmune encephalitis, and inflammatory bowel disease.[25-27] Blocking IL-23 with an antagonistic antibody reduced the inflammatory response seen in mouse models of autoimmune encephalitis, colitis, and ovalbumin challenge.[28-30]

Genome-wide association studies have demonstrated associations between polymorphisms of the gene for IL-23, or the gene for its receptor, and the diseases PsO, CD, UC, and PsA.[31-34] In addition, excessive expression of IL-23 has been reported in affected skin in PsO, in the gut mucosa in CD, and in the synovial tissue of subjects with PsA.[35-37]

This study is being conducted to evaluate the treatment of moderately to severely active PsA. The subject population will consist of no more than 50% of subjects with a demonstrated inadequate response (lack of efficacy after a minimum 12 week duration of therapy) or intolerance to 1 or 2 biologic therapies (Bio IR). The remaining study population will be subjects who have a demonstrated inadequate response (lack of efficacy after a minimum 12 week duration of therapy) or intolerance to at least 1 csDMARD (csDMARD-IR). A previous clinical study suggested that risankizumab 150 mg at Weeks 0, 4, and every 12 weeks (q12w) thereafter is effective in the treatment of PsA.

Clinical Hypothesis

Risankizumab will provide better efficacy compared to placebo and will be well tolerated in subjects with moderately to severely active PsA who have had an inadequate response or intolerance to biologic therapy and/or csDMARD therapy.

2.2 Benefits and Risks to Subjects

Despite the availability of various PsA therapies, many subjects still do not respond adequately to these treatments, or gradually lose response over time. Risankizumab is an antagonist specific for IL-23 which has been implicated in the pathophysiology of immune-mediated inflammatory diseases. Nonclinical studies have shown that risankizumab has minimal inhibitory effects on IL-12, the inhibition of which has been associated with increased risk of serious infections.[38,39] Selective IL-23 inhibition may not increase risk of serious infection, including mycobacterial infections.[40]

Interleukin-23 inhibition is not known to increase the risk of tuberculosis (TB) infection or impair the response to TB infection in animal models.[41,42] Thus, low-risk subjects with positive QuantiFERON testing do not need to be treated with anti-TB therapy prior to receiving risankizumab, but should be carefully monitored for any sign of TB reactivation. Absence of TB reactivation despite not receiving anti-TB prophylaxis will provide important information in humans as to whether TB testing is required prior to treatment with risankizumab.

Efficacy of risankizumab for the treatment of moderate to severe psoriasis was demonstrated in four Phase 3, randomized, placebo- and/or active-comparator (adalimumab or ustekinumab) controlled

pivotal studies in > 2000 subjects. Risankizumab response rates were consistent across all 4 studies: 72% to 75% of subjects achieved 90% reduction in Psoriasis Area and Severity Index score (PASI 90), and 84% to 88% achieved sPGA clear or almost clear at Week 16. In addition, nearly all subjects (85% to 90%) achieved PASI 75 at Week 16.

As of 29 March 2018, 2,471 subjects in the psoriasis studies were exposed to ≥ 1 dose of risankizumab at any dosage level (including subjects who received placebo for Weeks 0 to 16 and then switched to risankizumab), representing 3,352 patient years (PYs) of exposure. Of the 2,471 subjects, 1,671 have had exposure to risankizumab at any dosage for at least 1 year. In the pivotal global Phase 3 plaque psoriasis studies, over the initial 16 weeks of exposure, the frequencies of adverse events (AEs) were similar in subjects treated with risankizumab (48.9%) compared to placebo (48.3%). Through Week 52, the exposure-adjusted rate of AEs in subjects in the risankizumab group was comparable to the event rate in the ustekinumab group (228.0 E/100 PYs in the risankizumab group and 281.0 E/100 PYs in the ustekinumab group). Likewise, serious adverse events per 100 subject-years were 9.4 for subjects treated with risankizumab and 10.9 for those treated with ustekinumab. Approximately 2.0% of subjects discontinued due to AEs. Few subjects had AEs in the following areas of safety interest: major adverse cardiac events (MACE), infections, malignancies, hepatic events, injection site events, or hypersensitivity reactions.

The Phase 2 program in PsA with risankizumab demonstrated efficacy for improvement in signs and symptoms of PsA and the safety results were consistent with those known to be associated with IL-23 antagonists. Taken together, the safety and efficacy data from the Phase 2 program support further development of risankizumab in Phase 3 in subjects with PsA.

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

Increases in major adverse cardiovascular events (MACE), including myocardial infarction (MI), cerebrovascular accident, and cardiovascular death, reported initially with anti-IL-12/23 agents, such as ustekinumab, have not been observed in longer term studies. While the likelihood of increased MACE is small, all suspected cardiovascular events (serious or nonserious) observed in this study will be adjudicated by an independent committee. An independent Cardiovascular Adjudication Committee (CAC) will adjudicate all observed cardio- and cerebro-vascular events and will remain blinded to treatment allocation (Section 6.4).

Injection-site reactions to biologic therapies may be characterized by redness, swelling or induration at the injection site. Manifestations of anaphylaxis may include pruritus, hypotension, swollen lips and tongue, abdominal pain, and respiratory distress. Both local and systemic hypersensitivity reactions and anaphylaxis are readily detectable, transient in nature, and manageable with standard medical treatment. Subjects will be closely monitored during study drug administration. The duration of the post-drug-administration safety surveillance is of 2 hours post first dose and 1 hour post all other doses. An independent Anaphylaxis Adjudication Committee (AAC) will adjudicate suspected anaphylactic reactions. The AAC will remain blinded to treatment allocation (Section 6.5).

An external Independent Data Monitoring Committee (IDMC) will review unblinded safety data on a periodic basis.

For further details, please see findings from completed studies, including safety data, in the risankizumab Investigator Brochure.[43]

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 on the course of COVID-19 are not well defined.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

Primary

Period 1 Double-Blind

To compare the efficacy of risankizumab 150 mg versus placebo for the treatment of signs and symptoms of PsA in the study population (see Section 2.1 and Section 4.1).

Secondary

Period 1 Double-Blind

To compare the safety and tolerability of risankizumab 150 mg versus placebo in the study population.

Period 2 Open-Label

To evaluate the long-term safety, tolerability and efficacy of risankizumab 150 mg in subjects who have completed Period 1.

3.2 Primary Endpoint

The primary endpoint is the proportion of subjects achieving American College of Rheumatology (ACR)20 Response (ACR20) at Week 24.

3.3 Secondary Endpoints

Ranked secondary endpoints with multiplicity adjustment:

1. Change from Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24;
2. Proportion of subjects achieving Psoriasis Area Severity Index (PASI) 90 response at Week 24 (in the subset of subjects with a body surface area (BSA) ≥ 3% at Baseline);
3. Proportion of subjects achieving ACR20 at Week 16;
4. Proportion of subjects achieving Minimal Disease Activity (MDA) at Week 24;
5. Change from Baseline in 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) at Week 24;

6. Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue) Questionnaire at Week 24.

Other secondary endpoints without multiplicity adjustment are:

1. Proportion of subjects achieving ACR50 response at Week 24;
2. Proportion of subjects achieving ACR70 response at Week 24;
3. Proportion of subjects with resolution of enthesitis (LEI = 0) at Week 24 in subjects with enthesitis at Baseline;
4. Proportion of subjects with resolution of dactylitis (LDI = 0) at Week 24 in subjects with dactylitis at Baseline;

3.4 Additional Endpoints

Additional endpoints at the scheduled time points as indicated in Appendix D:

- Proportion of subjects achieving ACR20, ACR50, or ACR70 response;
- Change from Baseline in individual components of ACR response;
- Change from Baseline in LDI in subjects with dactylitis at Baseline;
- Change from Baseline in dactylitis count in subjects with dactylitis at Baseline;
- Proportion of subjects with resolution of dactylitis sites included in the LDI in subjects with dactylitis at Baseline;
- Change from Baseline in LEI in subjects with enthesitis in the LEI at Baseline
- Proportion of subjects with resolution of enthesitis sites included in the LEI in subjects with enthesitis in the LEI at Baseline;
- Change from Baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index in subjects with enthesitis in the SPARCC at Baseline;
- Proportion of subjects with resolution of enthesitis sites included in the SPARCC Enthesitis Index in subjects with enthesitis in the SPARCC at Baseline;
- Change from Baseline in total enthesitis count in subjects with enthesitis in the LEI or SPARCC at Baseline;
- Proportion of subjects with resolution of enthesitis in LEI and SPARCC in subjects with enthesitis in the LEI or SPARCC at Baseline;
- Proportion of subjects achieving PASI 75 response (in the subset of subjects with a BSA ≥ 3% at Baseline);
- Proportion of subjects achieving PASI 90 response (in the subset of subjects with a BSA ≥ 3% at Baseline);
- Proportion of subjects achieving PASI 100 response (in the subset of subjects with a BSA ≥ 3% at Baseline);

- Proportion of subjects with both ACR 50 and PASI 90 response (in the subset of subjects with a BSA ≥ 3% at Baseline)
- Change from Baseline in BSA-PsO (in the subset of subjects with a BSA ≥ 3% at Baseline);
- Proportion of subjects who achieve a Modified Psoriatic Arthritis Response Criteria (PsARC) response;
- Change from Baseline in Disease Activity Score 28 using high sensitivity C-Reactive Protein (DAS28-hsCRP);
- Change from Baseline in PsA Disease Activity Score (PASDAS);
- Change from Baseline in Disease Activity In Psoriatic Arthritis (DAPSA) score;
- Change from Baseline in FACIT-Fatigue Questionnaire;
- Change from Baseline in SF-36 Health Questionnaire;
- Change from Baseline in EuroQol-5D-5L (EQ-5D-5L) Health Questionnaire;
- Change from Baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire;
- Proportion of subjects with health resource utilization (HRU) since the last study visit;
- Change from Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (in subjects with axial spondylitis at Baseline);
- Proportion of subjects achieving BASDAI50 response (in subjects with axial spondylitis at Baseline);
- Change from Baseline in morning stiffness (mean of BASDAI Questions 5 and 6, in subjects with axial spondylitis at Baseline and all subjects);
- Change from Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS, in subjects with axial spondylitis at Baseline);
- Proportion of subjects with ASDAS Inactive Disease (in subjects with axial spondylitis at Baseline);
- Proportion of subjects with ASDAS Major Improvement (in subjects with axial spondylitis at Baseline);
- Proportion of subjects with ASDAS Clinically Important Improvement (in subjects with axial spondylitis at Baseline);
- Proportion of subjects achieving a clinically meaningful improvement in the HAQ-DI (change ≤ –0.35) in subjects with ≥ 0.35 HAQ-DI at Baseline.

3.5 Safety Endpoints

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

3.6 Pharmacokinetic Endpoints

Serum risankizumab concentrations, anti-drug antibodies (ADA), and neutralizing antibodies (nAb) will be determined at the visits indicated in the Activity Schedule (Appendix D). Serum risankizumab concentrations will be summarized at the sampling time points using descriptive statistics. Anti-drug antibody titers will be tabulated for each ADA positive subject at the respective study visits. The number and percentage of subjects with ADA and nAb will be calculated.

3.7 Biomarker Sampling

Optional whole blood and urine samples will be collected from subjects who provide consent to investigate prognostic, surrogate, predictive and pharmacodynamic biomarkers. The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the study drug (or drugs of the same or similar class) or the development and progression of PsA or related conditions. The samples may also be used to develop new diagnostic tests, therapies, research methods or technologies. Assessments may include but may not be limited to nucleic acids, proteins, metabolomic analytes, or lipids. Research on samples collected in Germany will be restricted to PsA and risankizumab.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3, global, multicenter study that will evaluate subjects with moderately to severely active PsA. The subject population will consist of no more than 50% with a demonstrated inadequate response (lack of efficacy after a minimum 12 week duration of therapy) or intolerance to 1 or 2 biologic therapies (Bio IR). The remaining study population will be subjects who have had an inadequate response (lack of efficacy after a minimum 12 week duration of therapy) or intolerance to at least 1 csDMARD.

The study consists of a Screening Period (approximately 35 days), Period 1, Period 2, and a 20-week Follow-up Period (Figure 1). Period 1 is a 24-week randomized, double-blind, placebo-controlled, parallel-group period. Period 2 starts at Week 24. To maintain the blind to the original treatment allocation, treatment at the Week 24 Visit will be blinded: subjects randomized to placebo will receive blinded risankizumab 150 mg, and subjects randomized to risankizumab will receive blinded placebo. At Week 28 and for the remaining dosing visits (to Week 208), all subjects will receive open-label risankizumab 150 mg q12w. Subjects will remain blinded to the original randomization allocation for the duration of the study. The total study duration is 228 weeks including a telephone call 140 days (20 weeks) after last dose of study drug.

Screening Period

Subjects will be screened for eligibility to enroll in the study until approximately 420 subjects (210/arm) have been randomized. Once 420 subjects have been randomized, subjects who have started screening but not yet been randomized will be allowed to enroll in the study if eligible. No further subjects will be

screened once sufficient numbers of subjects to fulfill the enrollment target have entered the screening process.

During the screening period, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures outlined in Appendix D. Subjects who do not meet all the laboratory eligibility criteria, but whose values are within 30% of the allowable laboratory value for any specific laboratory determination as defined in Section 5.1, at the principal investigator's discretion, may return for redraw of the specific laboratory test(s) that did not meet eligibility criteria. Other laboratory parameters associated with the Screening Visit should not be re-drawn.

In addition, subjects not meeting eligibility criteria may undergo a second Screening Visit at the discretion of the Investigator. The subject must meet all the eligibility criteria in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study. For consideration beyond two Screening Visits, AbbVie must be consulted. Most screening procedures will be repeated during this second Screening Visit. Possible exceptions are noted below.

If a subject has had an Interferon-Gamma Release Assay (IGRA; QuantiFERON Tuberculosis [TB] Gold test) and/or a purified protein derivative (PPD) test (or equivalent) (or both if required per local guidelines), and/or electrocardiogram (ECG) within the previous 90 days, these tests will not be required to be repeated for screening, provided the conditions noted in the Operations Manual are met.

If allowed by local regulation, radiographs of hands and feet may be repeated.

Period 1: Double-Blind Period

Eligible subjects will be randomized to receive blinded risankizumab or placebo in 1:1 ratio through Week 24. Study visits occur in Period 1 at Week 0, Week 4, Week 8, Week 12, Week 16, and dosing in Period 1 occurs at Week 0, Week 4, and Week 16 as outlined in Figure 1.

Period 2: Open-Label Period

During Period 2, all subjects will receive risankizumab. To maintain the blind to the original treatment allocation, treatment at the Week 24 Visit will be blinded: subjects randomized to placebo will receive blinded risankizumab 150 mg, and subjects randomized to risankizumab will receive blinded placebo. At Week 28 and for the remaining dosing visits, all subjects will receive open-label risankizumab 150 mg q12w.

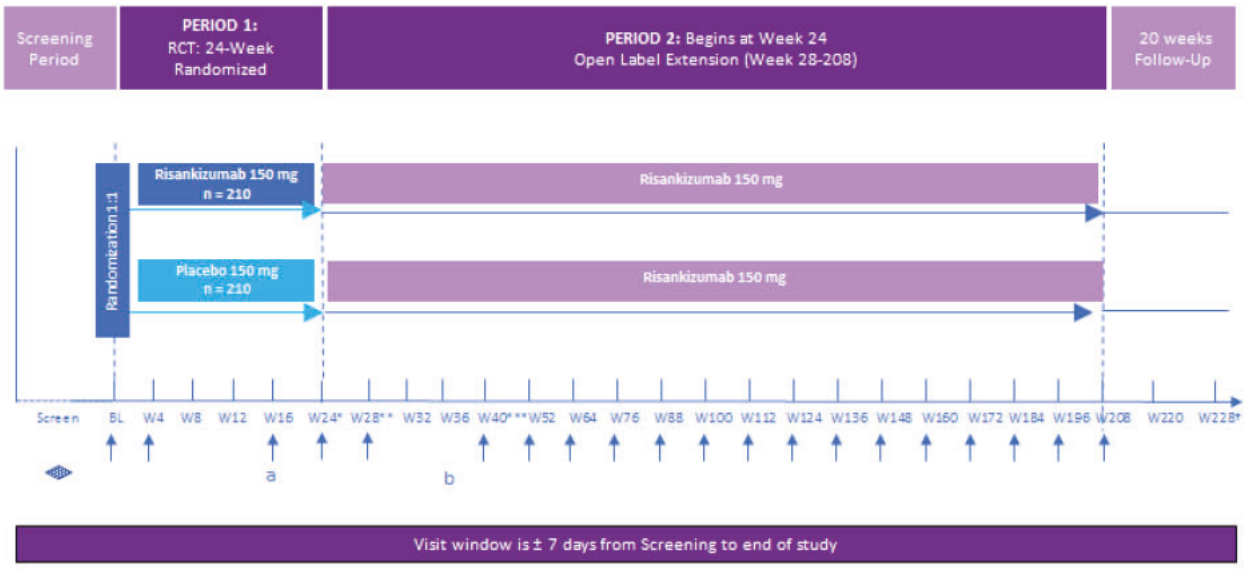
Study dosing in Period 2 occur at Week 24, Week 28, and q12w thereafter until the final dosing time point at Week 208 as outlined in Figure 1.

Follow-up Period

The Follow-up Period consists of a completion visit 12 weeks after the last study drug dose. An additional follow-up phone call will occur 8 weeks later, 20 weeks after last study drug dose, to determine the status of any ongoing AEs/serious adverse events (SAEs) or the occurrence of any new AEs/SAEs.

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

Figure 1. Study Schematic



LEGEND:

BL = Baseline; RCT = randomized clinical trial; W = Week

* At Week 24, subjects randomized to placebo in Period 1 will receive a blinded dose of risankizumab. Subjects randomized to risankizumab treatment in Period 1 will receive a blinded dose of placebo.

** At Week 28, subjects randomized to placebo in Period 1 will receive a 2nd dose of risankizumab. Subjects randomized to risankizumab in Period 1 will receive risankizumab (scheduled dose).

*** From Week 40 to Week 208 Visits, doses occur q12w.

† Follow up phone call.

↑ Dosing.

◈ Bilateral radiographs of hands and feet.

a. At Week 16, subjects classified as non-responders (defined as not achieving at least a 20% improvement in either or both tender joint count [TJC] and swollen joint count [SJC] at both Week 12 and Week 16) compared to Baseline will add or modify rescue concomitant medications/therapy as described in Section 5.4. Rescue therapy qualification occurs only at Week 16 Visit.

b. Starting at Week 36, subjects classified as non-responders will be discontinued from study drug. See Section 5.5 for details.

4.2 Discussion of Study Design

Choice of Control Group

Placebo control (with up to 2 background csDMARDs) will be used in this study to address potential confounding factors, such as placebo effect, potential investigator bias in safety and efficacy assessment, or regression to the mean in endpoint scoring. At Week 24, all subjects assigned to placebo at Baseline will be switched to risankizumab treatment.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with PsA.

Suitability of Subject Population

The intended study population is subjects with moderately to severely active PsA. No more than 50% will have had a demonstrated inadequate response or intolerance to 1 or 2 biologic therapies (Bio-IR). The rest of the study population will be subjects who have had an inadequate response or intolerance to at least 1 csDMARD.

Selection of Doses in the Study

Risankizumab dose of 150 mg subcutaneous (SC) administered at Week 0, 4, and q12w thereafter is selected for this study. Subjects randomized to placebo will receive risankizumab dose of 150 mg SC at the same dosing frequency starting Week 24 (at Week 24, 28, and q12w thereafter) as those randomized to risankizumab at Week 0.

The dose selection in this study was informed by analyses of safety and efficacy data from:

- Completed Phase 1 through 3 PsO studies (Studies 1311.1, 1311.2, M16-008, M15-995, M16-010);
- Ongoing Phase 3 PsO Study M15-992
- Phase 2 PsA Study M16-002 (1311.5)

As well as:

- Safety data from completed Phase 2 studies in subjects with ankylosing spondylitis (AS) (Study 1311.8) and CD (Study 1311.6)
- Analyses of the exposure-response relationship of efficacy in PsA Phase 2 study

In Phase 3 studies in subjects with PsO, a risankizumab dose of 150 mg SC administered at Weeks 0, 4, and q12w thereafter was evaluated. In the Phase 2 study in subjects with PsA, risankizumab 150 mg SC was administered as frequently as every 4 weeks over a period of 16 weeks. In Phase 2 studies in subjects with PsO, AS and CD, doses of risankizumab up to 180 mg SC were administered every 8 weeks or q12w for up to 24 weeks (Studies 1311.2, 1311.6, and 1311.8) and intravenous (IV) doses of up to 600 mg were administered every 4 weeks for 12 to 24 weeks (Study 1311.6 in subjects with CD).

In the Phase 2 study of risankizumab in subjects with PsA (Study M16-002), 4 risankizumab dosing regimens were evaluated: single dose of 75 mg at Week 0 (N = 20); 150 mg at Week 0 and 12 (N = 39); 150 mg at Week 0, 4, and 16 (N = 42); and 150 mg at Week 0, 4, 8, 12, and 16 (N = 42). In this study, risankizumab-treated subjects demonstrated significant improvement compared to placebo in key rheumatology endpoints (ACR20/50/70 and DAS28-CRP) and skin-related endpoints (PASI 75/90/100). At Week 16, ACR20/50/70 responses were 62%/24%/7% in subjects who received risankizumab doses of 150 mg SC at Weeks 0, 4, and 16 compared to 36%/12%/0% in subjects on placebo. The Week 16 PASI 75/90/100 responses, in subjects with baseline BSA of skin symptoms ≥ 3%, were 70%/67%/50% in

subjects who received risankizumab doses of 150 mg SC at Weeks 0, 4, and 16 compared to 10%/10%/10% in subjects on placebo. No further improvements in ACR or PASI responses were noted in subjects who received risankizumab doses of 150 mg at Weeks 0, 4, 8, 12, and 16.

Risankizumab exposures in subjects with PsA in the Phase 2 study (Study M16-002) were comparable to those in subjects with PsO in Phase 1 through 3 studies at similar dose and dosing frequency. The ADA incidence (approximately 12% [17/140] over 32 weeks) in risankizumab-treated subjects with PsA (Study M16-002) was comparable to that in subjects with PsO or CD, and presence of ADA did not affect risankizumab plasma exposures.

Exposure-response analyses were conducted to explore the relationship between risankizumab C_{avg} (the average plasma concentration from Week 0 – 16) and ACR20/50/70 and PASI 75/90/100 responses at Week 16 in subjects with PsA (Study M16-002). For this analysis, C_{avg} from Weeks 0 to 16 was used as an exposure metric, as it accounts for the differences in risankizumab dosing frequency across different arms in the study. A shallow trend for exposure-response relationship was observed for ACR20, PASI 75, and PASI 90 across the risankizumab regimens evaluated in the Phase 2 study.

Only 20 subjects received the risankizumab 75 mg dose in Study M16-002 and among these, PASI assessments were performed only in those subjects with skin symptoms on BSA ≥ 3%, and only 9 subjects met that criterion. Since very limited data were available at the 75 mg dose, these subjects were excluded from the exposure-responses analyses. Excluding these subjects showed a clear exposure-response relationship for ACR20 and PASI 75/90/100 responses, with plateau of efficacy at C_{avg} associated with the risankizumab dosing regimen of 150 mg at Weeks 0, 4, and 16. These results support that a risankizumab dosing regimen of 150 mg at Week 0, 4, and 16 is optimal for efficacy for subjects with PsA.

Risankizumab was well tolerated in the Phase 2 study in subjects with PsA, with no discernible differences in treatment-emergent AEs and laboratory abnormalities between risankizumab-treated and placebo-treated subjects and no dose-related trends in risankizumab-treated subjects across all dosing regimens with doses up to 150 mg SC every 4 weeks. Additionally, safety data from ongoing Phase 3 study (Study M15-992) and completed Phase 2 and 3 studies (Studies 1311.2, M15-995, M16-008, and M16-010) in subjects with PsO, and final safety data from completed Phase 2 studies (Studies 1311.6 and 1311.8) in subjects with CD (Study 1311.6) and AS (Study 1311.8) indicate that risankizumab administration was safe and generally well tolerated by study participants, with no dose limiting toxicities. It is noteworthy that approximately 2120 PsO subjects have been enrolled in Phase 3 studies at a dose of 150 mg SC administered at Week 0, 4, and q12w thereafter, for up to 2 years in duration. Risankizumab doses of up to 600 mg IV were administered every 4 weeks for 12 to 24 weeks and up to 180 mg SC were administered every 8 weeks or every 12 weeks for up to 24 weeks in Phase 2 studies in subjects with CD, PsO, or AS.

In addition, single doses of risankizumab up to 300 mg SC and 1200 mg intravenous (IV) have been administered to healthy subjects in a Phase 1 study (Study M16-513), and safety data indicate that risankizumab administration was safe and generally well tolerated by study participants with no dose-limiting toxicities. In addition, a single dose of risankizumab 1800 mg has been administered to healthy subjects in another Phase 1 study (Study M16-533), and preliminary safety data indicate that risankizumab administration was safe and generally well tolerated by study participants. Details of the

safety findings from completed or ongoing Phase 1 through 3 studies in healthy subjects or subjects with PsA, PsO, CD, and AS are provided in the Investigator's Brochure.

In summary, the risankizumab dose selected for evaluation in this Phase 3 study is expected to be efficacious based on data from Phase 2 PsA study (Study M16-002) with an acceptable safety profile based on data from completed and ongoing Phase 2 and 3 studies in subjects with PsO, CD, and AS.

Treatment Duration Rationale

Period 1 is a 24-week randomized, double-blind, placebo-controlled parallel-group period. It is designed to compare the efficacy, safety, and tolerability of risankizumab versus placebo in subjects with moderately to severely active PsA. The treatment duration of Period 1 is designed to test the superiority of risankizumab versus placebo for achieving the primary efficacy endpoint (ACR20 at Week 24) and several secondary endpoints. Period 2 begins at Week 24. It is designed to assess long-term safety and maintenance of treatment response to risankizumab for subjects who have completed Period 1.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

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

Consent

- 1. Subject must be functionally able to read and understand a written informed consent form, study-related instructions, and study questionnaires.
- 2. Subject 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. The use of Legally Authorized Representatives (LARs) is prohibited for this protocol.
- 3. Employees of the sponsor and/or study sites and their family members **may not** be enrolled in this study.

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 (ANC) > 1,500/µL;
- Platelet count > 100,000/µL;
- Hemoglobin > 8.0 g/dL;

6. Subject is willing and able to comply with procedures required in this protocol.

Disease Activity

7. Subject has a clinical diagnosis of PsA with symptom onset at least 6 months prior to the Screening Visit and fulfillment of the Classification Criteria for PsA (CASPAR) at Screening Visit.
8. Subject has active disease defined as ≥ 5 tender joints (based on 68 joint counts) and ≥ 5 swollen joints (based on 66 joint counts) at both the Screening Visit and Baseline.
9. Subject has diagnosis of active plaque psoriasis, with at least one psoriatic plaque of ≥ 2 cm diameter or nail changes consistent with psoriasis at Screening Visit.

Subject History

10. To be considered Bio-IR:

    - Subject must have demonstrated **an inadequate response** (lack of efficacy after minimum 12 week duration of therapy) or intolerance to treatment with 1 or 2 biologic therapies intended to treat psoriatic arthritis.

    To be considered csDMARD-IR:

    - Subject must have demonstrated **an inadequate response** (lack of efficacy after minimum 12 week duration of therapy) to previous or current treatment with at least 1 of the following csDMARDs at maximally tolerated dose: MTX, sulfasalazine (SSZ), leflunomide (LEF), apremilast, bucillamine and iguratimod, or ciclosporin A.
    - MTX-IR is defined as an inadequate response (lack of efficacy after minimum 12 weeks duration of therapy) at the following doses ranges: ≥ 15 mg/week, or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week after complete titration (for subjects in some countries, such as China, Korea, Malaysia, Singapore, Hong Kong, Taiwan, and Japan inadequate response to MTX is defined as ≥ 7.5 mg/week or as required per local authorities).
    - Alternatively, subject may have demonstrated an **intolerance or contraindication to** csDMARDs as determined by the investigator.
    - Subject enrolling in the csDMARD-IR population **must not have had any prior exposure** to biologic immunomodulation agents used to treat PsA.

11. No evidence of **hepatitis B virus (HBV), hepatitis C virus (HCV) infection, human immunodeficiency virus (HIV) infection, or TB** defined as:

    - HBV: Hepatitis B surface antigen (HBs Ag) positive (+) test or detected sensitivity on the HBV DNA polymerase chain reaction (PCR) qualitative test for subjects who are hepatitis B

core antibody (HBc Ab) positive (+) (and for hepatitis B surface antibody [HBs Ab] positive [+] subjects where mandated by local requirements).

- HCV: HCV RNA detectable in any subject with anti-HCV antibody (HCV Ab).
- HIV: Confirmed positive anti-HIV antibody (HIV Ab) test. Ineligibility due to a positive HIV test should be documented in the CRF as a screen failure due to criterion 16 to keep this test result private.
- TB: Subjects with a positive QuantiFERON® TB /PPD test result may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active TB. If presence of latent TB is established, subjects are not required to be treated with prophylactic anti-TB therapy prior to or during the study, if the subject is considered low risk for reactivation per the investigator judgment.

- 12. No **active systemic infection** during the last 2 weeks prior to Baseline Visit (exception: common cold), as assessed by the investigator.
- 13. No documented **active or suspected malignancy** or history of **any malignancy** within the last 5 years except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.
- 14. No history of organ transplantation requiring continued immunosuppression.
- 15. No **major surgery** performed within 12 weeks prior to randomization or planned during the conduct of the trial (e.g., hip replacement, aneurysm removal, stomach ligation).
- 16. No history of clinically significant medical conditions or any other reason, including any physical, psychological, or psychiatric condition that in the opinion of the Investigator would compromise the safety or interfere with the subject's participation in this study, including a positive HIV test, or would make the subject an unsuitable candidate to receive study drug or would put the subject at risk by participating in the protocol; or permanently wheelchair-bound or bedridden or very poor functional status which prevents the ability to perform self-care.
- 17. No **active skin disease other than psoriasis** which could interfere with the assessment of psoriasis.
- 18. No history of **extra-articular manifestations of PsA** (e.g., PsO, uveitis, or inflammatory bowel disease [IBD]) that is not clinically stable for at least 30 days prior to Screening.
- 19. No **prior joint surgery** at joints to be assessed within this study in the 8 weeks prior to the Baseline Visit or **treatment with** intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the 8 weeks prior to the Baseline Visit.
- 20. No history of fibromyalgia, any arthritis with onset prior to age 17 years, or current diagnosis of inflammatory joint disease other than PsA (including, but not limited to rheumatoid arthritis, gout, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, systemic lupus erythematosus.)
    - Prior history of reactive arthritis or axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis is permitted if documentation of change in diagnosis to PsA or additional diagnosis of PsA is made.

- Prior history of fibromyalgia is permitted if documentation of change in diagnosis to PsA or documentation that the diagnosis of fibromyalgia was made incorrectly.

21. No history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 6 months.

22. No history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.

Contraception

23. A **negative serum pregnancy test** is required at the Screening Visit for all female subjects of childbearing potential. In addition a **negative urine pregnancy test** is required at Baseline prior to the first dose of study drug for all female subjects of childbearing potential. Subjects with a borderline serum pregnancy test at Screening must have a negative serum pregnancy test ≥ 3 days later to document continued lack of a positive result.

24. **If female**, subject must be of non-childbearing potential (defined in Section 5.2) OR a female of childbearing potential practicing at least 1 protocol-specified **method of birth control** that is effective from Study Day 1 through at least 140 days (20 weeks) after the last dose of study drug (local practices may require 2 methods of birth control).

25. Female subject may not be **pregnant, breastfeeding, or considering becoming pregnant** during the study and for at least 140 days (20 weeks) after the last dose of study drug.

Concomitant Medications

26. No prior exposure to any **anti-IL-23 agent**, such as guselkumab, tildrakizumab, or risankizumab.

27. No prior exposure to anti-IL-12/23 agent, such as ustekinumab, or anti-IL-17, or IL-17 receptor antagonists such as secukinumab or ixekizumab.

28. Subjects must have **discontinued all biologic therapy** prior to first dose of study drug. Subjects who need to discontinue biologic therapy in order to comply with this inclusion criterion must have discontinued the listed biologic therapy for the amount of time noted below. If not noted below, subjects need to have discontinued biologic therapy at least five times the mean terminal elimination half-life of a drug prior to the Baseline Visit in order to be eligible for participation in this study.

- 4 weeks for etanercept;
- 8 weeks for adalimumab, infliximab, certolizumab, golimumab, and abatacept;
- 1 year for rituximab OR 6 months if B cells have returned to pretreatment level or normal reference range (local laboratory) if pretreatment levels are not available

29. Subjects are not required to be receiving csDMARD therapy to participate in the clinical trial. However, subjects on current treatment with concomitant csDMARDs at study entry **must be on ≤ 2 of only the following csDMARDs** for ≥ 12 weeks and at stable dose for ≥ 4 weeks prior to the Baseline Visit at the following doses:

- MTX (≤ 25 mg/week);
- SSZ (≤ 3000 mg/day);
- LEF (≤ 20 mg/day);
- apremilast (≤ 60 mg/day);
- hydroxychloroquine (HCQ) (≤ 400 mg/day);
- bucillamine (≤ 300 mg/day);
- iguratimod (≤ 50 mg/day)
- ciclosporin A (≤ 5 mg/kg/day)

No other csDMARDs are permitted. The combination of MTX and LEF is exclusionary.

Where mandated by local requirements only, treatment with at least one of the following medications is required: csDMARDs, NSAIDs, acetaminophen, low potency opioids (tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen), or oral corticosteroids at dose equivalent to prednisone ≤ 10 mg/day.

30. Subjects who need to **discontinue or modify dose or dosing interval of their csDMARD therapy** prior to the Baseline Visit in order to comply with Eligibility Criterion 29 must follow the procedure specified below:
    - LEF must be discontinued ≥ 8 weeks prior to baseline if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with cholestyramine or activated charcoal or as per local label);
    - Discontinuation or modification of all other csDMARDS must occur ≥ 4 weeks prior to Baseline or at least five times the mean terminal elimination half-life of the drug before undergoing the Baseline Visit, whichever is longer.
31. Subjects are **permitted** to take stable doses of NSAIDs, acetaminophen/paracetamol, low-potency opiates (tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen), oral corticosteroids (equivalent to prednisone ≤ 10 mg/day), or inhaled corticosteroids for stable medical conditions. However, these medications must have been at a stable dose for ≥ 1 week prior to the Baseline Visit without an anticipated dose adjustment during study duration.
32. Subjects must have **discontinued all opiates** (except for tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen) at least 1 week prior to the first dose of study drug (refer to Section 5.3).
33. No use of the following **concomitant psoriasis treatments** within the specified timeframe prior to Baseline Visit:
    - Oral retinoids within 4 weeks;
    - Fumarates within 1 week;
    - Psoralens and Ultraviolet A (PUVA) within 4 weeks;
    - Ultraviolet A (UVA) and Ultraviolet B (UVB) within 2 weeks;

- Topical treatments, including medicated shampoos, within 2 weeks, with the exception of the following:
  - Bland (without beta or alpha hydroxy acids) emollients
  - Low potency (Class VI or VII) topical corticosteroids on the palms, soles, face, inframammary area and groin only.
  - Topical anti-itch treatment with no expected effect on psoriatic skin lesions.

34. Subject must not have received **any live vaccine** within 6 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 140 days (20 weeks) after the last dose of study drug (refer to Section 5.3).

35. Subject must not have been treated with **any investigational drug** within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another interventional clinical study.

5.2 Contraception Recommendations

If female, subject must be either postmenopausal or practicing birth control methods outlined below.

Postmenopausal is defined as:

- 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 > 40 international units (IU)/L;

OR

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Women of childbearing potential are defined as having experienced menarche and are:

- Not postmenopausal (as defined above);
- Not permanently sterilized (e.g., hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

Women of childbearing potential must practice at least one of the following methods of birth control throughout the study, including 140 days (20 weeks) after the last study drug dose is given.

- Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline (Day 1);
- Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline (Day 1);

- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success for the procedure);
- Intrauterine device (IUD);
- Intrauterine hormone-releasing system (IUS);
- Vasectomized sexual partner(s) (provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the trial participant);
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

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

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

5.3 Prohibited Medications and Therapy

During the study all other investigational drugs are prohibited. In addition, the following drugs are prohibited.

JAK Inhibitors

Concomitant use of JAK inhibitors (including but not limited to ruxolitinib [Jakafi®], tofacitinib [Xeljanz®], baricitinib, upadacitinib, and filgotinib).

Corticosteroids

- Intravenous (IV), intramuscular (IM) and epidural corticosteroids
- Intra-articular, trigger point or tender point, intra-bursa, and intra-tendon sheath corticosteroids are exclusionary and NOT allowed in Period 1 up to Week 36 unless a subject qualifies for rescue therapy at the Week 16 visit;
- Oral corticosteroids (refer to Section 5.1 Eligibility Criterion 31 for more information).

Biologic Therapies

All concomitant biologic therapies and biosimilars versions of biologic drugs for the treatment of PsA are prohibited during the study (Period 1 and Period 2). Examples of biologic therapies include but are not limited to the following:

- Humira® (adalimumab)
- Enbrel® (etanercept)
- Remicade® (infliximab)

- Orencia® (abatacept)
- Cimzia® (certolizumab pegol)
- Simponi® (golimumab)
- Stelara® (ustekinumab)
- Taltz® (ixekizumab)
- Cosentyx® (secukinumab)
- Tremfya® (guselkumab)

Opiates

Opiates, with the exception of tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen, are not permitted during the study and subjects must have discontinued at least 1 week prior to the first dose of study drug.

Opiates including (but not limited to):

- buprenorphine
- fentanyl
- hydromorphone
- levophanol
- meperidine
- methadone
- morphine
- oxycodone
- oxymorphone
- propoxyphene

Vaccines

Live vaccines are not permitted during study participation including up to 140 days (20 weeks) after the last dose of study drug. Although not mandated by the protocol, it is recommended that subjects be up to date on vaccines recommended by local guidelines. If the subject and investigator choose to administer live vaccines, these vaccinations must be completed at least 6 weeks before first dose of study drug.

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

- Monovalent live attenuated influenza A (H1N1) (intranasal)
- Seasonal trivalent live attenuated influenza (intranasal)

- Herpes zoster (Zostavax®)
- Rotavirus
- Varicella (chicken pox)
- Measles-mumps-rubella or measles mumps rubella varicella
- Oral polio vaccine
- Smallpox
- Yellow fever
- Bacille Calmette-Guérin (BCG)
- Oral Typhoid

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

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with reasons 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) through the last follow-up telephone call (up to Week 228).

All prior drug therapies for PsA, since initial diagnosis, must be recorded in the eCRF along with the dates of first and last dose, maximum dosage taken, route of administration and reason for discontinuation, if known. Additionally, the investigator will record response to biologics and csDMARDs (e.g., no response, inadequate response, loss of response), intolerance to biologics and csDMARDs, and/or contraindication for biologics and csDMARDs.

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

Subjects must be able to safely discontinue any prohibited medications prior to initial study drug administration as specified in the Eligibility Criteria (Section 5.1); where not specified, discontinuation must occur 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

Subjects are allowed to be on 0, 1, or 2 background csDMARDs. They must continue on their stable background csDMARD treatment through Week 36, unless the subject qualifies for rescue therapy at the Week 16 Visit. Background csDMARDs should have been started ≥ 12 weeks prior to the Baseline Visit

and without dosing or administration changes ≤ 4 weeks prior to the Baseline Visit. **Subjects taking MTX should take a dietary supplement of oral folic acid (or equivalent) throughout study participation.**

At any time, the background csDMARD dose may be decreased for safety reasons.

Additionally subjects must also continue on their stable doses of the following, starting 4 weeks prior to Baseline through the Week 36 assessments:

- NSAIDs
- Acetaminophen/paracetamol
- Low-potency opiates (tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen)
- Oral corticosteroids (equivalent to prednisone ≤ 10 mg/day)

If an enrolled subject is not taking any of the above at Baseline Visit, these concomitant medications must not be initiated except where permitted by protocol (specific time period or protocol-defined rescue). If taking any of the above at Baseline on an as-needed basis (PRN), a subject should continue to use them for the same reason and same dose each time but they should not be taken within the 24 hours prior to any study visit to avoid bias in outcome measurements.

In the event of tolerability (or other safety) issues, these medications may be decreased, or discontinued with substitution of another permitted medication from that class.

In Period 2, at Week 24 (after Week 24 assessments have been performed) and thereafter, subjects may use any topical therapy for PsO per investigator judgment.

In Period 2, starting at Week 36 (after Week 36 assessments have been performed) and thereafter, 1 intra-articular, trigger point or tender point, intra-bursa, or intra-tendon sheath injection of corticosteroids, dosage and frequency per standard of care, is allowed every 12 weeks. However, corticosteroid injections should be avoided within 21 days prior to the next scheduled study visit to avoid confounding effects of systemic absorption of corticosteroids.

At Week 36 (after Week 36 assessments have been performed) and thereafter, initiation of or change in corticosteroids, NSAIDs, acetaminophen/paracetamol, low potency opiates (tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen) or adding or changing doses of csDMARDs (MTX, LEF, SSZ, apremilast, HCQ, bucillamine, iguratimod, or ciclosporin A) is allowed as per eligibility Criterion 29 or local label, whichever dose is lower. The combination of MTX and LEF is not allowed at any time during study conduct.

Allowed topical corticosteroids by World Health Organization classification[44] are listed below:

Potency	Class	Topical Corticosteroid	Formulation
Low	VI	Betamethasone valerate	Lotion, 0.05%
		Desonide	Cream, 0.05%
		Fluocinolone acetonide	Solution, 0.01%
	VII	Dexamethasone sodium phosphate	Cream, 0.1%
		Hydrocortisone acetate	Cream, 1%
		Methyprednisolone acetate	Cream, 0.25%

Rescue Concomitant Medications/Therapy

At Week 16, subjects classified as non-responders (defined as not achieving at least a 20% improvement in either or both tender joint count [TJC] and swollen joint count [SJC] compared to Baseline at both Week 12 and Week 16) will:

- Add or modify doses of NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen); OR
- Receive 1 intra articular, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroid injection for 1 peripheral joint or 1 enthesis. Corticosteroid injections should be avoided within 21 days prior to the next scheduled study visit. For the analysis of the TJC, SJC, and enthesitis sites, injected joints or enthesitis sites will be considered "not assessable" for 90 days from the time of the injection; OR
- Titrate current background csDMARD or add an additional csDMARD, as allowed by eligibility criteria (Section 5.1). Doses of csDMARDs may not exceed maximums defined in eligibility criteria. Addition of a biologic therapy is not permitted. No more than 2 csDMARDs may be used.

5.5 Withdrawal of Subjects and Discontinuation of Study

Lack of response within the context of this study is defined as not achieving at least a 20% improvement in either or both TJC and SJC, compared to Baseline, on 2 consecutive visits. This evaluation begins at Week 32; therefore, Week 36 is the first possible time point a subject might be discontinued for lack of response. From Week 36 onward, study subjects will continue to be evaluated for lack of response on two consecutive visits. Discontinued subjects will be followed through the remainder of the study.

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

- Clinically significant abnormal laboratory result(s) or AEs, which rule out continuation of the study drug, as determined by the Investigator or the AbbVie Therapeutic Area Medical Director (TA MD) (as applicable).
- The Investigator believes withdrawal from the study treatment or study is in the best interest of the subject.

- The subject requests withdrawal from the study treatment or study.
- Eligibility criteria violation(s) are noted after the subject started study drug, if continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD, after consultation with the investigator.
- Subject needs to initiate prohibited medication(s) or dosages, and continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
- The subject becomes pregnant while on study drug.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study (see Operations Manual, Section 3.12).
- Subject is diagnosed with a malignancy (Exception: localized non-melanoma skin cancer or carcinoma in-situ of the cervix, where continuation of the subject is at the discretion of the investigator).
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial as determined by the Investigator or AbbVie TA MD.
- Occurrence of following hepatic test abnormalities that is confirmed on a separate sample following a repeated blood draw:
  - ALT or AST > 8 × Upper Limit of Normal (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%).

Positive TB Screen

- If subject has a positive QuantiFERON®-TB Gold Test (or other Interferon-Gamma Release Assay [IGRA]) or TB Skin Test (Purified Protein Derivative [PPD] test) at Screening or prior documented positive test within 90 days prior to Screening Visit, the test should not be repeated.
- If subject has a positive QuantiFERON®-TB Gold Test (or IGRA equivalent) and/or positive PPD test, or if there is a repeat indeterminate QuantiFERON®-TB Gold test (or IGRA equivalent) upon retesting, subjects may participate or continue in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active TB.
- If presence of latent TB is established, subjects who are at low risk of reactivation, defined by local guidelines and investigator judgment, do not need to be treated with prophylactic anti-TB therapy prior to or during the trial.
- If a decision is made to treat based on the clinical judgment of the investigator, TB prophylaxis should be initiated according to local country guidelines. Subjects do not need to be discontinued from study participation if prophylaxis for latent TB is initiated.

- It is also necessary to report new diagnoses of latent or active TB as an AE in the source documents and eCRFs. In the case of a TB-related AE, a TB Supplemental Form that collects additional information will be completed by the investigator.
- Subjects who have had an ulcerating reaction to the TB Skin Test in the past should not be re-exposed and should not be tested by a PPD skin test.
- TB assessment and treatment must be considered in regards to the local practice guidelines of any concomitant csDMARDs in use.

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

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

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it may be necessary to 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 before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

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

5.6 Follow-Up for Subject Withdrawal from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent).

Subjects who prematurely discontinue study drug should complete a Premature Discontinuation Visit (PD Visit) as soon as possible. Afterwards, subjects should follow the regular visit schedule as outlined in the Activity Schedule (Appendix D) and adhere to all study procedures except for dispensing study drug, pharmacokinetic (PK) sample collection, and biomarker sample collection for optional exploratory research. Once the subject has discontinued study drug, all rescue- and efficacy-driven discontinuation criteria no longer apply. If at any point a subject no longer wants to provide assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD visit is not required.

If a subject prematurely discontinues study participation but is willing to receive a 140-day (20-week) follow-up phone call after the last dose of study drug, the phone call should be completed to ensure all treatment-emergent AEs/serious AEs (SAEs) have been resolved. The follow-up phone call will not be conducted for subjects who withdraw study consent.

All attempts must be made to determine the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these

procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the Investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study. Subjects who prematurely discontinue from the study will not be replaced.

5.7 Study Drug

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

Table 1. Description of Study Drug and Placebo

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Risankizumab (ABBV-066)	Solution for injection in pre-filled syringe	75 mg/0.83 mL (90 mg/mL)	SC injection	Boehringer-Ingelheim Pharma GmbH & Co. KG
Placebo for Risankizumab (ABBV-066)	Solution for injection in pre-filled syringe	N/A	SC injection	Boehringer-Ingelheim Pharma GmbH & Co. KG

N/A = not applicable; SC = subcutaneous

AbbVie will not supply drug other than risankizumab and matching placebo. If a subject is unable to come to the study site for a study visit due to the COVID-19 pandemic, study drug can be taken to the subject's residence and administered by trained site personnel under appropriate conditions.

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

Interruption/Discontinuation of Study Drug Due to COVID-19

Delays in study drug dosing due to a subject with COVID-19 must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from study drug. Follow Section 5.6 for subjects who discontinue study drug.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. For subjects who rescreen, the screening number assigned by the IRT at the initial Screening Visit should be used. Subjects will be randomized in a 1:1 ratio to one of two treatment groups:

- Group 1: Risankizumab 150 mg (N = 210)
- Group 2: Placebo (N = 210)

Randomization will be stratified by current use of csDMARD (0 vs ≥ 1), number of prior biologic therapies (0 vs ≥ 1), and extent of psoriasis (≥ 3% BSA or < 3% BSA) at Baseline.

The Investigator, study site personnel, and the subject will remain blinded to each subject's treatment in Period 1 throughout the study. AbbVie will carry out an analysis of the primary endpoint at Week 24. To maintain the blind during the blinded portion of the study, the risankizumab pre-filled syringe (PFS) and placebo PFS provided for the study will be identical in appearance.

In the event of a medical emergency in which the Investigator believes that knowledge of study drug treatment is required, reasonable efforts must be made to contact the AbbVie Emergency Contact prior to breaking the blind, as long as it does not compromise subject safety. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting AbbVie Emergency Contact, the Investigator can directly access the IRT system to break the blind without AbbVie agreement.

The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

5.9 Protocol Deviations

The Investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the Investigator is responsible for notifying the Independent Ethics Committee/Institutional Review Board (IEC/IRB), regulatory authorities (as applicable) and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

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

Product Complaint

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

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

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

Medical Complaints/Adverse Events and Serious Adverse Events

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

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

If any of the following events are reported, then the following applicable supplemental report must be completed (Table 2).

Table 2. Adverse Events that Require Supplemental Reports

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

AE = adverse event; eCRF = electronic case report form; SAE = serious adverse event; TB = tuberculosis

If an AE meets any of the following criteria, it is to be reported to AbbVie or contract research organization (CRO) (as appropriate) as an SAE within 24 hours of the site being made aware of the SAE: Death of Subject, Life-Threatening, Hospitalization or Prolongation of Hospitalization, Congenital Anomaly, Persistent or Significant Disability/Incapacity, Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome.

All adverse events reported from the time of study drug administration until 140 days or 5 half-lives after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

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

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each adverse event as described in the Operations Manual, Section 4.4 Adverse Event Definition of Severity Grade.

The investigators will assess the relationship of the adverse event to the use of study drug as Reasonable Possibility or No Reasonable Possibility.

Pregnancy

While not an adverse event, pregnancy in a study subject must be reported to AbbVie within 24 hours of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued from study drug. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy 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 of the site becoming aware of the event.

6.2 Toxicity Management

Monitoring of toxicity related to stable background csDMARDs, titration of csDMARDs, or addition of csDMARDs should comply with country level requirements.

6.3 Independent Data Monitoring Committee

An external Independent Data Monitoring Committee (IDMC) will review unblinded safety data at approximate 6 month intervals throughout the course of the study.

- A separate IDMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the IDMC members, frequency and triggers of data reviews, and relevant safety data to be assessed. Unblinded adjudicated cardio-cerebrovascular and anaphylaxis events will be presented to the IDMC for review on a periodic basis.
- Communications from the IDMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

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

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

6.5 Anaphylaxis Adjudication Committee

While systemic hypersensitivity reactions and anaphylaxis are not identified risks for risankizumab, the Sponsor has established an independent, blinded, expert committee to adjudicate events of anaphylaxis based on a pre-specified definition. An independent external AAC will adjudicate suspected anaphylactic reactions and will remain blinded to treatment allocation. The events that are adjudicated and the adjudication process will be detailed in the AAC Charter. A supplemental Hypersensitivity

Reaction 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 for relevant events.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

An unblinded analysis will be conducted after all subjects have completed Week 24 or have prematurely discontinued for the purpose of initial regulatory submission. Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all randomized subjects who received at least 1 dose of study drug. The FAS will be used for all efficacy and Baseline analyses. Subjects will be grouped according to treatment as randomized.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. For the Safety Analysis Set, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

7.3 Statistical Analyses for Efficacy

Imputation Methods

Non-Responder Imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C): Subjects with a missed scheduled assessment visit due to reasons other than the COVID-19 pandemic will be handled by non-responder imputation. In addition, subjects will be considered as non-responders after the initiation of concomitant medications for PsA that could meaningfully impact efficacy assessment or initiation of rescue therapy. Missing data due to a COVID-19 infection or logistical restrictions related to the COVID-19 pandemic will be handled through multiple imputation.

As Observed (AO): The AO analysis will not impute values for missing evaluations; therefore, a subject who does not have an evaluation on a scheduled visit will be excluded from the AO analysis for that visit. Regardless of premature discontinuation of study drug, initiation of concomitant medications for PsA that could meaningfully impact efficacy assessments, or initiation of rescue therapy, all observed data will be used in the AO analysis.

Statistical Analyses for Efficacy

The comparisons between the risankizumab and placebo treatment groups for the primary efficacy endpoint (ACR20 at Week 24) will be performed using the Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors.

For continuous efficacy endpoints, the treatment comparison will be conducted using a Mixed-Effect Model Repeated Measures (MMRM) method as primary inference purpose.

The MMRM analysis will be conducted using mixed-effect model with observed measurements at all visits prior to initiation of any concomitant medications for PsA that could meaningfully impact efficacy assessments or rescue medications. The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, main stratification factors, and the continuous fixed covariate of baseline measurement. An unstructured variance covariance matrix will be used. The parameter estimations are based on the assumption of data being missing at random and using the method of restricted maximum likelihood (REML).

Categorical efficacy variables will be analyzed using the CMH test controlling for stratification variables. NRI-C imputation will be used for missing data imputation.

The primary and ranked secondary efficacy endpoints will be tested with multiplicity adjustment to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided). The details of the testing procedure will be specified in SAP.

Long-term efficacy by time point will be summarized using descriptive statistics. For binary endpoints, frequencies and percentages will be summarized. For continuous endpoints, the mean, standard deviation, median, minimum, and maximum will be reported.

Additional subgroup analysis and sensitivity analysis will be specified in the SAP.

Sample Size Estimation

Approximately 420 subjects will be randomized to risankizumab 150 mg or placebo in a ratio of 1:1 (210 subject/treatment group). A sample size of 210 in each group will have 90% power to detect a difference in HAQ-DI mean change from baseline of 0.24 (the difference between risankizumab 150 mg mean change from baseline of –0.37 and placebo mean change from baseline of –0.13) assuming that the common standard deviation is 0.72 using a two-group Satterthwaite t-test with a two-sided significance level of 0.05.

This sample size also ensures that analyses will have at least a 90% power to detect a 20% treatment difference in ACR20 at Week 24, with assumed placebo response rate of 35%, using a two-sided test at a 0.05 significance level and accounting for a 10% dropout rate.

7.4 Statistical Analyses for Safety

Safety analyses will be carried out using the Safety Analysis Set. There will be two sets of planned safety analysis: safety analysis by Week 24, and long-term safety analysis. Safety will be assessed by AEs, physical examinations, laboratory assessments, and vital signs. Frequency tables and lists of subjects with treatment emergent AEs by preferred term as in the Medical Dictionary for Regulatory Activities (MedDRA), by system organ class and preferred term, by severity, and by relationship to the study drug as assessed by the Investigator will be provided. The changes from Baseline in vital signs, physical examination results, and clinical laboratory values will be analyzed in a descriptive manner. Shift of laboratory values from Baseline to defined time points will be tabulated.

7.5 Analysis of PK and Immunogenicity

Serum risankizumab concentrations will be summarized at the sampling time point using descriptive statistics. In addition, ADA titers will be tabulated for each ADA positive subject at the respective study visits. The number and percentage of subjects with ADA and nAb will be calculated. Additional analyses may be conducted if appropriate.

7.6 Analysis of Exploratory Variables

Data from exploratory research samples will be tabulated for each subject with a breakdown by dose group. Exploratory analyses will be performed on the data from exploratory research samples. These exploratory analyses are separate from the study statistical analysis plan and may not be reported in study report.

8 ETHICS

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

The protocol, informed consent form(s), recruitment materials, and all participant 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 participant is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

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

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

8.3 Subject Confidentiality

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

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

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

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

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

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

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

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

The end-of-study is defined as last protocol contact or last protocol follow-up, whichever is longer.

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AAC	Anaphylaxis Adjudication Committee
ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse Event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AO	As observed
AS	Ankylosing spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	Aspartate transaminase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BCG	Bacille Calmette-Guérin
BIO-IR	Inadequate response to 1 or 2 biologic therapies or intolerance
BSA	Body surface area
CAC	Cardiovascular Adjudication Committee
C_{avg}	Average plasma concentrations
CASPAR	Classification Criteria for PsA
CCP	Cyclic-citrullinated peptide
CD	Crohn's disease
CL/F	Apparent Clearance
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease of 2019
CRO	Contract research organization
csDMARD	Conventional synthetic DMARD
CTCAE	Common Terminology Criteria for Adverse Events
DAPSA	Disease Activity In Psoriatic Arthritis
DAS28	Disease Activity Score 28
DMARD	Disease modifying anti-rheumatic drug
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency

EQ-5D-5L	EuroQol-5D-5L
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBc-Ab	Hepatitis B core antibody
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis b virus
HCV	Hepatitis c virus
HCQ	Hydroxychloroquine
HIV	Human immunodeficiency virus
HRU	Health resource utilization
hsCRP	High sensitivity C-Reactive Protein
IBD	Inflammatory bowel disease
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IGRA	Interferon-Gamma Release Assay
IL	Interleukin
IM	Intramuscular
IMP	Investigational Medicinal Product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IU	International units
IUS	Intrauterine hormone-releasing system
IV	Intravenous
JAK	Janus kinase
LAR	Legally Authorized Representative

LDI	Leeds Dactylitis Index
LEF	Leflunomide
LEI	Leeds Enthesitis Index
mAb	Monoclonal antibody
MACE	Major adverse cardiac event
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed Effect Model Repeated Measures
MTX	Methotrexate
nAb	Neutralizing antibody
NMSC	Non-melanoma skin cancer
NRI-C	Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19
NSAID	Nonsteroidal anti-inflammatory drug
OC	Observed cases
PASDAS	PsA Disease Activity Score
PASI	Psoriasis Area Severity Index
PCR	Polymerase chain reaction
PCS	Physical Component Summary
PD	Premature Discontinuation
PFS	Pre-filled syringe
PK	Pharmacokinetic(s)
PPD	Purified protein derivative
PRN	Pro re nata (as-needed basis)
PsA	Psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
PsO	Psoriasis
PUVA	Psoralens and Ultraviolet A
PY	Patient years
q12w	Every 12 weeks
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	36-Item Short Form Health Survey
SJC	Swollen joint count
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
Th	T helper
TJC	Tender joint count
TNF	Tumor necrosis factor
UC	Ulcerative colitis
ULN	Upper limit of normal
UVA	Ultraviolet A
UVB	Ultraviolet B
VAS	Visual analogue scale
WBC	White blood cell
WPAI	Work Productivity and Activity Impairment

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M15-998: Psoriatic Arthritis: Risankizumab Therapy Vs Placebo in Bio-IR Subjects

Protocol Date: 10 September 2020

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

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

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Medical Writing
		Immunology Clinical Development
		Immunology Clinical Development
		Clinical Program Development
		Data Statistical Sciences
		Clinical Pharmacology and Pharmacometrics

APPENDIX D. ACTIVITY SCHEDULE

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

Study Activities Table

Activity	Screening D –35 to D –1	BASELINE D1	W4 D28	W8 D56	W12 D84	W16 D112	W24 D168	W28 D196	W32 D224	W36 D252	W40 D280	W52 to W208 (Every 12 Weeks) D364 to D1456	Completion or PD (12 Weeks Post Last Dose) D1540	F/U Call (20 Weeks Post Last Dose) D1596
INTERVIEWS & QUESTIONNAIRES														
Informed Consent and Subject Information	✓													
Eligibility criteria	✓	✓												
CASPAR	✓													
Medical history	✓	✓												
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior Biologic and csDMARD therapy	✓													
TB Screening questionnaire (annually after Screening)	✓											✓	✓	
Patient Reported Outcomes – SF-36,[a] EQ-5D-5L, FACIT-Fatigue,[a] WPAI,[a] BASDAI		✓			✓		✓			✓		✓	✓	
Patient Reported Outcomes – HAQ-DI, Patient's Assessment of Pain(VAS), PtGA of Disease Activity (VAS)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
HRU		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Activity	Screening D –35 to D –1	BASELINE D1	W4 D28	W8 D56	W12 D84	W16 D112	W24 D168	W28 D196	W32 D224	W36 D252	W40 D280	W52 to W208 (Every 12 Weeks) D364 to D1456	Completion or PD (12 Weeks Post Last Dose) D1540	F/U Call (20 Weeks Post Last Dose) D1596
LABS & EXAMS														
Weight[b]	✓						✓					✓	✓	
Height	✓													
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical exam (annually after W52)	✓	✓					✓					✓	✓	
12-lead ECG	✓													
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Investigator Assessments (PGA)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigator Assessments (TJC, SJC, BSA-PsO[a])	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigator Assessments (LDI, LEI, SPARCC)		✓			✓	✓	✓			✓		✓	✓	
Investigator Assessments (PASI[a])		✓	✓	✓	✓	✓	✓			✓		✓	✓	
Investigator Assessments (Psoriatic Spondylitis Question)		✓												
Bilateral radiographs of hands and feet[c]	✓													
Central Laboratory Test – Serum pregnancy	✓													
Local urine pregnancy test		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Activity	Screening	BASELINE	W4	W8	W12	W16	W24	W28	W32	W36	W40	W52 to W208 (Every 12 Weeks)	Completion or PD (12 Weeks Post Last Dose)	F/U Call (20 Weeks Post Last Dose)
	D –35 to D –1	D1	D28	D56	D84	D112	D168	D196	D224	D252	D280	D364 to D1456	D1540	D1596
Central Laboratory Tests – hsCRP, Clinical Chemistry, Hematology	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Central Laboratory Tests – Total Cholesterol, HDL-C, LDL-C, Triglyceride		✓												
Central Laboratory Tests – TB screen (QuantiFERON-TB Gold test [or IGRA equivalent] and/or local purified protein derivative [PPD] skin test)[d]	✓											✓	✓	
Central Laboratory Tests – HIV Screening, Hepatitis B and C Screening, Rheumatoid Factor, Anti-CCP antibodies, Urinalysis, FSH	✓													
Blood samples for Risankizumab PK assay[e]								✓				✓		
Blood samples for Risankizumab ADA assay and neutralizing antibody (nAb) assay[e]		✓						✓				✓		
Calculation of TJC/SJC responses					✓	✓			✓	✓	✓	✓		
Anaphylaxis Monitoring[f]		✓	✓			✓	✓	✓			✓	✓		

Activity	Screening	BASELINE	W4	W8	W12	W16	W24	W28	W32	W36	W40	W52 to W208 (Every 12 Weeks)	Completion or PD (12 Weeks Post Last Dose)	F/U Call (20 Weeks Post Last Dose)
	D –35 to D –1	D1	D28	D56	D84	D112	D168	D196	D224	D252	D280	D364 to D1456	D1540	D1596
Rx TREATMENT														
Randomization/ Drug assignment		✓												
Administer Study Drug		✓	✓			✓	✓	✓			✓	✓		

a. After Week 52, assessment is to be done every 24 weeks (at Week 76, Week 100, Week 124, Week 148, Week 172, Week 196, Week 220/PD visit).

b. Weight should be measured at screening, Week 24 and Week 52. After Week 52, assessment is to be done every 24 weeks (at Week 76, Week 100, Week 124, Week 148, Week 172, Week 196, Week 220/PD visit).

c. If required to meet CASPAR criteria.

d. TB testing will be performed at Screening, Week 52, and every 48 weeks thereafter. TB testing should be performed at the PD visit if it has not been performed within the past 48 weeks.

e. After Week 28, PK, ADA, and nAb samples will be collected **only at Week 208.**

f. Subjects will be closely monitored for approximately 2 hours after the first dose administration (Study Day 1) and Week 24 (first dose of risankizumab for subjects randomized to placebo) and 1 hour after all other dose administrations.

In case of a **suspected anaphylactic reaction**. A blood sample for risankizumab drug level, ADA, and nAb should be collected once within 24 hours of the reaction. In addition, blood tests to be conducted in the event of a suspected anaphylactic reaction are:

- Serum tryptase: 15 minutes to 3 hours of symptom onset, and no later than 6 hours (as tryptase may remain elevated for 6 or more hours after the onset and therefore may still be informative if obtained after 3 hours); it is also requested to collect a follow-up tryptase level a minimum of 2 weeks after the recorded event or at the next study visit.
- Plasma histamine: 5 to 15 minutes of symptom onset, and no later than 1 hour.

In the event that a suspected anaphylactic reaction occurs while the subject is not on site at the study clinic, please advise the treating facility to perform serum tryptase and histamine.

Note: Visit window is ± 7 days. Any of the procedures may be performed at an unscheduled visit at the discretion of the Investigator.

Optional Biomarker Study Activities Table

Activity	Screening D –35 to D –1	BASELINE D1	W4 D28	W8 D56	W12 D84	W16 D112	W24 D168	W28 D196	W32 D224	W36 D252	W40 D280	W52 D364	PD (if prior to W52) D 1540
Whole Blood: Transcriptomic (PG-RNA)		✓	✓		✓		✓					✓	✓
Whole Blood: genetic (PG-DNA)		✓											
Whole Blood: epigenetic (PG-DNAepi)		✓	✓		✓		✓					✓	✓
Whole Blood: Proteomic and targeted protein investigations (serum)		✓	✓		✓		✓					✓	✓
Urine biomarker		✓	✓		✓		✓					✓	✓

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	26 July 2018
Version 2.0	12 November 2018
Version 3.0	14 February 2019
Version 4.0	17 March 2020

The purpose of this version is to incorporate necessary protocol modifications due to the COVID-19 pandemic as follows:

- Section 2.2 – included information on the re-evaluation of the benefit and risk to subjects participating in the study.
- Section 5.5 – added instructions to refer to Operations Manual for necessary changes to activities or procedures.
- Section 5.7 – provided instructions in the event of temporary study drug interruption/halt due to COVID-19 and that in the event the subject cannot complete an onsite visit, administration of study drug at the subject's house is to be performed by study staff if feasible and permitted by local regulations.
- Section 5.9 – clarified that protocol deviations may include modifications due to COVID-19.
- Section 7.3 – replaced NRI with NRI-C to incorporate handling of missing data due to COVID-19.
- Section 8.2 – noted that AbbVie will modify the study protocol as necessary due to the pandemic, referring to the Operations Manual in Appendix F for additional details. Investigators must also notify AbbVie if any urgent safety measures are taken.
- Section 9 – noted that remote monitoring may be employed as needed.
- Appendix D – added reference to Operations Manual for allowed modification.
- Appendix F – Operations Manual updated to include details on how to perform specific activities/procedures that may be impacted by changes in global/local regulations due to the pandemic.

  Rationale for all of the above changes: *To make modifications to the protocol related to the COVID-19 pandemic that ensures subject safety, continuity of care for subjects, and data integrity within the study.*

The following changes not related to the COVID-19 pandemic were also made:

- Section 3.3 – Added the ranked secondary endpoint ACR20 at Week 16.

Rationale: *As a clinically meaningful measure of efficacy, ACR20 with multiplicity control at an earlier timepoint will provide additional data on treatment effect.*

- Section 3.3 – Modified resolution of enthesitis and dactylitis to be unranked additional secondary endpoints without multiplicity adjustment.

  Rationale: *Given the expected size of the subpopulations for these endpoints, the resulting date are not expected to provide adequate power to be clinically meaningful. No data from this study or any other ongoing study was used to make this determination.*

- Section 3.4 – Corrected the description of the endpoint "Change from Baseline in Modified Psoriatic Arthritis Response Criteria (PsARC)" to "Proportion of subjects who achieve a Modified Psoriatic Arthritis Response Criteria (PsARC) response."

  Rationale: *Change from baseline is not the correct method to evaluate a binary endpoint.*

- Section 7.3 – Modified wording on the NRI-C and AO imputation methods.

  Rationale: *To clarify differences between the NRI-C and AO methods.*

- Section 7.3 – Modified wording on MMRM analysis for continuous variables.

  Rationale: *To clarify which data will be used in the MMRM analysis.*

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M15-998

Psoriatic Arthritis: Risankizumab Therapy Vs Placebo in Bio-IR Subjects

SPONSOR:	For Non-EU Countries: AbbVie For EU Countries: AbbVie Deutschland.	ABBVIE INVESTIGATIONAL PRODUCT:	Risankizumab, ABBV-066

FULL TITLE: A Phase 3, Randomized, Double-Blind Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis Including Those Who Have a History of Inadequate Response or Intolerance to Biologic Therapy(ies) (KEEPsAKE 2)

1 CONTACTS

Sponsor Emergency Medical Contact	[redacted] AbbVie Avenida De Burgos 91 Madrid, Spain 28050 **EMERGENCY 24 hour Number:** **+1 (973) 784-6402**	Office/Mobile: Email: [redacted]
Safety Concerns	Immunology Safety Team Dept. R48S, Bldg. AP31-2 1 North Waukegan Road North Chicago, IL 60064	Phone: (847) 938-8737 Email: GPRD_SafetyManagement_Immunology@abbvie.com
SAE Reporting outside of RAVE	Email: PPDINDPharmacovigilance@abbvie.com	Fax: (847) 938-0660
Protocol Deviations	[redacted] AbbVie [redacted] 1 North Waukegan Road North Chicago, IL 60064	Office: Mobile: Email: [redacted]
Certified Clinical Lab	Covance Central Laboratory Services SA 8211 Scicor Drive Indianapolis, IN 46214	Phone: +001 866-762-6209 (Toll free) +001 317-271-1200 (Local calls) Fax: +001 317-616-2362 For country specific toll-free numbers please refer to Covance Lab Manual.
Pharmacokinetic Lab	AbbVie Deutschland GmbH & Co. KG Bioanalysis Large Molecules Knollstrasse 67061 Ludwigshafen, Germany	Phone: +49 621-589-4847 Fax: +49 621-589-3184
Exploratory Sample Lab	BioStorage Technologies, Inc. 2910 Fortune Circle West, Suite E Indianapolis, IN 46241	

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2 INVESTIGATION PLAN

2.1 Individual Treatment Period Visit Activities

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

Any of the procedures, excluding study drug administration and patient reported outcomes, may be performed at an unscheduled visit at the discretion of the investigator.

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

SCREENING:

INTERVIEW	• Informed consent • Demographics, where allowed by local regulations • Medical history • Prior biologic and conventional synthetic disease modifying anti-rheumatic drug (csDMARD) therapy	• Evaluation of eligibility criteria • Prior and concomitant medications assessment • Tuberculosis (TB) Screening questionnaire • Classification Criteria for Psoriatic Arthritis (CASPAR)
EXAM	• 12-lead electrocardiogram (ECG) • Vital signs • Physical examination • Adverse event (AE) assessment • Bilateral radiographs of hands and feet (if required to meet CASPAR criteria) • Body surface area (BSA)-psoriasis (PsO)	• Height • Weight • Tender joint count (TJC) • Swollen joint count (SJC)
LOCAL LAB	• TB screen (Purified Protein Derivative [PPD] Skin Test), if not completed by another method (QuantiFERON-TB Gold Test)	
CENTRAL LAB	• High sensitivity C-Reactive Protein (hsCRP) • Clinical chemistry • TB screen (QuantiFERON-TB Gold Test) • Human immunodeficiency virus (HIV) screening • Anti-cyclic-citrullinated peptide (CCP) antibodies	• Serum pregnancy test • Hematology • Follicle-stimulating hormone (FSH) • Hepatitis B and C screening • Rheumatoid factor • Urinalysis

BASELINE/STUDY DAY 1:

INTERVIEW	• Medical History • Health Resource Utilization (HRU)	• Evaluation of eligibility criteria • Prior and concomitant medications assessment
PRO	• EuroQol-5D-5L (EQ-5D-5L) • Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • 36-Item Short Form Health Survey (SF-36) • Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) • Work Productivity and Activity Impairment (WPAI)	• Health Assessment Questionnaire-Disability Index (HAQ-DI) • Patient's Assessment of Pain (Visual analogue scale [VAS]) • Patient's Global Assessment (PtGA) of Disease Activity (VAS)
EXAM	• Vital signs • Physical examination • AE assessment • Physician's Global Assessment (PGA) • BSA-PsO • Psoriasis Area Severity Index (PASI) • Psoriatic Spondylitis Question	• Leeds Enthesitis Index (LEI), Leeds Dactylitis Index (LDI), and Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index • TJC • SJC
LOCAL LAB	• Urine pregnancy test	
CENTRAL LAB	• hsCRP • Clinical chemistry • Total cholesterol, High-density lipoprotein-cholesterol (HDL-C), Low-density lipoprotein-cholesterol (LDL-C), Triglyceride • Hematology	• Anti-drug antibody (ADA) sample • Neutralizing antibody (nAb) sample • Optional biomarker samples: whole blood (DNA/RNA/serum proteomic) and urine • Anaphylaxis testing (if applicable)[a]
TREATMENT	• Administer study drug • Randomization/Drug Assignment	• Anaphylaxis monitoring

WEEK 4:

INTERVIEW	• Prior and concomitant medications assessment	• HRU
PRO	• HAQ-DI	• Patient's Assessment of Pain (VAS) • PtGA of Disease Activity (VAS)
EXAM	• Vital signs • AE assessment • PGA • BSA-PsO	• PASI • TJC • SJC
LOCAL LAB	• Urine pregnancy test	
CENTRAL LAB	• hsCRP • Clinical chemistry • Hematology	• Optional biomarker samples: whole blood (DNA/RNA/serum proteomic) and urine • Anaphylaxis testing (if applicable)[a]
TREATMENT	• Administer study drug	• Anaphylaxis monitoring

WEEK 8:

INTERVIEW	• Prior and concomitant medications assessment	• HRU
PRO	• HAQ-DI	• Patient's Assessment of Pain (VAS) • PtGA of Disease Activity (VAS)
EXAM	• Vital signs • AE assessment • PGA • BSA-PsO	• PASI • TJC • SJC
LOCAL LAB	• Urine pregnancy test	
CENTRAL LAB	• hsCRP • Clinical chemistry	• Hematology

WEEK 12:

INTERVIEW	• Prior and concomitant medications assessment	• HRU
PRO	• BASDAI • EQ-5D-5L • SF-36 • FACIT-Fatigue • WPAI	• HAQ-DI • Patient's Assessment of Pain (VAS) • PtGA of Disease Activity (VAS)
EXAM	• Vital signs • AE assessment • PGA • BSA-PsO • PASI	• LDI, LEI, and SPARCC • TJC • SJC • Interactive Response Technology (IRT) calculation of TJC/SJC responses
LOCAL LAB	• Urine pregnancy test	
CENTRAL LAB	• hsCRP • Clinical chemistry • Hematology	• Optional biomarker samples: whole blood (DNA/RNA/serum proteomic) and urine

WEEK 16:

INTERVIEW	• Prior and concomitant medications assessment	• HRU
PRO	• HAQ-DI	• Patient's Assessment of Pain (VAS) • PtGA of Disease Activity (VAS)
EXAM	• Vital signs • AE assessment • PGA • BSA-PsO • PASI	• LDI, LEI, and SPARCC • TJC • SJC • IRT calculation of TJC/SJC responses
LOCAL LAB	• Urine pregnancy test	
CENTRAL LAB	• hsCRP • Clinical chemistry	• Hematology • Anaphylaxis testing (if applicable)[a]
TREATMENT	• Administer study drug	• Anaphylaxis monitoring

WEEK 24:

INTERVIEW	• Prior and concomitant medications assessment	• HRU
PRO	• BASDAI • EQ-5D-5L • SF-36 • FACIT-Fatigue • WPAI	• HAQ-DI • Patient's Assessment of Pain (VAS) • PtGA of Disease Activity (VAS)
EXAM	• Vital signs • Physical examination • Weight • AE assessment • PGA	• BSA-PsO • PASI • LDI, LEI, and SPARCC • TJC • SJC
LOCAL LAB	• Urine pregnancy test	
CENTRAL LAB	• hsCRP • Clinical chemistry • Hematology	• Optional biomarker samples: whole blood (DNA/RNA/serum proteomic) and urine • Anaphylaxis testing (if applicable)[a]
TREATMENT	• Administer study drug	• Anaphylaxis monitoring

WEEK 28:

INTERVIEW	• Prior and concomitant medications assessment	• HRU
PRO	• HAQ-DI	• Patient's Assessment of Pain (VAS) • PtGA of Disease Activity (VAS)
EXAM	• Vital signs • AE assessment • PGA • BSA-PsO	• TJC • SJC
LOCAL LAB	• Urine pregnancy test	
CENTRAL LAB	• hsCRP • Clinical chemistry • Hematology	• Pharmacokinetic (PK) sample • ADA sample • nAb sample • Anaphylaxis testing (if applicable)[a]
TREATMENT	• Administer study drug	• Anaphylaxis monitoring

WEEK 32:

INTERVIEW	• Prior and concomitant medications assessment	• HRU
PRO	• HAQ-DI	• Patient's Assessment of Pain (VAS) • PtGA of Disease Activity (VAS)
EXAM	• Vital signs • AE assessment • PGA • BSA-PsO	• TJC • SJC • IRT calculation of TJC/SJC responses
LOCAL LAB	• Urine pregnancy test	
CENTRAL LAB	• hsCRP • Clinical chemistry	• Hematology

WEEK 36:

INTERVIEW	• Prior and concomitant medications assessment	• HRU
PRO	• BASDAI • EQ-5D-5L • SF-36 • FACIT-Fatigue • WPAI	• HAQ-DI • Patient's Assessment of Pain (VAS) • PtGA of Disease Activity (VAS)
EXAM	• Vital signs • AE assessment • PGA • BSA-PsO • PASI	• LDI, LEI, and SPARCC • TJC • SJC • IRT calculation of TJC/SJC responses
LOCAL LAB	• Urine pregnancy test	
CENTRAL LAB	• hsCRP • Clinical chemistry	• Hematology

WEEK 40:

INTERVIEW	• Prior and concomitant medications assessment	• HRU
PRO	• HAQ-DI	• Patient's Assessment of Pain (VAS) • PtGA of Disease Activity (VAS)
EXAM	• Vital signs • AE assessment • PGA • BSA-PsO	• TJC • SJC • IRT calculation of TJC/SJC response
LOCAL LAB	• Urine pregnancy test	
CENTRAL LAB	• hsCRP • Clinical chemistry	• Hematology • Anaphylaxis testing (if applicable)[a]
TREATMENT	• Administer study drug	• Anaphylaxis monitoring

WEEK 52 to WEEK 208
(Every 12 weeks):

INTERVIEW	• Prior and concomitant medications assessment • HRU	• TB Screening questionnaire (W52 & every 48 weeks thereafter)
PRO	• BASDAI • EQ-5D-5L • SF-36 (W52 & every 24 weeks thereafter) • FACIT-Fatigue (W52 & every 24 weeks thereafter) • WPAI (W52 & every 24 weeks thereafter)	• HAQ-DI • Patient's Assessment of Pain (VAS) • PtGA of Disease Activity (VAS)
EXAM	• Vital signs • Physical examination (W52 & annually thereafter) • Weight (W52 & every 24 weeks thereafter) • AE assessment • PGA • BSA-PsO (W52 & every 24 weeks thereafter)	• PASI (W52 & every 24 weeks thereafter) • LDI, LEI, and SPARCC • TJC • SJC • IRT calculation of TJC/SJC responses
LOCAL LAB	• Urine pregnancy test	• TB screen (PPD Skin Test, if not completed by another method [QuantiFERON TB Gold Test] W52 & every 48 weeks thereafter)
CENTRAL LAB	• hsCRP • Clinical chemistry • TB screen (QuantiFERON-TB Gold Test, W52 & every 48 weeks thereafter) • Hematology	• PK Sample (only at W208) • ADA sample (only at W208) • nAb sample (only at W208) • Optional biomarker samples: whole blood (DNA/RNA/serum proteomic) and urine (W52 Only) • Anaphylaxis testing (if applicable)[a]
TREATMENT	• Administer study drug	• Anaphylaxis monitoring

a. These laboratory assessments will be performed if the subject has a suspected anaphylactic reaction as determined by the site investigator.

Completion (12 weeks after last dose) or Premature Discontinuation:		
INTERVIEW	• Prior and concomitant medications assessment • HRU	• TB Screening questionnaire (only if subject has not had one within the past 48 weeks)
PRO	• BASDAI • EQ-5D-5L • SF-36 • FACIT-Fatigue • WPAI	• HAQ-DI • Patient's Assessment of Pain (VAS) • PtGA of Disease Activity (VAS)
EXAM	• Vital signs • AE assessment • Physical examination • Weight • PGA • BSA-PsO	• PASI • LDI, LEI, and SPARCC • TJC • SJC
LOCAL LAB	• Urine pregnancy test	• TB screen (PPD Skin Test, only if subject has not had one within the past 48 weeks and if not completed by QuantiFERON TB Gold Test)
CENTRAL LAB	• hsCRP • Clinical chemistry • TB screen (QuantiFERON-TB Gold Test, only if subject has not had one within the past 48 weeks)	• Hematology • Optional biomarker samples: whole blood (DNA/RNA/serum proteomic) and urine (if prior to W52)

F/U Call (20 weeks post last dose)		
INTERVIEW	• Prior and concomitant medications assessment	• HRU
EXAM	• AE assessment	

2.2 COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, if it is not possible for all study visits or procedures to be performed as specified due to travel restrictions or other reasons, Table 1 summarizes the modifications allowed per

the scenario. If a subject does not meet any of the scenarios described below, contact the sponsor for further guidance.

Table 1. Modifications to Study Visits Due to COVID-19 Pandemic

Scenario	Actions
If the subject can come to the study site	Perform the study visit procedures and study drug administration as planned. If laboratory samples cannot be shipped to the central laboratory, a local laboratory may be used for routine assessment. Biomarker assessments must still be shipped to the central laboratory. Local laboratory results should be reviewed by the Investigator as soon as possible. Local labs should be added to the Unscheduled local lab eCRF (see Section 3.12).
If the subject can come to the study site but a complete visit is not possible	Complete as many of the study procedures as possible as indicated in the planned study visit in Section 2.1.
For subjects who are not suspected or confirmed to have COVID-19, but are unable to attend an onsite visit (e.g., travel restrictions, quarantine)	1. Determine if the subject can perform an out of window (OOW) onsite visit (see Section 3.14). The study visits as described in the protocol should be conducted as close as possible to the scheduled study visit date. 2. Regardless of whether an onsite OOW visit can occur, a phone call from the site to the subject should be completed as close as possible to the date of the study visit. The phone call will query for any AEs and review concomitant medications. If possible, complete any ePRO assessment by interview (see Section 3.4). 3. If the visit is a dosing visit, an at-home visit is allowed to conduct study assessments and administer study drug (see Section 3.11).
For subjects who are well but have been quarantined due to exposure to a confirmed case of COVID-19	1. Follow the quarantine and travel restrictions as dictated by local health authority. 2. Study drug should not be administered while the subject has a suspected or confirmed COVID-19 infection. 3. Determine if the subject can perform an out of window (OOW) onsite visit (see Section 3.14). The study visits as described in the protocol should be conducted as close as possible to the scheduled study visit date. 4. Regardless of whether an onsite OOW visit can occur, a phone call from the site to the subject should be completed as close as possible to the date of the study visit. The phone call will query for any AEs and review concomitant medications. If possible, complete any ePRO assessment by interview (see Section 3.4).

Scenario	Actions
For subjects who have suspected or confirmed coronavirus disease (COVID-19)	1. Study drug should not be administered while the subject has an active COVID-19 infection. 2. Following recovery from illness, study visits and drug administration may be resumed after discussion with the sponsor. 3. Determine if the subject can perform an out of window (OOW) onsite visit (see Section 3.14). The study visits as described in the protocol should be conducted as close as possible to the scheduled study visit date. 4. Regardless of whether an onsite OOW visit can occur, a phone call from the site to the subject should be completed as close as possible to the date of the study visit. The phone call will query for any AEs and review concomitant medications. If possible, complete any ePRO assessment by interview (see Section 3.4). 5. Notify AbbVie of any subjects who are affected by this situation.

3 STUDY PROCEDURES

3.1 Subject Information and Informed Consent

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

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

Optional biomarker research samples will only be collected if the subject has voluntarily signed and dated a written consent form describing the research. The written consent may be part of the main consent form. If the subject does not consent to providing optional samples, the subject will still be allowed to participate in the study. A subject may withdraw consent for optional biomarker samples at any time and remain in the clinical study. Data generated from the optional biomarker samples before subject withdrawal of consent will remain part of the study results.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

3.2 Medical History

A complete medical history including the subtype of psoriatic arthritis (PsA), cardiovascular history and cardiovascular risk factors, history of hepatitis B vaccination, tobacco (including e-cigarettes) and alcohol will be taken at Screening. A detailed history of prior biologic(s) and csDMARD(s) and reasons for discontinuing will also be collected. The subject's medical history will be updated at the Study Day 1 visit. This updated medical history will serve as the Baseline for clinical assessment.

The subject's demographic data, including year of birth, gender, race, and ethnicity will be collected, when allowed per local regulatory guidelines.

3.3 Adverse Event Assessment

Please refer to Section 4.2.

3.4 Patient-Reported Outcomes

Subjects will complete the self-administered patient-reported outcome (PRO) instruments. Subjects should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

All PROs are collected electronically. The subject should complete the questionnaires before site personnel perform any clinical assessments and preferably before any interaction with site personnel has occurred to avoid biasing the subject's response. Data stored on the central server will be considered source. The investigator and delegated staff will be able to access uploaded subject-entered data via a password protected website until the generation, receipt, and confirmation of the study archive. Data from the ePRO system will be archived and provided to the investigator at that time as a durable record of the site's ePRO data.

Subjects will complete the following questionnaires as specified in the Study Activities Table (Appendix D of protocol). A validated translation will be provided in their local language, as applicable:

BASDAI

The BASDAI is composed of 6 items investigating 5 domains (fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, morning stiffness), with 1 item for each of the first 4 domains and 2 items for the last domain (morning stiffness). A lower score indicates less disease activity.

EQ-5D-5L Health Questionnaire

The EQ-5D-5L is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-5L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on 5 levels of severity. Responses to the 5 items encode a discrete health state which is mapped to a preference (utility) specific for different societies. Subjects also rate their perception of their overall health on a separate visual analogue scale.

FACIT-Fatigue

Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue is a 13-item questionnaire that evaluates fatigue/tiredness and its impact on daily activities and functioning in chronic diseases. This instrument includes items such as tiredness, weakness, listlessness, lack of energy, and the impact of these feelings on daily functioning (e.g., sleeping, and social activities). A lower score indicates less negative impact on daily activities.

HAQ-DI

Health Assessment Questionnaire Disability Index (HAQ-DI) is a self-reported assessment of how the patient's illness affects their ability to function in their daily life over the past week. The HAQ-DI for a patient is calculated as the mean of the following 8 category scores: Dressing and Grooming, Rising, Eating, Walking, Hygiene, Reach, Grip, and Activities. A lower score demonstrates less disability.

Patient's Assessment of Pain (VAS)

The Patient's Assessment of Pain (VAS) allows patients score on a 100 mm horizontal scale (0 being no pain and 100 being severe pain) to assess the patient's overall assessment of pain due to the disease condition during the past 24 hours.

PtGA of Disease Activity (VAS)

Patient's Global Assessment (PtGA) of Disease Activity (VAS) allows patients to score on a 100 mm horizontal scale (0 being very well and 100 being very poorly) to assess the patient's overall functionality assessment considering the disease activity within the past 24 hours.

SF-36 Health Questionnaire

The SF-36 Health Questionnaire is a 36-item survey of patient health consisted of 8 scaled scores, which are weighted sums of the questions in their section. The 8 sections are physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems,

emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. A higher score indicates a more favorable health state.

WPAI

The WPAI Questionnaire is a well-validated instrument to measure impairments in work and activities. The questionnaire includes 6 questions to assess the effect of psoriatic arthritis (PsA) on the patient's ability to work and perform regular activities in the past 7 days.

Patient reported outcome assessments are provided in Appendix Q.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If electronic PRO instruments (ePROs) cannot be completed on the tablet, they are permitted to be completed via phone or video interview.

Site staff will record the subject's responses on the screen shot of the PRO in the subject's language. The date, time and interviewer name should be recorded in the source document. The investigator or study coordinator must transcribe the PRO responses into the TrialManager website. No other site roles will receive access to enter data into TrialManager. Training will be required for investigator data entry into TrialManager and will be provided upon request of the sponsor.

If appropriate site personnel can travel to the subject's home, the tablet can be taken to the subject's home for ePRO completion. All ePROs should be completed for the assigned visit.

3.5 Investigator Assessments

The investigator assessments will be conducted at the study visits specified in the Study Activities Table. The results of the assessments, with the exception of the Physician Global Assessment (PGA) of Disease Activity (VAS), will be recorded on paper forms and entered into the electronic case report form (eCRF). The PGA will be entered into the ePRO device. If possible, the investigator assessments should be performed by an independent and blinded assessor who should not perform any other study related procedures.

In order to minimize variability, the same assessor should evaluate the subject at each visit for the duration of the trial. A back-up assessor should be identified. The assessor should be an independent qualified medical professional (i.e., nurse, physician's assistant, physician, or other qualified person). It is the responsibility of the Investigator to ensure that all assessors are qualified and trained to perform assessments and that all training is documented. If the assessor is not available, the pre-identified back-up assessor should perform such assessments.

Assessors must complete the following training modules provided by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA):

- Assessment of Enthesitis and Dactylitis in Psoriatic Arthritis
- PASI/BSA--Psoriasis Area and Severity Index (PASI)
- Assessment of Synovitis in Psoriatic Arthritis – Joint Count

The training modules will be provided via web portals. The training for PASI/BSA is to be completed at 3 time points and may be completed in either Study M16-011 or Study M15-998. The time points are as follows for each assessor at the site:

1. Prior to the first subject screened
2. Between randomization and the first Week 4 visit
3. Between Week 12 and the first Week 24 visit.

If an assessor has been certified for any of the above GRAPPA trainings in the previous 6 months, the respective GRAPPA training module(s) required prior to screening the first subject may be waived upon providing the training certificate. The PASI/BSA training required at the second and third time points described above may not be waived.

HRU Questionnaire

Sites will complete a HRU questionnaire at the study visits specified in the Study Activities Table. The questionnaire will be an interview administered by the site. The answers will be completed on the source worksheet provided by the sponsor and entered in the eCRF.

The assessor is not required to be independent and should be a qualified medical professional or a study coordinator.

Psoriasis Assessments

PASI

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

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

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

The assessor should be an independent qualified medical professional.

BSA–PsO

The subject's right or left hand should be selected as the measuring device. For purposes of clinical estimation, the total surface of the palm plus five digits will be assumed to be approximately equivalent to 1%. Measurement of the total area of involvement by the assessor is aided by imagining if scattered plaques were moved so that they were next to each other and then estimating the total area involved.

The assessor should be an independent qualified medical professional.

TJC and SJC Assessment

TJC Assessment

An assessment of 68 joints will be done for tenderness by pressure manipulation on physical examination. Joint pain/tenderness will be classified as: present, absent, replaced, or no assessment. Joints injected with corticosteroid will be considered non-evaluable for 90 days from the time of the injection.

The assessor should be an independent qualified medical professional.

SJC Assessment

An assessment of 66 joints will be done by directed physical examination. The hip joints are not assessed for swelling; all other joints that are assessed for tenderness will also be assessed for swelling. Joint swelling will be classified as present, absent, replaced, or no assessment. Joints injected with corticosteroid will be considered non-evaluable for 90 days from the time of the injection.

The assessor should be an independent qualified medical professional.

Dactylitis

LDI

This evaluation will be conducted to assess the presence or absence of dactylitis in all 20 of the subject's digits. The assessment should begin with visual inspection of the hands and feet. For each pair of digits in which one or both digits appear dactylitic, the circumference of the affected digits (both right and left side) will be assessed using a dactylometer. Additionally, the affected digit pairs will be assessed for tenderness by squeezing the digital shaft mid-way between the metacarpophalangeal and proximal interphalangeal joints and will be recorded as tenderness, yes or no. Tenderness should not be assessed by squeezing the joint lines. Digits injected with corticosteroid will be considered non-evaluable for 90 days from the time of the injection. If a digit is missing and its contralateral digit is dactylitic, "digit

absent" will be recorded for the missing digit. For any digit without an available dactylometer measurement, the standard reference value will be utilized in calculation of the LDI. The standard reference values will not be entered into the eCRF. A dactylometer will be provided to sites for use.

The assessor should be an independent qualified medical professional.

Enthesitis

LEI

LEI is a validated enthesitis index that uses 6 sites for evaluation of enthesitis: lateral epicondyle humerus left and right, Achilles tendon insertion left and right, and medial condyle femur left and right. Tenderness on examination is recorded as either present, absent, or not assessed for each of the 6 sites, for an overall score range of 0 – 6.

Enthesitis sites injected with corticosteroid will be considered non-evaluable for 90 days from the time of the injection.

The assessor should be an independent qualified medical professional.

SPARCC Enthesitis Index

This evaluation will be conducted to assess the presence or absence of enthesitis at 8 bilateral sites: medial epicondyle, lateral epicondyle, supraspinatus insertion to the greater tuberosity of the humerus, greater trochanter, quadriceps insertion into the superior border of the patella, patellar ligament insertion into the inferior pole of the patella or tibial tubercle, Achilles tendon insertion into calcaneum, and plantar fascia insertion into calcaneum. Tenderness on examination is recorded as either present, absent, or not assessed for each of the 16 sites. For scoring purposes, the inferior patella and tibial tuberosity are considered to be one site due to their anatomical proximity. The overall score range is 0 – 16. Enthesitis sites injected with corticosteroid will be considered non-evaluable for 90 days from the time of the injection. The lateral epicondyle and Achilles tendon insertion will only need to be assessed once since the 2 bilateral sites overlap between the LEI and SPARCC.

The assessor should be an independent qualified medical professional.

Psoriatic Spondylitis

This evaluation will be conducted at Baseline only as part of assessing PsA subtype. If the investigator determines that a subject has psoriatic spondylitis, how the diagnosis was made should be recorded (i.e., clinical evaluation, radiography and/or MRI).

Where possible, this evaluation should be assessed by a rheumatologist.

CASPAR

This is a validated set of criteria used for the classification of PsA based on the presence of inflammatory arthritis (joints, spine, or entheses) with ≥ 3 points from 5 categories as specified in Appendix B.

Subjects may receive bilateral radiographs of the hands and feet if needed to determine whether the subject fulfills item 5 of the CASPAR criteria (Appendix B). Radiographs will be locally read for CASPAR scoring.

PGA

Physician Global Assessment (PGA) of Disease Activity (VAS) allows physicians to score on a 100 mm horizontal scale (0 being very well and 100 being very poorly) to assess the patient's overall functionality assessment considering the disease activity within the past 24 hours.

The assessor is not required to be independent but should be a qualified medical professional, preferably a physician.

Investigator assessments are shown in Appendix D through Appendix P.

3.6 Biomarker Sampling

Optional whole blood and urine samples will be collected for exploratory research throughout the study as outlined in Section 2.1. All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will store the samples and data in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on risankizumab (or drugs of this class) or psoriatic arthritis and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

3.7 12-Lead Electrocardiogram

A 12-lead ECG will be performed at Screening using local equipment, as specified in Section 2.1. If a subject has had an ECG within the previous 90 days, it will not be required to be repeated for screening provided the conditions noted in this section are met. The ECG should be performed prior to blood collection.

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

- Normal ECG

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

In case of an abnormal ECG, the abnormal finding will be documented. Clinically significant ECG findings noted at screening will be captured in Medical History.

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

3.8 Height and Weight

Height and weight will be measured without shoes. The subject will wear lightweight clothing and no shoes during weighing. Weight should be measured at screening, Week 24 and Week 52. After Week 52, weight should be measured every 24 weeks (at Week 76, Week 100, Week 124, Week 148, Week 172, Week 196, and the Week 220/PD visit).

3.9 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure (BP) and pulse rate will be obtained at visits as specified in Section 2.1 before blood draws are performed. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes. Any significant abnormal vital signs findings will be reported as AEs.

3.10 Physical Examination

A complete physical examination will be performed at the designated study visits as specified in Section 2.1. The physical examination performed on Study Day 1 will serve as the Baseline physical examination for the entire study. Any significant physical examination findings after the first dose will be recorded as AEs. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any visits that do not require a full physical examination, a symptom-directed physical examination can be performed as deemed necessary by the Investigator.

3.11 Administer Study Drug

Study drug will be administered to subjects beginning at Baseline (Study Day 1) and as specified in Section 2.1. All subcutaneous (SC) doses of risankizumab and placebo will be administered by study site personnel under the direction of the Investigator. The date and time (to the nearest minute) of onset of study drug administration will be recorded in the subject's medical record. The first dose of study drug will be administered after all other Baseline (Study Day 1) procedures are completed.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If a subject cannot travel to the site for a visit when study drug administration is planned, site personnel may travel to the subject's home to conduct an at-home visit. Study drug may be transported under appropriate storage conditions and administered by trained site personnel. The site must contact the Sponsor to obtain instructions on how to dispense drug in the IRT system for at-home visits or for visits when a joint count assessment cannot be made.

If an at-home visit is scheduled, site staff should also bring the ePRO tablet to the home for the subject to complete those assessments, see Section 3.4 for more details.

Monitoring for Hypersensitivity Reactions

Therapeutic protein products, such as biologics, may elicit a range of acute effects, from symptomatic discomfort to sudden, fatal reactions that have often been grouped as 'infusion reactions' in the past. Although the term implies a certain temporal relationship, infusion reactions are otherwise not well defined and may encompass a wide range of clinical events, including anaphylaxis and other events that may not be directly related to antibody responses, such as cytokine release syndrome.

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

In the event of a suspected anaphylactic reaction, in addition to the standard AE eCRF, the supplemental Hypersensitivity Reaction Signs and Symptoms eCRF should also be completed by the site. The clinical criterion for diagnosing anaphylaxis is provided in Appendix C for reference; symptoms of anaphylactic reaction usually occur within 24 hours after exposure to an allergen. These are guidelines that are used to help diagnose anaphylaxis. The investigator is encouraged to report any suspected reactions.

Subjects will be monitored throughout the study for signs and symptoms suggestive of hypersensitivity reactions, including allergic reactions and anaphylaxis. A medical person qualified in the treatment of acute hypersensitivity reactions must be present during the injections. Subjects will be closely monitored for approximately 2 hours after the first dose administration (Study Day 1) and Week 24 (first dose of risankizumab for subjects randomized to placebo) and 1 hour after all other dose administrations.

Anaphylaxis Testing

In the event of a suspected anaphylactic reaction, a blood sample for risankizumab drug level, ADA, and nAb should be collected once within 24 hours of the reaction. In addition to risankizumab drug level, ADA and nAb assays, blood tests to be conducted in the event of a suspected anaphylactic reaction are:

- Serum tryptase: 15 minutes to 3 hours of symptom onset, and no later than 6 hours (as tryptase may remain elevated for 6 or more hours after the onset and therefore may still be informative if obtained after 3 hours); it is also requested to collect a follow-up tryptase level a minimum of 2 weeks after the recorded event or at the next study visit.
- Plasma histamine: 5 to 15 minutes of symptom onset, and no later than 1 hour.

3.12 Clinical Laboratory Tests

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study. The Baseline (Day 1) laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

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

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

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

Clinical Laboratory Tests		
Hematology	**Clinical Chemistry**	**Other Tests**
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands, if detected Lymphocytes Monocytes Basophils Eosinophils Platelet count Coagulation: International Normalized Ratio (INR)[a]	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Direct and indirect bilirubin[c] Alanine transaminase (SGPT/ALT) Aspartate transaminase (SGOT/AST) Gamma-glutamyl transferase (GGT) Alkaline phosphatase Sodium Potassium Calcium Cholesterol[d] Total protein Glucose Triglycerides[d] LDL[d] HDL[d] Albumin Chloride Bicarbonate/CO^2 Estimated glomerular filtration rate (eGFR) Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)	Hepatitis B surface antigen (HBs Ag, qualitative)[b] Hepatitis B core antibody (HBc Ab)/anti-HBc (qualitative)[b] HBs Ab/anti-HBs (qualitative)[b] Hepatitis B Virus DNA (reflex, quantitative)[b] Hepatitis C Antibodies (qualitative)[b] Hepatitis C Virus RNA (reflex, quantitative)[b] HIV-1 and HIV-2 Antibody (qualitative)[b] Human Chorionic Gonadotropin (hCG)[b,e] for females (quantitative) Rheumatoid Factor[b] Anti-CCP antibodies[b] hsCRP FSH[b,f] TB screen (QuantiFERON-TB Gold Test) **Anaphylaxis Testing**[g] Tryptase[g] Histamine[g] Serum risankizumab concentrations[g] ADA/nAb sample[g] **Local Labs** TB screen (PPD Skin Test), if needed Urine hCG for females[e]
Urinalysis[b]		
Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocyte esterase Nitrite Microscopic (reflex)		

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

b. Performed only at Screening.

c. Direct and indirect bilirubin is reflex if total bilirubin ≥ ULN.

d. Performed only at Baseline.

e. Pregnancy testing is required only for females of childbearing potential.

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

g. **Only performed** in case of a suspected anaphylactic reaction. A blood sample for risankizumab drug level, ADA, and nAb should be collected once within 24 hours of the reaction. In addition, blood tests to be conducted in the event of a suspected anaphylactic reaction are:

- Serum tryptase: 15 minutes to 3 hours of symptom onset, and no later than 6 hours (as tryptase may remain elevated for 6 or more hours after the onset and therefore may still be informative if obtained after 3 hours); it is also requested to collect a follow-up tryptase level a minimum of 2 weeks after the recorded event or at the next study visit.
- Plasma histamine: 5 to 15 minutes of symptom onset, and no later than 1 hour.

  In the event that a suspected anaphylactic reaction occurs while the subject is not on site at the study clinic, please advise the treating facility to perform serum tryptase and histamine.

Serum Pregnancy Test

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

If the repeat serum pregnancy test is:

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

Determination of postmenopausal status will be made during the Screening period based on the subject's history and confirmed by FSH if appropriate.

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

Urine Pregnancy Test

Additional urine pregnancy tests for female subjects of childbearing potential will be performed at visits indicated in Section 2.1. More frequent pregnancy tests will be performed throughout the study if required per local/country requirements.

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

Chemistry

Blood samples at Baseline will be collected following a minimum 8-hour fast. If a subject is not able to fast due to unforeseen circumstances, the nonfasting status will be recorded in study source documentation and lab requisition. Subjects are not required to fast before laboratory assessments at other time points.

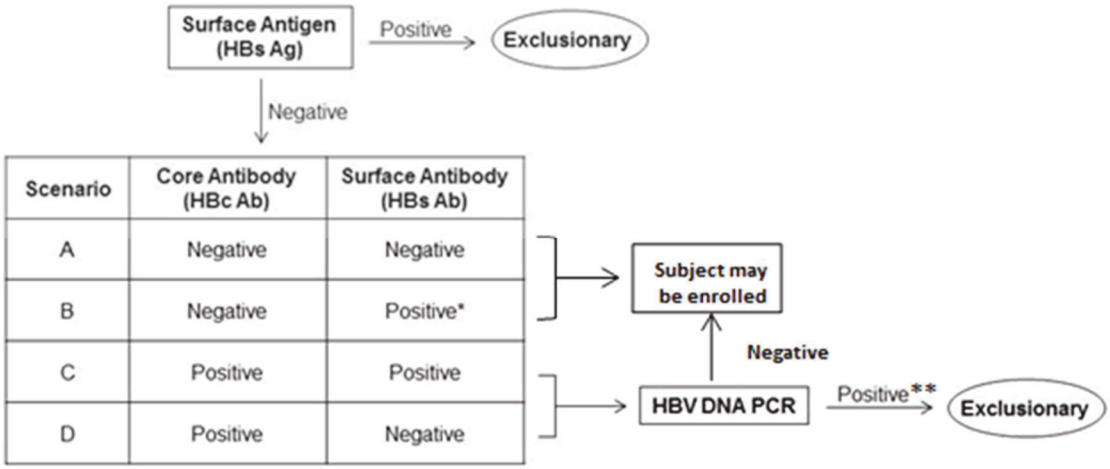
Urinalysis

Dipstick urinalysis will be completed by the central laboratory at the Screening Visit. Specified abnormal macroscopic urinalyses dipstick results will be followed up with a microscopic analysis at the central laboratory.

Hepatitis B and C Testing

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

Figure 1. Interpretation and Management of HBV Serologic Test Results



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

** Where mandated by local requirements; subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at screening should have HBV DNA PCR testing performed q12w. HBV DNA PCR testing q12w is not necessary when the subject has a history of HBV vaccine and is HBs Ab+ and HBc Ab-.

HIV Testing

HIV testing will be performed at Screening. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health and subject should receive or be referred for clinical care promptly. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result. Ineligibility due to a positive HIV test should be documented in the CRF as a screen failure due to criterion 16 to keep this test result private.

TB Screen

Subjects will be tested for TB by either the QuantiFERON-TB Gold Test (or IGRA equivalent) or a TB Skin Test (PPD) at the Screening visit. Subjects who have had a TB test performed within 90 days of the Screening Visit will not need to have the test repeated, provided all of the protocol-required documentation is available at the site, and no new TB risk factors have been identified.

At Screening, all subjects will be assessed for evidence of TB, and if positive, additional risk factors will be assessed. At Week 52, subjects with no prior positive TB test will be tested for TB by either the QuantiFERON-TB Gold Test (or IGRA equivalent) or a TB Skin Test (PPD).

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

- If the **QuantiFERON-TB Gold Test (or IGRA equivalent) is NOT possible**, or if both the QuantiFERON-TB Gold Test (or IGRA equivalent) and the PPD Skin Test are required per local guidelines, the PPD Skin Test will be performed according to standard clinical practice.
  - The PPD Skin Test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test.
  - The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm," not "negative."
- If subject had a positive QuantiFERON-TB Gold (or IGRA equivalent) or PPD test at Screening, the test should not be repeated. Subjects who have had an ulcerating reaction to the TB Skin Test in the past should not be re-exposed and should not be tested by a PPD skin test.
- If the **TB screening test** (either PPD or the QuantiFERON-TB Gold test [or IGRA equivalent]) **is positive, or** if there is a **repeat indeterminate** QuantiFERON-TB Gold test (or IGRA equivalent) upon retesting, subjects may participate in the study if **further work-up** (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active TB.
- If the subject is diagnosed with **active TB**, the subject should not be randomized in the study and should not receive study drug. Subject will be considered as a **screening failure**.
- If presence of **latent TB** is established, subjects who are considered at low risk for reactivation defined by local guidelines and investigator judgment are not required to be treated with prophylactic anti-TB therapy prior to or during the study.
- If the subject is diagnosed with **active TB** after being randomized, the subject should not receive any further study drug, and a Premature Discontinuation (PD) Visit procedures should be followed (Section 2.1).

- If **TB (latent or active)** is diagnosed during the study, it is also necessary to report it as an AE in the source documents and eCRFs. In the case of a TB-related AE, a TB supplemental form that provides additional information will be completed by the investigator or designee.

FSH

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

Anaphylaxis Testing

In the event of a suspected anaphylactic reaction or other systemic post-dose reaction, blood samples should be collected as stated in Section 3.11.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results. In addition, the Investigator must review and confirm the subject has no additional issues that would impact the ability of the subject to safely continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible.

3.13 Drug Concentration and Anti-Drug Antibody Measurements

Pharmacokinetic, ADA, and nAb samples should be collected within 60 minutes prior to the dose at dosing visits.

Collection of Blood Samples for Risankizumab Analysis, ADA Assay, and nAb Assay

Blood samples for analysis of risankizumab serum concentrations, ADA assay, and nAb assay will be collected during the treatment period on the study days and time points specified in the protocol. Samples will be collected by venipuncture into appropriately labeled, evacuated serum collection tubes. The time that each blood sample (PK and ADA/nAb) is collected will be recorded to the nearest minute.

Measurement Methods

Serum concentrations of risankizumab and ADA and nAb assessments will be done using validated methods at or under the supervision of the Bioanalysis Department at AbbVie. The presence of ADA to risankizumab will be assessed via a tiered approach with an electrochemiluminescence assay using screening, confirmatory, and titration analyses. Samples that are confirmed positive may be further characterized in a validated nAb assay. Any additional analytes may be analyzed using nonvalidated methods. Serum samples collected for risankizumab PK and ADA analysis may be used for future assay development or validation activities. Risankizumab nAb samples upon request may be used for the analysis of neutralizing ADAs.

Disposition of Samples

The frozen serum samples for risankizumab analysis, ADA and nAb assays will be packed in dry ice sufficient to last during transportation and shipped from the study site to the central lab according to instructions from AbbVie.

3.14 Out of Window Visits Due to COVID-19 Pandemic

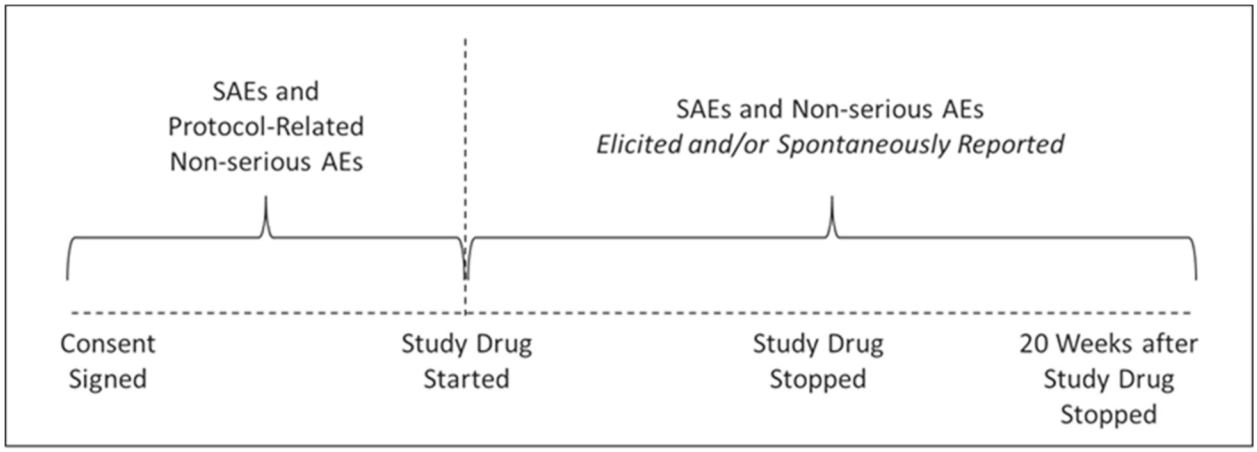
If a visit can be performed onsite but OOW, consult with the sponsor to determine if the OOW visit is permitted.

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

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious adverse events (SAEs) as well as protocol-related nonserious AEs (e.g., bruising related to blood draw) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 140 days (20 weeks) following discontinuation of study treatment has elapsed, all AEs and SAEs will be collected, whether solicited or spontaneously reported by the subject.



4.2 Definition of Adverse Event

An AE can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol specific criteria (see Section 6.2 in the **Protocol** regarding toxicity management), and/or if the investigator considers them to be AEs.

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

4.3 Serious Adverse Events

Classification of Serious Adverse Events is defined as follows:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

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

4.4 Adverse Event Definition of Severity Grade

When criteria are available, events should be graded to the 5 criteria as described in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0,[1] which can be accessed at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

If no grading criteria are provided for the reported event, the event should be graded as mild, moderate, or severe per the Investigator's judgment.

Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
Severe	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Life-threatening consequences; urgent intervention indicated. Death related to AE.

4.5 Definition of Relationship to Study Drug

Relationship to study drug is defined as follows:

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

4.6 Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent AEs (i.e., any event that begins or worsens in severity after initiation of study drug through 140 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT). The tabulation of the number of subjects with treatment-emergent AEs by severity grade and relationship to study drug also will be provided. Subjects reporting more than one AE for a given MedDRA preferred term will be counted only once for that term using the most severe grade for the severity grade table and the most related for the relationship to study drug tables. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC.

4.7 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

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

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team Dept.
R48S, Bldg. AP31-2
1 North Waukegan Road North Chicago, Illinois 60064
Office: +1 847-938-8737
Email: GPRD_SafetyManagement_Immunology@abbvie.com

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

[redacted]

AbbVie
Avenida De Burgos 91,
Madrid, Spain 28050

Contact Information:

Office/Mobile: [redacted]
Email:

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

HOTLINE: +1 (973) 784-6402

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

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

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

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

4.8 Reporting Product Complaints

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

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

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

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

5.2 Additional Eligibility Criteria

For subjects in some countries, such as China, Korea, Malaysia, Singapore, Hong Kong, Taiwan, and Japan, inadequate response to MTX is defined as lack of efficacy after minimum 12 weeks duration of therapy at MTX dose ≥ 7.5 mg/week or as required per local authorities.

5.3 Additional Requirements-France

Collection of race and ethnicity information is not required.

5.4 Additional Laboratory Requirements

If required by country regulatory authorities, subjects who initiate or increase dose of MTX during the study should undergo ALT, AST, creatinine and complete blood count (CBC) testing every 4 weeks for a 12 week period.

6 STUDY DRUG

6.1 Treatments Administered

The study drug (risankizumab or placebo) will be administered by a healthcare professional in the form of 2 subcutaneous injections of 75 mg per injection at the visits listed in Section 2.1. For additional details on dispensing study drug in the event of home administration due to the COVID-19 pandemic, see Section 3.11.

Risankizumab will be provided by AbbVie as solution for injection in pre-filled syringes (PFS).

Risankizumab will be administered as an initial dose, a second dose 4 weeks later, and q12w thereafter.

Study drug administration instructions will be provided separately.

6.2 Packaging and Labeling

Study drug packaged in 75 mg PFS will be provided in both open-label and blinded fashion and packaged in cartons containing 1 syringe per carton. Each kit will be labeled as required per local requirements. Each kit label will contain a unique kit number. This kit number is assigned to a subject via Interactive Response Technology (IRT) and encodes the appropriate study drug to be administered at the subjects corresponding study visit.

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

Storage and Disposition of Study Drug

Risankizumab or placebo PFS must be kept protected from light in the original packaging, in a refrigerator between 2° to 8°C (36° to 46°F). Study drug must not be frozen at any time. The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate. A temperature log must be maintained for documentation.

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

6.3 Method of Assigning Subjects to Treatment Groups

This is a Phase 3, global, multi-center study that will evaluate subjects with moderately to severely active psoriatic arthritis. Period 1 is a 24-week randomized, double-blind, placebo-controlled, parallel-group period. Eligible subjects will be randomized to risankizumab or placebo in a 1:1 ratio for Period 1. After the Week 24 assessments are performed, Period 2 begins. During Period 2, all subjects will receive risankizumab. To maintain the blind to the original treatment allocation, treatment at the Week 24 Visit will be blinded: subjects who were randomized to placebo will receive blinded risankizumab, and those randomized to risankizumab will receive 1 dose of blinded placebo. At Week 28 and for the remaining dosing visits all subjects will receive open-label risankizumab 150 mg q12w.

At the Screening Visit, all subjects will be assigned a unique subject number through the use of the IRT. Randomization will be stratified by current use of csDMARD (0 vs ≥ 1), number of prior biologic therapies (0 vs ≥ 1), and extent of psoriasis (≥ 3% BSA or < 3% BSA) at Baseline.

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

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

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

6.4 Selection and Timing of Dose for Each Subject

Risankizumab 150 mg or matching placebo dose subcutaneously (SC, 2 × 75 mg PFS) administered at Week 0, 4, 16, 24, 28, and q12w thereafter is selected for this study.

6.5 Drug Accountability

The investigator or his/her designated and qualified representatives will administer study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the treatment period. The monitor will review study drug accountability on an ongoing basis. Final accountability will be verified by the monitor at the end of study drug treatment at the site.

Stand-alone investigational product administration guidelines for sites will be provided by the sponsor.

The study drug start date and the last dose of the regimen will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each kit and the date of reconciliation will be documented in the IRT system. The monitor will review study drug accountability on an ongoing basis.

Upon completion of or discontinuation from the treatment, all study drug will be returned to AbbVie (or designee) or destroyed on site. All destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of drug accountability procedures.

7 References:

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	Antibody
ADA	Anti-drug antibody
AE	Adverse event
Ag	Antigen
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BIO-IR	Inadequate response to 1 or 2 biologic therapies or intolerance
BP	Blood pressure
BSA-PsO	Body surface area-psoriasis
BUN	Blood urea nitrogen
CASPAR	Classification Criteria for PsA
CBC	Complete blood count
CCP	Cyclic-citrullinated peptide
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
csDMARD	Conventional synthetic disease modifying anti-rheumatic drug
DAS28	Disease Activity Score 28
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	EuroQol-5D-5L
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FSH	Follicle-stimulating hormone
GGT	Gamma-glutamyl transferase
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBc	Hepatitis B core
HBs	Hepatitis B surface
hCG	Human Chorionic Gonadotropin

HCV	Hepatitis C virus
HDL-C	High-density lipoprotein-cholesterol
HIV	Human immunodeficiency virus
HRU	Health Resource Utilization
hsCRP	High sensitivity C-Reactive Protein
IMP	Investigational Medical Product
IRT	Interactive Response Technology
LDI	Leeds Dactylitis Index
LDL-C	Low-density lipoprotein-cholesterol
LEI	Leeds Enthesitis Index
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing antibody
OOW	Out of window
PASI	Psoriasis Area Severity Index
PD	Premature Discontinuation
PFS	Pre-filled syringe
PGA	Physician's Global Assessment
PK	Pharmacokinetic(s)
PPD	Purified Protein Derivative
PRO	Patient-reported outcome
PsA	Psoriatic Arthritis
PsARC	Psoriatic Arthritis Response Criteria
PT	Preferred term
PtGA	Patient's Global Assessment
RBC	Red blood cell
SAE	Serious adverse event
SC	Subcutaneous(ly)
SF-36	36-Item Short Form Health Survey
SJC	Swollen joint count
SOC	System Organ Class
SPARCC	Spondyloarthritis Research Consortium of Canada
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	Therapeutic Area Medical Director

TB	Tuberculosis
TJC	Tender joint count
ULN	Upper limit of normal
VAS	Visual analogue scale
WBC	White blood cell
WPAI	Work Productivity and Activity Impairment

APPENDIX B. CASPAR CRITERIA

Table. The CASPAR classification criteria for PsA

To be classified as having PsA, a patient must have inflammatory articular disease (joint, spine, entheseal) with ≥ 3 of the following 5 points:

Criterion	Description
1. Evidence of psoriasis (one of a, b, c):	
(a) Current psoriasis[a]	Psoriatic skin or scalp disease currently present, as judged by a rheumatologist or a dermatologist
(b) Personal history of psoriasis	A history of psoriasis obtained from patient or family physician, dermatologist, rheumatologist, or other qualified health care professional
(c) Family history of psoriasis	A history of psoriasis in a first- or second-degree relative by patient report
2. Psoriatic nail dystrophy	Typical psoriatic nail dystrophy, including onycholysis, pitting, and hyperkeratosis observed on current physical examination
3. Negative test result for RF	By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range
4. Dactylitis (one of a, b):	
(a) Current	Swelling of an entire digit
(b) History	A history of dactylitis recorded by a rheumatologist
5. Radiological evidence of juxta-articular new bone formation	Ill-defined ossification near joint margins (excluding osteophyte formation) on plain x-ray films of hand or foot

CASPAR, CIASsification criteria for Psoriatic ARthritis; PsA, psoriatic arthritis; RF, rheumatoid factor; ELISA, enzyme-linked immunosorbent assay.

[a] Current psoriasis scores 2; all other items score 1.

APPENDIX C. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis[2] is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
    - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    - Reduced BP or associated symptoms or end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen (study drug) for a subject within minutes to several hours:
    - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    - Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen (study drug) for that subject (within minutes to several hours), with systolic BP of less than 90 mmHg or greater than 30% decrease from that subject's baseline BP (Day 1).

APPENDIX D. JOINT ASSESSMENT

Joint counts will be performed by assessor(s) who must be well trained and part of the site personnel. Whenever possible, the same evaluator should perform these assessments at all visits.

Number of Tender Joints:

The 68 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 10 metacarpophalangeal, 10 proximal interphalangeal, 8 distal interphalangeal joints of the hands, the 2 hips, 2 knees, 2 ankles 2 mid-tarsal, 10 metatarsophalangeal, and 10 proximal interphalangeal joints of the feet.

Joints are to be scored as either tender (1) or not tender (0), replaced (9) or not assessed (99).

Number of Swollen Joints:

The 66 joints to be examined for swelling are the same as those examined for tenderness, however excluding both hip joints.

Joints are to be scored as either swollen (1) or not swollen (0), replaced (9) or not assessed (99).

Synovial fluid and/or soft tissue swelling but not bony overgrowth represents a positive result for swollen joint count.

APPENDIX E. AMERICAN COLLEGE OF RHEUMATOLOGY 20 RESPONSE (ACR20)

ACR RESPONSE CRITERIA[3,4]

ACR 20:

- At least 20% improvement in SJC* compared to baseline **AND**
- At least 20% improvement in TJC* compared to baseline **AND**
- At least 20% improvement in at least 3 out of the following 5 variables:
    1. Patient's assessment of pain on VAS
    2. Patient's global assessment of the disease on VAS
    3. Investigator's global assessment of the disease on VAS
    4. Patient's assessment of disability on HAQ
    5. Acute phase reactant (serum CRP)

ACR 50:

- At least 50% improvement in SJC* compared to baseline **AND**
- At least 50% improvement in TJC* compared to baseline **AND**
- At least 50% improvement in at least 3 out of the following 5 variables:
    1. Patient's assessment of pain on VAS
    2. Patient's global assessment of the disease on VAS
    3. Investigator's global assessment of the disease on VAS
    4. Patient's assessment of disability on HAQ
    5. Acute phase reactant (serum CRP)

ACR 70:

- At least 70% improvement in SJC* compared to baseline **AND**
- At least 70% improvement in TJC* compared to baseline **AND**
- At least 70% improvement in at least 3 out of the following 5 variables:
    1. Patient's assessment of pain on VAS

2. Patient's global assessment of the disease on VAS
3. Investigator's global assessment of the disease on VAS
4. Patient's assessment of disability on HAQ
5. Acute phase reactant (serum CRP)

* SJC and TJC are evaluated according to the complete joint count (see Appendix D).

APPENDIX F. DISEASE ACTIVITY SCORE(DAS)28 – HSCRP

DAS28-hsCRP[5] will be calculated taking the following variables into account:

- TJC (on 28 joints)
- SJC (on 28 joints)
- Patient's global assessment of the disease on VAS (0 – 100)
- Serum hsCRP level (mg/L)

APPENDIX G. PASI SCORE DEFINITIONS AND USE

The PASI score is an established measure of clinical efficacy for psoriasis medications.[6]

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

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

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

The **area of psoriatic involvement** of these four areas (Ah, At, Au, and Al) is given a numerical value: 0 = no involvement, 1 = < 10%, 2 = 10 to < 30%, 3 = 30 to < 50%, 4 = 50 to < 70%, 5 = 70 to < 90%, and 6 = 90 to 100% involvement.

The **signs of severity, erythema (E), induration (I) and desquamation (D)** of lesions are assessed using a numeric scale 0 – 4 where 0 is a complete lack of cutaneous involvement and 4 is the severest possible involvement; scores are made independently for each of the areas, h, t, u and l and represents a composite score for each area. An illustration of judging erythema follows: 0 = no erythema, 1 = slight erythema, 2 = moderate erythema, 3 = marked erythema, and 4 = very marked erythema.

The PASI score is calculated according to the following formula:

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

APPENDIX H. LEEDS DACTYLITIS INDEX

The LDI basic measures the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot, using a minimum difference of 10% to define a dactylitic digit.[7,8] The ratio of circumference is multiplied by a tenderness score, using a modification of LDI which is a binary score (1 for tender, 0 for non-tender). If both sides are considered involved, or the circumference of the contralateral digit cannot be obtained, AbbVie will input and utilize a circumference provided in the standard reference tables. This modification is referred to as LDI basic and will be applied in this study. The LDI requires a finger circumference gauge or a tape measure to measure digital circumference.

Dactylitis Count

The dactylitis count is the number of fingers and toes with dactylitis, with a range of 0 – 20.

Presence of Dactylitis

If dactylitis is present with any finger or toe, the subject is counted as a subject with dactylitis.

APPENDIX I. LEEDS ENTHESITIS INDEX (LEI)

LEI is a validated enthesitis index that uses 6 sites for evaluation of enthesitis: lateral epicondyle humerus left and right, Achilles tendon insertion left and right and medial condyle femur left and right. The LEI demonstrated substantial to excellent agreement with other scores in the indication of psoriatic arthritis.[9]

Enthesitis Count

Tenderness on examination is recorded as either present (1) or absent (0) for each of the 6 sites, for an overall score range of 0 – 6.

Presence of Enthesitis

If enthesitis is present with any of the 6 sites (lateral epicondyle humerus left and right, Achilles tendon insertion left and right and medial condyle femur left and right), the subject is counted as a subject with enthesitis.

APPENDIX J. SPONDYLOARTHRITIS RESEARCH CONSORTIUM OF CANADA (SPARCC) ENTHESITIS INDEX

Enthesial sites examined include medial epicondyle (left and right), lateral epicondyle (left and right), supraspinatus insertion into greater tuberosity of humerus (left and right), greater trochanter (left and right), quadriceps insertion into superior border of patella (left and right), patellar ligament insertion into inferior pole of patella or tibial tubercle (left and right), Achilles tendon insertion into calcaneum (left and right), plantar fascia insertion into calcaneum (left and right).[10]

Enthesitis Count

Tenderness on examination is recorded as either present (1) or absent (0) for each of the 16 sites, for an overall score range of 0 – 16.

APPENDIX K. PSORIATIC ARTHRITIS RESPONSE CRITERIA (PSARC)

A subject is defined as a PsARC responder if, and only if, they have an improvement in two of the following four factors (with at least one factor being a joint count) and no worsening in the remaining factors:[11]

- Patient global assessment of disease activity (0 – 100 mm VAS scale, improvement defined as decrease of ≥ 20 mm)
- Physician global assessment of disease activity (0 – 100 mm VAS scale, improvement defined as decrease ≥ 20 mm)
- Tender 68-joint count (improvement defined as decrease of ≥ 30%)
- Swollen 66-joint count (improvement defined as decrease of ≥ 30%)

APPENDIX L. MINIMAL DISEASE ACTIVITY

The proportion of subjects achieving minimal disease activity (MDA) will be analysed.[12] A patient is classified as achieving MDA when at least 5 of the 7 following criteria are met.

- Tender joint count ≤ 1
- Swollen joint count ≤ 1
- PASI ≤ 1 or BSA ≤ 3%
- Patient Assessment of Pain-VAS ≤ 15
- Patient Global Assessment of Disease Activity VAS ≤ 20
- HAQ-DI ≤ 0.5
- Tender entheseal points ≤ 1

APPENDIX M. PSA DISEASE ACTIVITY SCORE (PASDAS)

The PASDAS is a weighted index incorporating patient and physician global VAS scores, TJC and SJC, dactylitis and enthesitis, health-related quality of life, and CRP levels.[13] The following formula is used:

(((0.18*√PGA) + (0.159 x √PtGA) – (0.253*√SF36/PCS) + (0.101 x LN (SJC + 1)) + (0.048*LN(TJC +1)) + (0.23 x LN (LEI + 1)) + (0.377 LN (TDC +1)) + (0.102 x LN (CRPmg/dl +))+2)*1.5

LN = natural logarithm; TDC = tender dactylitis count

APPENDIX N. DISEASE ACTIVITY IN PSORIATIC ARTHRITIS (DAPSA)

DAPSA is an assessment of disease activity in PsA based on the following variables: TJC68, SJC66, PtGA of Disease Activity (VAS), Patient's Assessment of Pain (VAS), and CRP.[14] Minor, moderate, and major response in DAPSA are defined as 50%, 75%, and 85% improvement from baseline (Day 1) respectively.

Calculation: SJC + TJC + PtGA + PP + CRP [mg/dl]

APPENDIX O. ANKYLOSING SPONDYLITIS DISEASE ACTIVITY (ASDAS)

ASDAS will be calculated taking the following variables into account:

- Back pain (question 2 from BASDAI)
- Duration of morning stiffness (question 6 from BASDAI)
- Patient's global assessment of the disease on VAS (0 - 10 cm)
- Peripheral joint pain/swelling (question 3 from the BASDAI)
- Serum CRP level (mg/L)

ASDAS calculation[15]

The ASDAS formulas are as follows:

ASDAS-CRP (the preferred version):

0.12 × Back Pain + 0.06 × Duration of Morning Stiffness + 0.11 × Patient Global + 0.07 × Peripheral Pain/Swelling + 0.58 × Ln(CRP + 1)

CRP is in mg/litre; the range of other variables is from 0 to 10; Ln represents the natural logarithm; √ represents the square root.

APPENDIX P. HEALTH RESOURCE UTILIZATION QUESTIONNAIRE (HRU)

Since the last study visit has the subject had any visits for their psoriatic arthritis other than the protocol required visit?

YES: ____

NO: ____

If YES, please provide the following:

1. Since the last protocol required visit, has the subject been seen by a health care professional for their psoriatic arthritis?

   YES: ____

   NO: ____

   If YES, how many times: ____

2. Since the last protocol required visit, has the subject been seen in the Emergency Room for their psoriatic arthritis?

   YES: ____

   NO: ____

   If YES, how many times: ____

3. Since the last protocol required visit, has the subject been admitted to the hospital due to their psoriatic arthritis?

   YES: ____

   NO: ____

If YES, please list the ADMISSION DATE: __ __/___ ___ ___/ ___ ___ ___ __
DD MMM YYYY

DISCHARGE DATE: __ __/___ ___ ___/ ___ ___ ___ __
DD MMM YYYY

APPENDIX Q. PATIENT-REPORTED OUTCOMES

BASDAI (Bath Ankylosing Spondylitis Disease Activity Index)[16]

Each question is answered on a 0 to 10 scale. For Questions 1 – 5, 0 means none and 10 means very severe; for Question 6, 0 means 0 hours and 10 means 2 or more hours. All questions refer to last week.

1. How would you describe the overall level of fatigue/tiredness you have experienced?
2. How would you describe the overall level of AS neck, back or hip pain you have had?
3. How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?
4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?
5. How would you describe the overall level of morning stiffness you have had from the time you wake up?
6. How long does your morning stiffness last from the time you wake up?

Calculation of BASDAI: compute the mean of Questions 5 and 6. Calculate the sum of the values of Questions 1 – 4 and add the result to the mean of Questions 5 and 6. Divide the result by 5.

Patient's Global Assessment of Disease Activity[17]

The patient global assessment VAS will be self-administered by the patient.

The patient's global assessment of disease activity will be performed using a horizontal 100 mm VAS, ranging from 0 (very well) to 100 (very poor) after the question:

"Considering all the ways psoriatic arthritis affects you, please indicate with a vertical mark (|) through the horizontal line how well you are doing today."

Health Assessment Questionnaire Disability Index (HAQ-DI)[18]

HAQ-DI is a self-reported patient outcome measurement tool commonly used in RA clinical trials to measure physical functioning in RA patients. The HAQ-DI composite score is calculated as the mean of the scores from the 8 following categories with a range of 0 – 3 (0 = no disability; 3 = worst disability): Dressing and Grooming, Rising, Eating, Walking, Hygiene, Reach, Grip, and Activities. The higher the score, the more likely to associate with morbidity and mortality for the RA patient. Under each category there are 2 - 3 items on the amount of difficulty they have in performing specific activities with four response options from 0 (no difficulty) to 3 (unable to do). In addition to these eight categories, there is an AIDS OR DEVICES/HELP FROM OTHER PERSON section ("companion items") that is used to

record the type of assistance, if any, a subject uses for his/her usual activities in each of the eight categories.

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)[19,20]

Response options/scale: Answers are based on a 5-point Likert scale. Responses of "not at all," "a little," "somewhat," "quite a bit," and "very much" are available for each question, and correspond to scores of 0, 1, 2, 3, and 4, respectively. Recall period for items: 7 days.

1. I feel fatigued.
2. I feel weak all over.
3. I feel listless ("washed out").
4. I feel tired.
5. I have trouble starting things because I am tired.
6. I have trouble finishing things because I am tired.
7. I have energy.
8. I am able to do my usual activities.
9. I need to sleep during the day.
10. I am too tired to eat.
11. I need help doing my usual activities.
12. I am frustrated by being too tired to do the things I want to do.
13. I have to limit my social activity because I am tired.

Short Form-36[21,22]

The Short Form-36 (SF-36) is a 36-item patient reported measure of overall health. The SF-36 consists of eight domains:

- vitality
- physical functioning
- bodily pain
- general health perceptions
- physical role functioning
- emotional role functioning
- social role functioning

- mental health

A scaled score is calculated for each domain as the weighted sum of the questions in the domain. The score for each domain ranges from 0 to 100. The higher the score the less disability; a score of 100 is equivalent to no disability and a score of 0 is equivalent to maximum disability.

EQ-5D-5L[23]

Under each heading, please check the ONE box that best describes your health TODAY:

Mobility

I have no problems walking ☐

I have slight problems walking ☐

I have moderate problems walking ☐

I have severe problems walking ☐

I am unable to walk ☐

Self-Care

I have no problems washing or dressing myself ☐

I have slight problems washing or dressing myself ☐

I have moderate problems washing or dressing myself ☐

I have severe problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

Usual Activities (e.g., work, study, housework, family, or leisure activities)

I have no problems with doing my usual activities ☐

I have slight problems with doing my usual activities ☐

I have moderate problems with doing my usual activities ☐

I have severe problems with doing my usual activities ☐

I am unable to do my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐

I have slight pain or discomfort ☐

I have moderate pain or discomfort ☐

I have severe pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐

I am slightly anxious or depressed ☐

I am moderately anxious or depressed ☐

I am severely anxious or depressed ☐

I am extremely anxious or depressed ☐

The patient's assessment of health will be performed using a horizontal 100 mm visual analog scale (VAS), ranging from 0 (worst health patient can imagine) to 100 (best health patient can imagine) after the question:

"Please indicate with a vertical mark (|) through the horizontal line how your health is today."

Patient's Assessment of PsA Pain Intensity[24]

The patient's assessment of PsA pain intensity will be performed using a horizontal 100 mm visual analog scale (VAS), ranging from 0 (no pain) to 100 (severe pain) after the question:

"Please indicate with a vertical mark (|) through the horizontal line the most pain you had from your psoriatic arthritis today."

Work Productivity and Activity Impairment (WPAI) Questionnaire[25]

The following questions ask about the effect of your psoriatic arthritis on your ability to work and perform regular activities. Please fill in the blanks or circle a number, as indicated.

1. Are you currently employed (working for pay)? _____ No ___ Yes

   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your psoriatic arthritis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your psoriatic arthritis. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____ HOURS

4. During the past seven days, how many hours did you actually work?

   _____ HOURS *(If "0," skip to question 6.)*

5. During the past seven days, how much did your psoriatic arthritis affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If psoriatic arthritis affected your work only a little, choose a low number. Choose a high number if psoriatic arthritis affected your work a great deal.

   Consider only how much psoriatic arthritis affected productivity while you were working.

Psoriatic arthritis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Psoriatic arthritis completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your psoriatic arthritis affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If psoriatic arthritis affected your activities only a little, choose a low number. Choose a high number if psoriatic arthritis affected your activities a great deal.

Consider only how much psoriatic arthritis affected your ability to do your regular daily activities, other than work at a job.

Psoriatic arthritis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Psoriatic arthritis completely prevented me from doing my daily activities

CIRCLE A NUMBER