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Protocol for Study M19-977

OptIMMize-1: A Phase 3, Randomized, Active-controlled Study of Risankizumab in Pediatric Patients With Moderate to Severe Plaque Psoriasis

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FULL TITLE: OptIMMize-1: A Randomized, Active-controlled, Efficacy Assessor-blinded Study to Evaluate Pharmacokinetics, Safety, and Efficacy of Risankizumab in Patients From 6 to Less Than 18 Years of Age With Moderate to Severe Plaque Psoriasis

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 SYNOPSIS

Title: OptIMMize-1: A Randomized, Active-controlled, Efficacy Assessor-blinded Study to Evaluate Pharmacokinetics, Safety, and Efficacy of Risankizumab in Patients From 6 to Less Than 18 Years of Age With Moderate to Severe Plaque Psoriasis	
Background and Rationale:	Risankizumab is a humanized monoclonal antibody of the immunoglobin G1 subclass directed towards interleukin (IL)-23p19 approved for the treatment of moderate to severe plaque psoriasis in adults. There is an unmet medical need for effective treatments in pediatric patients with chronic plaque psoriasis. This study is being conducted to evaluate risankizumab in subjects from 6 to less than 18 years of age with moderate to severe plaque psoriasis.
Objective(s) and Endpoint(s):	The objective of this study is to evaluate the pharmacokinetics (PK), safety, and efficacy of risankizumab in subjects from 6 to less than 18 years of age with moderate to severe plaque psoriasis. The following co-primary endpoints will be evaluated: • Achievement of Psoriasis Area and Severity Index (PASI) 75 (defined as at least 75% improvement from baseline in PASI) at Week 16 of initial treatment • Achievement of static physician global assessment (sPGA) clear or almost clear (0 or 1) at Week 16 of initial treatment (US only: and ≥ 2 grade improvement from baseline)
Investigator(s):	Multicenter
Study Site(s):	Approximately 50 sites (globally)
Study Population and Number of Subjects to be Enrolled:	A total of at least 132 pediatric patients with moderate to severe plaque psoriasis.
Investigational Plan:	This is a multicenter, Phase 3, 4-part, active-controlled, efficacy assessor-blinded study. • Part 1 will be a sentinel cohort of 12 adolescents with severe plaque psoriasis who will undergo PK sampling for 16 weeks and continue risankizumab treatment until Week 40. Pharmacokinetic data up to Week 16 will inform the risankizumab dosing regimen for Part 2 and Part 3. • Part 2 will be a randomized, efficacy assessor-blinded assessment of efficacy, comparing risankizumab to ustekinumab in at least 80 adolescents with moderate to severe plaque psoriasis. A 16-week initial treatment period (Period A) will be followed by an up to 36-week randomized treatment or withdrawal period (Period B) for risankizumab responders, and in case of disease flare a 16-week re-treatment period (Period C). Risankizumab non-responders and subjects who received ustekinumab in Period A will receive risankizumab (Period B) until Week 40.

	• Part 3 will be a sentinel cohort of 12 children with severe plaque psoriasis who will undergo PK sampling for 16 weeks and then continue risankizumab treatment until Week 40. Pharmacokinetic data from Week 16 will inform the risankizumab dosing regimen for Part 4. • Part 4 will be a single-arm, 52-week, open-label safety study of 28 children with moderate to severe plaque psoriasis. (Japan only: Approximately 2 adolescents age 12 to less than 18 years will be included.) Enrollment will be triggered by Week 16 data from Part 3.
Key Eligibility Criteria:	Pediatric patients with stable severe or moderate to severe plaque psoriasis as defined in each study part by body surface area (BSA) psoriasis involvement and scores on the PASI and sPGA.
Study Drug and Duration of Treatment:	Study duration will be approximately 65 weeks for Part 1, 3 and 4 and approximately 81 weeks for Part 2. Risankizumab will be administered at Weeks 0, 4 and then every 12 weeks for 40 weeks in Part 1, and planned for Parts 3, and 4 (contingent on PK data obtained in Part 1). The dose will be based on body weight in pediatric patients and is equivalent to the adult exposure at the approved efficacious therapeutic dose of [redacted] mg. For subjects ≥ 40 kg the risankizumab dose is [redacted] mg. For subjects < 40 kg the risankizumab dose is [redacted] mg. In Part 2 only, subjects will be randomized to receive either risankizumab or ustekinumab for 16 weeks during Period A. The ustekinumab dose administered will be based on weight: 0.75 mg/kg for subjects < 60 kg; 45 mg for subjects 60 to < 100 kg; and 90 mg for subjects ≥ 100 kg. Subjects previously randomized to ustekinumab in Period A, risankizumab subjects who are non-responders at Week 16, and risankizumab subjects re-randomized to continue risankizumab treatment will receive risankizumab for 36 weeks in Period B in order to collect additional safety information for risankizumab. Subjects who are randomized to withdraw risankizumab treatment in Period B will receive risankizumab for 16 weeks if they meet the re-treatment criteria (Period C). Subjects who complete the current study and meet the eligibility criteria of the Study M19-973 open-label extension (OLE) study will be able to continue treatment for 216 additional weeks.
Date of Protocol Synopsis:	16 October 2023

2 INTRODUCTION

2.1 Background and Rationale

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

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

Why Is This Study Being Conducted?

There is an unmet medical need for effective treatments in pediatric patients with chronic plaque Ps who are candidates for systemic therapy. This study will evaluate the pharmacokinetics (PK), safety, and efficacy of risankizumab in subjects with moderate to severe plaque Ps from 6 to less than 18 years of age.

2.2 Benefits and Risks to Subjects

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

Subjects with a positive QuantiFERON®-tuberculosis (TB) (or interferon gamma release assay [IGRA] equivalent)/TB skin test result for TB must fulfill entry criteria as specified in Section 5.1 of this protocol. Interleukin-23 inhibition is not known to increase the risk of TB infection or impair the response to TB infection in animal models.

Published literature indicates that inhibition of IL-23 is unlikely to increase the risk for cancer. Expression of IL-23 is increased in human tumors.[4-6] Moreover, preclinical data have demonstrated a beneficial effect of IL-23 p19 inhibition in animal models, both for pre-existing and tumor-induction models.[7] While there is not enough clinical information at this time to rule out a risk of cancer with risankizumab, this risk is considered small.

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

Potential Increases in major adverse cardiovascular (major adverse cardiac event) events, including myocardial infarction (MI), cerebrovascular accident, and cardiovascular death, reported initially with anti-IL-12/23 agents have not been observed in longer term studies with risankizumab.

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

In conclusion, the benefit-risk profile of risankizumab is considered appropriate for this stage of clinical development.[8] Based on data from the integrated safety analyses, risankizumab is safe and well -tolerated and demonstrates a favorable benefit-risk profile.

As this is the first study to use risankizumab in patients under the age of 18, specific risks for this population have yet to be identified; however, no significant risks are expected as planned dosing will be equivalent to the adult efficacious dose that is considered safe and well-tolerated. Due to potential immunological issues in very young children, it was determined that children under the age of 6 should not be included in this study.

For further details on the safety profile of risankizumab, please see findings from completed studies including safety data in the current Investigator's Brochure (IB).[1]

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 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

The objective of this study is to evaluate the PK, safety, and efficacy of risankizumab in subjects from 6 to less than 18 years of age with moderate to severe plaque Ps.

Primary Efficacy

The primary efficacy objective is to assess the rate of subjects who achieve a) PASI 75 (defined as at least 75% improvement from baseline in PASI) and b) sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 16 of initial treatment with study drug based on the Intent-to-Treat (ITT) population (as defined in Section 7.2).

There are no statistical hypotheses corresponding to the co-primary efficacy objectives as efficacy will be assessed descriptively, providing estimates with confidence intervals without performing statistical testing.

The estimands corresponding to the co-primary efficacy objectives are defined as follows for Part 1, Part 3, and Part 4:

- Percentage of subjects achieving at least 75% reduction in PASI (PASI 75) from Baseline at Week 16 of initial treatment with risankizumab without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population
- Percentage of subjects achieving sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 16 of initial treatment with risankizumab without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population

The estimands corresponding to the co-primary efficacy objectives are defined as follows for Part 2:

- Difference in the percentage of subjects achieving at least 75% reduction in PASI (PASI 75) from Baseline at Week 16 of initial treatment with risankizumab compared to ustekinumab without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population
- Difference in the percentage of subjects achieving sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 16 of initial treatment with risankizumab compared to ustekinumab without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population

Secondary Efficacy

The secondary efficacy objectives are to assess the rate of subjects who achieve the ranked secondary endpoints specified in Section 3.3 below in the ITT population.

There are no statistical hypotheses corresponding to the secondary efficacy objectives as efficacy will be assessed descriptively, providing estimates with confidence intervals without performing statistical testing.

The estimands corresponding to the secondary efficacy objectives are defined as follows for Part 1, Part 3, and Part 4:

- Percentage of subjects achieving at least 90% reduction in PASI (PASI 90) from Baseline at Week 16 of initial treatment with risankizumab without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population
- Percentage of subjects achieving 100% reduction in PASI (PASI 100) from Baseline at Week 16 of initial treatment with risankizumab without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population

The estimands corresponding to the secondary efficacy objectives are defined as follows for Part 2:

- Difference in the percentage of subjects achieving at least 90% reduction in PASI (PASI 90) from Baseline at Week 16 of initial treatment with risankizumab compared to ustekinumab without

the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population

- Difference in the percentage of subjects achieving 100% reduction in PASI (PASI 100) from Baseline at Week 16 of initial treatment with risankizumab compared to ustekinumab without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population
- Percentage of subjects achieving sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 0 and Week 16 of the re-treatment phase in Part 2 with risankizumab without the use of rescue medication and regardless of premature discontinuation of study drug in the ITT population

Rescue medication for the purposes of this analysis will be considered any systemic (oral or parenteral) medication used specifically for the treatment of psoriasis.

3.2 Co-primary Endpoints

- Achievement of PASI 75 (defined as at least 75% improvement from baseline in PASI) at Week 16 of initial treatment
- Achievement of sPGA clear or almost clear (0 or 1) at Week 16 of initial treatment (US only: and ≥ 2 grade improvement from baseline)

3.3 Ranked Secondary Endpoints

- Achievement of PASI 90 (defined as at least 90% improvement from baseline in PASI) at Week 16 of initial treatment
- Achievement of PASI 100 (defined as 100% improvement from baseline in PASI) at Week 16 of initial treatment
- Achievement of sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 0 and Week 16 of the re-treatment phase in Part 2

3.4 Non-ranked Secondary Efficacy Endpoints

- Achievement of PASI 50 (defined as at least 50% improvement from baseline in PASI) at Week 16 of initial treatment
- Achievement of PASI 50 (defined as at least 50% improvement from baseline in PASI) at Week 0 and Week 16 of the re-treatment phase in Part 2
- Achievement of PASI 90 (defined as at least 90% improvement from baseline in PASI) at Week 0 and Week 16 of the re-treatment phase in Part 2
- Achievement of PASI 100 (defined as 100% improvement from baseline in PASI) at Week 0 and Week 16 of the re-treatment phase in Part 2

- Achievement of a PASI 75 (defined as at least 75% improvement from baseline in PASI) at Week 0 and Week 16 of the re-treatment phase in Part 2
- Change in Children's Dermatology Life Quality Index (CDLQI) from Week 0 to Week 16 of initial treatment in Part 2
- Change in CDLQI from Week 0 to Week 16 of re-treatment phase of Part 2
- Change in Family Dermatology Life Quality Index (FDLQI) from Week 0 to Week 16 of initial treatment in Part 2
- Change in FDLQI from Week 0 to Week 16 of re-treatment phase of Part 2
- Change in Itch Numerical Rating Scale (Itch NRS) from Week 0 to Week 16 of initial treatment in Part 2
- Change in Itch NRS from Week 0 to Week 16 of re-treatment phase in Part 2
- Achievement of ≥ 4-point improvement from baseline in the Itch Numerical Rating Scale (in patients with Baseline score ≥ 4) at Week 16 of initial treatment in Part 2.

3.5 Other Endpoints

- Achievement of PASI 75 at Week 12 during the treatment or withdrawal period of Part 2
- Achievement of sPGA clear or almost clear (0 or 1) at Week 12 during the treatment or withdrawal period of Part 2
- Achievement of PASI 50/75/90/100 at all other visits collected
- Achievement of sPGA clear (0) at all other visits collected
- Achievement of sPGA clear or almost clear (0 or 1) at all other visits collected
- Change in Itch Numerical Rating Scale (Itch NRS) at each study visit from Week 0
- Achievement of ≥ 4-point improvement from baseline in the Itch Numerical Rating Scale (in patients with baseline score ≥ 4) at each study visit in Part 2
- Change in CDLQI at each study visit from Week 0
- Change in FDLQI at each study visit from Week 0

3.6 Safety Endpoints

- Treatment emergent adverse events (TEAEs)
- Serious adverse events (SAEs)
- Areas of safety interest (ASI)
- TEAEs leading to discontinuation
- Vital signs and laboratory tests (hematology, chemistry, and urinalysis)

3.7 Pharmacokinetic and Immunogenicity Endpoints

Serum risankizumab concentrations, antidrug antibody (ADA), and neutralizing antibody (nAb) will be determined at the visits indicated in the Study Activities Table (Appendix D).

Serum risankizumab concentrations will be summarized at each timepoint by cohort using descriptive statistics. Population PK analyses combining the data from this study and other studies may be performed. Relationships between risankizumab exposure and efficacy or safety variables of interest may be explored.

The number and percentage of subjects (i.e., incidence) with positive ADA and nAb will be summarized by cohorts and study visits. Anti-drug Abs titers will be tabulated for each subject by regimen at the respective study visits. The effect of immunogenicity on risankizumab exposure, efficacy, and/or safety variables may be explored.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

The study consists of 4 parts, each with distinct patient populations. Further details regarding study procedures are in the Operations Manual. See Section 5 for information regarding eligibility criteria.

Subjects who initially do not meet all eligibility criteria for the study may be permitted to repeat the Screening Visit one time following re-consent. There is no minimum period of time that a subject must wait prior to the repeat Screening Visit. The subject must meet all eligibility criteria on the repeat Screening Visit in order to qualify for the study. A repeat of all screening procedures is needed at this repeat Screening Visit with these exceptions:

- If the repeat Screening Visit is within 30 days of the initial Screening Visit, clinical laboratory parameters assessed as normal at the initial Screening Visit do not need to be repeated at the repeat Screening Visit
- If the subject had a complete initial screening evaluation, including the assessment of an Interferon-Gamma Release Assay (IGRA; QuantiFERON TB Gold In Tube test) or a purified protein derivative (tuberculin) (PPD) test (or equivalent), and electrocardiogram (ECG), these tests do not need to be repeated at the repeat Screening Visit if they were completed within 90 days since the initial Screening Visit.

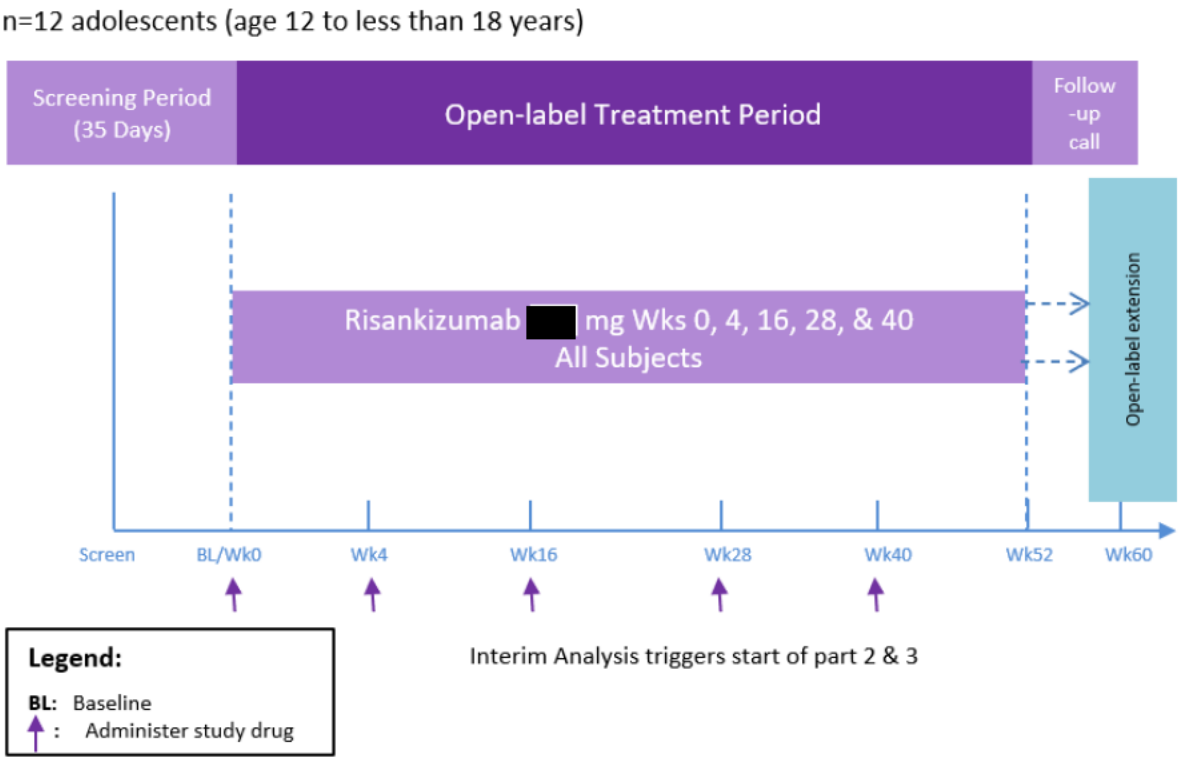
Part 1

Part 1 will be a sentinel (open-label) cohort of 12 adolescents (age 12 to less than 18 years) with severe disease. At least 1 subject with a body weight less than 50 kg at baseline will be enrolled in Part 1 to ensure good representation of the lower body weight range. Subjects will undergo PK sampling for 16 weeks and continue treatment until Week 40 (subjects will receive [redacted] mg risankizumab subcutaneously [SC] at Weeks 0, 4, 16, 28, and 40). A follow-up call will take place 20 weeks after the last dose of study drug (Week 40) if the subject does not enroll into Study M19-973, the open-label

extension (OLE) study. Pharmacokinetic data up to Week 16 informed the dosing regimen for Part 2 in adolescents and triggered the start of Part 3 in children 6 to less than 12 years of age.

A schematic of Part 1 is shown in Figure 1.

Figure 1. Part 1 Schematic



Wk = week

Part 2

Part 2 will be a randomized, efficacy assessor-blinded assessment of efficacy, comparing risankizumab with ustekinumab in at least 80 adolescents (age 12 to less than 18 years) with moderate to severe disease. Enrollment into Part 2 will be triggered by the Week 16 data from Part 1. In Part 2, a 16-week initial treatment period (Period A) will be followed by an up to 36-week randomized treatment or withdrawal period (Period B) for risankizumab responders, and then a potential 16-week re-treatment period (Period C) for subjects who experience a disease flare (defined as sPGA ≥ 3 on or after Week 28). Risankizumab non-responders and subjects who received ustekinumab in Period A will receive risankizumab (Period B) until Week 40.

In Period A, subjects will be randomized (2:1) to receive risankizumab SC based on weight (subjects who weigh ≥ 40 kg will receive [redacted] mg risankizumab, while subjects who weigh < 40 kg will receive [redacted] mg risankizumab) or ustekinumab SC based on weight (0.75 mg/kg for subjects < 60 kg; 45 mg for subjects 60 to < 100 kg; 90 mg for subjects ≥ 100 kg) at Weeks 0 and 4. At Week 16, risankizumab

non-responders (sPGA ≥ 2) and subjects initially randomized to ustekinumab will enter Period B and will receive risankizumab every 12 weeks until Week 40 in order to collect additional safety information for risankizumab. Risankizumab responders (sPGA = 0 or 1) will enter Period B and will be re-randomized (1:1) to receive no medication until a disease flare or risankizumab every 12 weeks until Week 40. Subjects randomized to the withdrawal arm in Period B who experience a disease flare on or after Week 28 will enter Re-Treatment Period C to receive risankizumab at Weeks 0 and 4 of the 16-week re-treatment period. Randomization and re-randomization will not be stratified due to the small sample size.

For subjects initially randomized to risankizumab in Period A, study duration will be up to approximately 81 weeks:

- Screening period of up to 35 days
- Period A: 16-week treatment period (dosing at Weeks 0 and 4)
- Period B: maximum of 36-week treatment or withdrawal period
  - Risankizumab non-responders: risankizumab dosed at Weeks 16, 28, and 40
  - Risankizumab responders: either no treatment or risankizumab dosed at Weeks 16, 28, and 40
- Period C: 16-week re-treatment period if a disease flare occurs in subjects randomized to the no treatment group
- The follow-up call with take place 20 weeks after the last dose of study drug unless the subject enrolls into Study M19-973, the OLE study.

For subjects initially randomized to ustekinumab, study duration will be up to approximately 65 weeks:

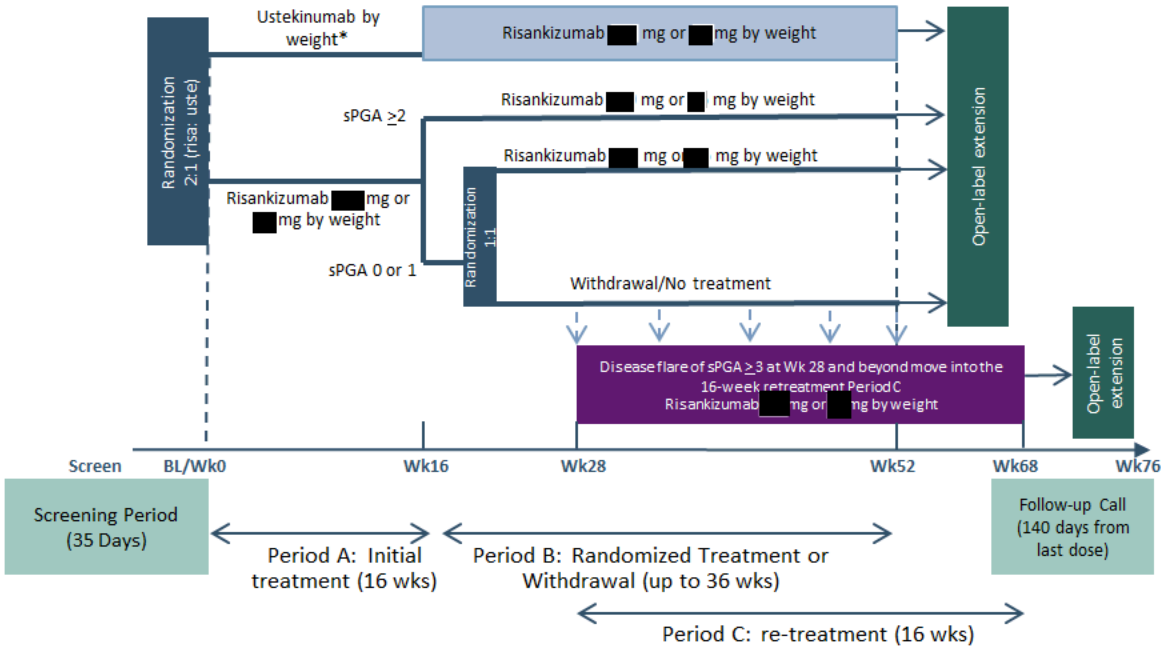
- Screening period of up to 35 days
- 52-week treatment period (16 weeks on ustekinumab followed by risankizumab with the last dose at Week 40)
- The follow-up call will take place 20 weeks after the last dose of study drug unless the subject enrolls into Study M19-973, the OLE study.

Subjects who complete either the Week 52 visit for those in Period B or 16 weeks of the re-treatment Period C have the option to enroll into Study M19-973, the OLE study.

A schematic of Part 2 is shown in Figure 2.

Figure 2. Part 2 Schematic

n=80 adolescents (age 12 to less than 18 years)



* Ustekinumab dose: 0.75 mg/kg for subjects < 60 kg; 45 mg for subjects 60 to < 100 kg; 90 mg for subjects ≥ 100 kg.

Legend:

BL: Baseline; sPGA = static physician global assessment; Wk = week

Administer study drug: dosed by weight

Initial treatment Period A: BL and Wk 4

Randomized Treatment or Withdrawal Period B:

- Week 16 risankizumab non-responders and all ustekinumab subjects will continue dosing every 12 weeks - Weeks 16, 28, and 40. All ustekinumab subjects will be switched to risankizumab at Week 16.
- Risankizumab responders will be re-randomized at a 1:1 ratio to continue risankizumab dosing or withdraw from the study drug.
- Risankizumab responders who are randomized to withdrawal of treatment will receive no study drug until subjects experience a disease flare. Once a disease flare has occurred, subjects will enter into the 16-week re-treatment Period C. The earliest timepoint in which a subject can switch to re-treatment Period C is on or after Week 28. The latest timepoint to switch to re-treatment Period C is at the Week 52 visit.

Re-treatment Period C: Re-treatment BL and Wk 4

Subjects who complete either Week 52 without disease flare or 16-week re-treatment from Period C are eligible to enroll into Study M19-973, the open-label extension study.

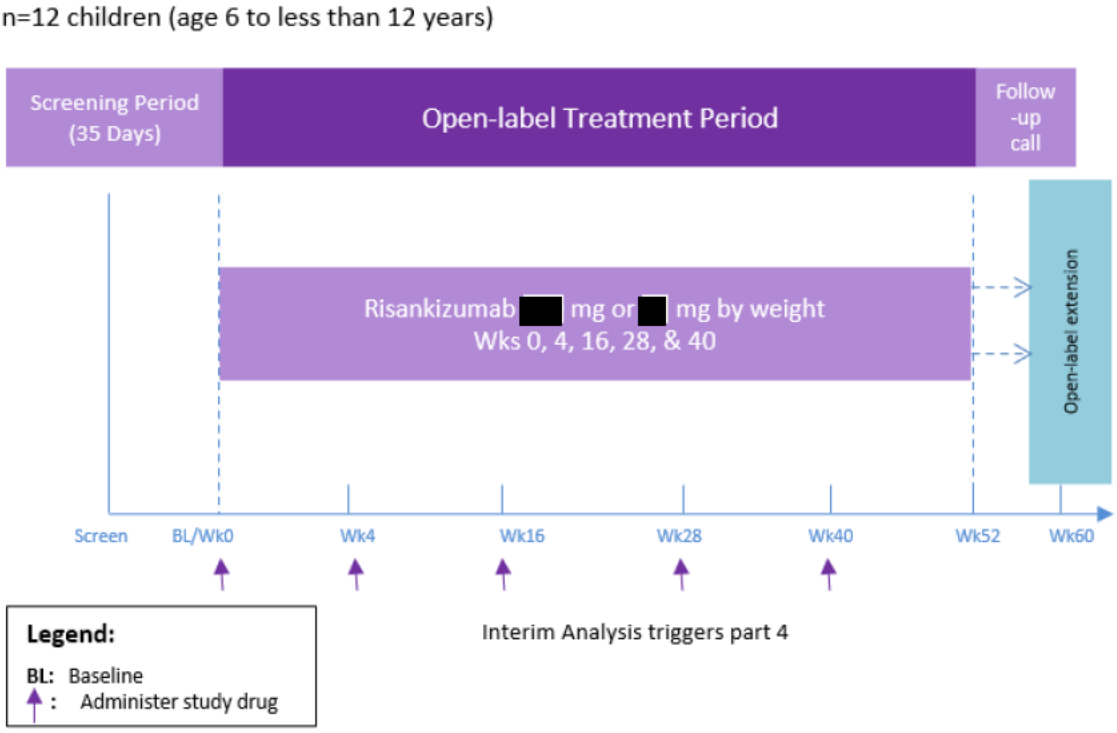
Part 3

Part 3 will be a sentinel (open -label) cohort of 12 children (age 6 to less than 12 years) with severe disease. At least 3 subjects aged between 6 to < 9 years old will be enrolled in Part 3 to ensure good representation of the lower age range. Subjects will undergo PK sampling for 16 weeks and then

continue treatment until Week 40 with dosing planned at Weeks 0, 4, 16, 28, and 40. Risankizumab will be administered based on body weight. Subjects who weigh ≥ 40 kg will receive [redacted] mg risankizumab, while subjects who weigh < 40 kg will receive [redacted] mg risankizumab. Pharmacokinetic data up to Week 16 informed the dosing regimen for the start of Part 4. Enrollment was triggered by the Week 16 data from Part 1. A schematic of Part 3 is shown in Figure 3.

A follow-up call will take place 20 weeks after the last dose of study drug (Week 40) if the subject does not enroll into Study M19-973, the OLE study.

Figure 3. Part 3 Schematic



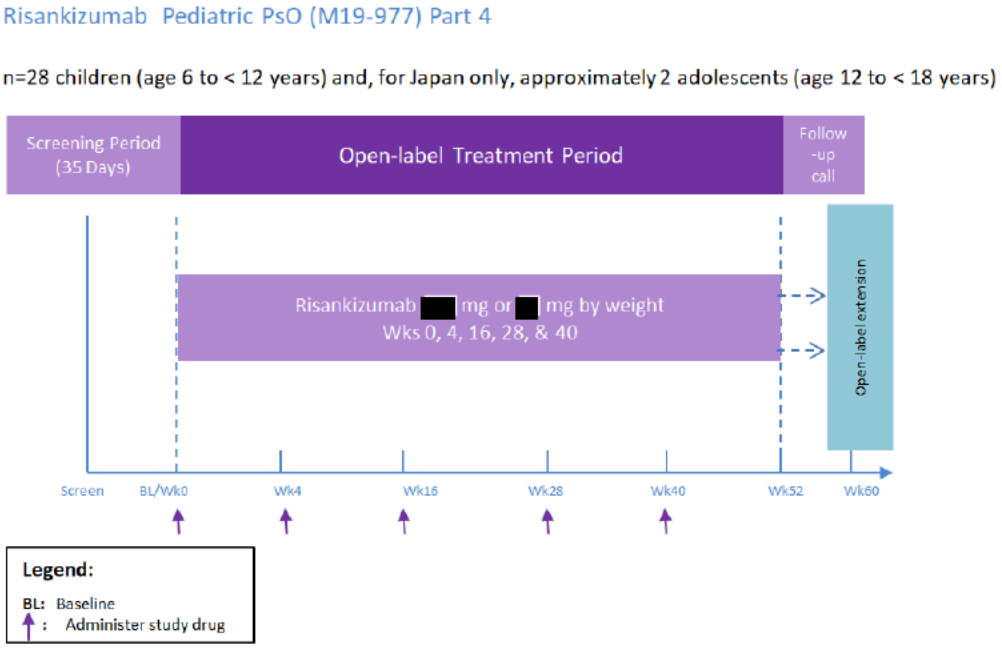
Wk = week

Part 4

Part 4 will be a single-arm, 52-week, open-label safety study of 28 children (age 6 to less than 12 years) with moderate to severe disease with dosing at Weeks 0, 4, 16, 28, and 40. (Japan only: Approximately 2 adolescents age 12 to less than 18 years will be included.) The risankizumab dose in Part 4 was based on the results of the PK data collected in Part 3. Enrollment will be triggered by Week 16 data from Part 3. A schematic of Part 4 is shown in Figure 4.

A follow-up call will take place 20 weeks after the last dose of study drug (Week 40) if the subject does not enroll into Study M19-973, the OLE study.

Figure 4. Part 4 Schematic



Wk = week

Subjects who have completed the current study and who meet the eligibility criteria will be offered the option to participate in Study M19-973, the OLE study. Assessments from the Final Visit of Study M19-977 will serve as the Baseline Visit assessments for Study M19-973.

Study duration during Parts 1, 3, and 4 will be up to approximately 65 weeks: a screening period of up to 35 days, a 52-week treatment period, and a 20-week follow-up call that will occur at Week 60 (20 weeks after the last dose of study drug at Week 40). The 20-week follow up call will not be completed if the subject enrolls into Study M19-973, the OLE study.

The investigator should consider discontinuing risankizumab treatment in subjects who have shown no response after 16 weeks of treatment.

No formal interim analysis is planned that would require type 1 error control. Data will be cleaned and analyzed as detailed in Section 7.6.

An external Data Monitoring Committee (DMC) and AAC will be used to monitor study activities as detailed in Section 6.2 and Section 6.3, respectively.

4.2 Discussion of Study Design

Choice of Control Group

In study Part 2, an active control group is used to assess efficacy and safety of risankizumab compared with an approved product for the same indication. Ustekinumab (Stelara®) is a human IL-12 and -23 antagonist indicated for the treatment of moderate to severe plaque Ps.[9]

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 plaque Ps. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Pediatric subjects 6 through < 18 years of age with plaque Ps who meet all inclusion criteria and who do not meet any of the exclusion criteria are eligible for this study. The specific subject population chosen was based on knowledge that IL-23 is involved in the pathogenesis of Ps in the adult population. Data from adult studies have shown that risankizumab is effective and well tolerated in the adult Ps population. This study is intended to confirm safety and efficacy in pediatric subjects as well as to identify the most appropriate dose based on subject weight.

Selection of Doses in the Study

Due to the similarity between children and adults in disease pathophysiology and the mechanism of action of risankizumab, the objective of dose selection in this study is to approximate a dose based on body weight in pediatric patients with plaque Ps to be equivalent to the adult exposure at the approved efficacious therapeutic dose of [redacted] mg SC at Week 0, 4, and every 12 weeks thereafter. A population PK model of risankizumab identified body weight as the primary covariate and therefore body weight range-based dosing has been selected for this study.[10] The population PK model was also used to identify a balance between maximizing the best approximate with adult exposure and minimizing complexity of dosing schemes. Further rationale by study part is provided below.

Selection of doses for Part 2 and Part 3 is based on PK modeling from Part 1. Subjects who weigh ≥ 40 kg will receive [redacted] mg risankizumab, while subjects who weigh < 40 kg will receive [redacted] mg risankizumab.

During the conduct of the study, if any subject initially assigned to the lower dose of risankizumab has a recorded weight ≥ 40 kg at a dosing visit, they will receive the standard risankizumab dose ([redacted] mg).

Part 1

The main objective of Part 1 is to evaluate the PK and safety of the proposed risankizumab pediatric dose based on extrapolation from adult data. According to an adalimumab study in pediatric patients with Ps (Study M04-717),[11] the median body weight of adolescent patients (age 12 to less than 18 years) was 59 kg with a minimum to maximum range of 38 kg to 108 kg. This largely overlaps with the body weight range observed in the risankizumab adult Phase 3 studies in Ps (38.5 kg to 193 kg) and supports the use of the same adult therapeutic dose of [redacted] mg risankizumab in Part 1 of this study without a

specific body weight cutoff. Data collected up to Week 16 from subjects in Part 1 will be useful for PK assessments and to guide dose selection for Parts 2 and 3.

Part 2

The risankizumab doses to be administered in Part 2 have been determined by the first 16 weeks of data from Part 1 and are [redacted] mg for subjects who weigh ≥ 40 kg and [redacted] mg for subjects who weigh < 40 kg.

Part 3

Similar to Part 1, the main objective of Part 3 is to evaluate PK and safety of the selected risankizumab pediatric doses in the 6 to < 12 -year-old patients based on extrapolation from adult data as well as the available data from Part 1 of the study. Due to the lower body weight in many of the younger patients compared with adult patients, body weight ranges will be used to determine the dose. The doses to be administered in Part 3 have been determined by the first 16 weeks of data from Part 1 and are [redacted] mg for subjects who weigh ≥ 40 kg and [redacted] mg for subjects who weigh < 40 kg.

Part 4

The doses to be administered in Part 4 have been determined by an updated population PK data analysis from Parts 1-3 and are [redacted] mg for subjects who weigh ≥ 40 kg and [redacted] mg for subjects who weigh < 40 kg.

During Parts 2, 3, and 4 of the study, the body weight measured prior to each dose administration will be used to determine the dose for each subject, with the exception of the doses administered at or prior to Week 4 in Part 3, when the baseline body weight will be used to determine the dose.

The target exposures at these doses will be within the range of the risankizumab exposures evaluated as safe and well-tolerated in adult programs across multiple indications.

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's parent or legal guardian 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. Subject will be included in all discussions to obtain verbal or written assent.

Demographic and Laboratory Assessments

- 2. Subject is judged to be in good general health, as determined by the investigator based upon the results of a medical history, physical examination, laboratory profile, and a 12-lead ECG performed during the Screening period.
- 3. Subject is male or female, 6 to < 18 years old:
  - Parts 1 and 2: ages include 12 to < 18 years at the time of enrollment;
  - Parts 3 and 4: ages include 6 to < 12 years at the time of enrollment.
- 4. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum aspartate transaminase and serum alanine transaminase ≤ 2 × upper limit of normal;
  - Serum total bilirubin ≤ 2.0 mg/dL; except for subjects with isolated elevation of indirect bilirubin related to Gilbert syndrome;
  - Total white blood cell count ≥ 3,000/µL;
  - Absolute neutrophil count ≥ 1,500/µL;
  - Platelet count ≥ 100,000/µL;
  - Hemoglobin ≥ 10 g/dL.
- 5. Subject is willing and able to comply with procedures required in this protocol and is not an employee of the sponsor and/or study site or a family member of an employee.

Disease/Condition Activity

- 6. Diagnosis of chronic plaque Ps for at least 6 months before the Baseline Visit.
- 7. Subject must be a candidate for systemic therapy as assessed by the investigator and meet the following disease activity criteria at both the Screening and Baseline Visits:
  - Part 1: Subject has severe disease defined as ≥ 20% body surface area (BSA) Ps involvement with sPGA score of 4; OR ≥ 10% BSA Ps involvement that includes facial or genital areas with sPGA score of 4; OR PASI ≥ 20;
  - Part 2: Subject has moderate to severe disease defined as ≥ 10% BSA Ps involvement with sPGA score of ≥ 3 or PASI ≥ 12;
  - Part 3: Subject has severe disease defined as ≥ 20% BSA Ps involvement with sPGA score of 4; OR ≥ 10% BSA Ps involvement that includes facial or genital areas with sPGA score of 4; OR PASI ≥ 20;
  - Part 4: Subject has moderate to severe disease defined as ≥ 10% BSA Ps involvement with sPGA score of ≥ 3 or PASI ≥ 12;
- 8. Subject must be a candidate for the treatment with ustekinumab according to local label. For Japan, this includes subjects ≥ 15 years old.
  - Subjects in Part 2 age < 15 years should meet the safety requirements of the local label.

Subject History

- 9. Subject must not have a history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 6 months.
- 10. Subject must not have a history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 11. No history of:
  - Erythrodermic Ps, generalized or localized pustular Ps, medication-induced or medication-exacerbated Ps, or new onset guttate Ps;
  - Active skin disease other than Ps that could interfere with the assessment of Ps;
  - Clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months;
  - An allergic reaction or hypersensitivity to a biologic agent or its excipients;
  - A latex allergy;
  - An organ transplant that requires continued immunosuppression;
  - **Any malignancy** except for successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix
- 12. No evidence of the following medical diseases or disorders:
  - Hepatitis B (HB) (hepatitis B virus [HBV]) or hepatitis C (hepatitis C virus [HCV]) infection, defined as
    - HBV: Hepatitis B surface antigen (HBs antigen) positive (+) test or detected sensitivity on the HBV DNA polymerase chain reaction qualitative test for subjects who are HB core Ab (HB core Ab) positive (+) (and for HB surface Ab [HBs Ab] positive [+] subjects where mandated by local requirements);
    - HCV: hepatitis C virus RNA detectable in any subject with anti-hepatitis C virus antibody;
  - Human immunodeficiency virus (HIV), defined as confirmed positive anti-HIV antibody (HIV Ab) test. Note: In case a screened subject has a confirmed positive HIV Ab test, eligibility criterion 2 regarding good general health criteria should be selected in the electronic case report form (eCRF) as the reason for screening failure;
  - COVID-19: In subjects who test positive for COVID-19, at least 5 days have passed since a positive test result in asymptomatic patients. Subjects with mild/ moderate COVID-19 symptoms can be enrolled if fever-free without use of antipyretics for 24 hours and improvement of other symptoms or 5 days have passed since the positive test result (whichever comes last). Subjects may be rescreened if judged to be in good general health, as determined by the investigator based on medical history and physical examination.
  - Active TB: For subjects with latent TB, please see the Operations Manual for details;
  - Active systemic infection/clinically important infection during the last 2 weeks prior to Baseline Visit as assessed by the investigator.

- Genetic deficiency in IL-12/IL-23;
- Active or suspected malignancy;
- Recent (within past 6 months) cerebrovascular accident or MI;
- Major surgery performed within 12 weeks prior to randomization or planned during the conduct of the study.

- 13. Subject does not have concurrent clinically significant medical conditions other than the indication being studied or any other reason that the investigator determines would interfere with the subject's participation in this study, would make the subject an unsuitable candidate to receive study drug, or would put the subject at risk by participating in the study.
- 14. Subject has an updated immunization schedule according to local immunization guidelines

Contraception

- 15. For all females of child-bearing potential; a **negative serum pregnancy test** at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug.
- 16. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is effective from Study Day 1 through at least 140 days (20 weeks or as guided by the local drug label, whichever is longer) after the last dose of study drug (local practices may require 2 methods of birth control). Female subjects of non-childbearing potential do not need to use birth control.
- 17. Female subjects may not be **pregnant, breastfeeding, or considering becoming pregnant** during the study or for approximately 140 days (20 weeks or as guided by the local drug label, whichever is longer) after the last dose of study drug.

Concomitant Medications

- 18. Subject must not have received **any live viral or bacterial vaccine** except non-replicating live vaccines (e.g., JYNNEOS monkeypox vaccine) within 4 weeks prior to the first dose of study drug or expect the need for live vaccination during study participation including at least 140 days (20 weeks or as guided by the local drug label, whichever is longer) after the last dose of study drug.
- 19. Subject has not had any previous exposure to risankizumab (all study parts) or ustekinumab (study Part 2).
- 20. 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

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential
  - A female who is considered of non-childbearing potential does not need to use birth control during or following study drug treatment.
  - Premenopausal female with permanent sterility or permanent infertility due to one of the following:
    - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy;
    - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
  - Premenarchal female
    - Females who have not experienced menarche (at least one menstrual period).

      (Note: If the childbearing potential changes after start of the study [e.g., a premenarchal female participant experiences menarche], the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception. If reproductive status is questionable, additional evaluation should be considered.)
- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 140 days (20 weeks or as guided by the local risankizumab or ustekinumab label (if approved), whichever is longer) after the last dose of study drug.
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device.
    - Intrauterine hormone-releasing system.
    - Vasectomized sexual partner(s) (the vasectomized partner should have received medical assessment of the surgical success and is the sole sexual partner of the trial participant).

- Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

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

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

5.3 Prohibited Medications and Therapy

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

1. Any systemic biologic therapy (other than the study drug);
2. Systemic non-biologic therapy for Ps, 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 Ps 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 Ps treatment) emollients and shampoos and/or low potency topical corticosteroids (US Class 6 - 7) on the palms, soles, face, inframammary area, and groin only. In areas where available topical corticosteroids are not easily identified by United States (US) Class, a list of acceptable low potency topical corticosteroids will be provided to sites.
5. Treatment with an experimental non-biologic for Ps within 4 weeks or five half-lives of the drug (whichever is longer);
6. Treatment with an experimental biologic for Ps within 12 weeks or five half-lives of the drug (whichever is longer);
7. Live attenuated vaccines (except non-replicating live vaccines (e.g., JYNNEOS monkeypox vaccine) are NOT allowed during the study and including up to 140 days (20 weeks or as guided by local drug label (if approved), whichever is longer) after the last dose of study drug. Examples of live attenuated vaccines include but are not limited to the following:
    - Bacille Calmette-Guérin;
    - Zoster vaccine live (Zostavax);

- Measles-mumps-rubella or measles mumps rubella varicella;
- Monovalent live attenuated influenza A (intranasal);
- Oral polio vaccine;
- Rotavirus;
- Seasonal trivalent live attenuated influenza (intranasal);
- Smallpox;
- Oral typhoid vaccine;
- Varicella (chicken pox);
- Yellow fever;
- Dengue (Dengvaxia®).

5.4 Prior and Concomitant Therapy

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation, are permissible. Concomitant therapies should not be administered with the intent to treat Ps or have demonstrated efficacy for the treatment of Ps (except for permitted low-potency topical corticosteroids). 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 electronic case report form (eCRF).

A detailed history of all prior biologic use needs to be documented in the source notes and captured in the EDC.

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

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

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

When possible, first dose of study drug should be given at least ± 7 days from non-live SARS-CoV-2 vaccine administration. The potential impact of risankizumab on SARS-CoV-2 vaccination is unknown.

The decision to receive a locally available non-live vaccine should be based on local guidance and an individual discussion between the treating physician and the subject and/or guardian.

5.5 Withdrawal of Subjects and Discontinuation of Study

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

- The subject or the subject's parent or legal guardian requests withdrawal from the study.
- The investigator believes it is in the best interest of the subject.
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie Therapeutic Area Medical Director (TA MD).
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix, where discontinuation is at the discretion of the Investigator.
- The subject becomes pregnant while on study drug.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.
- Post-Baseline occurrence of one or more of the following hepatic test abnormalities (confirmed on a second separate sample at least 48 hours apart):
    - ALT (alanine aminotransferase) or AST (alanine aminotransferase) > 8 × ULN (upper limit of normal);
    - ALT or AST > 5 × ULN for more than 2 weeks;
    - ALT or AST > 3 × ULN and Total Bilirubin > 2 × ULN or international normalized ratio [INR] > 1.5;
    - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented (in the eCRF if reported as an AE). If ALT or AST values return to the normal reference range or its Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is expected to be safe. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found

or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug.

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

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

COVID-19 Pandemic-Related Acceptable Protocol Modification

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

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

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

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

During the study drug dosing period, for a subject with confirmed (viral test positive) or suspected COVID-19 infection, the timing of next administration of study drug or possibility of premature discontinuation would be at the discretion of the investigator. Follow subsequent protocol Section 5.6 for subjects who discontinued study drug.

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

Discontinuation of Study Drug and Continuation of Study Participation

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

Premature Discontinuation of Study (Withdrawal of Informed Consent)

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks.

In addition, if subject is willing, a follow-up phone call 140 days (20 weeks) after the last dose of study drug may be completed to ensure all treatment-emergent AEs/serious adverse events (SAEs) have been

resolved. The 140-day (20 week) follow-up phone call following the last dose of risankizumab study drug during the trial will not be required for any subject who initiates commercially available risankizumab after completion of the study Completion Visit or PD visit or enters Study M19-973, the OLE study.

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

5.7 Study Drug

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

Table 1. Identity of Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Risankizumab (ABBV-066)	Solution for injection in pre-filled syringe	[redacted] mg/[redacted] mL	Subcutaneous injection	AbbVie
Risankizumab (ABBV-066)	Solution for injection in pre-filled syringe	[redacted] mg/[redacted] mL	Subcutaneous injection	AbbVie
Ustekinumab	Solution for injection in pre-filled syringe	45 mg/0.5 mL	Subcutaneous injection	Janssen
Ustekinumab	Solution for injection in vial	45 mg/0.5 mL	Subcutaneous injection	Janssen

AbbVie will not supply drug other than risankizumab and ustekinumab.

Open-label risankizumab and ustekinumab 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.

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.

Study Parts 1, 3, and 4 are open-label single arm and all subjects will receive the same dose exposure equivalent based on body weight (Parts 3 and 4) and the same frequency of study drug.

For Part 2 only, the IRT will assign a randomization number that will encode the subject's treatment group assignment in Period A according to the randomization schedule generated by the statistics department at AbbVie. For subjects re-randomized in Period B of Part 2, the IRT will assign a separate randomization number that will encode the subject's treatment group assignment in Period B according to a separate randomization schedule generated by the statistics department at AbbVie. Randomization for Period A will be done in a 2:1 ratio of risankizumab vs. ustekinumab. The re-randomization ratio of continued treatment with risankizumab vs. no treatment for Period B will be 1:1. Randomization and re-randomization will not be stratified due to the small number of subjects.

The blinded efficacy assessor must be independent from all other study activities. 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.

5.9 Protocol Deviations

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

5.10 EU CTR Publication Policy

AbbVie as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and sponsor personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final clinical study report of the multicenter study except as agreed with the sponsor.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.

Investigators are NOT employed by the organization sponsoring the study. There is an agreement between investigators and the sponsor (or its agents) that restricts the investigator's rights to discuss or publish study results after the study is completed.

AbbVie requests that any investigator or institution that plans on presenting/publishing results, provide written notification of their request 60 days prior to their presentation/publication. AbbVie requests that no presentation/publication will be instituted until 12 months after a study is completed or after the first presentation/publication, whichever occurs first. A delay may be proposed for a presentation/publication if AbbVie needs to secure patent or proprietary protection.

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 damage or not working properly, or packaging issues.

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

Medical Complaints/Adverse Events and Serious Adverse Events

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

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

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

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

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

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

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

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

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

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

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements, including reporting to Eudravigilance database in accordance with EU Clinical Trial Regulation 536/2014.

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

Areas of Safety Interest/Safety Topics of Interest

Subjects will be screened and monitored throughout the study for Areas of Safety interest (ASI)/Safety Topics of Interest. Screening procedures are outlined in the Activity Schedule (Appendix D). In consideration of the ASI, the following supplemental eCRF(s) must be completed if AEs in any of the following areas are reported during the study (Table 2).

Table 2. Supplemental Adverse Events eCRFs

Adverse Event	Supplemental Report
In the case of any of the following AEs, the appropriate supplemental eCRFs should be completed: • **Discontinuation or interruption of study drug due to any hepatic-related AE** • **Hepatic-related SAE** • **A subject experiencing an ALT/AST > 8 × ULN** • **A subject experiencing an ALT/AST > 3 × ULN with a total bilirubin > 2 × ULN**	• Hepatic AE eCRF
Suspected anaphylactic/systemic hypersensitivity reactions	• Hypersensitivity Reaction Signs and Symptoms eCRF
TB Subjects with events of latent TB or suspected active TB after initiation of study drug should have a TB Supplemental Form completed.	• TB Supplemental eCRF
Death	• Death eCRF

AE = adverse event; ALT = alanine aminotransferase; AST = alanine aminotransaminase; eCRF = electronic case report form; SAE = serious adverse event; TB = tuberculosis; ULN = upper limit of normal

Adverse Event Severity and Relationship to Study Drug

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

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

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

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

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

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected. The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Independent Data Monitoring Committee

An external DMC will review safety data throughout the course of the study.

A separate DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC members, frequency and triggers of data reviews, and relevant safety data to be assessed. Unblinded ASI events will be presented to the DMC for review on a periodic basis.

6.3 Anaphylaxis Adjudication Committee

While no concerns with anaphylaxis/systemic hypersensitivity have been identified with the use of risankizumab, the sponsor has established an independent, blinded, expert committee to adjudicate events of anaphylaxis based on pre-specified definitions. This independent external AAC will adjudicate suspected anaphylactic reactions and will remain blinded to treatment allocation. The event terms to be adjudicated and the adjudication process are detailed in the AAC Charter. A supplemental Hypersensitivity Reactions Signs and Symptoms eCRF will be used to collect information pertinent to the events. In addition, the site may be contacted for additional source documentation.

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

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

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

7.2 Definition for Analysis Populations

The Intent to Treat (ITT) Population in each study part includes all enrolled subjects from Parts 1, 3, and 4, and all randomized subjects from Part 2. The ITT Set will be used for all efficacy and baseline analyses. For analyses by study period in Part 2, only subjects enrolled into the respective study period will be included for that period.

The Safety Analysis Population in each study part consists of all subjects who received at least 1 dose of study drug and will be used for all safety analyses.

7.3 Handling Potential Intercurrent Events for the Primary and Secondary Endpoints

The efficacy endpoints (defined in Section 3.2, Section 3.3, Section 3.4, and Section 3.5) will be analyzed on the ITT population to address the following potential intercurrent events:

1. Binary Endpoints
    - For subjects with the use of rescue medication, values after the start of rescue medication will be excluded from analysis and subjects will be considered non-responders at all time points after the start of rescue medication.
    - Data collected will be used regardless of premature discontinuation of study drug.
2. Continuous endpoints
    - Values after the use of rescue medication will be excluded.
    - Data collected will be used regardless of premature discontinuation of study drug.

7.4 Statistical Analyses for Efficacy

Descriptive statistics will include counts and proportions for categorical data, and median, mean, standard deviation, first and third quartiles, and minimum/maximum for continuous data. In addition, two-sided 95% confidence intervals (CI) will be reported. For continuous endpoints, CIs for means and differences between means, respectively, will be based on the normal distribution. For dichotomous endpoints, exact CIs will be provided based on the Clopper-Pearson method for proportions and by the Miettinen-Nurminen method for differences in proportions.[12]

No statistical testing will be performed in this study.

The efficacy analyses in the ITT population for the different study parts will be performed separately, as described in Section 7.6.

Primary Efficacy Analysis

The primary efficacy analyses will be conducted by providing descriptive statistics and 95% CI as described above.

Secondary Efficacy Analysis

Secondary efficacy analyses will be conducted by providing descriptive statistics and 95% CI as described above.

Other Efficacy Analyses

Other efficacy analyses will be conducted providing descriptive statistics and 95% CI as described above.

Subgroup Analysis for Efficacy

Details regarding subgroup analyses will be specified in the SAP.

7.5 Statistical Analyses for Safety

The safety analyses will be carried out using the Safety Analysis Population and will be based on treatments the subjects actually received. Safety will be assessed by AEs, physical examination, laboratory assessments, and vital signs. The safety analyses in the safety population for the different study parts will be performed separately as described in Section 7.6. Analysis details will be specified in the SAP.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as those that began or worsened in severity after the first dose of study drug and within 140 days/20 weeks after the last dose of study drug. The number and percentage of subjects experiencing TEAEs will be tabulated using the MedDRA system organ class and preferred term, by severity, and by relationship to the study drug as assessed by the investigator. Summaries (including percentages and events per 100 patient-years) of SAEs, deaths, AEs leading to discontinuation and ASI will be provided as well. Pre-treatment AEs will be summarized separately.

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

7.6 Interim Analysis

No statistical test will be performed, therefore no formal interim analysis that would require type 1 error control will be done. Analyses will be performed at the following timepoints:

Part 1 data up to Week 16 will be cleaned and analyzed after all subjects have reached Week 16 or have prematurely discontinued the study. Week 16 data will inform the dose(s) and the initiation for Part 2 and Part 3. A final analysis of Part 1 will be performed when all subjects have completed Part 2.

Part 2 data, Part 1 data, and all available Part 3 or Part 4 data will be analyzed separately when all subjects have completed Part 2 and will be submitted for regulatory purposes.

Part 3 data up to Week 16 have been cleaned and analyzed after all subjects have reached Week 16 or have prematurely discontinued the study. Week 16 data informed the dose(s) and the initiation for Part 4. A final analysis of Parts 3 and 4 will be performed together when all subjects have completed Part 4 or have prematurely discontinued from the study.

An external DMC composed of persons independent of AbbVie and with relevant expertise in their field will review unblinded safety data from the ongoing study. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

A separate DMC charter was prepared outside of the protocol and describes the roles and responsibilities of the DMC members, frequency of data reviews and relevant safety data to be assessed.

7.7 Multiplicity Adjustment and Overall Type I Error Control

Not applicable for this study.

7.8 Sample Size Determination

The sample sizes for the 4 study parts are per the risankizumab Ps pediatric investigational plan (PIP), in which it has also been agreed the study does not need to be powered to demonstrate superiority. The current study design meets the PIP commitment of at least 120 subjects evaluable for the primary endpoint of which at least 40 subjects are age 6 to less than 12 years and at least 80 subjects are age 12 to less than 18 years.[13]

All enrolled (for Part 2, all randomized) subjects will be considered evaluable for the primary endpoint. Subjects discontinued from the study prior to Week 16 will be included in the analysis as non-responders.

Part 1 (age 12 to less than 18 years with severe Ps) and Part 3 (age 6 to less than 12 years with severe Ps) are being conducted primarily for PK purposes and will each enroll 12 subjects. Enrollment of 12 subjects, a sample size typical of Phase 1 PK and safety/tolerability studies, will be sufficient to evaluate and confirm if the dosing is able to provide exposures in pediatric subjects consistent with exposures at the therapeutic dose in adult subjects, and to provide sentinel efficacy and safety data before exposing additional subjects with moderate to severe disease.

Assuming observed response rates for each of the co-primary endpoints of 66.7% (8 of 12), 75% (9 of 12) or 83.3% (10 of 12), the 95% exact CI will have a width of 34.9 to 90.1, 42.8 to 94.5, or 51.6 to 97.9, respectively.

Part 2 will enroll 80 subjects ages 12 to less than 18 years in a 2:1 ratio (i.e., 53 subjects will be randomized to risankizumab, 27 subjects to ustekinumab). The assumptions for response rates are based on the results for the 2 ustekinumab-controlled risankizumab studies in adult subjects with moderate to severe plaque Ps and apply to both co-primary endpoints, PASI 75 and sPGA clear or almost clear (0 or 1). Assuming an observed response rate of 59% (16 of 27) or 70% (19 of 27) for the ustekinumab group and a response rate of 79% (42 of 53) for the risankizumab group, the 95% exact CI for the difference between treatment groups will have a width of –2.7 to 42.4 or –13.9 to 31.9, respectively.

Part 4 will enroll 28 subjects (age 6 to less than 12 years). (Japan only: Approximately 2 adolescents aged 12 to <18 years will be included.) As the design of Parts 3 and 4 only differs by the intensity of the PK sampling, the 40 subjects (aged 6 to <12 years) enrolled into Parts 3 and 4 can be analyzed together if it is confirmed in Part 3 that the same dosing regimen is used for both Parts 3 and 4. Assuming observed response rates for each of the co-primary endpoints of 65% (26 of 40), 75% (30 of 40) or 85% (34 of 40), the 95% exact CI will have a width of 48.3 to 79.4, 58.8 to 87.3, or 70.2 to 94.3, respectively. Results from the approximately 2 Japanese adolescents (ages 12 to < 18 years) will be assessed separately, as applicable.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

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

8.2 Ethical Conduct of the Study

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

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab) and shipping investigational product and/or supplies to ensure continuity of treatment where allowed. 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.

For the personal data that AbbVie Deutschland GmbH & Co acting as sponsor of the submitted study ("AbbVie") controls and maintains, AbbVie has developed a robust security program focused on due diligence in design, managed change, and information security governance. Information Security policies govern the Information Security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's Information Security policies taking into account the sensitivity of the data.

Before patient data is shared with AbbVie, the study doctor and staff will replace any information that could directly identify a patient (such as name, address, and contact information) with a generic code which AbbVie cannot link to that patient's identity to protect the confidentiality of the data.

AbbVie has a data protection impact assessment (DPIA) program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains and these processing activities respect privacy of clinical trial subjects. AbbVie also maintains robust security incident response policies and procedures, including requirements for the containment of any data related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

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 follows the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s) including EU Clinical Trial Regulation 536/2014. During the COVID-19 pandemic, remote data review and verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

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

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data

will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements, including EU Clinical Trial Regulation 536/2014.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later.

12 REFERENCES

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AAC	Anaphylaxis Adjudication Committee
Ab	Antibody
ADA	antidrug antibody
AE	adverse event
Ag	antigen
ASI	areas of safety interest
BP	blood pressure
BSA	Body surface area
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
COVID	Coronavirus disease of 2019
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
DMC	Data monitoring committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
FDLQI	Family Dermatology Life Quality Index
GCP	Good clinical practice
HB	hepatitis B
HBc	Hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematopoietic stem cell transplantation
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIV	Human immunodeficiency virus
HIV Ab	HIV antibody
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC/IRB	Independent Ethics Committee/Institutional Review Board

IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGRA	interferon gamma release assay
IL	interleukin
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
nAb	neutralizing antibody
NRS	Numerical Rating Scale
OLE	open-label extension
PASI	Psoriasis Area Severity Index
PCR	polymerase chain reaction
PD visit	Premature Discontinuation visit
PE	physical examination
PFS	pre-filled syringe
PIP	pediatric investigational plan
PK	Pharmacokinetic(s)
PPD	purified protein derivative (tuberculin)
PRO	patient-reported outcome
Ps	psoriasis
PT	preferred term
q12w	every 12 weeks
QOL	quality of life
RBC	red blood cell
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

SC	subcutaneous
SOC	system organ class
sPGA	Static Physician's Global Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TBM	T cells, B cells, and monocytes
TEAE	Treatment emergent adverse event
WBC	white blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M19-977: OptIMMize-1: A Randomized, Active-controlled, Efficacy Assessor-blinded Study to Evaluate Pharmacokinetics, Safety, and Efficacy of Risankizumab in Patients From 6 to Less Than 18 Years of Age With Moderate to Severe Plaque Psoriasis.

Protocol Date: 16 October 2023

Clinical research studies sponsored by AbbVie are subject to the ICH 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 IRB/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 IB/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]	Clinical Program Development
		Clinical Development, Immunology
		Clinical Development, Immunology
		Data and Statistical Sciences
		Data and Statistical Sciences
		Clinical Pharmacology

APPENDIX D. ACTIVITY SCHEDULE

The following tables show the required activities for the indicated study parts. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed within the Operations Manual.

Study Parts 1, 3 and 4

Activity	Screening	Baseline	Week 4	Week 8	Week 12	Week 16	Week 28	Week 40	Week 52 Premature Discontinuation	Week 60 (140-Day) Follow Up Call
	Day –35 to Day –1	Day 1	Day 28	Day 56	Day 84	Day 112	Day 196	Day 280	Day 364	Day 420
Visit window			± 3 days				± 7 days			
INTERVIEWS & QUESTIONNAIRES										
Informed consent	✓									
Eligibility criteria	✓	✓								
Medical/surgical history	✓	✓								
Alcohol and nicotine use	✓									
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SARS-CoV-2 Infection Risk Assessment Tool	✓									
Latent TB risk assessment form	✓									
LOCAL LABS & EXAMS										
12-lead ECG	✓									
Height and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination	✓	✓	✓	✓	✓	✓	✓	✓	✓	
BSA	✓	✓								
PASI, sPGA	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Urine pregnancy test (prior to dose administration for females of childbearing potential only)		✓	✓			✓	✓	✓	✓	

Activity	Screening	Baseline	Week 4	Week 8	Week 12	Week 16	Week 28	Week 40	Week 52 Premature Discontinuation	Week 60 (140-Day) Follow Up Call
	Day –35 to Day –1	Day 1	Day 28	Day 56	Day 84	Day 112	Day 196	Day 280	Day 364	Day 420
Visit window			± 3 days				± 7 days			
CENTRAL LABS										
HBV/HCV/HIV screening (HBV DNA PCR testing q12w per local requirements)	✓									
Serum pregnancy test	✓									
QuantiFERON-TB Gold test (and/or local PPD skin test)	✓								✓	
Clinical chemistry, hematology, urinalysis	✓	✓	✓	✓		✓	✓	✓	✓	
Blood samples for risankizumab PK (Parts 1 and 3)		✓	✓	✓	✓	✓			✓	
Blood samples for risankizumab PK (Part 4)		✓	✓			✓			✓	
Blood sample for risankizumab ADA/nAb assays		✓	✓			✓			✓	
TREATMENT										
Enrollment/drug assignment		✓								
Administer study drug		✓	✓			✓	✓	✓		
Hypersensitivity monitoring		✓	✓			✓	✓	✓		

Part 2, Initial Treatment Period A

Activity	Screening	Baseline	Week 4	Week 12	Week 16	Premature Discontinuation	Follow Up Call
	Day –35 to Day –1	Day 1	Day 28	Day 84	Day 112		
Visit window			± 3 days			± 7 days	
INTERVIEWS & QUESTIONNAIRES							
Informed consent	✓						
Eligibility criteria	✓	✓					

Activity	Screening	Baseline	Week 4	Week 12	Week 16	Premature Discontinuation	Follow Up Call
	Day −35 to Day −1	Day 1	Day 28	Day 84	Day 112		
Visit window			± 3 days			± 7 days	
Medical/surgical history	✓	✓					
Alcohol and nicotine use	✓						
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓
Patient Reported Outcomes: CDLQI, FDLQI, and Itch NRS		✓			✓	✓	
SARS-CoV-2 Infection Risk Assessment Tool	✓						
Latent TB risk assessment form	✓						
LOCAL LABS & EXAMS							
12-lead ECG	✓						
Height and weight	✓	✓	✓	✓	✓	✓	
Vital signs	✓	✓	✓	✓	✓	✓	
Physical examination	✓	✓	✓	✓	✓	✓	
BSA	✓	✓					
PASI, sPGA	✓	✓	✓	✓	✓	✓	
Urine pregnancy test (prior to dose administration for females of childbearing potential only)		✓	✓		✓	✓	
CENTRAL LABS							
HBV/HCV/HIV screening (HBV DNA PCR testing q12w per local requirements)	✓						
Serum pregnancy test	✓						
QuantiFERON-TB Gold test (and/or local PPD skin test)	✓						
Clinical chemistry, hematology, urinalysis	✓	✓	✓		✓	✓	
T cell, B cell, and monocytes (TBM)		✓			✓		
Immunoglobulin G, M, and A (IgG, IgM, and IgA)		✓			✓		
Blood samples for risankizumab PK		✓	✓		✓	✓	
Blood sample for risankizumab ADA/nAb assays		✓	✓		✓	✓	
TREATMENT							
Randomization		✓					
Administer study drug		✓	✓		✓		

Activity	Screening	Baseline	Week 4	Week 12	Week 16	Premature Discontinuation	Follow Up Call
Visit window	Day –35 to Day –1	Day 1	Day 28 ± 3 days	Day 84 ± 3 days	Day 112 ± 3 days	± 7 days	± 7 days
Hypersensitivity monitoring		✓	✓		✓		
Re-randomization for Treatment or Withdrawal Period B (risankizumab responders only)					✓		

Part 2, Treatment or Withdrawal Period B

Activity	Week 22	Week 28	Week 34	Week 40	Week 46	Week 52/ Premature Discontinuation (Period B)	Follow up call
	Day 154	Day 196	Day 238	Day 280	Day 322	Day 364	Day 420
Visit window	± 7 days						
INTERVIEWS & QUESTIONNAIRES							
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓
Patient Reported Outcomes: CDLQI, FDLQI, and Itch NRS						✓	
LOCAL LABS & EXAMS							
Height and weight	✓	✓	✓	✓	✓	✓	
Vital signs	✓	✓	✓	✓	✓	✓	
Physical examination	✓	✓	✓	✓	✓	✓	
BSA							
PASI, sPGA	✓	✓	✓	✓	✓	✓	
Urine pregnancy test (prior to dose administration for females of childbearing potential only)		✓		✓		✓	
CENTRAL LABS							
QuantiFERON-TB Gold test (and/or local PPD skin test)						✓	
Clinical chemistry, hematology, urinalysis		✓		✓		✓	
Blood samples for risankizumab PK		✓				✓	
Blood sample for risankizumab ADA/nAb assays		✓				✓	
TREATMENT							
Administer study drug		✓		✓			
Hypersensitivity monitoring		✓		✓			

Part 2, Retreatment Period C

Activity	Retreatment Baseline	Week 4	Week 8	Week 12	Week 16/ Premature Discontinuation (Period C)	Week 24 (140-Day) Follow Up Call
	Day 1	Day 28	Day 56	Day 84	Day 112	Day 168
Visit window		± 3 days				± 7 days
INTERVIEWS & QUESTIONNAIRES						
Adverse event assessment	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓
Patient Reported Outcomes: CDLQI, FDLQI, and Itch NRS	✓				✓	
LOCAL LABS & EXAMS						
Height and weight	✓	✓	✓	✓	✓	
Vital signs	✓	✓	✓	✓	✓	
Physical examination	✓	✓	✓	✓	✓	
PASI, sPGA	✓	✓	✓	✓	✓	
Urine pregnancy test (prior to dose administration for females of childbearing potential only)	✓	✓			✓	
CENTRAL LABS						
QuantiFERON-TB Gold test (and/or local PPD skin test)					✓	
Clinical chemistry, hematology, urinalysis	✓	✓	✓		✓	
T cell, B cell, and monocytes (TBM)	✓				✓	
Immunoglobulin G, M, and A (IgG, IgM, and IgA)	✓				✓	
Blood samples for risankizumab PK	✓	✓			✓	
Blood sample for risankizumab ADA/nAb assays	✓	✓			✓	
TREATMENT						
Administer study drug	✓	✓				
Hypersensitivity monitoring	✓	✓				

APPENDIX E. SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	18 March 2020
Version 2.0	06 January 2021
Version 3.0	27 May 2021
Administrative Change 1	24 June 2021
Version 3.1 (Japan Only)	25 June 2021
Version 4.0	02 February 2023
Administrative Change 2	23 February 2023

The purpose of this version is to correct minor typographical errors and to update the following sections:

Protocol

- Updated the Sponsor Emergency Medical Contact information on protocol title page.

  Rationale: *To reflect personnel changes for this study*.

- The EU CT number was updated on the title page and footer throughout the protocol and operations manual.

  Rationale: *To provide the EU CT number*.

- Added "For European Union countries: the sponsor is AbbVie Deutschland GmbH & Co. KG" to title page.

  Rationale: *To clarify the MAH in the European Union.*

- Added Section 5.10 EU CTR Publication Policy.

  Rationale: *To provide a binding sponsor statement that the clinical trial will be conducted in compliance with EU Clinical Trial Regulation 536/2014* .

- In Section 6.1 added that SUSAR reporting for the IMP will be done to the Eudravigilance database in accordance with EU Clinical Trial Regulation 536/2014 as part of the global and local requirements that AbbVie is applying to.

  Rationale: *To describe the procedure for reporting of suspected unexpected adverse reactions (SUSAR) by the sponsor to the Eudravigilance database as per EU Clinical Trial Regulation 536/2014.*

- Updated to include new program lead, therapeutic area MD, and clinical pharmacology contacts Appendix C (List of Protocol Signatories).

  Rationale: *To reflect personnel changes for this study.*

Operations Manual

- Updated the Sponsor Emergency Medical Contact in Section 1 and Section 4.3.

  Rationale: *To reflect personnel changes for this study.*

- Removed the address and phone number for the Safety team from Section 1.

  Rationale: *To remove unnecessary information from contacts.*

- In Section 3.14, under Table 1 - Clinical Laboratory Testing changed "gamma glutamyl transferase/γ-genotype" to "GGT."

  Rationale*: To address a typographical error*.

- In Section 4.3 and Section 5.1, added that SUSAR reporting for the IMP will be done to the Eudravigilance database in accordance with EU Clinical Trial Regulation 536/2014.

  Rationale: *To describe the procedure for reporting of suspected unexpected adverse reactions (SUSAR) by the sponsor to the Eudravigilance database as per EU Clinical Trial Regulation 536/2014.*