Statistical Analysis Plan for Study 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

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Version 4.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for risankizumab Study 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."

Study M19-977 examines the efficacy and safety of risankizumab in subjects from 6 to less than 18 years of age with moderate to severe plaque psoriasis.

The study consists of four parts with distinct subject populations (see Section 2.0). The analyses described here will be conducted for each of the parts separately as specified in Section 12.0.

The analyses of biomarker research endpoints, pharmacokinetic and immunogenicity endpoints will not be covered in this SAP.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analyses.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

This SAP includes no changes to analyses described in the protocol with following exception:

- For the other efficacy endpoints "Achievement of sPGA clear or almost clear (0 or 1)" at Week 12 during the treatment or withdrawal period of Part 2 and at all other visits collected "(US only: and ≥ 2 grade improvement from baseline)" was added.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

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 (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 4.0).

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 (PASI75) 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 (PASI75) 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 3.2 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 (PASI90) 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 (PASI100) 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 (PASI90) 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 (PASI100) 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.

Of note: the reference to the US in "sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline)" does not refer to the individual subjects' location of residence but implies that this is an additional endpoint relevant for US regulatory purposes, while the endpoint relevant ex-US does not require a minimum improvement from baseline.

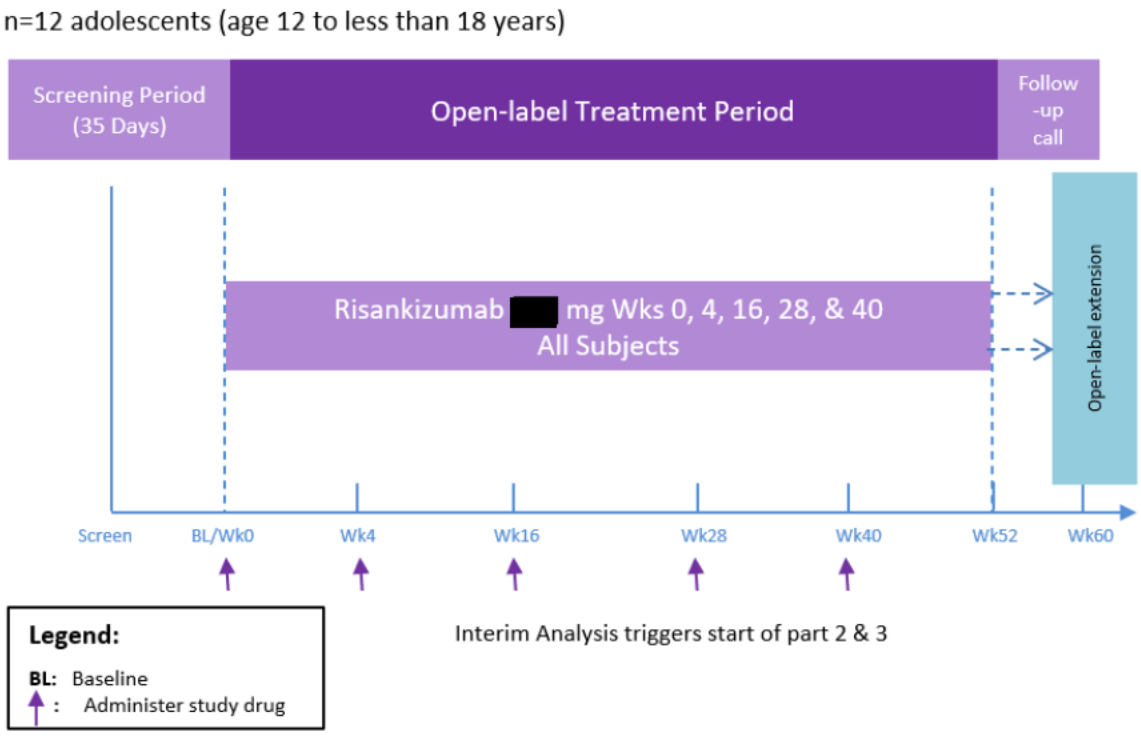
2.2 Study Design Overview

The study consists of 4 parts, each with distinct patient populations.

Part 1

Part 1 will be a sentinel, open-label cohort of 12 adolescents (age 12 to less than 18 years) with severe disease who 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 will inform the dosing regimen for Part 2 in adolescents and trigger 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



Part 2

Part 2 will be a randomized, evaluator-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. 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 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.

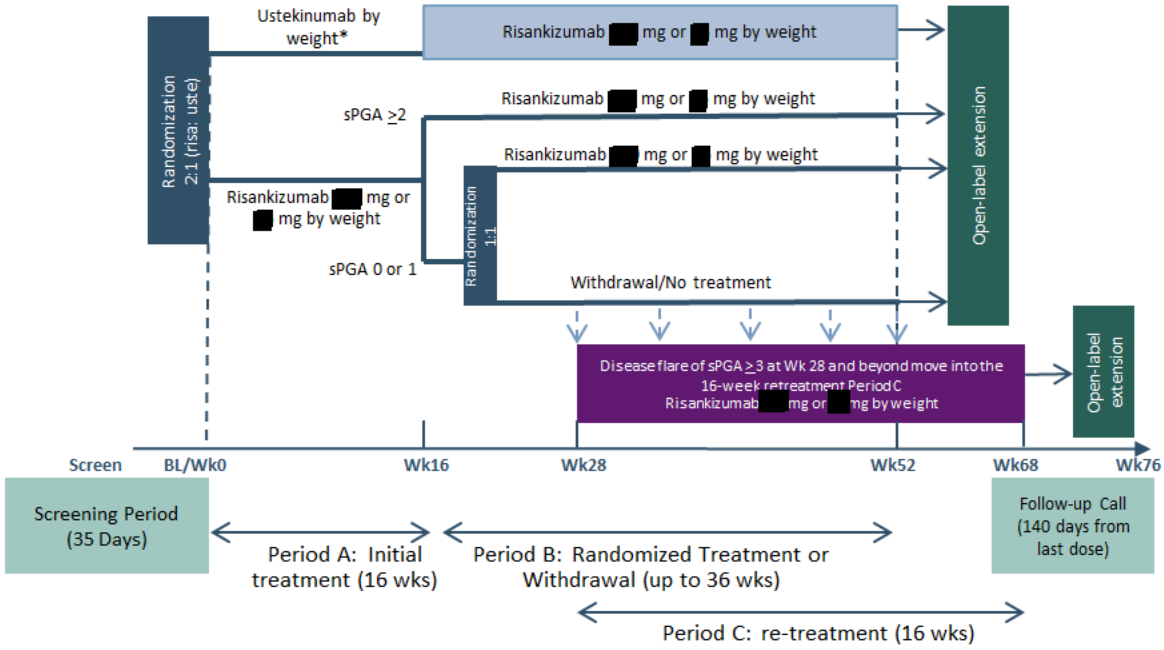
In Period A, subjects will be randomized (2:1) to receive risankizumab SC based on weight (subjects who weigh ≥ 40 kg will receive [redacted] mg risankizumab, while subjects who weigh < 40 kg will receive [redacted] mg risankizumab) or ustekinumab SC based on weight (0.75 mg/kg for subjects < 60 kg; 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. 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 (sPGA ≥ 3 on or after Week 28) 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.

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- Wks 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

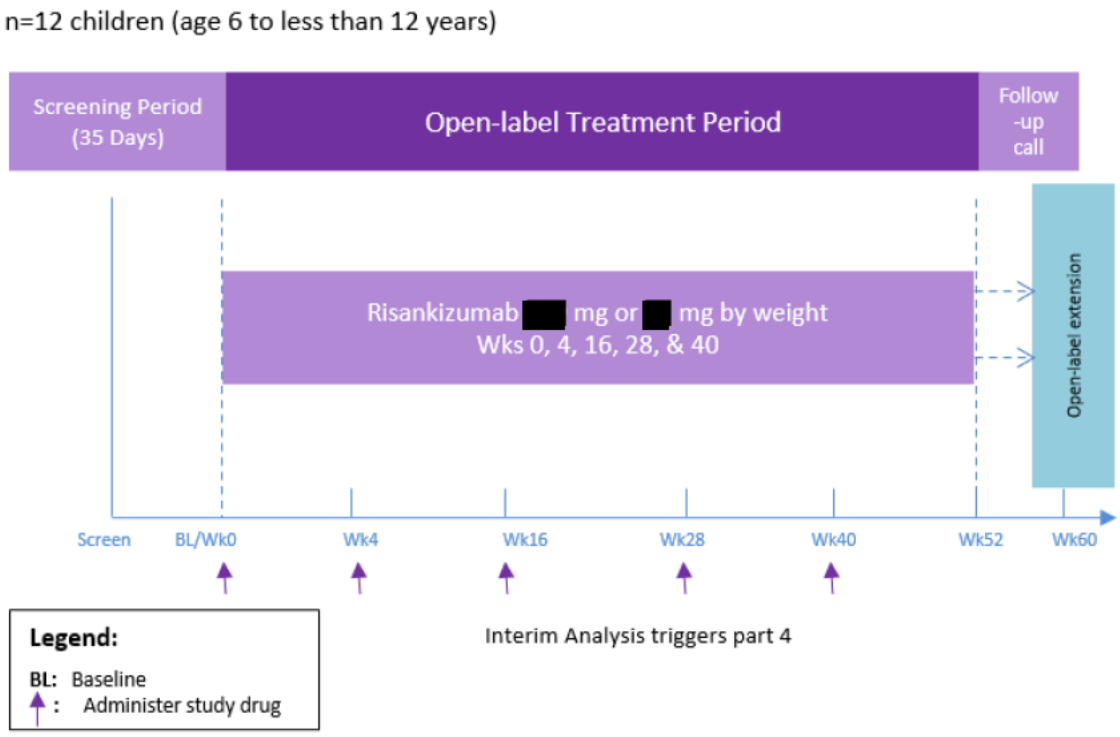
Subjects who complete either Week 52 without disease flare or 16-week re-treatment from Period C are eligible to enroll into Study M19-973, the open-label extension study.

Part 3

Part 3 will be a sentinel (open-label) cohort of 12 children (age 6 to less than 12 years) with severe disease who 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 will inform the dosing regimen for the start of Part 4. Enrollment will be 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

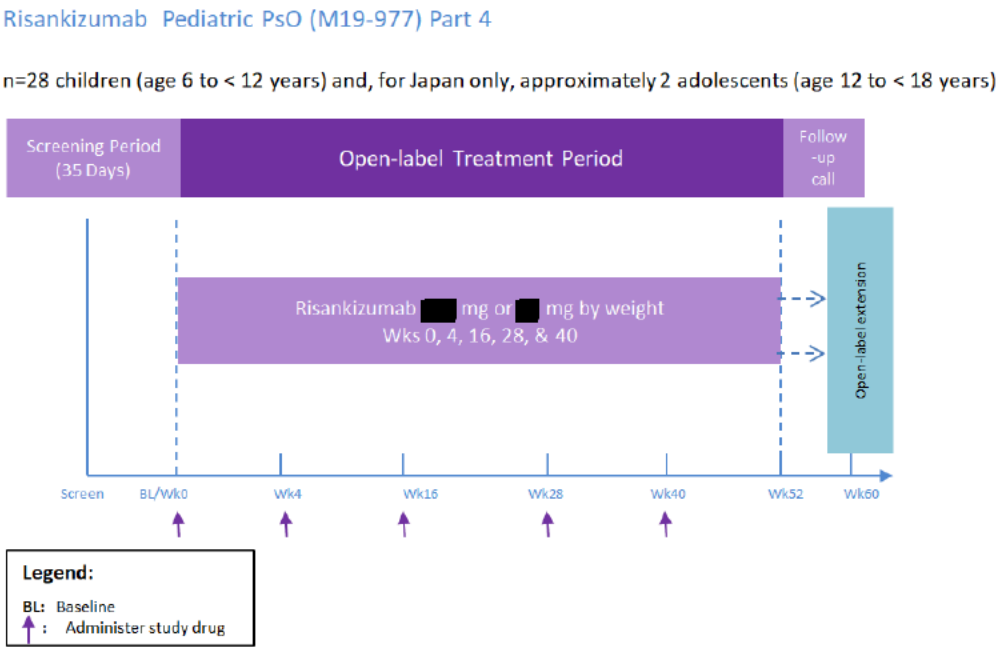


Part 4

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. The risankizumab dose in Part 4 will be 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



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.

2.3 Treatment Assignment and Blinding

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 (for 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.

2.4 Sample Size Determination

The sample sizes for the 4 study parts are per the risankizumab psoriasis 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.[1]

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. Thus, 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 will be fulfilled with the current study.

Part 1 (age 12 to less than 18 years with severe psoriasis) and **Part 3** (age 6 to less than 12 years with severe psoriasis) 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 age 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 psoriasis and apply to both co-primary endpoints, PASI75 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). As the design of Parts 3 and 4 only differs by the intensity of the PK sampling, the 40 subjects 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.

3.0 Endpoints

3.1 Primary Endpoint(s)

The co-primary endpoints of this study are:

- 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) (US only: and ≥ 2 grade improvement from baseline) at Week 16 of initial treatment.

3.2 Secondary Endpoint(s)

The ranked secondary endpoints of this study are:

- 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

The non-ranked secondary endpoints are:

- 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 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 Numeric 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 of Part 2
- Achievement of ≥ 4-point improvement from baseline in the Itch Numeric Rating Scale (in patients with Baseline score ≥ 4) at Week 16 of initial treatment in Part 2

3.3 Other Efficacy Endpoint(s)

The other efficacy endpoints of this study are:

- 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) (US only: and ≥ 2 grade improvement from baseline) 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) (US only: and ≥ 2 grade improvement from baseline) at all other visits collected

- Change in Itch Numeric Rating Scale (Itch NRS) at each study visit from Week 0
- Achievement of ≥ 4-point improvement from baseline in the Itch Numeric 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

3.4 Safety Endpoint(s)

The following endpoints will be included in the safety analyses:

- 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).

3.5 Additional Endpoint(s)

Not applicable.

4.0 Analysis Populations

The following population sets will be used for the analyses.

Part 1, Part 3, Part 4:

The **Intent to Treat (ITT) Population** in each study part includes all enrolled subjects. The ITT Population will be used for all efficacy and baseline analyses.

The **Safety Analysis Population** consists of all subjects who received at least 1 dose of study drug.

For Part 4, the two Japanese adolescents aged 12 to <18 years, if enrolled, will not be included in the Intent to Treat (ITT) and the Safety Analysis Population. Their results will be listed separately.

Part 2:

The **Intent to Treat (ITT) Population** includes all randomized subjects. The ITT Population will be used for all efficacy and baseline analyses. Subjects will be analyzed according to treatment as randomized.

The **Safety Analysis Population** in each study part consists of all subjects who received at least 1 dose of study drug. Subjects will be included in the analysis according to the study drug that they actually received. For Period A, a subject's actual treatment will be determined by the first dose of study drug. For subjects re-randomized in Period B, only subjects who received no drug are included in the withdrawal arm, subjects who received at least one dose of study drug are included in the treatment continuation arm.

For analyses by study period in Part 2, only subjects enrolled into the respective study period will be included for that period.

For displays by treatment group for Part 2, treatment groups will be based on randomization and re-randomization assignments.

5.0 Subject Disposition

Part 1, Part 3, Part 4:

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized:

- Subjects screened
- Subjects enrolled
- Subjects who took at least one dose of study drug

- Only for analyses conducted prior to the completion of the respective study part, see Section 12.0: Subjects who completed Week 16
- Only for analyses conducted prior to the completion of the respective study part, see Section 12.0: subjects ongoing at the time of analysis
- Subjects who completed the study
- Subjects who prematurely discontinued the study (all reasons and primary reason)
- Subjects who prematurely discontinued study drug (all reasons and primary reason)

Part 2:

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized overall and by treatment group:

- Subjects screened
- Subjects randomized
- Subjects who completed Period A
- Subjects enrolled (re-randomized) into Period B (note: subjects randomized to ustekinumab and subjects randomized to risankizumab who are non-responders at Week 16 in Period A are enrolled for OL risankizumab treatment, subjects randomized to risankizumab who are responders at Week 16 in Period A are re-randomized between withdrawal/no treatment and OL risankizumab treatment continuation)
- Subjects who completed Period B
- *Only for subjects re-randomized to treatment withdrawal:* Subjects completed 36 weeks in withdrawal Period B without disease flare
- *Only for subjects re-randomized to treatment withdrawal:* Subjects completed withdrawal Period B with disease flare
- Subjects enrolled into re-treatment Period C
- Subjects who completed re-treatment Period C

- Subjects who prematurely discontinued the study by period and overall (all reasons and primary reason)
- Subjects who prematurely discontinued study drug by period and overall (all reasons and primary reason)

6.0 Study Drug Duration and Compliance

Part 1, Part 3, Part 4:

For the ITT population, **duration of treatment** will be summarized using the number of subjects treated, mean, standard deviation, median, minimum and maximum. Duration of treatment is defined for each subject as last dose date minus first dose date + 84 days.

Treatment compliance will be summarized for the ITT population as follows:

There will be a summary of the number of subjects receiving study drug and dose at each study drug administration visit. This will be repeated on the cumulative number of doses.

When computing compliance at each study drug administration visit, the denominator will include all subjects who have not prematurely discontinued the study drug prior to the scheduled study drug injection.

Part 2:

For the ITT population, **duration of treatment** will be summarized by treatment group using the number of subjects treated, mean, standard deviation, median, minimum and maximum. Duration of treatment is defined for each subject as last dose date minus first dose date + 84 days. For subjects re-randomized to treatment withdrawal in Period B, treatment duration will be counted until last dose date in Period A + 84 days and then restarted at the first re-treatment dose after the treatment withdrawal, if applicable. **Duration of risankizumab treatment** is defined for each subject as last risankizumab dose date minus first risankizumab dose date + 84 days. For subjects re-randomized to treatment withdrawal in Period B, risankizumab treatment duration will be counted until

last risankizumab dose date in Period A + 84 days and then restarted at the first risankizumab re-treatment dose after the treatment withdrawal, if applicable.

Treatment compliance will be summarized for the ITT population by treatment group as follows:

There will be a summary of the number of subjects receiving study drug and dose at each study drug administration visit. This will be repeated on the cumulative number of doses.

When computing compliance at each study drug administration visit, the denominator will include all subjects in a specific study period who have not prematurely discontinued the study drug prior to the scheduled study drug injection.

In addition to the analyses by study part, analyses of duration of risankizumab treatment will be created that combine subjects enrolled into Part 1 and Part 2 (adolescents) and subjects enrolled into Part 3 and Part 4 (children), respectively.
The two Japanese adolescents aged 12 to < 18 years enrolled into Part 4 are not included in the Safety Analysis Population (see Section 4.0) and listed separately throughout. They are therefore not included in the above.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics and patient reported outcomes, medical history, and prior and concomitant medications will be summarized for the ITT population overall and by treatment group (for Part 2).

Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Continuous demographic variables include age (years), weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Categorical demographic variables include sex, ethnicity, race, age (12 to < 15, 15 to < 18 years for Part 1 and 2; 6 to < 9, 9 to < 12 years for Part 3 and 4), weight (< 40 kg or ≥ 40 kg), region (Europe, North America, or rest of world).

Disease characteristics include prior systemic biologic for psoriasis (0 vs. ≥ 1), PASI (Psoriasis Area and Severity Index), BSA (Body Surface Area), sPGA categories, history of psoriatic arthritis (yes, no), duration of plaque psoriasis (in years).

In addition to the analyses by study part, analyses of demographics will be created that combine subjects enrolled into Part 1 and Part 2 (adolescents) and subjects enrolled into Part 3 and Part 4 (children), respectively.

The two Japanese adolescents aged 12 to < 18 years enrolled into Part 4 are not included in the Safety Analysis Population (see Section 4.0) and listed separately throughout. They are therefore not included in the above.

Patient Reported Outcomes (PROs) analyzed at baseline include CDLQI (Children's Dermatology Life Quality Index), FDLQI (Family's Dermatology Life Quality Index) and Itch Numeric Rating Scale (Itch NRS). In addition to the analysis of Itch Numeric Rating Scale (Itch NRS) as a continuous variable, Itch NRS ≥ 4 will be analyzed as a categorical baseline variable.

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized overall and by treatment group. The system organ class (SOC) will be

presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name. A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken on or after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug plus 140 days. The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

In addition, a table will be generated that displays the number of subjects by visit who started rescue medication on or prior to the respective visit. Rescue medication for the purposes of this analysis will be considered any systemic (oral or parenteral) medication used specifically for the treatment of psoriasis.

8.0 Handling of Potential Intercurrent Events for the Primary and Secondary Endpoints

The efficacy endpoints (defined in Section 3.1, Section 3.2, and Section 3.3) 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.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted in the ITT Population separately for each study part, as described in Section 12.0. For analyses by study period in Part 2, only subjects enrolled into the respective study period will be included.

No statistical testing will be performed. All confidence intervals will be two-sided with 95% confidence probability.

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.[2]

The primary analysis for each study part will be performed at the time points described in Section 12.0. This will be the only and final analysis for the co-primary efficacy endpoints for each part.

"Baseline" refers to the last non-missing observation before the first administration of study drug or the date of enrollment (Part 1, 3, 4) or randomization (Part 2) if no study drug is given.

9.2 Handling of Missing Data

Missing data will be imputed using the following methods for the efficacy analyses:

- Non-Responder Imputation (NRI): the NRI analysis will categorize any subject who does not have evaluation during a specific visit window as a non-responder for that visit. NRI will be the primary approach in the analyses of categorical variables.
- Last Observation Carried Forward (LOCF): the LOCF analysis will impute a missing value with the last value observed previously. Baseline observations are not carried forward. LOCF will be the primary approach in the analyses of continuous variables.
- As Observed (AO): The AO analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the AO analysis for that visit. AO will include all values collected in the study. AO will exclude all values collected in the study after the first dose of rescue medication (see also Section 8.0). AO will be used as sensitivity analysis in the analyses of categorical and continuous variables.

9.3 Primary Efficacy Endpoint(s) and Analyses

9.3.1 Primary Efficacy Endpoint(s)

The co-primary endpoints to assess the efficacy of risankizumab for the treatment of moderate to severe plaque psoriasis are:

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

9.3.2 Main Analysis Primary Efficacy Endpoint(s)

The attributes of the estimands corresponding to the co-primary efficacy endpoints are summarized in Table 1.

Table 1. Summary of the Estimand Attributes of the Co-Primary Efficacy Endpoints

Estimand Label	Attributes of the Estimands				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
PASI75 at Week 16 of initial treatment	Risankizumab and Ustekinumab*	PASI75 at Week 16 of initial treatment	ITT	• Subjects with the use of rescue medication on or prior to Week 16 will be considered as non-responders • For subjects who prematurely discontinue study drug on or prior to Week 16, data will be used regardless	Part 1, 3 and 4: Percentage of subjects achieving PASI75 at Week 16 in the Risankizumab group Part 2: Difference in the percentage of subjects achieving PASI75 at Week 16 in the Risankizumab group in comparison with the Ustekinumab group

Estimand Label	Attributes of the Estimands				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 16 of initial treatment		sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 16 of initial treatment			Part 1, 3 and 4: Percentage of subjects achieving sPGA 0/1 (US only: and ≥ 2 grade improvement from baseline) at Week 16 in the Risankizumab group Part 2: Difference in the percentage of subjects achieving sPGA 0/1 (US only: and ≥ 2 grade improvement from baseline) at Week 16 in the Risankizumab group in comparison with the Ustekinumab group

* Ustekinumab is only applicable for Part 2.

For analysis of the co-primary endpoints, exact CIs will be provided based on the Clopper-Pearson method for proportions (Part 1, 3 and 4) and by the Miettinen-Nurminen method for differences in proportions[2] (Part 2).

NRI will be used as the primary approach for the analyses of the co-primary endpoints.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint(s)

For dealing with missing data, AO will be used as sensitivity analysis for the analyses of the co-primary endpoints.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Key Secondary Efficacy Endpoints

The key (ranked) secondary efficacy endpoints are specified in Section 3.2.

9.4.2 Main Analyses of Key Secondary Efficacy Analyses

The attributes of the estimands corresponding to the key secondary efficacy endpoints are summarized in Table 2.

Table 2. Summary of the Estimand Attributes of the Ranked Secondary Efficacy Endpoints

Estimand Label	Attributes of the Estimands				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
PASI90 at Week 16 of initial treatment	Risankizumab and Ustekinumab*	PASI90 at Week 16 of initial treatment	ITT	• Subjects with the use of rescue medication on or prior to Week 16 will be considered as non-responders • For subjects who prematurely discontinue study drug on or prior to Week 16, data will be used regardless	Part 1, 3 and 4: Percentage of subjects achieving PASI90 at Week 16 in the Risankizumab group Part 2: Difference in the percentage of subjects achieving PASI90 at Week 16 in the Risankizumab group in comparison with the Ustekinumab group
PASI100 at Week 16 of initial treatment		PASI100 at Week 16 of initial treatment			Part 1, 3 and 4: Percentage of subjects achieving PASI100 at Week 16 in the Risankizumab group Part 2: Difference in the percentage of subjects achieving PASI100 at Week 16 in the Risankizumab group in comparison with the Ustekinumab group

Table 2. Summary of the Estimand Attributes of the Ranked Secondary Efficacy Endpoints (Continued)

Estimand Label	Attributes of the Estimands				
	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 0 of the re-treatment phase in Part 2	Risankizumab	sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 0 of the re-treatment phase in Part 2	ITT	• Subjects with the use of rescue medication on or prior to Week 0 of the re-treatment period will be considered as non-responders • For subjects who prematurely discontinue study drug on or prior to Week 0 of the re-treatment period, data will be used regardless	Percentage of subjects achieving sPGA 0/1 (US only: and ≥ 2 grade improvement from baseline) at Week 0 of the re-treatment period in the Risankizumab group
sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 16 of the re-treatment phase in Part 2		sPGA clear or almost clear (0 or 1) (US only: and ≥ 2 grade improvement from baseline) at Week 16 of the re-treatment phase in Part 2		• Subjects with the use of rescue medication on or prior to Week 16 of the re-treatment period will be considered as non-responders • For subjects who prematurely discontinue study drug on or prior to Week 16 of the re-treatment period, data will be used regardless	Percentage of subjects achieving sPGA 0/1 (US only: and ≥ 2 grade improvement from baseline) at Week 16 of the re-treatment period in the Risankizumab group

* Ustekinumab is only applicable for Part 2

For analysis of the ranked secondary endpoints, exact CIs will be provided based on the Clopper-Pearson method for proportions (Part 1, 3 and 4) and by the Miettinen-Nurminen method for differences in proportions[2] (Part 2).

9.4.3 Sensitivity and Supplementary Analyses for Key Secondary Efficacy Endpoint(s)

For dealing with missing data, AO will be used as sensitivity analysis for secondary endpoints.

9.4.4 Supportive Secondary Efficacy Endpoints and Analyses

The non-ranked secondary efficacy endpoints are specified in Section 3.2.

Analyses of non-ranked secondary efficacy endpoints will be conducted by providing descriptive statistics and 95% CI as described above.

9.5 Additional Efficacy Analyses

The other efficacy endpoints are specified in Section 3.3.

Analyses of other efficacy endpoints will be conducted by providing descriptive statistics and 95% CI as described above.

9.6 Efficacy Subgroup Analyses

Due to the small sample sizes and the uncontrolled design of Part 1, Part 3, and Part 4, no efficacy subgroup analyses will be performed.

For Part 2, the co-primary endpoints will be analyzed for the following subgroups, using NRI for imputation of missing data:

- age group (12 to < 15, 15 to < 18 years)
- sex (male, female),
- race (white, non-white)
- weight group (< 40 kg, ≥ 40 kg),

- region (Europe, North America, rest of world),
- baseline PASI (< 20, ≥ 20)
- baseline sPGA (≤ 3, 4)
- baseline BSA (< 20, ≥ 20)
- prior biologic Psoriasis therapy (yes, no)
- prior systemic Psoriasis therapy (yes, no)
- anti-drug antibodies (ADA) (positive, negative)
- neutralizing antibodies (nAb) (positive, negative)

Analyses within subgroups will be conducted providing descriptive statistics and 95% CI as described above.

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Safety Analysis Population. Safety summaries will be presented overall and by treatment group (Part 2). For the safety analysis in Part 2, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized. Safety analyses will include adverse events, laboratory, and vital sign measurements. For Part 2, safety analyses will be presented by study period as well as overall, unless otherwise specified.

For Part 2 Period A, a subject's actual treatment will be determined by the first dose of study drug. For subjects re-randomized in Part 2 Period B, only subjects who received no drug are included in the withdrawal arm, subjects who received at least one dose of study drug are included in the treatment continuation arm.

Missing safety data will not be imputed.

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any event with an onset that is after the first dose of study drug and with an onset date within 20 weeks (140 days) after the last dose of study drug. Events where the onset date is the same as the study drug start date and no start times are available are assumed to be treatment-emergent. For subjects re-randomized to treatment withdrawal in Part 2 Period B, AEs are only considered treatment emergent until last dose date in Period A + 140 days and then from the first re-treatment dose after the treatment withdrawal onwards, if applicable.

For the analysis of TEAEs as exposure-adjusted AEs per 100 patient-years of risankizumab exposure, all TEAS prior to the first risankizumab dose will be excluded (i.e., the TEAEs observed in the ustekinumab group in Part 2 Period A).

Pre-treatment AEs will be summarized separately in a listing.

10.2.2 Adverse Event Overview

An overview of TEAEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study drug according to the investigator

- Any severe treatment-emergent AE
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to discontinuation of study drug
- Any serious infection
- Opportunistic infection excluding tuberculosis and herpes zoster
- Active tuberculosis
- Herpes Zoster
- Any malignant tumor
- Any malignant tumor excluding NMSC
- Any NMSC
- Any hepatic event
- Any serious hypersensitivity
- Any injection site reaction
- Any adjudicated Anaphylactic Reaction
- Any Suicidal Ideation Behavior (SIB)
- Any treatment-emergent AE leading to death
- All deaths
- Deaths occurring ≤ 140 days after last dose of study drug
- Deaths occurring > 140 days after last dose of study drug

An overview of TEAEs will also be presented as exposure-adjusted AEs per 100 patient-years of risankizumab exposure, where AEs per 100 patient-years of exposure are defined as the number of AEs divided by the total exposure in 100 patient-years. This analysis will not be broken down by period in Part 2.

Note that one event per preferred term per day per subject will be counted in the calculation of the number of AEs (i.e., a preferred term will not be counted twice on the same day for the same subject). See the calculation method below.

$$100 \times \frac{\text{Number of TEAEs}}{\text{Total Patient Years}}$$

where total patient years is defined as the sum of the risankizumab exposure (defined as date of last risankizumab dose – date of first risankizumab dose + 140 days (5 half-lives)) of all subjects normalized by 365.25, and rounded to one decimal place. For subjects re-randomized to treatment withdrawal in Period B, risankizumab exposure will be counted until last risankizumab dose date in Period A + 140 days and then restarted at the first risankizumab re-treatment dose after the treatment withdrawal, if applicable. For subjects initially randomized to ustekinumab, only TEAEs from the date of first risankizumab dose onwards will be included for this analysis which is exposure adjusted for risankizumab exposure.

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency.

10.2.4 Treatment-Emergent Adverse Events per Patient-Years of Risankizumab Exposure

In addition to the exposure-adjusted Overview of TEAS described in Section 10.2.2, exposure-adjusted AEs per 100 patient-years of risankizumab exposure will also be provided by SOC and PT, where AEs per 100 patient-years of exposure are defined as the number of TEAEs divided by the total risankizumab exposure in 100 patient-years.

Note that one event per preferred term per day per subject will be counted in the calculation of the number of AEs (i.e., a preferred term will not be counted twice on the same day for the same subject). See the calculation method below.

$$100 \times \frac{\text{Number of TEAEs}}{\text{Total Patient Years}}$$

where total patient years is defined as the sum of the risankizumab exposure (defined as date of last risankizumab dose – date of first risankizumab dose + 140 days (5 half-lives)) of all subjects normalized by 365.25, and rounded to one decimal place. For subjects re-randomized to treatment withdrawal in Period B, risankizumab exposure will be counted until last risankizumab dose date in Period A + 140 days and then restarted at the first risankizumab re-treatment dose after the treatment withdrawal, if applicable.

This analysis will not be broken down by period in Part 2.

10.2.5 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and in listing format. Exposure-adjusted SAEs per 100 patient-years of risankizumab exposure will also be provided by SOC and PT.

10.2.6 Areas of Safety Interest

Detailed information about the search criteria for areas of safety interest (ASIs) are provided in Appendix B.

The final list will be based on the most updated final version of risankizumab Product Safety Statistical Analysis Plan.

Tabular listings of selected area of safety interest will be provided.

10.2.7 Combined Analyses for Adolescents/Children

In addition to the analyses by study part, the following tables of exposure-adjusted AEs per 100 patient-years of risankizumab exposure will be created that combine subjects enrolled into Part 1 and Part 2 (adolescents) and subjects enrolled into Part 3 and Part 4 (children), respectively:

- Overview of TEAEs,
- TEAEs summarized by SOC and PT,
- TEAEs summarized by SOC and PT by decreasing frequency.

The two Japanese adolescents aged 12 to < 18 years enrolled into Part 4 are not included in the Safety Analysis Population (see Section 4.0) and listed separately throughout. They are therefore not included in the above.

10.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline where SAE-related laboratory assessments on or before the first dose of study drug will be excluded. The clinical laboratory tests defined in the protocol operations manual (e.g., hematology and clinical chemistry) will be summarized.

Mean change from baseline to each applicable post-baseline visit will be summarized for selected laboratory variables, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group and difference between treatment groups (differences only applicable for Part 2 Period A).

Changes in laboratory parameters will be tabulated using shift tables categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline either to the worst value during treatment and to minimum and

maximum value (based on normal range), will be created. A similar shift table will be provided to summarize shifts from baseline to the final post-baseline value.

Laboratory abnormalities meeting CTC v4.03 criteria grade 3 and 4 will be summarized.

The following analyses will be done combining subjects enrolled into Part 1 and Part 2 (adolescents) and subjects enrolled into Part 3 and Part 4 (children), respectively:

The two Japanese adolescents aged 12 to < 18 years enrolled into Part 4 are not included in the Safety Analysis Population (see Section 4.0) and listed separately throughout. They are therefore not included in the above.

Laboratory abnormalities will be evaluated based on Potentially Clinically Significant (PCS) criteria (Appendix C). For each laboratory PCS criterion, the number and percentage of subjects who have a laboratory value meeting the criteria will be summarized. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCS criteria.

In addition, the number and percentage of subjects meeting criteria for potential hepatotoxicity will be provided.

- ALT > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- AST > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- TBL > 1.5 × ULN, > 2 × ULN
- ALT and/or AST > 3 × ULN and TBL > 1.5 × ULN
- ALT and/or AST > 3 × ULN and TBL > 2 × ULN
- ALT > 3 × ULN and TBL > 1.5 × ULN
- ALT > 3 × ULN and TBL > 2 × ULN
- Alkaline phosphatase > 1.5 × ULN

For criteria involving multiple parameters, the values do not need to be concurrent to meet the defined criteria.

A listing of potentially clinically important liver function laboratory values will include all subjects who met any of the following four criteria:

- ALT > 3 × ULN, or
- AST > 3 × ULN, or
- ALP > 1.5 × ULN, or
- Total bilirubin > 1.5 × ULN.

A listing of potential biochemical Hy's Law cases, defined as those who meet all of the following conditions at any post-baseline visit, not necessarily concurrent, will be provided.

- ALT of > 3 × ULN or AST of > 3 × ULN
- Total bilirubin > 2 × ULN

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure as well as height will be summarized.

Mean change from baseline to each applicable post-baseline visit will be summarized for the above mentioned vital sign variables, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group and difference between treatment groups (Period A, Part 2).

The following analyses will be done combining subjects enrolled into Part 1 and Part 2 (adolescents) and subjects enrolled into Part 3 and Part 4 (children), respectively:

The two Japanese adolescents aged 12 to < 18 years enrolled into Part 4 are not included in the Safety Analysis Population (see Section 4.0) and listed separately throughout. They are therefore not included in the above.

Vital sign variables will be evaluated based on potentially clinically significant (PCS) criteria (Appendix D). For each vital sign PCS criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCS criteria.

10.5 Safety Subgroup Analyses

Counts and percentages of hypersensitivity reactions and injection site reactions will be presented for the following subgroups:

- Anti-drug antibodies (ADA) (positive, negative)
- Neutralizing antibodies (nAb) (positive, negative)

10.6 Other Safety Analyses

Not applicable.

11.0 Other Analyses

Not applicable.

12.0 Interim Analyses

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 and Part 2 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 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 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 data monitoring committee (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 will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC members, frequency of data reviews, relevant safety data to be assessed, and expectations for blinded communications.

12.1 Data Monitoring Committee

An external data monitoring committee (DMC) composed of persons independent of AbbVie and with relevant expertise in their field will review 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 will be prepared outside of the protocol and will describe the roles and responsibilities of the IDMC members, frequency and triggers of data reviews, and relevant safety data to be assessed. Unblinded ASI events will be presented to the IDMC for review on a periodic basis.

Since there are no efficacy analyses for early stopping, no alpha adjustment is needed.

13.0 Overall Type-I Error Control

Not applicable for this study as no statistical testing will be performed.

14.0 Version History

Table 3. SAP Version History Summary

Version	Date	Summary
1.0	12 August 2020	Original version
2.0	18 August 2021	Updated SAP to align with edits in protocol version 3.0; addition of Itch NRS endpoints; addition of estimands language; updated Itch endpoint; updated safety (ASIs and hepatotoxicity criteria) wording to align with most current version of PSSAP (v4.1)
3.0	01 May 2023	Updated SAP to align with edits in protocol version 4.0; added ≥ 2-grade improvement from baseline of sPGA (US only), update list of ASIs, summary for height added

4.0	16 October 2023	Section 6.0: added analyses of duration of risankizumab treatment that combine subjects enrolled into Part 1 and Part 2 (adolescents) and subjects enrolled into Part 3 and Part 4 (children) rationale: to provide integrated exposure information for adolescents and children, respectively Section 7.1: added analyses of demographics that combine subjects enrolled into Part 1 and Part 2 (adolescents) and subjects enrolled into Part 3 and Part 4 (children) rationale: to provide integrated demographics information for adolescents and children, respectively Section 10.2.2: removed assessment of treatment-emergent COVID-19 related events and COVID-19 related deaths from Adverse Event Overview rationale: to align with general company approach Section 10.2.7: added analyses of exposure-adjusted AEs per 100 patient-years of risankizumab exposure that combine subjects enrolled into Part 1 and Part 2 (adolescents) and subjects enrolled into Part 3 and Part 4 (children) rationale: to provide integrated safety information for adolescents and children, respectively Section 10.3: Replaced analyses of PCS hematology, chemistry, hepatoxicity by Part with analyses by age cohort (adolescents, children) rationale: to provide integrated safety information for adolescents and children, respectively Section 10.4: Replaced analyses of PCS for vital signs by Part with analyses by age cohort (adolescents, children) rationale: to provide integrated safety information for adolescents and children, respectively Section 10.5: Removed subgroup analyses by gender rationale: small number of subjects Appendix D Updated criteria for potentially clinically significant vital sign values rationale: to align with general company approach

15.0 References

1. European Medicines Agency. P/0205/2016. Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral and a waiver. 2016.
2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication.

Appendix B. Definition of Area of Safety Interest

Area of safety interest (ASI) will be identified using the following search criteria:

Area of Safety Interest	Search Criteria		Include in AE Overview (Y/N)
Serious Infections	Serious AEs in the Infections and Infestations SOC		Y
Tuberculosis	Active TB CMQ (code 10000002)		Y
Opportunistic Infections	Opportunistic Infection Excluding Tuberculosis and Herpes Zoster CMQ (code 10000105)		Y
Herpes Zoster	Herpes Zoster CMQ (code 10000079)		Y
Malignant Tumours	Narrow	Malignant tumours (SMQ 20000194)	Y
Non-melanoma Skin Cancer (NMSC)	Broad	Skin malignant tumours (SMQ 20000204) excluding terms identified by the Melanoma CMQ (code 10000100)	Y
Malignant Tumours excluding NMSC	'Malignant Tumours excluding NMSC' is identified by the 'Malignant Tumours' search excluding terms identified by the 'Non-melanoma skin cancer (NMSC)' search.		Y
Hypersensitivity	Narrow	Hypersensitivity (SMQ 20000214)	Y – serious events only
Adjudicated Anaphylactic Reaction*	Adjudicated terms will be identified using SDTM data (e.g., CE and PR domains).		Y
Hepatic Events	Broad	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ 20000013)	Y
	Broad	Hepatitis, non-infectious (SMQ 20000010)	
	Broad	Cholestasis and jaundice of hepatic origin (SMQ 20000009)	
	Broad	Liver related investigations, signs and symptoms (SMQ 20000008)	
	Narrow	Liver-related coagulation and bleeding disturbances (SMQ 20000015)	
Injection Site Reaction		Injection site reaction CMQ (code 10000091)	Y
Suicidal Ideation and Behavior (SIB)	Narrow	Suicide/self-injury (SMQ 20000037)	Y

* Events will be identified for adjudication by Anaphylactic Reaction SMQ Broad search as specified in the RISA AAC Charter.

Appendix C. Potentially Clinically Significant Criteria for Safety Endpoints

The criteria for Potentially Clinically Significant (PCS) laboratory findings are described in Table C-1 and Table C-2.

Table C-1. Potentially Clinically Significant Chemistry Values

		Definition of Potentially Clinically Significant Current (Version 4) NCI CTCAE Grade 3 or Greater	
Chemistry Variables	**Units**	**Very Low**	**Very High**
TBL	mcmol/L		> 3.0 × ULN
ALP	U/L		> 5.0 × ULN
SGOT/AST	U/L		> 5.0 × ULN
SGPT/ALT	U/L		> 5.0 × ULN
Albumin	g/L	< 20	
Glucose	mmol/L	< 2.2	> 13.9
Triglycerides	mmol/L		> 5.7
Creatinine	mcmol/L		> 3.0 × ULN (> 3.0 × BL)
Sodium	mmol/L	< 130	> 155
Potassium	mmol/L	< 3.0	> 6.0
Calcium	mmol/L	< 1.75	> 3.1
CPK	U/L		> 5.0 × ULN
Total Cholesterol	mmol/L		> 10.34
GGT			> 5.0 × ULN

Note: A post-baseline value must be more extreme than the baseline value to be considered a potentially clinically significant finding.

Table C-2. Potentially Clinically Significant Hematology Values

		Definition of Potentially Clinically Significant Current (Version 4) CTCAE Grade 3 or Greater
Hematology Variables	**Units**	**Very Low**
Hemoglobin	g/L	< 80.0
Platelets count	10^9/L	< 50.0
WBC count	10^9/L	< 2.0
Neutrophils	10^9/L	< 1.0
Lymphocytes	10^9/L	< 0.5

Note: A post-baseline value must be more extreme than the baseline value to be considered a potentially clinically significant finding.

Appendix D. Criteria for Potentially Clinically Significant Vital Sign Values

Vital signs values will be categorized as follows:

Systolic Blood Pressure (mmHg)

Age Group	Category	Criteria for Potentially Clinically Significant Vital Signs
12 to < 18 years	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from baseline
10 and 11 years	Low	Value ≤ 80 mmHg and decrease ≥ 20 mmHg from baseline
	High	Value ≥ 140 mmHg and increase ≥ 20 mmHg from baseline
Less than 10 years	Low	Value ≤ 80 mmHg and decrease ≥ 20 mmHg from baseline
	High	Value ≥ 130 mmHg and increase ≥ 20 mmHg from baseline

Diastolic Blood Pressure (mmHg)

Age Group	Category	Criteria for Potentially Clinically Significant Vital Signs
12 to < 18 years	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from baseline
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from baseline
10 and 11 years	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from baseline
	High	Value ≥ 90 mmHg and increase ≥ 10 mmHg from baseline
Less than 10 years	Low	Value ≤ 50mmHg and decrease ≥ 10 mmHg from baseline
	High	Value ≥ 85 mmHg and increase ≥ 10 mmHg from baseline

For categorization purposes in case of age specific ranges, age at enrollment will be used.