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Protocol for Study M16-766

Risankizumab versus Secukinumab for Subjects with Moderate to Severe Plaque Psoriasis

VERSION:	1.1 (France Only)	DATE:	16 August 2019
SPONSOR:	AbbVie, Inc.* 1 North Waukegan Road North Chicago, IL 60064, USA	NUMBER OF SITES:	80
ABBVIE INVESTIGATIONAL PRODUCT:	Risankizumab, ABBV-066	EudraCT:	2017-004932-12

FULL TITLE: A Multicenter, Randomized, Open Label, Efficacy Assessor-Blinded Study of Risankizumab Compared to Secukinumab for the Treatment of Adult Subjects with Moderate to Severe Plaque Psoriasis who are Candidates for Systemic Therapy

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

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1 SYNOPSIS

Title: A Multicenter, Randomized, Open Label, Efficacy Assessor-Blinded Study of Risankizumab Compared to Secukinumab for the Treatment of Adult Subjects with Moderate to Severe Plaque Psoriasis who are Candidates for Systemic Therapy	
Background and Rationale:	Psoriasis is a chronic debilitating immune-mediated disease characterized by marked inflammation of the skin that results in thick, erythematous, scaly plaques. This study will provide essential data comparing risankizumab (anti-IL-23 therapy) vs. secukinumab (anti-IL-17A therapy) for the treatment of patients with moderate to severe plaque psoriasis who are candidates for systemic therapy.
Objective(s) and Endpoint(s):	The objective of this study is to evaluate the efficacy and safety of risankizumab compared with secukinumab for the treatment of adult subjects with moderate to severe plaque psoriasis who are candidates for systemic therapy. The two primary endpoints are: • Proportion of subjects achieving a Psoriasis Area Severity Index (PASI) 90 response at Week 52; superiority of risankizumab vs. secukinumab. • Proportion of subjects achieving a PASI 90 response at Week 16; non-inferiority of risankizumab vs. secukinumab with a non-inferiority margin of 12%. The multiplicity-controlled key secondary endpoints are: • Proportion of subjects achieving a PASI 100 response at Week 52; superiority of risankizumab vs. secukinumab; • Proportion of subjects achieving a static physician global assessment (sPGA) 0 or 1 at Week 52; superiority of risankizumab vs. secukinumab; • Proportion of subjects achieving a PASI 75 response at Week 52; superiority of risankizumab vs. secukinumab. Other efficacy endpoints include change and percent change from baseline in PASI and body surface area (BSA) as well as multiple levels of PASI and sPGA response at all visits.
Investigator(s):	Multi-center

Study Site(s):	**Country**	**Number of Sites**
	Australia	5
	Canada	7
	France	5
	Germany	7
	Italy	5
	Netherlands	5
	Spain	5
	United States	30
	United Kingdom	5
	Poland	6
Study Population and Number of Subjects to be Enrolled:	Adult subjects with moderate to severe plaque psoriasis who are candidates for systemic therapy and who are eligible for this study, will be randomized to receive risankizumab or secukinumab in a 1:1 ratio. The study is designed to randomize approximately 310 subjects (155 subjects/arm).	
Investigational Plan:	This is a Phase 3, global, multicenter, randomized, open-label, efficacy assessor-blinded, active comparator study examining the effect of 150 mg risankizumab every 12 weeks vs. 300 mg secukinumab every 4 weeks in patients with moderate to severe plaque psoriasis. The study compromises a 30-day screening period, a 52-week open-label study period and a 16-week follow-up period. The follow-up period consists of a follow-up phone call 20 weeks after the last study drug dose. Subjects in France who were randomized to risankizumab will have two additional dosing visits at Week 52 and Week 64 and a follow-up phone call 20 weeks after the last study drug dose.	
Key Eligibility Criteria:	Subjects must be ≥ 18 years old at screening with a clinical diagnosis of chronic plaque psoriasis with or without psoriatic arthritis for at least 6 months before the Baseline Visit. Subjects must have stable moderate to severe chronic plaque psoriasis with or without psoriatic arthritis at both Screening and Baseline Visit, defined as follows: • ≥ 10% BSA psoriasis involvement • sPGA score of ≥ 3 • PASI score ≥ 12. Subjects must be candidates for systemic therapy as assessed by the investigator and must be an acceptable candidate to receive secukinumab according to the local label for the compound.	

Study Drug and Duration of Treatment:	Participants randomized to receive secukinumab will receive 2 injections of active secukinumab (300 mg total dosage) subcutaneously at Weeks 0, 1, 2, 3, and 4, and then every 4 weeks thereafter until the last dose at Week 48. Participants randomized to receive risankizumab will receive 2 injections of active risankizumab (150 mg total dosage) subcutaneously at Weeks 0, 4, and then every 12 weeks (q12w) thereafter until the last dose at Week 40. Subjects in France who were randomized to risankizumab will have two additional dosing visits at Week 52 and Week 64.
Date of Protocol Synopsis:	16 August 2019

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

This study will provide essential data comparing risankizumab vs. secukinumab for the treatment of patients with moderate to severe plaque psoriasis who are candidates for systemic therapy.

Psoriasis is a chronic debilitating immune-mediated disease characterized by marked inflammation of the skin that results in thick, erythematous, scaly plaques involving the skin. In most developed countries, prevalence is between 1.5 and 5%.[1] Twenty-five percent of patients have moderate to severe disease with a considerable negative impact on psychosocial and economic status.[2] It is increasingly recognized that psoriasis is more than a superficial disease, with 30% of patients having joint involvement and a high correlation between psoriasis and obesity, diabetes, depression, metabolic syndrome, and cardiovascular disease.[3] While the majority of mild psoriasis patients are managed with topical therapies, those with moderate or severe and/or refractory disease usually require phototherapy and/or systemic therapy.

Oral systemic agents provide modest efficacy; therefore, patients are increasingly being treated with biologic agents such as tumor necrosis factor (TNF)-alpha inhibitors (etanercept and adalimumab), the interleukin (IL)-12/23 inhibitor (ustekinumab),[4] and IL-17 receptor A (IL-17RA) inhibitors (secukinumab and ixekizumab). Ustekinumab, a monoclonal antibody (mAb) targeting the common p40 subunit of IL-12 and IL-23, was approved for the treatment of psoriasis and psoriatic arthritis in 2009, and for Crohn's disease in 2016. Secukinumab, an anti-IL-17A antibody was approved in the US for the treatment of psoriasis in 2015 and for the treatment of psoriatic arthritis and ankylosing spondylitis in 2016. In addition, other recently approved systemic agents for the treatment of psoriasis include an IL-17RA inhibitor (brodalumab) and an IL-23p19 inhibitor (guselkumab), which are also under investigation for psoriatic arthritis. Another anti-IL-23p19 antibody, tildrakizumab, has been studied in Phase 3 psoriasis trials.

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

There is still clinical need for increased efficacy as the most effective anti-TNF and anti-IL-12/23 agents provide approximately 75% improvement in psoriasis in about 50 to 80% of patients and these responses can be lost over time. While the anti-IL-17A, -IL-17RA, and -IL-23p19 agents (i.e., secukinumab, ixekizumab, brodalumab and guselkumab) may provide better efficacy than anti-TNF therapies and ustekinumab, they require monthly or every other month injections.[6,9]

Risankizumab is currently being developed for the treatment of psoriasis (Phase 3 studies concluded) and Crohn's disease (currently in Phase 3 studies) and the treatment of ulcerative colitis, psoriatic arthritis, and asthma (in Phase 2 studies). Risankizumab is a humanized mAb of the immunoglobin

(Ig)G1 subclass directed towards the p19 subunit of IL-23. The antibody has been engineered to reduce Fc γ receptor and complement binding and potential charge heterogeneity. Risankizumab binds with high affinity to human IL-23.

The current study compares the safety and efficacy of risankizumab vs. secukinumab in subjects with moderate to severe plaque psoriasis. For a more detailed description of the risankizumab drug profile, refer to the latest version of the investigator's brochure (IB).[10] For a more detailed description of the secukinumab drug profile, refer to the latest version of the approved labeling information in your country.

Clinical Hypothesis

Risankizumab will be superior to secukinumab in subjects with moderate to severe plaque psoriasis in the achievement of ≥ 90% reduction from baseline Psoriasis Area Severity Index (PASI 90) at Week 52 and will be non-inferior to secukinumab in the achievement of PASI 90 at week 16 with non-inferiority margin of 12%.

2.2 Benefits and Risks to Patients

Despite the availability of various psoriasis 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. Non-clinical 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.[11,12] Selective IL-23 inhibition may not increase risk of serious infection, including mycobacterial infections.[13]

In Phase 1 and Phase 2 studies of risankizumab in patients with psoriasis, the majority of subjects receiving risankizumab achieved 90% improvement of their disease and risankizumab was well tolerated. Recently, positive top-line results were observed from 3 pivotal Phase 3 clinical trials evaluating risankizumab compared to ustekinumab, placebo, or adalimumab, for the treatment of patients with moderate to severe plaque psoriasis.[14-16] After 16 weeks of treatment, all 3 studies met their co-primary endpoints of at least a 90% improvement in the Psoriasis Area and Severity Index (PASI 90) and a static physician global assessment (sPGA) score of clear or almost clear (sPGA 0 or 1) for risankizumab (150 mg) treatment vs. ustekinumab, placebo and adalimumab.[14-16] The safety profile was consistent with that observed in Phase 2 clinical trials, with no important identified risks for risankizumab. As with many immune modulating agents, risankizumab may impair immune function resulting in a risk of infection. This will be monitored by collection of all AEs during the treatment and observation periods. In addition, subjects with active infection will not be included in the study.

IL-23 inhibition is not known to increase the risk of tuberculosis (TB) infection or impair the response to TB infection in animal models. No cases of active TB were reported across all risankizumab studies. Across all Phase 3 psoriasis studies, of the 71 subjects with latent tuberculosis (TB) who were concurrently treated with risankizumab and appropriate TB prophylaxis treatment, none developed active TB during the mean follow-up of 67.9 weeks. In 2 Phase 3 psoriasis studies (Studies M15-992 and M15-997), of 31 subjects with latent TB at screening who did not receive prophylaxis during the study, none developed active TB over a mean follow-up of 58.5 weeks. Thus, low risk subjects with positive QuantiFERON®-TB Gold testing do not need to be treated with antituberculosis therapy prior to

receiving risankizumab, but should be carefully monitored for any sign of TB reactivation. However, to address the label of secukinumab, subjects with latent TB may only be randomized to this trial if sufficient treatment has been initiated according to local routine clinical practice (please refer to the TB Screen section of the Operations Manual for further guidance).

There is not enough information at this time to rule out a risk of cancer with risankizumab, but this risk is considered small with this type of compound as experience with the anti-IL-12/23 mAb ustekinumab has not suggested significant risk for cancer or serious infection.

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

Increases in major adverse cardiovascular (MACE) events, including myocardial infarction, cerebrovascular accident, and cardiovascular death, were initially reported with anti-IL-12/23 agents, such as ustekinumab, although an increased incidence of MACE events was not observed in longer term studies. While the likelihood of increased MACE is small, all suspected cardiovascular events (serious or non-serious) observed in this study will be adjudicated. An independent Cardiovascular Adjudication Committee (CAC) will be adjudicating all observed cardio- and cerebro-vascular events and will remain blinded to treatment allocation (Section 6.2). Although Study M16-766 is an open-label study, information for adjudication purposes will be provided to the CAC in a blinded manner to ensure unbiased assessment.

Local reactions to subcutaneously (SC) administered biologic therapies are uncommon, and are usually limited to redness, swelling, or induration at the injection site. Manifestations of systemic hypersensitivity reactions include anaphylaxis, pruritus, hypotension, and respiratory distress. Both local and systemic hypersensitivity reactions are usually readily detectable, transient in nature, and manageable with standard medical treatment. Subjects will be closely monitored during study drug administration. An independent Anaphylaxis Adjudication Committee (AAC) will be adjudicating observed systemic hypersensitivity and anaphylactic events. The AAC will remain blinded to treatment allocation (Section 6.3).

There are no important identified risks for risankizumab.[10]

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

For further details, please see findings from completed studies, including safety data in the risankizumab Investigator Brochure.[10]

Secukinumab (Cosentyx®) has been approved as a safe and efficacious product for the treatment of plaque psoriasis in a number of countries for at least 3 years. Please refer to the local label available to you for information regarding the efficacy and safety of this product.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The main objective of this study is to evaluate the efficacy and safety of risankizumab compared with secukinumab for the treatment of adult subjects with moderate to severe plaque psoriasis who are candidates for systemic therapy.

3.2 Primary Endpoint

The 2 primary endpoints are:

- Proportion of subjects achieving a PASI 90 response at Week 52; superiority of risankizumab vs. secukinumab.
- Proportion of subjects achieving a PASI 90 response at Week 16; non-inferiority of risankizumab vs. secukinumab with non-inferiority margin of 12%.

3.3 Secondary Endpoints

The multiplicity-controlled key secondary endpoints are:

- Proportion of subjects achieving a PASI 100 response at Week 52; superiority of risankizumab vs. secukinumab;
- Proportion of subjects achieving an sPGA 0 or 1 at Week 52; superiority of risankizumab vs. secukinumab;
- Proportion of subjects achieving a PASI 75 response at Week 52; superiority of risankizumab vs. secukinumab.

Other efficacy endpoints include change and percent change from baseline in PASI and body surface area (BSA) as well as multiple levels of PASI and sPGA responses at all visits.

3.4 Safety Parameters

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

3.5 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 each sampling time point using descriptive statistics. Anti-drug

antibody titers will be tabulated for each subject at the respective study visits. The number and percentage of subjects with ADA and NAb will be calculated.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3, global, multicenter, randomized, open-label, efficacy assessor-blinded, active comparator study examining the effect of 150 mg risankizumab every 12 weeks vs. 300 mg secukinumab every 4 weeks in patients with moderate to severe plaque psoriasis.

Eligible subjects will be randomized to receive risankizumab or secukinumab in a 1:1 ratio. The study is designed to randomize approximately 310 subjects (155 subjects/arm). Participants randomized to receive secukinumab will receive 2 injections of active secukinumab (300 mg total dosage) subcutaneously at Weeks 0, 1, 2, 3, and 4, and then every 4 weeks (q4w) thereafter until the last dose at Week 48. Participants randomized to receive risankizumab will receive 2 injections of active risankizumab (150 mg total dosage) subcutaneously at Weeks 0 and 4, and then every 12 weeks (q12w) thereafter until the last dose at Week 40. Subjects in France who were randomized to risankizumab will have two additional dosing visits at Week 52 and Week 64 and a follow-up phone call 20 weeks after the last study drug dose.

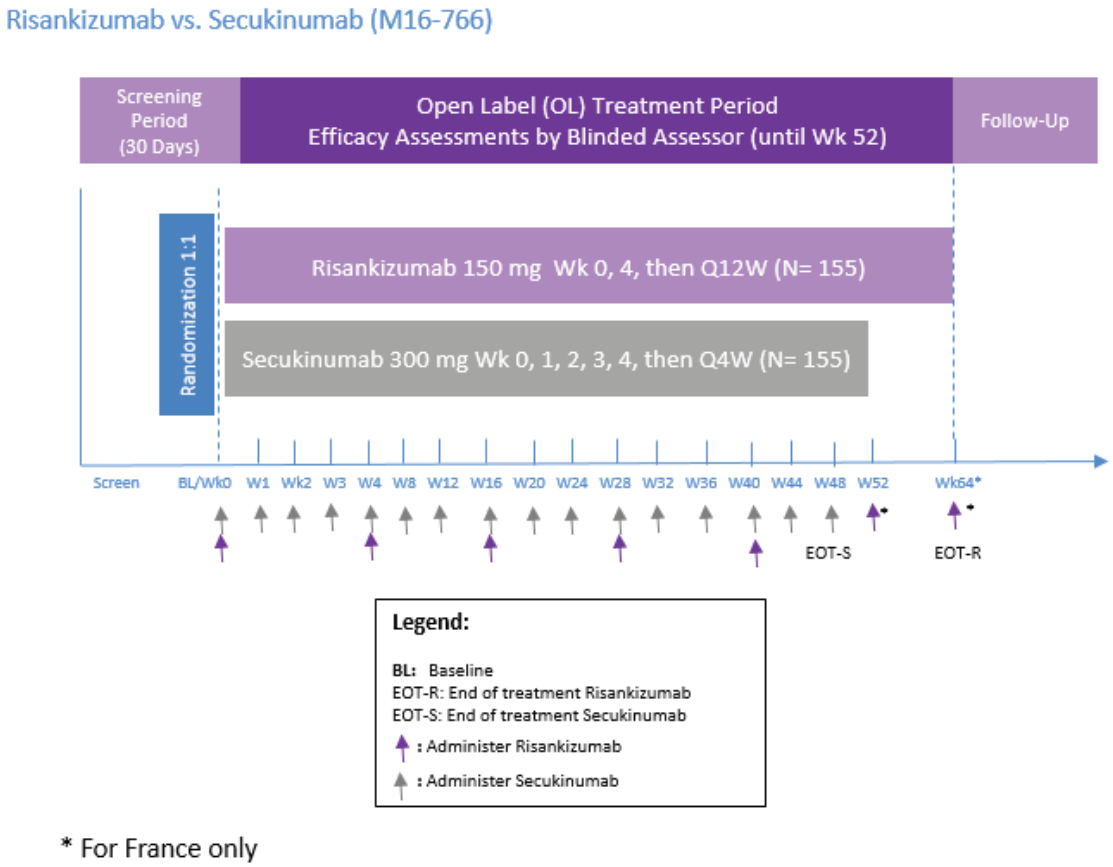
The study duration will be up to 88 weeks. The study comprises a 30-day Screening Period, a 52-week open-label study period and a 16-week follow-up period. The follow-up period consists of a follow-up phone call 20 weeks after the last dose of study drug. Subjects in France who were randomized to risankizumab will have two additional dosing visits at Week 52 and Week 64 and a follow-up phone call 20 weeks after the last study drug dose.

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

See Section 5 for information regarding eligibility criteria.

The first primary analysis will be performed when the last subject completes the Week 16 visit. There will not be a modification to trial conduct based on the results of the analysis. Efficacy accessors will remain blinded for the duration of the study.

Figure 1. Study Schematic



* For France only

4.2 Discussion of Study Design

Choice of Control Group

An active comparator group randomized to receive secukinumab will be used in this study to examine the effect of 150 mg risankizumab every 12 weeks vs. 300 mg secukinumab every 4 weeks in patients with moderate to severe plaque psoriasis.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with moderate to severe plaque psoriasis. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Subjects who have stable moderate to severe chronic plaque psoriasis with or without psoriatic arthritis (definition includes ≥ 10% BSA psoriasis involvement, sPGA score of ≥ 3, and PASI ≥ 12 at Screening and

Baseline Visit) and who are candidates for systemic therapy are eligible for this study. The selection criteria relating to safety guarantee that subjects enrolled can safely be treated with risankizumab based on the current knowledge of this drug.

Selection of Doses in the Study

The selected dose for risankizumab is aligned with the dose tested in Phase 3 global studies in subjects with moderate to severe plaque psoriasis. The dose selected for evaluation is expected to be efficacious with an acceptable safety profile and considered appropriate for the treatment of patients with plaque psoriasis. For secukinumab, the selected dose is as recommended in the approved product labeling for the treatment of plaque psoriasis.

Blinded Efficacy Assessor

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

Table 1. Tasks of the Efficacy Assessor and Investigator

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

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

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

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

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

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

Consent

- 1. Subjects must voluntarily **sign and date an informed consent**, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, at least 18 years old.
- 3. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:

- Serum aspartate transaminase (AST) < 2 × ULN;
- Serum alanine transaminase (ALT) < 2 × ULN;
- Serum direct bilirubin ≤ 2.0 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to a confirmed diagnosis of Gilbert syndrome;
- Total white blood cell (WBC) count > 3,000/µL;
- Absolute neutrophil count (ANC) > 1,500/µL;
- Platelet count > 100,000/µL;
- Hemoglobin > 8 g/dL.

✓ 4. Are willing or able to comply with procedures required in this protocol.

Disease Activity

✓ 5. Diagnosis of chronic plaque psoriasis with or without psoriatic arthritis for at least 6 months before the Baseline Visit;

✓ 6. Subject has stable moderate to severe chronic plaque psoriasis with or without psoriatic arthritis

- Subject has ≥ 10% BSA psoriasis involvement, sPGA score of ≥ 3, and PASI ≥ 12 at Screening and Baseline Visit;

✓ 7. Subject must be a candidate for systemic therapy as assessed by the investigator;

✓ 8. Subject must be an acceptable candidate to receive secukinumab according to the local label for this compound.

Subject History

✓ 9. No history of:

- Erythrodermic psoriasis, generalized or localized pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis;
- Active skin disease other than psoriasis that could interfere with the assessment of psoriasis;
- Chronic infections including HIV, viral hepatitis (hepatitis B, hepatitis C), and/ or active tuberculosis. 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 tuberculosis. If presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local country guidelines. The patient will not be eligible for randomization if latent tuberculosis is present and is untreated as per local guidelines.

  Active systemic infection during the last 2 weeks prior to Baseline Visit (exception: common cold) prior to Baseline Visit, as assessed by the investigator;

- 10. No history of **any documented active or suspected malignancy** or history of any malignancy within the last 5 years except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix;
- 11. No history of clinically significant (per Investigator's judgment) **drug or alcohol abuse** within the last 6 months.
- 12. No history of inflammatory bowel disease.
- 13. No history of underlying medical diseases or problems including but not limited to the following:
  - Subject has been a previous recipient of a solid organ transplant;
  - Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than psoriasis, surgical procedure (i.e., organ transplant), medical examination finding (including vital signs and ECG), or laboratory value at the screening visit outside the given range that, in the opinion of the investigator, is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data.
- 14. 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.
- 15. No major surgery performed within 12 weeks prior to randomization or planned to be performed during the conduct of the trial (e.g., hip replacement, aneurysm removal, stomach ligation) as assessed by the Investigator.

Contraception

- 16. Women of childbearing potential must have a negative serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Baseline Visit and following visits (as outlined in the Study Activity Table of this protocol) prior to study drug administration;
- 17. If female, subject must be postmenopausal OR permanently surgically sterile OR for a woman of child bearing potential be practicing at least one protocol-specified method of birth control (Section 5.2) that is effective from the Baseline Visit through at least 140 days (20 weeks) after the last dose of study drug;
- 18. Female subjects must not be pregnant, breastfeeding or considering becoming pregnant during the study and for approximately 140 days (20 weeks) after the last dose of the study drug;
- 19. Additional local requirements may apply.

Concomitant Medications

- 20. No previous exposure to risankizumab;
- 21. No previous exposure to secukinumab;
- 22. No use of any restricted medication as specified in the prohibited medications/therapy section or any drug considered likely to interfere with the safe conduct of the study.

- 23. 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 currently be enrolled in another clinical study.

5.2 Contraception Recommendations

If female, subject must be either postmenopausal or practicing a birth control method 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 an FSH level > 40 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 1 of the following methods of birth control through 20 weeks after the last study drug dose is given.

- Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal) 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.
- 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).

5.3 Prohibited Medications and Therapy

Prohibited medications and therapy are defined as using the following prohibited concomitant psoriasis treatments within the specified timeframe prior to Baseline Visit and throughout the study.

1. Any systemic biologic to treat psoriasis:
    - Adalimumab, infliximab and biosimilar versions within 12 weeks;
    - Etanercept and biosimilar versions within 6 weeks;
    - Ixekizumab, brodalumab, and other IL-17 inhibitors within 16 weeks;
    - Ustekinumab, efalizumab, guselkumab, tildrakizumab, mirikizumab, and other IL-23 inhibitors within 24 weeks.
2. Systemic non-biologic therapy for psoriasis, including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, apremilast, and fumaric acid derivatives within 4 weeks.
3. Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks.
4. Topical psoriasis treatments, including but not limited to corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, urea, alpha- or beta-hydroxyl acids, and medicated shampoos (for example those that contain > 3% salicylic acid, corticosteroids, coal tar or vitamin D3 analogues) within 2 weeks.
    - *Exception:* Subjects are allowed to use bland (containing no psoriasis treatment) emollients and shampoos and/or low potency topical corticosteroids on the palms, soles, face, inframammary area, and groin only.
5. Treatment with an experimental non-biologic for psoriasis within 4 weeks or five half-lives of the drug (whichever is longer).
6. Treatment with an experimental biologic for psoriasis within 12 weeks or five half-lives of the drug (whichever is longer).

Receipt of any live vaccine within 6 weeks or is expected to need live vaccination during study participation, including at least 20 weeks after the last dose of study drug.

5.4 Prior and Concomitant Therapy

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

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the subject has received from 4 weeks prior to screening or receives during

the study must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route, and frequency on the appropriate eCRF.

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

Subjects must be able to safely discontinue any prohibited medications 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.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject will be discontinued from study drug if any of the following occurs:

- Clinically significant abnormal laboratory result(s) or adverse event(s) that preclude continuation of the study medication, as determined by the Investigator and the Therapeutic Area Medical Director (TAMD) (as applicable).
- The Investigator believes withdrawal from the study is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and/or exclusion 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 TAMD, after consultation with the Investigator
- Subjects need to initiate a prohibited medications and continuation of the study drug would place the subject at risk as determined by the AbbVie TAMD
- Subject develops active TB at any time during the study.
- Subject becomes pregnant while participating in the study.
- Subject is diagnosed with a malignancy. Exception: localized non-melanoma skin cancer or carcinoma in-situ of the cervix, where discontinuation is at the discretion of the Investigator.
- Subject is significantly non-compliant with study procedures.
- Post baseline occurrence of any of the following laboratory tests:
  - ALT or AST > 8 × ULN;
  - ALT or AST > 5 × ULN for more than 2 weeks;
  - ALT or AST > 3 × ULN and Total Bilirubin > 2 × ULN or 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%).

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.

5.6 Follow-Up for Subject Withdrawal from Study

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

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 140-day follow-up phone call after the last dose of study drug will be completed to ensure all treatment-emergent AEs/serious AEs (SAEs) have been resolved.

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

5.7 Study Drug

Study site staff will administer study drug or comparator subcutaneously (risankizumab 150 mg [2 × 75 mg pre-filled syringe] or secukinumab 300 mg [2 × 150 mg pre-filled syringe]) (Table 2).

Table 2. Identity of Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Risankizumab (ABBV-066)	Solution for injection in pre-filled syringe	75 mg/0.83 mL	Subcutaneous injection	Boehringer Ingelheim
Secukinumab	Solution for injection in pre-filled syringe	150 mg/mL	Subcutaneous injection	Novartis

AbbVie will not supply drug other than risankizumab and secukinumab. Risankizumab and secukinumab 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 stored as

specified on the label in their original packaging and kept in a secure location. A temperature log must be maintained for documentation. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff prior to dispensing to subjects. Study drug will only be used for the conduct of this study. Instructions for drug preparation will be provided by AbbVie.

5.8 Randomization/Drug Assignment

Each subject 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 may only be rescreened one time. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie. Subjects will be randomized in a 1:1 ratio to one of two treatment groups:

- Group 1: Risankizumab 150 mg (N = 155)
- Group 2: Secukinumab 300 mg (N = 155)

The randomization will be stratified by weight (≤ 100 kg vs. > 100 kg) and prior systemic biologic for psoriasis.

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

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

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

5.9 Protocol Deviations

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

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

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

Medical Complaints/Adverse Events and Serious Adverse Events

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event 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 adverse events on a routine basis throughout the study. All adverse events will be followed to a satisfactory conclusion.

If an adverse event meets any of the following criteria, it is to be reported to AbbVie or CRO (as appropriate) as a serious adverse event within 24 hours of the site being made aware of the serious adverse event:

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

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events reported from the time of study drug administration until 140 days or 5 half-lives (taking both risankizumab and secukinumab half-lives into consideration) after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related non-serious adverse events will be collected from the time the subject signs the study-specific informed consent.

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

Areas of Safety Interest

Infections, especially opportunistic infections, are a theoretical risk with immunomodulators. Subjects will be screened and monitored throughout the study for Areas of Safety Interest (ASI) (Table 3). Screening procedures are outlined in the Activity Schedule (Appendix D).

If any of the following serious adverse events (SAEs) are reported, then the following supplemental report must be completed.

Table 3. Areas of Safety Interest

Serious Adverse Event	Supplemental eCRF
Hepatic Adverse Events • Discontinuation or interruption of study drug due to a hepatic related AE (please see individual subject discontinuation criteria pertinent to hepatic lab abnormalities) • A hepatic related SAE	Hepatic AE
Suspected Hypersensitivity/Anaphylactic Reaction	Hypersensitivity Reaction Signs and Symptoms
Cardiac and Vascular Events • Cardiovascular history and risk factors • Cardiovascular (cardiac) adverse event • MI and unstable angina adverse event • Heart failure • Cerebral vascular accident and transient ischemic attack • Combination thrombotic event • Arrhythmias • Death	Major Adverse Cardiovascular Events (MACE)
Cardiovascular procedures	Serious Adverse Event Supplemental Procedure
Tuberculosis Infections, especially opportunistic infections, are a theoretical risk with immunomodulators. Subjects will be screened for tuberculosis (using the TB risk factors questionnaire) and those with active tuberculosis will be excluded from participation in the study.	Tuberculosis

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each adverse event as mild, moderate, or severe. The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

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

When criteria are available, events should be graded as described in the National Cancer Institute Common Terminology Criteria for Adverse Events.[17] 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.

Pregnancy

While not an adverse event, pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5).

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 Cardiovascular Adjudication Committee

An independent adjudication committee will be adjudicating 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. Dedicated eCRFs will be used for:

- Myocardial Infarction or Unstable Angina Adverse Event;
- Heart Failure Adverse Event;
- Cerebral Vascular Accident and Transient Ischemic Attack Adverse Event;
- Death;
- Cardiovascular procedures.

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

6.3 Anaphylaxis Adjudication Committee

While no concerns with systemic hypersensitivity have been identified with the use of risankizumab, the sponsor has established an independent, blinded, expert committee to adjudicate events of anaphylaxis based on pre-specified definition. This independent external AAC will be adjudicating observed suspected anaphylactic reactions and will remain blinded to treatment allocation. The events that are adjudicated and the adjudication process will be detailed in the Anaphylaxis Adjudication Committee Charter. A supplemental Hypersensitivity/Anaphylactic reactions 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.

In the event a serious systemic hypersensitivity reaction such as anaphylaxis occurs while the subject/patient is not on site, every effort should be made to obtain serum tryptase and histamine levels from the treating facility to help better understand and characterize the diagnosis.

6.4 Product Complaint

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

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

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

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The objectives of the statistical analyses are to evaluate the efficacy and safety of risankizumab versus secukinumab in patients with moderate to severe plaque psoriasis both short- and long-term.

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

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

The Primary Analysis for all efficacy endpoints in Period B will be conducted after all continuing subjects have completed Week 52 and all data pertaining to Week 52 are cleaned and when a database lock will occur to enable the analysis.

The efficacy assessors will remain blinded for the duration of the entire study.

The statistical analyses will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock for the Primary Analysis for Period A. Complete and specific details of the statistical analyses will be described in the Statistical Analysis Plan Supplement (SAP-S), which will be finalized prior to database lock for the Primary Analysis for Period A as well. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Intent-to-Treat (ITT) Population will be used for the efficacy analyses.

The ITT Population is defined as all subjects who are randomized at Baseline.

The following populations will be used for safety analysis:

- The Safety Population is defined as all subjects who are randomized at Baseline and received at least one dose of study drug.
- The All Risankizumab Treated (All_RZB) Population is defined as subjects who receive at least one dose of risankizumab in the study.

In order to evaluate the impact of major protocol violations on the primary efficacy endpoint in Period A, additional sensitivity analyses will be performed on a Per-protocol Population, which excludes subjects with major protocol deviations that potentially affect the primary efficacy endpoints. The criteria for exclusion of subjects from the Per-protocol Population will be fully defined in the classification plan and the exclusion of subjects from the Per-protocol Population for the analysis in Period A will be finalized before the database lock. Additional sensitivity analysis for the primary endpoint in Period B may be performed if deemed necessary.

7.3 Statistical Analyses for Efficacy

Primary Analysis

The efficacy analysis will be conducted in the ITT Population, and Per-protocol Population for Period A, and for Period B if defined. The ITT Population will be analyzed by treatment group as randomized.

Comparison of the primary endpoint will be made between risankizumab group and secukinumab group using the Cochran-Mantel-Haenszel test adjusting for the stratification factors. For the primary analysis, Non-Responder Imputation (NRI) will be used. The analysis will be repeated using last observation carried forward (LOCF) and Multiple Imputation (MI).

A graphic approach will be utilized for multiplicity control. Details of multiplicity control and analyses methods are provided in the SAP. Specifically, the initial alpha spending between the two primary endpoints will be 0.0375 for Period A, and 0.0125 for Period B.

Sample Size Estimation

The assumptions for the secukinumab Week 16 and Week 52 PASI 90 response rates of 69.7% and 60.6%, respectively, are based on weighted average from secukinumab studies SCULPTURE, ERASURE, FIXTURE, JUNCTURE, and CLEAR. The assumptions for the risankizumab Week 16 and Week 52 PASI 90 response rates of 75.1% and 81.3%, respectively, are based on weighted average from UltiMMa-1 and UltiMMa-2 trials.

The non-inferiority margin was chosen based on the treatment effect of secukinumab versus placebo in PASI 90 response rate at Week 16. A 12% non-inferiority margin preserves 80% of the treatment effect of secukinumab over placebo.

Approximately 310 subjects (155 subjects per treatment group) will provide more than 90% power to detect the difference of risankizumab and secukinumab at Week 52 using a two-sided alpha level of 0.0125, and 90% power to determine the non-inferiority of risankizumab relative to secukinumab using a tolerance limit of 12% and a two-sided alpha level of 0.0375 at Week 16.

7.4 Analyses of Pharmacokinetics and Immunogenicity

Serum risankizumab concentrations will be summarized at each sampling time point using descriptive statistics. For immunogenicity assessment, the number and percentage of subjects with ADA and NAb will be calculated. In addition, ADA titers will be tabulated for each subject at the respective study visits. Additional analyses combining PK, ADA, and NAb data from this study and other studies may be conducted if appropriate.

7.4 Statistical Analyses for Safety

All safety analyses will be performed in the safety populations.

Pre-treatment AEs will be summarized separately.

All treatment-emergent adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, and Areas of Safety Interest (ASI) will be collected during the study. A treatment-emergent AE (TEAE) is defined as an event with onset or worsening after the first study dose of study drug and within 140 days after the last dose of injection for risankizumab or secukinumab administrations. The number and percentages of subjects experiencing TEAE will be tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class and preferred term. Summaries (including percentages and event per 100 patient-year) of SAEs, deaths, AEs leading to discontinuation, and Areas of Safety Interest will be provided as well. For selected laboratory and vital signs parameters, mean change from baseline and percentage of subject with evaluations meeting pre-defined criteria for Potentially Clinically Important values will be summarized.

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.

8.3 Subject Confidentiality

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

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

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

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted 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 Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

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

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ADA	anti-drug antibody
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASI	areas of safety interest
AST	aspartate aminotransferase
BCG	Bacille Calmette-Guérin
BSA	body surface area
CAC	Cardiovascular Adjudication Committee
CV	cardiovascular
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
IB	Investigator's brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
Ig	immunoglobin
IL	interleukin
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-treat
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
NAb	neutralizing antibody
PASI	Psoriasis Area Severity Index
PD	Premature discontinuation
PFS	Pre-filled syringe

PK	pharmacokinetic
PsO	psoriasis
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
sPGA	static Physician Global Assessment
SUSAR	suspected unexpected serious adverse reactions
TA MD	Therapeutic Area Medical Director
TB	tuberculosis
TEAE	Treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-766: Risankizumab versus Secukinumab for Subjects with Moderate to Severe Plaque Psoriasis

Protocol Date: 16 August 2019

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]		International Development
		Clinical Program Development
		Clinical Program Development
		Pharmacokinetics
		Data and Statistical Sciences
		Medical Writing

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the eight Period 1 subject encounters. The individual activities are described in detail in the **Operations Manual**.

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Study Activities Table

	Screening	BASELINE/WK0	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48	Wk52/ PD[a]	Wk 64[s]	Follow Up Call[b]
Activity	**D–30 to D–1**	**D0**	**D7**	**D14**	**D21**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	**D196**	**D224**	**D252**	**D280**	**D308**	**D336**	**D364**	**D448**	
Informed consent[c]	✓																			
Demographics	✓																			
Medical history[d]	✓	✓																		
Nicotine use and alcohol history	✓																			
Psoriasis & PSA history	✓																			
Eligibility criteria	✓	✓																		
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height,[e] weight, and waist circumference	✓								✓									✓		
Vital signs[f]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Complete Physical exam[g]	✓	✓							✓						✓			✓		
12-lead ECG[h]	✓																	✓		
Adverse event assessment[i]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

	Screening	BASELINE/WK0	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48	Wk52/ PD[a]	Wk 64[s]	Follow Up Call[b]
Activity	**D–30 to D–1**	**D0**	**D7**	**D14**	**D21**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	**D196**	**D224**	**D252**	**D280**	**D308**	**D336**	**D364**	**D448**	
Blinded Efficacy assessor assessments (PASI, sPGA, BSA)	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
FSH,[j] serum pregnancy test at central lab[k]	✓																			
Local urine pregnancy test[l]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Central laboratory tests – clinical chemistry, hematology	✓	✓				✓			✓			✓			✓		✓	✓	✓	
Central Lab – Total cholesterol, HDL-C, LDL-C, and triglycerides[m]		✓																✓		
Central Lab – TB Screening (QuantiFERON®-TB Gold test and local PPD skin test if required)[n]	✓																		✓	

	Screening	BASELINE/WK0	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48	Wk52/ PD[a]	Wk 64[s]	Follow Up Call[b]
Activity	**D–30 to D–1**	**D0**	**D7**	**D14**	**D21**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	**D196**	**D224**	**D252**	**D280**	**D308**	**D336**	**D364**	**D448**	
Central Lab - HIV,[o] Hepatitis B and C Screening, urinalysis[p]	✓																			
Blood samples for risankizumab PK assay[q]						✓			✓						✓			✓		
Blood samples for risankizumab ADA assay[q]		✓							✓						✓			✓		
Randomization/ drug assignment		✓																		
Administer secukinumab[r]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Administer risankizumab[r]		✓				✓			✓			✓			✓			✓[s]	✓	

a. Subjects that prematurely discontinue from the study (withdrawal of informed consent), will have a premature discontinuation (PD) visit within 2 weeks after the decision to discontinue and no dose of risankizumab will be administered.

b. For those subjects who prematurely discontinue from the study, a follow up call will occur approximately 20 weeks after the last dose of study medication. The follow-up phone call will be to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

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

d. Note hepatitis B vaccination status in medical history.

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

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

g. If appropriate, a targeted physical exam should be performed at any other visit (e.g., to evaluate a reported adverse event).

h. The ECG should be performed prior to blood collection. For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required; provided all protocol-required documentation is available, and nothing has changed in the subject's health status since the time of the test that warrants a repeat test.

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

j. 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.

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

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

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

n. TB testing will be performed at Screening Visit and at Week 64 visit. Refer to TB Screen section of the operations manual for further information.

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

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

q. PK and ADA samples should be collected prior to the dose at dosing visits. For subjects who prematurely discontinue from study drug treatment prior to Week 52, PK and ADA samples will be collected at any time during the PD visit.

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

s. Only applies to subjects in France who were randomized to risankizumab.

Note: Visit window is ± 3 days. Any of the procedures may be performed at an unscheduled visit at the discretion of the Investigator.

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	15 February 2018

The purpose of this version is to:

- Extend the study to provide two additional dosing visits at Week 52 and Week 64 for active subjects on risankizumab in France only (Section 1, Synopsis; Section 4.1, Overall Study Design and Plan and Figure 1, Appendix D, Activity Schedule).

  Rationale: *Provide continued risankizumab therapy to subjects who were randomized to risankizumab and successfully completed the study until risankizumab is available in France. Data from the IMMhance study (Study M15-992) showed that patients receiving continuous risankizumab treatment had significantly longer median time to relapse compared with those who withdrew risankizumab (and received placebo).*

- Revise wording on timing of the primary analysis for all efficacy endpoints in Period B (Section 7.1, Statistical and Analytical Plans).

  Rationale: *To clarify that the timing of the planned primary analysis of all efficacy endpoints in Period B has not changed.*

- Add Week 64 measurements for prior/concomitant therapy, vital signs, adverse event assessment, local urine pregnancy test, central laboratory tests (clinical chemistry, hematology), and central lab – TB screening (Appendix D, Activity Schedule).

  Rationale: *To continue to monitor routine safety parameters.*

- Add that no dose of risankizumab will be administered at the PD visit (Appendix D, Activity Schedule Footnote a).

- ***Rationale:*** *To clarify that additional dosing of risankizumab has been added to Week 52/PD visit; however this should only apply to the Week 52 and not the PD visit.*

In addition to these modifications, this amendment contains the following minor change:

- Update contact information for emergency medical contact and updated list of protocol signatories (Appendix C, List of Protocol Signatories).
- Correct minor clerical errors for consistency throughout the protocol.