1.0 Title Page

Statistical Analysis Plan

Study 1311.4

Risankizumab Versus Placebo in a Multicenter Randomized Double-Blind Study in Patients with Moderate to Severe Chronic Plaque Psoriasis Evaluating the Efficacy and Safety with Randomized Withdrawal and Re-Treatment (IMMhance)

Date: 12 Sep 2017

Version 2.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analysis to be completed by the AbbVie Clinical Statistics Department for study Protocol 1311.4 dated 28 July 2016.

This SAP will provide details to further elaborate statistical methods as outlined in the Protocol 1311.4 and will describe analysis conventions to guide the statistical programming work. The SAP will be signed off before the study database is locked.

Analyses will be performed using SAS® version 9.4 (SAS Institute, Inc., Cary, NC 27513) or higher using the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Primary Study Objective

The primary objective of the initial randomized phase of the study (Part A1; see Section 4.2) is to assess the efficacy of risankizumab 150 mg in comparison to placebo in subjects with moderate to severe chronic plaque psoriasis. The primary objective of the second randomized phase of the study (Part B; see Section 4.2) is to evaluate the maintenance of response with continuous risankizumab treatment compared with withdrawal of treatment.

The primary efficacy evaluation will be performed at 16 weeks. The maintenance of response following drug withdrawal will be assessed after Week 28 through the end of the study (primary evaluation at Week 52). Subsequent to drug withdrawal, subjects who experience relapse will be retreated with risankizumab to assess response after retreatment.

Evaluations of risankizumab efficacy and safety in various populations will be performed in the study to provide a full picture of risankizumab benefits and risks. These populations and the intent of the related analyses is specific in Section 5.2.

In addition, this trial will assess pharmacokinetics (PK) and the emergence of anti-drug antibodies (ADA) and their effect on efficacy and safety. Moreover, it will be explored how the use of risankizumab may influence gene and protein expression levels and disease specific protein markers. PK and ADA analyses, as well as DNA banking, exploratory biomarker, and metabolic risk factor analyses, will not be included in this SAP.

4.2 Design Diagram

This is a confirmatory, multinational, multicenter, randomized, double-blind, placebo controlled study with randomized withdrawal and retreatment, evaluating the safety and efficacy of risankizumab 150 mg subcutaneous (SC) in patients with moderate to severe chronic plaque psoriasis.

The study consists of an up to 42 day screening period, a 16-week double-blind, placebo-controlled initial treatment period (Part A1), a 12-week treatment period (Part A2), an up to 60-week continuous treatment and treatment withdrawal period (Part B) with possible retreatment with risankizumab for up to 16 weeks, and a 16 week follow-up period.

Part A1: A 16-week double-blinded, placebo-controlled treatment period during which subjects will be randomized at a ratio of 4:1 to one of two treatment arms as shown in Figure 1. Arm 1 refers to those subjects originally randomized to risankizumab and Arm 2 refers to those subjects originally randomized to placebo. The first dose of study drug will be administered on Day 1 (Visit 2; Baseline) and the second dose will be administered at Week 4. The randomization will be stratified with respect to weight (≤ 100 kg vs. > 100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1).

Part A2: A 12-week treatment period. At Week 16, all subjects will receive one dose of risankizumab 150 mg.

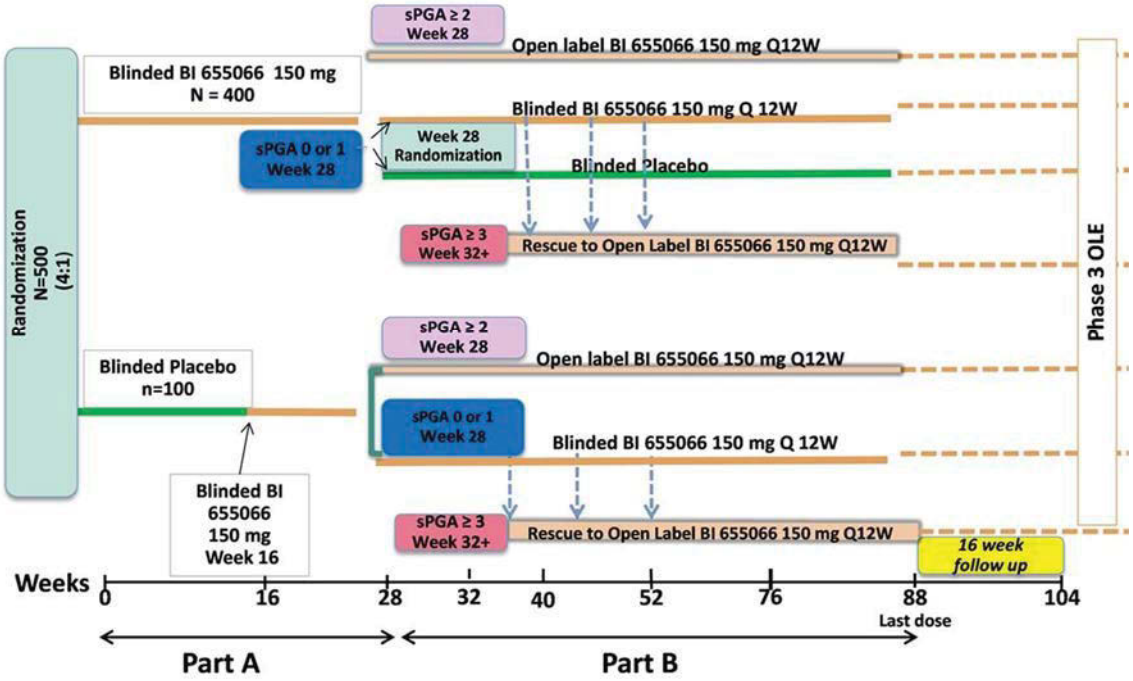
Part B: At Week 28, non-responders (static Physician Global Assessment [sPGA] ≥ 2) will receive open label risankizumab 150 mg every 12 weeks with a last dose at Week 88 (end-of-treatment, EOT), while responders (sPGA of 0 or 1) from Arm 1 will be

re-randomized in a 1:2 ratio to either maintain risankizumab 150 mg or matching placebo every 12 weeks with a last dose at Week 88 (EOT). The re-randomization will be stratified with respect to weight (≤ 100 kg vs. > 100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1). Responders from Arm 2 will continue to receive blinded risankizumab 150 mg every 12 weeks with a last dose at Week 88 (EOT) to maintain the blind. Throughout the SAP, "re-randomized" or "re-randomization" refers to the randomization at Week 28 among subjects from Arm 1 of Part A.

Retreatment: Starting from Week 32, subjects experiencing relapse (defined as an sPGA of ≥ 3), will receive open label risankizumab 150 mg. If this relapse occurs anytime between Week 32 through Week 70, open label risankizumab 150 mg will be administered at 0, 4, and 16 weeks (EOT) after relapse. If this relapse occurs after Week 70 through Week 82, open label risankizumab 150 mg will be administered 0 and 4 weeks (EOT) after relapse. If the relapse occurs after Week 82 through Week 88 the subject will immediately have the EOT procedures performed, including the final dose of study drug.

Follow-Up Period: Subjects who have completed their EOT visit will be followed up for 16 weeks. Follow-up Visit 1 is scheduled at 6 weeks after EOT. And Follow-up Visit 2 is scheduled at 16 weeks after EOT, which is the end of observation (EOO) visit. Subjects who have completed the EOO visit within the specified window, who have not discontinued drug prematurely, and who also meet the eligibility criteria will be offered to roll over into an open label extension study.

Figure 1. Trial Design



BI 655066 is risankizumab.

4.3 Sample Size

This study is designed to show a difference between risankizumab and placebo in terms of achieving 90% reduction in Psoriasis Area and Severity Index (PASI 90) response and sPGA of clear or almost clear (sPGA of 0 or 1) at Week 16. This study was also powered to show a difference in sPGA response at Week 52 between the subjects re-randomized to continue on risankizumab vs. subjects randomized to placebo at Week 28.

Based on the interim results from Study 1311.2, it is assumed at most 10% of the subjects in the re-randomized risankizumab arm and approximately 25% of subjects in the re-randomized placebo arm will lose response. Using a 1:2 re-randomization scheme (risankizumab:placebo), 102 subjects in the risankizumab arm and 204 subjects in the

placebo arm will provide at least 90% power to detect the difference in sPGA response rate at Week 52. Assuming that 80% of subjects initially randomized to risankizumab at baseline will achieve sPGA of 0 or 1 at Week 28, the total sample size required for the initial risankizumab arm at Visit 2 is (102)(3) ÷ 0.8 = 383.

A total sample size of 500 = 400:100 for risankizumab: placebo was planned at Visit 2.

Based on the outcome from Trials 1311.1 and 1311.2, the PASI 90 response rate at Week 16 is assumed to be at least 65% in the risankizumab arm and approximately 5% for placebo. For sPGA clear or almost clear at Week 16, the response rate is assumed to be at least 80% for the risankizumab arm and approximately 5% for placebo. This trial will have > 99% power for comparing risankizumab arm to placebo on both of these endpoints.

All calculations were performed using ADDPLAN Version 6.0.4, an Aptiv Solutions Company.

4.4 Interim Analysis

Unblinded data will be reviewed during the study by an independent data monitoring committee (DMC). The membership, roles and responsibilities and activities of the DMC will be defined in a written charter. The DMC will include representatives from external safety experts who do not directly involve in the study. Clinical site personnel and the study team will remain blinded to the randomized treatment assignments during the course of the study. Communications from the DMC to the study team will not contain information that could potentially unblind the study personnel. Since there is no efficacy analyses for early stopping, no alpha adjustment is needed.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Efficacy Population:

Intent-to-Treat (ITT) Population: The ITT Populations will be used for the efficacy analyses in different parts.

- The ITT Population in Part A1 (ITT_A1) is defined as all subjects who are randomized at Baseline. This Population will be analyzed for the efficacy of initial treatment.
- The ITT Population in Part A2 from Arm 1 (ITT_A2) is defined as all subjects who were randomized to Arm 1 at Baseline. Data from Part A2 will be used to evaluate the mid-term efficacy.
- The ITT Population across Part A2 and B from Arm 2 (ITT_ARM2) is defined as all subjects who were randomized to Arm 2 at Baseline and received at least one dose of study drug on or after Week 16. This Population will be analyzed for short and long term efficacy without initial loading dose.
- The ITT Population in Part B for re-randomized subjects (ITT_B_R) is defined as all subjects who were randomized to Arm 1 and re-randomized at Week 28. The ITT_B_R Population will mainly be used to compare efficacy of continued treatment with risankizumab vs withdrawal from the treatment. The risankizumab arm will also be summarized (including data after retreatment) for long-term efficacy with the option of re-load.
- The ITT Population in Part B for Arm 1 non-responders at Week 28 (ITT_B_NR) is defined as all subjects who were randomized to Arm 1 at Baseline, were non-responders (sPGA $\geq$ 2) at Week 28, and receive at least one dose of risankizumab on or after Week 28. This population will be summarized for potential delayed response.
- The ITT Population for Part B placebo patients who received retreatment (ITT_B_PBO_RT) is defined as all subjects who were re-randomized to placebo and received at least one dose of retreatment with open label risankizumab after relapse, and have the opportunity to have retreatment Week 16 assessments.

- The ITT Population for Part B risankizumab patients who receive retreatment (ITT_B_RZB_RT) is defined as all subjects who were re-randomized to risankizumab and received at least one dose of retreatment with open label risankizumab after relapse, and have the opportunity to have retreatment Week 16 assessment. The population will be summarized to examine the efficacy of re-treatment with loading dose upon relapse on risankizumab.

ITT Populations will be analyzed by the treatment group as randomized.

In addition, additional analysis will be performed on ITT_B_R subjects who are re-randomized to risankizumab 150 mg, in which all evaluations after re-randomization (including evaluations after retreatment with open label risankizumab after relapse) will be included along with the blinded assessments to evaluate the efficacy of continuous treatment.

Per-Protocol (PP) Population: To evaluate the impact of protocol deviations on the primary and ranked secondary endpoints, additional analyses will be performed on the Per-protocol Populations. The Per-protocol Population will include those who were most compliant with the protocol in ways that could impact the primary and ranked secondary endpoints. Final results and the criteria for exclusion of subjects will be finalized prior to database lock for data pertaining to the DB period.

The PP Population at Part A1 (PP_A1; a.k.a. the PPS in study Protocol 1311.4) is defined as all subjects from the ITT_A1 Population who meet all the following criteria:

- Subjects must receive at least 75% of planned study drug injections, per randomization, in Part A1.
- Subjects must have either a PASI or sPGA assessment post-baseline in Part A1.
- Inclusion Criterion 4: Subjects must have stable moderate to severe chronic plaque psoriasis at baseline:
  - Have an BSA ≥ 10% and
  - Have a PASI ≥ 12 and

- Have an sPGA ≥ 3.

Primary and ranked secondary efficacy endpoints at Part A1 at Week 16 will be analyzed on the PP_A1 Population.

The PP Population at Part B for re-randomized subjects (PP_B_R; a.k.a. RRS-PPS in study Protocol 1311.4) is defined as all subjects from the ITT_B_R Population who meet all the following criteria:

- Subjects must receive at least 75% of planned study drug injections, per re-randomization, in Part B.
- Subjects must have at least one sPGA assessment post re-randomization in Part B.
- Subjects must have sPGA < 2 at re-randomization.

The primary efficacy endpoint for Part B at Week 52 and ranked secondary endpoint for Part B at Week 104 will be analyzed on the PP_B_R Population.

PP Populations will be analyzed by the treatment group as randomized (or re-randomized).

Safety Population:

The Safety Populations will be used for safety analyses in different study parts.

Each ITT population will have a corresponding safety population (Safety) of the same study part, which includes all subjects who receive at least one dose of study drug during the analysis period.

Complete safety tables will be provided for the Safety_A1 Population and the Safety_B_R population. Only AE overview tables will be provided for other safety populations.

The Safety Population will be analyzed based on the actual treatment received at the randomization visit (Part A) and at the re-randomization visit (Part B).

In addition, an All Risankizumab Treated Population (ALL_RZB) is defined as all subjects who receive at least one dose of risankizumab in the study. The ALL_RZB Population will be used for safety analyses. Complete safety tables will be provided in the ALL_RZB Population.

Table 1. Notations for Treatment Groups

Population	Treatment Code	Definition
ITT_A1/PP_A1/ Safety_A1	RZB	Subjects who randomized to risankizumab 150 mg.
	PBO	Subjects who randomized to placebo.
ITT_A2/Safety_A2	RZB/RZB	Subjects who randomized to risankizumab 150 mg.
ITT_ARM2/ Safety_ARM2	PBO/RZB	Subjects who randomized to placebo and received at least one dose of study drug on or after Week 16.
ITT_B_R/PP_B_R/ Safety_B_R	RZB/RZB/RZB	Subjects who re-randomized to risankizumab 150 mg at Week 28.
	RZB/RZB/PBO	Subjects who re-randomized to placebo at Week 28.
ITT_B_NR/Safety_B_NR	RZB/RZB/RZB	Subjects who randomized to risankizumab and are non-responders at Week 28.
ITT_B_PBO_RT/ Safety_B_PBO_RT	RZB/RZB/PBO/RZB	Subjects who received open-label risankizumab 150 mg as retreatment, after re-randomized to placebo in Part B.
ITT_B_RZB_RT/ Safety_B_RZB_RT	RZB/RZB/RZB/RZB	Subjects who received open-label risankizumab 150 mg as retreatment, after re-randomized to risankizumab in Part B.
ALL_RZB	RZB	Subjects who received at least one dose of risankizumab 150 mg.

5.2 Variables Used for Stratification of Randomization

At Visit 2, subjects will be randomized in blocks to double-blind treatment to either risankizumab 150 mg or placebo in a 4:1 ratio. Randomization will be stratified with respect to weight (≤ 100 kg vs. > 100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1).

Subjects originally randomized to risankizumab 150 mg (Arm 1) who are responders at Week 16 will be re-randomized at Week 28 in a 1:2 ratio to either risankizumab 150 mg or placebo. Re-randomization will also be stratified with respect to weight (≤ 100 kg vs. > 100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1).

6.0 Analysis Conventions

Definition of Baseline

The last non-missing measure collected on or before the date of the first dose of study drug injection will be used as Baseline for summary of demographics and disease characteristics, efficacy analyses, and safety analyses in each period, with the exception that:

- The last evaluation on or prior to the first dose date of risankizumab will be used for the safety analyses for Safety_ARM2 and ALL_RZB populations.
- For all vital sign assessments, only assessments prior to first dose time will be considered, since vital signs are to be assessed both pre- and post-dose in some visits.

For subjects who are randomized but do not take any study drug during the study, the last non-missing measurement collected on or before the date of randomization will be used as Baseline.

Definition of Final Observation (Applicable to Safety Analyses)

Final observation for the Part A1 is defined as:

- The last non-missing observation collected within 105 days following the last dose of study drug in Part A1, for subjects who were not dosed in Part A2.
- The last non-missing observation collected on or before the first dose date of study drug on or after Week 16 and within 105 days following the last dose of study drug in Part A1, for subjects who were dosed in Part A2. For vital sign assessments, only assessments prior to the first dose of study drug injection in Part A2 will be included in the analysis for Part A1.

Final observation for the Part A2 is defined as:

- The last non-missing observation collected within 105 days following the Week 16 dose of study drug in Part A2, for subjects who were not dosed in Part B.
- The last non-missing observation collected on or before the first dose date of Part B, or within 105 days following the last dose of study drug in Part A2, whichever comes first, for subjects who were dosed in Part B. For vital sign assessments, only assessments prior to the first dose of study drug injection in Part B will be included in the analysis for Part A2.

Final observation in Part B is defined as the last non-missing observation collected within 105 days following the last dose of study drug, and on or prior to the date first dose of retreatment with risankizumab for relapsed subjects, with the following exception:

For vital sign assessments, only assessments prior to the first dose of retreatment will be included in the analysis for Part B.

Final observation in the retreatment period is defined as the last non-missing observation collected within 105 days after the last dose of retreatment with risankizumab.

Final observation in the entire study is defined as the last non-missing observation collected within 105 days after the last dose of study drug.

Definition of Rx Days (Days Relative to the Date of First Dose of Study Drug)

Rx days are calculated for each time point relative to the date of first dose of study drug. They are defined as the number of days between the day of the first dose of study drug and the specific time point. Rx days are negative values when the time point of interest is prior to the first study drug dose day. Rx days are positive values when the time point of interest is on or after the first study drug dose day. The day of the first dose of study drug is defined as Rx Day 1, while the day prior to the first study drug dose is defined as Rx Day –1 (there is no Rx Day 0).

For analysis in each Part (A1, A2, or B), the Rx Day is calculated relative to the first dose of study drug in the specific study Part. For analysis across Part A2 and Part B, the Rx days are calculated relative to the date of first dose of risankizumab injection in Part A2.

Definition of Analysis Windows

All time points and corresponding time windows are defined based on Rx Days.

For efficacy analyses, local tolerability, ECG, laboratory parameters, and vital sign variables, analysis windows are constructed using the following algorithm:

- Determine the nominal Rx day for each visit (e.g., Week 4 [4 weeks after Baseline visit] equals Rx Day 29).
- In order to include all post baseline data, the first post-baseline interval starts on the first day after the first dose of study drug (Rx Day 2).
- Determine the window around a specific nominal Rx day by adding or subtracting half of the interval between adjacent visits (e.g., days between Week 2 and Week 4 is 14). The threshold between adjacent visits is determined by splitting the interval evenly between the visits. If the resulting split is between Rx days, then the threshold is determined as the midpoint between the adjacent visits. If the resulting split is on an Rx day, then the threshold is determined as being between that Rx day and the Rx day prior to it (e.g., the split between Week 2 and Week 4 would be between Rx Days 22 and 23).
- If more than one assessment is included in a time window the assessment closest to the nominal day will be used. If there are two observations equidistant to the nominal day, the one after the nominal day will be used in analyses. If more than one assessment is included on the same day, then the worst assessment on that day will be used in analyses, except those specified in Section 11.0.

The protocol specified visits and corresponding time windows used in the efficacy analyses, local tolerability, ECG, laboratory parameters, and vital sign variables, are

presented in the following Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15 and Table 16.

Table 2. Visit Windows for Analysis of PASI, sPGA, Local Tolerability, and Vital Signs in Part A1 (ITT_A1/PP_A1/Safety_A1 Populations)

Window Label	Target Day	Interval
Baseline	1	≤ 1[a]
Week 4	29	[2, 43]
Week 8	57	[44, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 127[b]]

Rx Day calculated relative to first dose date of study drug. For subjects randomized but not dosed, Rx Day calculated relative to Randomization.

a. There is no baseline for local tolerability measurements. If time is collected in vital signs, restrict to records prior to the first dose of study drug.

b. The minimum of upper bound and first dose date of study drug on or after Week 16 (and within 105 days of last dose for safety analyses). If time is collected in vital signs, restrict to records prior to the first dose of study drug on or after Week 16.

Table 3. Visit Windows for Analysis of DLQI in Part A1 (ITT_A1/PP_A1 Populations)

Window Label	Target Day	Interval
Baseline	1	≤ 1
Week 12	85	[2, 99]
Week 16	113	[100, 127[a]]

Rx Day calculated relative to first dose date of study drug. For subjects randomized but not dosed, Rx Day calculated relative to Randomization.

a. The minimum of upper bound and first dose date of study drug on or after Week 16.

Table 4. Visit Windows for Analysis of Safety Laboratory Tests and ECG in Part A1 (Safety_A1 Population)

Window Label	Target Day	Interval
Baseline	1	≤ 1
Week 4	29	[2, 71]
Week 16	113	[72, 155[a]]

Rx Day calculated relative to first dose date of study drug. For subjects randomized but not dosed, Rx Day calculated relative to Randomization.

a. The minimum of upper bound and first dose date of study drug on or after Week 16 (and within 105 days of last dose for safety analyses).

Table 5. Windows for Analysis of Efficacy Variables Collected Only at Week 16 After Baseline in Part A1 (ITT_A1 Population)

Window Label	Target Day	Interval
Baseline	1	≤ 1
Week 16	113	[2, 225[a]]

Rx Day calculated relative to first dose date of study drug. For subjects randomized but not dosed, Rx Day calculated relative to Randomization.

a. The minimum of upper bound and first dose date/time on or after Week 16 study drug.

Table 6. Visit Windows for Analysis of PASI and sPGA in Part A2 (ITT_A2 Population)

Window Label	Target Day	Interval
Entry of A2	1	≤ 1
Week 20	29	[2, 43]
Week 24	57	[44, 71]
Week 28	85	[72, 99[a]]

Rx Day calculated relative to the date of Week 16 visit.

a. The minimum of upper bound and first dose date on or after the first re-randomized dose for subjects with re-randomization or the first open label risankizumab dose for those who were not re-randomized.

Table 7. Visit Windows for Analysis of Efficacy Variables Only Collected at Week 28 in Part A2 (ITT_A2 Population)

Window Label	Target Day	Interval
Baseline	1	≤ 1
Week 28	85	[2, 169[a]]

Rx Day calculated relative to the date of Week 16 visit.

a. The minimum of upper bound and first dose date on or after the first re-randomized dose for subjects with re-randomization or the first open label risankizumab dose for those who were not re-randomized.

Table 8. Visit Windows for Analysis of PASI and sPGA, Local Tolerability, and Vital Signs in Part B (ITT_B_R/ITT_B_NR/PP_B_R/Safety_B_R/Safety_B_NR Populations)

Window Label	Target Day	Interval
Entry of B	1	≤ 1[a]
Week 32	29	[2, 43]
Week 36	57	[44, 71]
Week 40	85	[72, 99]
Week 44	113	[100, 127]
Week 48	141	[128, 155]
Week 52	169	[156, 190]
Week 58	211	[191, 232]
Week 64	253	[233, 274]
Week 70	295	[275, 316]
Week 76	337	[317, 358]
Week 82	379	[359, 400]
Week 88	421	[401, 442]
Week 94	463	[443, 498]
Week 104	533	[499, 568[b]]

Rx Day calculated relative to the first dose date of study drug in Part B. For subjects re-randomized but not dosed in Part B, Rx Day calculated relative to the IRT date of Re-randomization evaluation.

a. There is no local tolerability at re-randomization and after EOT. If time is collected in vital signs, restrict to records prior to the first dose of study drug in Part B.

Table 8. Visit Windows for Analysis of PASI and sPGA, Local Tolerability, and Vital Signs in Part B (ITT_B_R/ITT_B_NR/PP_B_R/Safety_B_R/Safety_B_NR Populations) (Continued)

b. The minimum of upper bound, the first dose date of retreatment with risankizumab for relapsed subjects (except the additional analysis as in footnote a), and within 105 days of last dose of study drug for safety analyses. If time is collected in vital signs, restrict to records prior to the first dose of retreatment.

Note: For additional PASI and sPGA analysis on ITT_B_R subjects re-randomized to risankizumab to evaluate continuous treatment, evaluations after retreatment with open label risankizumab will also be included along with blinded assessments.

Table 9. Visit Windows for Analysis of Safety Laboratory Tests and ECG in Part B (Safety_B_R/Safety_B_NR Populations)

Window Label	Target Day	Interval
Entry of B	1	≤ 1
Week 40	85	[2, 127]
Week 52	169	[128, 211]
Week 64	253	[212, 295]
Week 76	337	[296, 379]
Week 88	421	[380, 477]
Week 104	533	[478, 589[a]]

Rx Day calculated relative to the first dose date of study drug in Part B. For re-randomized subjects not dosed in Part B, Rx Day calculated relative to the IRT date of Re-randomization evaluation.

a. The minimum of upper bound and first dose date of retreatment with risankizumab for relapsed subjects (and within 105 days of last dose of study drug for safety analyses).

Table 10. Visit Windows for Analysis of Other Efficacy Endpoints Only Collected at Week 52, 76, and 104 in Part B (ITT_B_R/ITT_B_NR/PP_B_R Populations)

Window Label	Target Day	Interval
Entry of B	1	≤ 1
Week 52	169	[2, 253]
Week 76	337	[254, 435]
Week 104	533	[436, 631[a]]

Rx Day calculated relative to the first dose date of study drug in Part B. For re-randomized subjects not dosed in Part B, Rx Day calculated relative to the IRT date of Re-randomization evaluation.

a. The minimum of upper bound and first dose date of retreatment with risankizumab for relapsed subjects.

Table 11. Visit Windows for Analysis of PASI and sPGA Across Part A2 and B (ITT_ARM2 Population)

Window Label	Target Day	Interval
Entry of A2	1	≤ 1
Week 20	29	[2, 43]
Week 24	57	[44, 71]
Week 28	85	[72, 99]
Week 32	113	[100, 127]
Week 36	141	[128, 155]
Week 40	169	[156, 183]
Week 44	197	[184, 211]
Week 48	225	[212, 239]
Week 52	253	[240, 274]
Week 58	295	[275, 316]
Week 64	337	[317, 358]
Week 70	379	[359, 400]
Week 76	421	[401, 442]
Week 82	463	[443, 484]
Week 88	505	[485, 526]
Week 94	547	[527, 582]
Week 104	617	[583, 652]

Rx Day calculated relative to first dose date of risankizumab.

Table 12. Visit Windows for Analysis of Other Efficacy Endpoints Collected at Week 28, 52, 76, and 104 in Part A2 and B (ITT_ARM2 Population)

Window Label	Target Day	Interval
Entry of A2	1	≤ 1
Week 28	85	[2, 169]
Week 52	253	[170, 337]
Week 76	421	[338, 519]
Week 104	617	[520, 715]

Rx Day calculated relative to first dose date of risankizumab.

Table 13. Visit Windows for Analysis of PASI and sPGA During Retreatment with Risankizumab (ITT_B_PBO_RT/ITT_B_RZB_RT Populations)

Window Label	Target Day	Interval
Entry of RTS	1	≤ 1
Week 8R	57	[2, 85]
Week 16R	113	≥ 86

Rx Day calculated relative to first dose date of retreatment with risankizumab.

Table 14. Visit Windows for Analysis of Other Efficacy Variables Only Collected at EOT and EOO Visits During Retreatment with Risankizumab (ITT__B_PBO_RT/ITT_B_RZB_RT Populations)

Window Label	Target Day	Interval
Entry of RTS	1	≤ 1
Week 16R	113	≥ 2

Rx Day calculated relative to first dose date of retreatment with risankizumab.

Table 15. Visit Windows for Analysis of Vital Signs and Local Tolerability in the ALL_RZB Population

Window Label	Target Day	Interval
Baseline	1	≤ 1[a]
Week 4	29	[2, 43]
Week 8	57	[44, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 155]
Week 28	197	[156, 239]
Week 40	281	[240, 323]
Week 52	365	[324, 407]
Week 64	449	[408, 491]
Week 76	533	[492, 575]
Week 88	617	[576, 673]
Week 104	729	[674, 785[b]]

Rx Day calculated relative to first dose date of risankizumab.

a. Local tolerability not measured at Baseline and at Week 104. If time is collected in vital signs, restrict to records prior to the first dose of risankizumab.

b. The minimum of upper bound and within 105 days of last dose of risankizumab.

Table 16. Visit Windows for Analysis of Safety Laboratory Tests and ECG in the ALL_RZB Population

Window Label	Target Day	Interval
Baseline	1	≤ 1
Week 4	29	[2, 71]
Week 16	113	[72, 155]
Week 28	197	[156, 239]
Week 40	281	[240, 323]
Week 52	365	[324, 407]
Week 64	449	[408, 491]
Week 76	533	[492, 575]
Week 88	617	[576, 673]
Week 104	729	[674, 785[a]]

Rx Day calculated relative to first dose date of risankizumab.

a. The minimum of upper bound and within 105 days of last dose of risankizumab.

The time windows specified in Table 17, Table 18, Table 19, Table 20, Table 21 and Table 22 will be used for the summary of study drug injections of each period.

Table 17. Visit Windows for Summary of Study Drug Injections for Part A1

Window Label	Target Day	Interval
Week 0	1	≤ 1
Week 4	29	[2, 57[a]]

Rx Day calculated relative to the first dose date of study drug.

a. Before the first dose date of study drug on or after Week 16.

Table 18. Visit Windows for Summary of Study Drug Injections for Part A2

Window Label	Target Day	Interval
Week 16	1	≤ 1

Rx Day calculated relative to the Week 16 dose date.

Table 19. Visit Windows for Summary of Study Drug Injections for Part B

Window Label	Target Day	Interval
Week 28	1	≤ 1
Week 40	85	[2, 127]
Week 52	169	[128, 211]
Week 64	253	[212, 295]
Week 76	337	[296, 379]
Week 88	421	[380, 463[a]]

Rx Day calculated relative to the first dose date of study drug in Part B.

a. Before retreatment.

Table 20. Visit Windows for Summary of Study Drug Injections for Subjects Retreated with Risankizumab for Relapse from Week 32 Through Week 70 (Inclusive)

Window Label	Target Day	Interval
Week 0	1	≤ 1
Week 4R	29	[2, 71]
Week 16R	113	[72, 155]

Rx Day calculated relative to the first dose date of retreatment.

Table 21. Visit Windows for Summary of Study Drug Injections for Subjects Retreated with Risankizumab for Relapse from Week 70 Through Week 82 (Inclusive)

Window Label	Target Day	Interval
Week 0	1	≤ 1
Week 4R	29	[2, 57]

Rx Day calculated relative to the first dose date of retreatment.

Table 22. Visit Windows for Summary of Study Drug Injections for Subjects Retreated with Risankizumab for Relapse After Week 82

Window Label	Target Day	Interval
Entry of retreatment	1	≤ 1

Rx Day calculated relative to the first dose date of retreatment.

Definition of Missing Data Imputation

No global imputation is taking place at the database level. Efficacy related imputations are outlined in Section 10.0. There is no imputation for missing values in the safety analyses.

Rounding of Numeric Results

Rounding will be performed for presentation of results. No rounding will be performed before or during analyses. The ROUND function of SAS will be used to round results.

When dichotomizing continuous variables, associated continuous variables will be rounded to 9 decimal points before applying the cutoff point to determine the response status (for example, percent change from baseline in PASI score will be rounded to 9 decimal places before comparing to 90%).

The mean and median will be rounded for presentation to 1 decimal more than the data entered into the database. The standard deviation will be rounded to 2 decimal places more than the data entered into the database. The minimum and maximum values will be presented as entered into the database.

Probabilities will be rounded to 3 decimal places before assignment of statistical significance and will be presented in rounded format. Probabilities that round to zero or are reported by SAS as zero will be presented as "< 0.001." Probabilities that round to 1 or are reported by SAS as 1 will be presented as "> 0.999."

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

7.1 Demographic and Baseline Characteristics

Demographics and Baseline characteristics will be summarized for each arm and for overall of the ITT populations. Continuous variables will be summarized with the number of non-missing observations by mean, standard deviation, first quartile, median,

third quartile, minimum and maximum values. Categorical data will be summarized using frequencies and percentages. Statistical tests will be performed to assess the comparability of the two arms at Randomization on ITT_A1 and at Re-Randomization on ITT_B_R. Per Protocol Populations will only be summarized in the accountability table. Treatment comparison will be made based on non-missing information. Continuous variables will be analyzed using one-way analysis of variance (ANOVA). Categorical variables will be analyzed using a two-sided Pearson's Chi-Square test (or an appropriate exact test if expected cell count < 5).

The following demographic and baseline parameters will be summarized.

Subject Demographics

- Sex (male, female)
- Age (years), defined as the number of years from date of birth to date of first drug
- Age categories (< 40 years, ≥ 40 – < 65 years, ≥ 65 years.)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multi Race)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Body weight (kg)
- Body weight category (≤ 100 kg, > 100 kg)
- Height (cm)
- BMI (kg/m^2)
- BMI category (< 25, ≥ 25 – < 30, ≥ 30)
- Prior exposure to TNF antagonists (0 versus ≥ 1)

General Baseline Characteristics

- PASI (Psoriasis Area and Severity Index)
- BSA (Body Surface Area)
- sPGA categories

- NAPSI (Nail Psoriasis Severity Index)
- PSSI (Psoriasis Scalp Severity Index)
- PPASI (Palmoplantar Psoriasis Area Severity Index)
- Dermatology Life Quality Index (DLQI)
- HAQ-DI (HAQ Disability Index)
- Pain VAS (Visual Analog Scale)/Patient Global Assessment (PtGA) VAS (Visual Analog Scale)
- TJC/SJC (Tender/Swollen Joints)
- DAS28 (Disease Activity)

Psoriasis and Cardiovascular History

- Psoriatic arthritis (diagnosed, suspected, no)
- Cardiovascular Diseases (myocardial infarction, angina pectoris, transient ischemic attack, stroke, deep vein thrombosis)
- Cardiovascular Risk Factors (hypertension, hyperlipidemia, diabetes mellitus, obesity)

General Use

- Smoking status (Never-smoked, Ex-smoker, Currently smokes)
- Alcohol status (Non-drinker, drinks – no interference with participation in trial, drinks – possible interference with participation in clinical trial)

Prior Treatment

- Psoriasis Biologic Treatment History – by Response to Prior Treatment
- Psoriasis Treatment – by Therapy Type (topical therapy, phototherapy, photochemotherapy, non-biologic systemic therapy, TNF antagonist, other biologic)

Also, Physical Exam and Pregnancy Test will be presented in listing format.

7.2 Medical History

Medical history will be summarized using body systems and condition/diagnosis as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized for each treatment arm. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Previous Treatment 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 first dose of study drug. A concomitant medication is defined as any medication that started prior to the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started after the first dose of study drug, but not after the last dose of study drug plus 21 days. The number and percentage of subjects who had taken medications will be summarized by generic drug name assigned by the World Health Organization (WHO) for both prior and concomitant medications.

7.4 Protocol Deviations

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 she/he did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded or prohibited concomitant treatment

8.0 Patient Disposition

The number of subjects for each of the following categories will be summarized, for overall and for each treatment group in the ITT_A1 Population:

- Number of subjects randomized
- Number of subjects treated during Part A1
- Number of subjects who completed Part A1
- Number of subjects who discontinued study drug during Part A1
- Number of subjects who prematurely discontinued from Part A1

The number of subjects for each of the following categories will be summarized, for overall and for each treatment group in the ITT_B_R population:

- Number of subjects re-randomized
- Number of subjects treated at Part B
- Number of subjects who completed the Part B
- Number of subjects who received retreatment with risankizumab during Part B at different time points
- Number of subjects who discontinued study drug during Part B
- Number of subjects who prematurely discontinued from the Part B

In addition, the reasons for premature discontinuation will be summarized with frequencies and percentages.

Disposition tables will also be summarized in the ITT_A2, ITT_ARM2, and ITT_B_NR Populations.

In addition to patient disposition, number of screening failures and reasons for screening failure will also be summarized among all screened subjects in a subject screening status table.

9.0 Study Drug Exposure and Compliance

Summary of study drug exposure will be provided for each treatment arm for all ITT_A1, ITT_A2, ITT_ARM2, ITT_B_R, and ITT_B_NR populations, and the ALL_RZB population. Study drug compliance will be summarized in ITT_A1, ITT_A2, and ITT_B_R populations.

Study drug exposure (days) will be summarized using the sample size, mean, standard deviation, minimum, median and maximum for each treatment part. In addition cumulative exposure of RZB will be also summarized in the ALL_RZB Population. Study drug exposure will be summarized as follows:

Study Drug Exposure (in Days) in Each Period:

Part A1:

For subjects who did not continue into Part A2:

- Date of last injection in Part A1 – Date of first injection in Part A1 + 84.

For subjects who continued into Part A2: the minimum of

- Date of first injection in Part A2 – Date of first injection in Part A1.
- Date of last injection in Part A1 – Date of first injection in Part A1 + 84 days.

Part A2:

For subjects who did not continue into Part B:

- Date of last injection in Part A2 – Date of first injection in Part A2 + 84 days.

For subjects who continued into Part B: the minimum of

- Date of first injection in Part B – Date of first injection in Part A2.
- Date of last injection in Part A2 – Date of first injection in Part A2 + 84 days.

Part B:

For subjects who did not receive retreatment with risankizumab: the minimum of

- Date of last injection in Part B – Date of first injection in Part B + 84 days.
- Cutoff date of 01 September 2017 – Date of first injection in Part B (only for the primary analysis after the last patient either has completed Week 52 visit or discontinues from the study)

For subjects who received retreatment with risankizumab: the minimum of

- Date of first injection of retreatment – Date of first injection in Part B.
- Date of last injection in Part B – Date of first injection in Part B + 84 days.
- Cutoff date (01 September 2017) – Date of first injection in Part B (only for the primary analysis after the last patient either has completed Week 52 visit or discontinues from the study)

ALL_RZB:

For subjects who were re-randomized to placebo in Part B and received retreatment with risankizumab: the minimum of

- Date of last injection of risankizumab in Part A – Date of first injection of risankizumab + 84 days + Date of last retreatment of risankizumab – Date of first retreatment of risankizumab + 84 days.
- Date of last injection of risankizumab in Part A – Date of first injection of risankizumab + 84 days + Cutoff date for retreatment (22 September 2017) – Date of first retreatment of risankizumab (only for the primary analysis after the last patient either has completed Week 52 visit or discontinues from the study).

For all other subjects: the minimum of

- Date of last injection of risankizumab – Date of first injection of risankizumab + 84 days.

- Cutoff date (01 September 2017) – Date of first injection of risankizumab (only for the primary analysis after the last patient either has completed Week 52 visit or discontinues from the study)

Compliance

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 scheduled time point, the denominator for each week will include all subjects in each analysis population who have not prematurely discontinued study drug prior to the scheduled study drug injection. Subjects who have prematurely discontinued the study drug but have not prematurely discontinued the study are not used in the denominator.

10.0 Efficacy Analysis

10.1 General Considerations

The treatment effect will be evaluated based on a two-sided significance level of 0.05 (when rounded to three decimal places).

The Primary Analysis for Period B re-randomized subjects will be conducted after the last patient either has completed Week 52 visit or discontinues from the study, and at the time approximate to the database lock of all other global pivotal Phase 3 psoriasis studies, whichever occurs later. All endpoints will be analyzed up to Week 52, with the following exception:

- Categorical endpoints related to PASI and sPGA, using the LOCF method (defined in Section 10.1.4), will be analyzed up to the last visit that at least one subject has observed PASI and sPGA measurements, respectively.

To best maintain the study integrity for data beyond Week 52, blinded treatment assignments will not be disseminated to the sites, investigators, and patients until the end of study database lock.

Efficacy variables will be summarized in all efficacy populations. The efficacy analysis will be conducted in the ITT_A1 and the ITT_B_R populations. Only the primary and ranked secondary variables will be analyzed for the per-protocol populations using primary approach to handle missing data as described below.

Subjects' actual weight category and prior TNF antagonist exposure will be used as the strata in the stratified analyses.

10.1.1 Analyses of Categorical Variables

For categorical variables, frequencies and percentages will be summarized. Treatment comparison will be conducted using a Cochran-Mantel-Haenszel (CMH) test with stratification factors as strata for the analysis. The CMH test will use weights proposed by Greenland & Robins, which is calculated as follows:

$\hat{\delta}_{MH} = \frac{\sum_{i=1}^{u} w_i \cdot \hat{\delta}_i}{\sum_{i=1}^{u} w_i}$, where

$\hat{\delta}_i = \frac{x_i}{n_i} - \frac{y_i}{m_i}$ denotes the risk difference in stratum $i, i = 1, \cdots, u$

$w_i = \frac{n_i \cdot m_i}{n_i + m_i}$ denotes the weight of stratum $i, i = 1, \cdots, u$

x_i denotes the number of patients with event in treatment_1 in stratum i, $i = 1, \cdots, u$

y_i denotes the number of patients with event in treatment_2 in stratum i, $i = 1, \cdots, u$

n_i denotes the number of patients on treatment_1 in stratum i, $i = 1, \cdots, u$

m_i denotes the number of patients on treatment_2 in stratum i, $i = 1, \cdots, u$

The estimated variance of $\hat{\delta}_{MH}$ is calculated as:

$$\widehat{var}(\hat{\delta}_{MH}) = \frac{\sum_{i=1}^{u} L_i}{(\sum_{i=1}^{u} w_i)^2}$$

where $L_i = \frac{x_i(n_i - x_i)\, m_i^3 + y_i(m_i - y_i)\, n_i^3}{n_i \cdot m_i \cdot (n_i + m_i)^2}$, $i = 1, \cdots, u$

Assuming a normal distribution of $\hat{\delta}_{MH}$, an approximate 95% CI is given as follows, where $z_{0.975}$ is the 97.5% quantile of the standard normal distribution:

$$CI = \left[\hat{\delta}_{MH} \pm z_{0.975} \cdot \sqrt{\widehat{var}(\hat{\delta}_{MH})}\right]$$

Also, the approximate p-value can be calculated using the following:

$$\text{pvalue} = 2 \cdot \Pr\left[Z > \left|\frac{\hat{\delta}_{MH}}{\sqrt{\widehat{var}(\hat{\delta}_{MH})}}\right|\right], \text{where } Z \sim N(0,1)$$

If there is a stratum for a treatment group that has 0 subjects in any cell in the contingency table, all cells from the stratum will be added by 0.1 in order to prevent dividing by 0 in the above equations, as suggested in Greenland & Robins.

10.1.2 Analyses of Continuous Variables

For continuous variables, the model based mean and standard error will be presented. The Baseline and visit means will also be presented for each treatment group for subjects who have both Baseline and post Baseline visit values. The treatment groups will be compared using ANCOVA with treatment group, Baseline value, and stratification factors in the model.

10.1.3 Analyses of Time-to-Event Variables

Time to first achievement of endpoints will only be performed in ITT_A1 up to Week 16. The time to event will be calculated as:

- Time to first achievement (with observed event) = [date of first achievement] – [date of first dose] + 1
- If a subject never attains Endpoint at the end of evaluation period, that subject's time to first achievement will be censored at the last visit where the variable was measured

Time to loss-of-response (and time to relapse) endpoints will only be performed in ITT_B_R Population among those who achieved response at Re-Randomization. The time to failure events will be calculated as:

- Subjects will be a considered as failures if they subsequently lost the response, or discontinue from the study due to AE of "Worsening of disease under study," or receive retreatment with risankizumab.
- Time to failure events = [date of failure] – [date of first dose in Part B] + 1
- Subjects who maintain Endpoint throughout the study, or discontinued from the study due to reasons other than above, will be censored at their last measurement.

Both time to first achieving endpoints and time to loss-of-response endpoints will be analyzed using Kaplan-Meier estimates for each treatment group. In the ITT_A1 and ITT_B_R populations, treatments will be compared using stratified Log-rank test.

10.1.4 Missing Data Imputations

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. The only exception is when the subject is a responder both before and after a specific visit window, then the subject will be categorized as a responder for the visit. Only observations within the same analysis period will be used except for summary of ITT_A2 from ARM 1, where subjects' observation from Part A1 can be used since the treatment is the

same. The NRI will be the primary approach in the analyses of categorical variables.

- Last Observation Carried Forward (LOCF): The LOCF analyses will use the last observed non-missing evaluation (last completed non-missing evaluation, from composite endpoint) from the previous visit within the particular period for efficacy measures assessed to impute missing data at later visits in the same period. Baseline efficacy evaluations will not be carried forward. Of note, post-baseline observations from Part A1 can be carried forward to ITT_A2 subjects from ARM 1 since treatment is the same. LOCF will be the primary approach in the analyses of continuous variables, and the secondary approach in the analysis of categorical variables.
- As-Observed Cases (OC): The as-observed 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 as-observed analysis for that visit. As-observed analysis will be the secondary approach in the analysis of continuous variables.
- Multiple Imputation (MI): The MI will be used as sensitivity approach to impute missing data in primary and ranked secondary endpoints. The variables to be included in the imputation model are listed below. If MI is not applicable due to the nature of our data (e.g., MCMC algorithm does not converge), logistic regression or mixed effect model repeat measurement (MMRM) methods will be applied as sensitivity approach, whichever applicable.

The Multiple Imputation analysis will be carried out in three steps.

- Imputation of missing data. The imputation will be generated for each efficacy endpoint measurement. The variables to be included in the imputation model are: Baseline disease severity (PASI and sPGA), Baseline weight (continuous variable), treatment group, actual prior TNF antagonist exposure, and measurements at each visit from randomization (or re-randomization) up to the end of the analysis period. For each endpoint, 20 'complete' datasets will be generated using SAS PROC MI. The imputed post-baseline measurements

will be rounded to the same precision as the observed data before the determination of responder status (e.g., PASI 90).

- Analysis of imputed data sets. A CMH test, stratified by stratification factors, will be used to analyze categorical endpoints in each imputed dataset.
- Synthesis of imputation and analysis results. SAS PROC MIANALYZE will be used to generate the final inferences of the risk difference between treatment groups.

Of note, subjects who discontinued due to AE of "Worsening of disease under study," or received retreatment with risankizumab for relapse during Part B, will be counted as non-responders in all visits thereafter in the NRI and MI analyses, and will have their last observation prior to discontinuation or retreatment with risankizumab carried forward in the LOCF analyses.

10.2 Primary Efficacy Analysis

10.2.1 Primary Efficacy Analysis in Part A

There are two co-primary endpoints to assess the efficacy of risankizumab 150 mg for the treatment of moderate to severe plaque psoriasis in Part A. These are as follows:

- Achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 16
- Achievement of an sPGA of clear or almost clear (0 or 1) at Week 16

The primary null hypotheses are that risankizumab 150 mg is not different from placebo in achieving PASI 90 and in achieving sPGA of clear or almost clear at Week 16.

The achievement of PASI 90 at Week 16 is the first co-primary endpoint. The difference in proportion of subjects achieving PASI 90 between treatment arms will be estimated and tested using the Cochran-Mantel-Haenszel risk difference estimate stratified by the stratification factors of baseline weight (≤ 100 kg vs. > 100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1).

The achievement of a sPGA of clear or almost clear at Week 16 is the second co-primary endpoint. The analysis method for the sPGA co-primary endpoint will be identical to that of the PASI 90 co-primary endpoint detailed above.

The co-primary endpoints of PASI 90 and sPGA clear or almost clear need to be significant simultaneously. Both endpoints will be tested using a two-sided test with a type I error rate of 0.05.

The primary analysis will be carried out in the ITT_A1 Population and the PP_A1 Population. Non-responder imputation will be used as the primary approach for missing values. LOCF and MI will be performed as sensitivity analyses.

10.2.2 Primary Efficacy Analysis in Part B

Achievement of an sPGA of clear or almost clear (0 or 1) at Week 52 is the primary endpoint for Part B under re-randomization. This endpoint will be tested independently with a type I error rate of 0.05, for the ITT_B_R Population. A sensitivity analysis will also be performed on the same endpoint for the PP_B_R Population.

10.3 Secondary Efficacy Analyses

10.3.1 Ranked Secondary Efficacy Analysis

10.3.1.1 Ranked Secondary Efficacy Analysis in Part A

The ranked secondary endpoints in Part A are in ranked order as follows:

1. Achievement of ≥ 75% reduction from baseline PASI score (PASI 75) at Week 16
2. Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 16
3. Achievement of sPGA of clear at Week 16
4. Achievement of DLQI score of 0 or 1 at Week 16

Ranked secondary endpoints above will be analyzed for the ITT_A1 Population. The same methods as discussed for the primary analyses will be used. The following null hypotheses will be tested in a hierarchical order using two-sided tests with a type I error of 0.05 only if the null hypothesis for the co-primary endpoints in Part A1 has been rejected:

1. Risankizumab is not different from placebo with respect to PASI 75 response at Week 16
2. Risankizumab is not different from placebo with respect to PASI 100 response at Week 16
3. Risankizumab is not different from placebo with respect to achieving an sPGA of clear at Week 16
4. Risankizumab is not different from placebo with respect to achieving a DLQI score of 0 or 1 at Week 16.

10.3.1.2 Ranked Secondary Efficacy Analysis in Part B

The ranked secondary endpoint for Part B is the achievement of sPGA of clear or almost clear (0 or 1) at Week 104.

This ranked secondary endpoint will be analyzed for the ITT_B_R Population. The same methods as discussed for the primary analyses will be used.

The null hypotheses below will be tested in a hierarchical order in the final analysis only, using two-sided tests with a type I error of 0.05 only if the null hypothesis for the primary endpoint in Part B has been rejected:

- Continuation of risankizumab is not different from switching to placebo with respect to sPGA of clear or almost clear (0 or 1) response at Week 104.

10.3.2 Other Secondary Efficacy Analysis

The other secondary endpoints are as follows:

- Achievement of PASI 75 at Week 52
- Achievement of PASI 90 at Week 52
- Achievement of PASI 100 at Week 52

Other secondary endpoints will be analyzed among the ITT_B_R Population.

10.3.3 Further Efficacy Endpoints

The further endpoints are as follows:

- Achievement of PASI 50 at all visits collected
- Achievement of PASI 75 at all visits collected
- Achievement of PASI 90 at all visits collected
- Achievement of PASI 100 at all visits collected
- Time to the first achievement of PASI 50, PASI 75, PASI 90, and PASI 100
- Time to loss of PASI 50, PASI 75, PASI 90, and PASI 100 response for subjects re-randomized at Week 28
- Change and percent change from baseline in PASI at all visits collected
- Achievement of PASI < 3 at all visits collected
- Proportion of subjects with at least 25% increase in PASI from baseline within 60 days after re-randomization for subjects re-randomized to placebo at Week 28
- Achievement of sPGA of clear or almost clear at all visits collected
- Achievement of sPGA of clear at all visits collected
- Time to the first achievement of sPGA of clear or almost clear
- Time to loss of sPGA of clear or almost clear response for subjects re-randomised at Week 28
- Time to sPGA of ≥ 3 (relapse) for subjects re-randomised at Week 28
- Change from baseline in DLQI at all visits collected

- Achievement of a DLQI score of 0 or 1 at all visits collected
- Achievement of a reduction of 5 or more points from baseline in DLQI score at all visits collected, among subjects with baseline DLQI ≥ 5
- Change from baseline in HAQ-DI at all visits collected, among subjects with PsA confirmed via ClASsification of Psoriatic Arthritis (CASPAR) and had baseline value > 0
- Achievement of a reduction of 0.3 or more from baseline HAQ-DI at all visits collected, among subjects with PsA confirmed via CASPAR and had baseline value ≥ 0.3
- Change and percent change from baseline on patient Pain VAS, among subjects with PsA confirmed via CASPAR and had baseline value > 0
- Achievement of a reduction of 10 or more from baseline Pain VAS at all visits collected, among subjects with PsA confirmed via CASPAR and had baseline value ≥ 10
- Change and percent change from baseline on patient Global Assessment VAS, among subjects with PsA confirmed via CASPAR and had baseline value > 0
- Change from baseline in Swollen or Tender Joint Count (28 joints) at all visits collected, among subjects with PsA confirmed via CASPAR and had baseline value > 0
- Change from baseline in DAS28 at all visits collected, among subjects with PsA confirmed via CASPAR and had baseline value > 0
- Change and percent change from baseline in Nail Psoriasis Severity Index (NAPSI) at all visits collected, in subjects with baseline NAPSI > 0
- Change and percent change from baseline in Palmoplantar Psoriasis Severity Index (PPASI) at all visits collected, in subjects with baseline PPASI > 0
- Change and percent change from baseline in Psoriasis Scalp Severity Index (PSSI) at all visits collected, in subjects with baseline PSSI > 0

10.4 Handling of Multiplicity

The statistical comparisons for the primary efficacy variable and the ranked secondary variables will be carried out in the hierarchical order. This means that statistically

significant results (P value ≤ 0.05) for the comparison in the higher rank (primary, then ranked secondary variables) are necessary to initiate the testing of the next comparison in the lower rank. Since a step-down procedure is used, each comparison will be tested at a significance level of 0.05 and overall alpha level of 0.05 will be preserved.

10.5 Efficacy Subgroup Analysis

To evaluate the consistency of the efficacy over demographic and other baseline characteristics, summaries and analyses will be performed for selected subgroups for the primary efficacy endpoints in Part A and the primary efficacy endpoint in Part B.

- Age group (< 40 years, ≥ 40 – < 65 years, ≥ 65 years)
- Sex (male, female)
- Race (white, non-white)
- Smoking (current, ex or never)
- BMI (normal: < 25, over weight: ≥ 25 – < 30, obese: ≥ 30)
- Region (US, Asia, Other)
- Baseline PASI score (by median)
- Baseline sPGA (3, 4)
- Psoriatic arthritis (yes [diagnosed or suspected], no)
- Ps Therapy History (Phototherapy or Photochemotherapy, TNF Antagonist, Other biologics, Non-biologic systemic therapy, All biologics, Naïve to all)

11.0 Safety Analysis

11.1 General Considerations

Safety analyses will include adverse events, laboratory, local tolerability, ECG, and vital sign measurements. Safety summaries will be provided using the safety population in each period as defined in Section 5.1. Comparison between risankizumab group and placebo group will be performed in the Safety Population in Safety_A1 and Safety_B_R populations. Continuous variables will be analyzed using one-way ANOVA and

categorical variables will be analyzed using Fisher's exact test. For analyses of AEs, only P values ≤ 0.100 when rounded to three digits will be presented.

Missing safety data will not be imputed.

11.2 Analysis of Adverse Events

11.2.1 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 105 days after the last dose of study drug in the analysis period, or prior to the first dose in the subsequent period for subjects who entered in to the subsequent period. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless the adverse event start time is prior to the study drug start time with the following exception:

- If an AE onset date is the same as the first dose of Part B and the AE time is missing, the AE is considered TEAE for the Part A2.

If an incomplete onset date is collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event is not treatment-emergent (e.g., the event end date is prior to the study drug start date).

Treatment-emergent adverse events (TEAE) for each safety population are defined as follows:

TEAEs of Safety_A1:

For subjects who do not enter Part A2, TEAEs are defined as any event with an onset after the first dose of study drug and no more than 105 days after the last dose of study drug.

For subjects who enter Part A2, TEAEs are defined as any event with an onset after the first dose of study drug and before the first dose of study drug in Part A2.

TEAEs of Safety_A2 for Subjects from ARM 1:

For subjects who do not enter Part B, TEAEs are defined as any event with an onset after the first dose of study drug in Part A2 and no more than 105 days after the last dose of study drug in Part A2.

For subjects who enter Part B, TEAEs are defined as any event with an onset after the first dose of study drug in Part A2 and prior to the first dose of study drug in Part B.

TEAE of Safety_ARM2:

TEAEs are defined as any event with an onset after the first dose of study drug in Part A2 or Part B and no more than 105 days after the last dose of study drug in the study.

TEAEs of Safety_B_NR:

TEAEs are defined as any event with an onset after the first dose of study drug in Part B and no more than 105 days after the last dose of study drug in the study.

TEAEs of Safety_B_R:

For subjects who do not receive retreatment with risankimumab, TEAEs are defined as any event with an onset after the first dose of study drug in Part B and no more than 105 days after the last dose of study drug in Part B.

For subjects who receive retreatment with risankimumab, TEAEs are defined as any event with an onset after the first dose of study drug in Part B and before the first dose of retreatment with risankimumab.

TEAEs of Safety_B_PBO_RT and Safety_B_RZB_RT:

TEAEs are defined as any event with an onset that is after the first dose of retreatment and no more than 105 days after the last dose of study drug.

TEAE of ALL_RZB:

TEAEs are defined as any event with an onset after the first dose of risankizumab through 105 days after the last dose of risankizumab, except for AEs with an onset during protocol-designed treatment gaps (i.e., placebo period) that was more than 105 days from the last dose of the previous risankizumab treatment and before the first dose of retreatment.

Summary tables will be presented as follows:

1. **Adverse Event Overview**

   The number and percentage of subjects experiencing treatment-emergent adverse events will be summarized for the following adverse event categories:

   - Any AE
   - Any AE that was assessed as related to study drug by the investigator
   - Any severe AE
   - Any serious AE (SAE)
   - Any serious AE that was assessed as related to study drug by the investigator
   - Any AE leading to discontinuation of study drug
   - Any AE leading to death
   - Any deaths
   - Areas of Safety Interest

2. **Adverse Events by System Organ Class and Preferred Term**

   TEAEs will be summarized and presented using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs). The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

   Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting

more than one type of adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one type of adverse event will be counted only once in the overall total.

In addition, the number and percentage of adverse events with causal relationship between the events and the study drug will be summarized using the same conventions described above.

3. Adverse Events by Maximum Severity

The severity grading of AEs follows Rheumatology Common Toxicity Criteria (RCTC).

- Grade 1 – mild
- Grade 2 – moderate
- Grade 3 – severe
- Grade 4 – life threatening

Adverse events will also be summarized by maximum severity. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity (Life threatening). In this case, the subject will be counted under the "Life-threatening" category.

4. Adverse Events by Maximum Relationship

Adverse events will be summarized by maximum relationship to study drug, as assessed by the investigator. Relationship of an AE to study drug is assessed by the investigator and collected in the CRF as 'Yes' or 'No.' If a subject has an adverse event with unknown relationship, the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship of "No." If the subject has another occurrence

of the same adverse event with a relationship assessment of "Yes," the subject will be counted under the "yes" category.

A listing of all pretreatment (i.e., events start prior to the first study drug injection) serious adverse events will be provided.

The following tables are planned.

Treatment-emergent adverse events will be summarized as follows:

- Grouped by SOC and PT
- Grouped by SOC, PT and maximum relationship to study drug
- Grouped by SOC, PT and maximum severity

Treatment-emergent serious adverse events will be summarized as follows:

- Grouped by SOC and PT
- A by-subject listing will be provided

Pre-treatment serious adverse events will be summarized as follows:

- A by-subject listing will be provided

Treatment-emergent adverse events leading to death or premature discontinuation of study drug will be summarized as follows:

- Grouped by SOC and PT
- Separate listings by subject for deaths and premature terminations of study drug due to adverse events will be provided.

Treatment-emergent areas of safety interest will be summarized as follows:

- Grouped by SOC and PT
- A listing by subject will be provided.

Areas of Safety Interest:

Areas of Safety Interest groupings are listed in Table 23. These events are of interest due to a higher rate in the moderate to severe psoriasis population, or of interest for all Ig products or products in general.

The final list will be based on the most updated final version of risankizumab Product Safety Statistical Analysis Plan, which is consistent to the most updated risankizumab Risk Management Plan.

Table 23. Areas of Safety Interest

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Adjudicated CV Events	Major adverse cardiovascular events (MACE)	Adjudicated events	Display underlined terms defined by the following adjudicated terms: • CV Death which includes CETERM values: Fatal CV, Fatal PE, Fatal Non-Cardiac/Non-Neuro Arterial Thrombosis/ Thromboembolism, Undetermined Death, Not assessable death (cardiac/neuro/thrombotic), Fatal Stroke • Myocardial infarction • Stroke	Y
	Extended MACE	Adjudicated events	Display underlined terms from MACE and underlined terms below: • Hospitalization for Unstable Angina • Coronary Revascularization Procedures	N

Table 23. Areas of Safety Interest (Continued)

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Adjudicated CV Events (continued)	Other CV events	Adjudicated events	Display underlined terms defined by the following adjudicated terms: • Thrombotic events which includes CETERM values: Deep Vein Thrombosis, TIA, Pulmonary Embolism, Non-fatal Non-Cardiac/Non-Neurological Arterial Thrombosis/ Thromboembolism, Other Venous Thrombosis, specified (non-fatal) • Cardiac arrhythmia which includes CETERM of: Clinically Significant Arrhythmia • Congestive heart failure which includes CETERM of Heart Failure • Hypertensive emergency	N
Serious infections, TB, fungal and opportunistic infections (including herpes zoster)	Serious infections	Serious PTs of the CMQ (company MedDRA query) Infections (CMQ 80000018)	PTs	Y
	TB	Tuberculosis (including Investigations) CMQ (code 80000033)	PTs	Y
	Opportunistic infections	Opportunistic infections CMQ (code 80000073	PTs	N

Table 23. Areas of Safety Interest (Continued)

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Serious infections, TB, fungal and opportunistic infections (including herpes zoster) (continued)	Fungal infections	Fungal infections CMQ (code 80000063)	PTs	N
	Herpes Zoster	Herpes zoster CMQ (code 80000175)	PTs	N
Malignancies	All possible malignancies	Narrow – Malignancies (SMQ 20000090)	PTs	N
	Malignant Tumours	Narrow – Malignant tumours (SMQ 20000194)	PTs	Y
	Non-melanoma skin cancer (NMSC)	Broad – Skin malignant tumours (SMQ 20000204) excluding terms identified by the Melanoma CMQ (code 80000119)	PTs	N
	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.	PTs	Y

Table 23. Areas of Safety Interest (Continued)

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Hypersensitivity Reaction	Hypersensitivity	Narrow – Hypersensitivity (SMQ 20000214)	PTs	Y – serious events only
	Anaphylactic Reaction	Narrow – Anaphylactic reaction (SMQ 20000021)	PTs	N
Hepatic Events	Hepatic Events	Broad – Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ 20000013) 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)	PTs	N

Adverse Event per 100 Patient-Years of Exposure

Adverse events occurring during the entire study will be presented by event rate per 100 patient-years. These will be presented for any TEAEs, serious adverse events, and Areas of Special Interest.

AEs per 100 patient-years of exposure is defined as the number of AEs divided by the total 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 study drug exposure (defined as date of last dose – date of first dose + 105 days (5 half-lives)) of all subjects normalized by 365.25, and rounded to one decimal place.

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

Deaths and all SAEs will be presented in listing format. In addition, SAEs and AE leading to study drug discontinuation will be summarized by System Organ Class and MedDRA Preferred Term.

11.2.3 Safety Subgroup Analysis

The AE overview and AE by SOC and PT in Safety_A1 and Safety_B_R populations will also be analyzed with respect to the actual values of stratification factors:

- Dichotomous weight (≤ 100 kg vs. > 100 kg)
- Prior exposure to TNF antagonists (0 versus ≥ 1)

11.3 Analysis of Laboratory Data

For the assessments of laboratory data, values observed more than 105 days after the last dose of study drug will be excluded.

Listing and descriptive statistics of laboratory values over time, changes from baseline, and extreme abnormal value on treatment will be provided. Extreme abnormal value is the value which is most significantly away from the reference range. Frequency of subjects with transitions relative to reference range and listing of subjects with significant abnormal laboratory values will be presented as well.

Analyses will be conducted in the Safety_A1 Population, the Safety_B_R Population, and the ALL_RZB Population.

For subjects who were re-randomized to placebo in Part B, laboratory values evaluated after 105 days from the last dose of risankizumab in Part A and before the first dose of retreatment will not be included in the summaries for the ALL_RZB Population.

11.3.1 Variables and Criteria Defining Abnormality

Clinical laboratory tests conducted in the study are listed in Table 24.

Table 24. Clinical Laboratory Tests

Category	Test Name
Haematology	Hematocrit (Hct) Hemoglobin (Hb) Glycosylated Hb (HbA1c) White Blood Cells/Leukocytes Platelet Count/Thrombocytes
Diff. Automatic	Neutrophils (relative and absolute count) Eosinophils (relative and absolute count) Lymphocytes (relative and absolute count)
Enzymes	AST (GOT) ALT (GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Amylase Lipase
Electrolytes	Calcium Sodium Potassium
Substrates	Glucose BUN Uric acid Creatinine eGFR (estimated by CKD-EPI formula) Bilirubin Total Albumin C-Reactive Protein (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol (calculated) HDL-Cholesterol
Urinalysis (Stix)	Urine Protein Urine Glucose

11.3.2 Statistical Methods

Analysis of Quantitative Laboratory Parameters (Hematology and Chemistry)

Though the protocol indicates utilizing the Rheumatology Common Toxicity Criteria (RCTC) scale for grading laboratory values, given that the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) scale includes a more comprehensive list of laboratory values; the lab analyses based on the NCI CTCAE scale will be presented. Changes from Baseline to each scheduled visit and to the final value in continuous laboratory parameters will be summarized with the mean, standard deviation and median. The Baseline and visit/final value means will also be presented for subjects who have both the Baseline and visit/final values (see Section 6.0 for the definition of Baseline and final values).

If there are multiple post-baseline measurements on the same day, average value will be used.

Shift Tables

Shift tables for changes from Baseline according to the normal range will be provided for each hematology, and clinical chemistry parameter. Shifts from Baseline to the following endpoints will be considered: minimum value, maximum value and final value. Categories of "low or normal" and "high or normal" will be included at Baseline in addition to the categories of "low," "normal," "high" and "missing."

If there are multiple post-baseline measurements on the same day, the last value will be used.

Potentially Clinically Important Laboratory Values

Frequencies and percentages of subjects with post Baseline lab values meeting the following criteria in Table 25 and Table 26 will be summarized. Of note, a post baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table 25. Criteria for Potentially Clinically Important Chemistry Values

		Definition of Potentially Clinically Important Current (Version 4) NCI CTCAE Grade 3 or Greater	
Chemistry Variables	**Units**	**Very Low**	**Very High**
TBL	mcmol/L		> 3.0 × 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
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
ALP			> 5.0 × ULN

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

Table 26. Criteria for Potentially Clinically Important Hematology Values

		Definition of Potentially Clinically Important Current (Version 4) Grade 3 or Greater
Hematology Variables	**Units**	**Very Low**
Hemoglobin	g/dL	< 8.0
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 important finding.

A separate listing will be provided that presents all of the subjects and values that are NCI CTCAE toxicity grade 3 or above. For each of these subjects, the whole course of the respective parameter will be listed. The NCI CTCAE grading is shown in Table 27 below:

Table 27. NCI CTCAE Grading

Test	Grade 1	Grade 2	Grade 3	Grade 4
SGPT/ALT increased	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
SGOT/AST increased	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
GGT increased	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
ALP increased	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
TBL increased	> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 10.0 × ULN	> 10.0 × ULN
Creatinine increased	> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 6.0 × ULN	> 6.0 × ULN
CPK increased	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 10.0 × ULN	> 10.0 × ULN
Hemoglobin decreased	< LLN – 100.0 g/L	< 100.0 – 80.0 g/L	< 80.0	
Neutrophil count decreased	< LLN – 1.5 × 10^9/L	< 1.5 – 1.0 × 10^9/L	< 1.0 – 0.5 × 10^9/L	< 0.5 × 10^9/L
WBC decreased	< LLN – 3.0 × 10^9/L	< 3.0 – 2.0 × 10^9/L	< 2.0 – 1.0 × 10^9/L	< 1.0 × 10^9/L
Lymphocyte count decreased	< LLN – 0.8 × 10^9/L	< 0.8 – 0.5 × 10^9/L	< 0.5 – 0.2 × 10^9/L	< 0.2 × 10^9/L

If there are multiple post-baseline measurements on the same day, the worst value will be used.

Liver Function Tests

Additional summaries will be presented for liver function tests including ALT or serum glutamic-pyruvic transaminase (SGPT), AST or serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase, and total bilirubin. Each laboratory value will be categorized as follows:

- < 1.5 × ULN
- ≥ 1.5 × ULN – < 3.0 × ULN
- ≥ 3.0 × ULN – < 5.0 × ULN
- ≥ 5.0 × ULN – < 10.0 × ULN
- ≥ 10.0 × ULN – < 20.0 × ULN
- ≥ 20.0 × ULN

Shift tables of Baseline to the maximum (relative to the normal range, i.e., the largest multiple relative to the upper limit of normal) values, and from Baseline to final value will be presented using these categories. A listing of potentially clinically important liver function laboratory values will be provided. The listing will include all subjects who met any of the following four criteria:

- ALT ≥ 3 × ULN, or
- AST ≥ 3 × ULN, or
- Alkaline phosphatase ≥ 1.5 × ULN, or
- Total bilirubin ≥ 2 × ULN.

A listing of possible Hy's Law cases, defined as those who meet all of the following conditions will be provided:

- ALT > 3 × ULN or AST > 3 × ULN
- Associated with an increase in bilirubin ≥ 2 × ULN
- Alkaline phosphatase < 2 × ULN.

11.4 Analysis of Vital Signs and Weight

Analyses will be conducted in the Safety_A1 Population, the Safety_B_R Population, and the ALL_RZB Population.

For subjects who were re-randomized to placebo in Part B, vital sign values evaluated after 105 days from the last dose of risankizumab in Part A and before the first dose of retreatment will not be included in the summaries for the ALL_RZB Population.

11.4.1 Variables and Criteria Defining Abnormality

The following vital sign parameters will be assessed: Systolic blood pressure [mmHg], Diastolic blood pressure [mmHg], Pulse [beats per minute], Respiratory rate [breaths per minute], Temperature [°C], Weight [kg]. The following table presents the Criteria for Potentially Clinically Important Vital Sign Findings. Of note, a post baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table 28. Criteria for Potentially Clinically Important Vital Sign Findings

Vital Sign	Category	Criteria for Potential Clinically Important Vital Signs
Systolic Blood Pressure	Low Value	≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High Value	≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic Blood Pressure	Low Value	≤ 50 mmHg and decrease ≥ 15 mmHg from Baseline
	High Value	≥ 105 mmHg and increase ≥ 15 mmHg from Baseline
Pulse	Low Value	≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High Value	≥ 120 bpm and increase ≥ 15 bpm from Baseline

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

11.4.2 Statistical Methods

Changes from Baseline to each visit and to the final value in vital sign parameters will be summarized with the mean, standard deviation and median. The Baseline and final value means will also be presented for subjects who have both the Baseline and final values (see Section 6.0 for the definition of Baseline and final values).

For baseline, if there are multiple measurements on the same day, the last measurement prior to the first dose of study drug will be used as the Baseline vital sign value. If there are multiple post-baseline measurements on the same day, average value will be used.

For systolic blood pressure, diastolic blood pressure and pulse, a listing of all subjects with any vital sign value meeting criteria for potentially clinically important values will be provided. For each of these subjects, the whole course of the respective parameter will be listed. The number and percentage of subjects who have at least one value meeting criteria for potentially clinically important values will be provided for each selected vital sign parameter.

11.5 Analysis of ECG Parameters

The ECG parameters will be assessed as scheduled in the study protocol.

Summary statistics for mean change from baseline for corrected QT interval (QTc) using Bazett (QTcB) and Fridericia (QTcF) corrections, aggregated, will be provided by analysis visits.

- Values for both QTcF and QTcB interval measurements will be categorized into the following: ≤ 450 ms, > 450 ms, > 480 ms, > 500 ms, or missing. For the scheduled visits, as well as baseline, the number and percentage of subjects within each category will be presented. Additionally, for each category, the number and percentage of subjects with a maximum QTcF interval falling into the category will be presented; a similar summary will be presented for QTcB intervals.
- For QTcF and QTcB intervals, the changes from baseline will be categorized into the following: < 30 ms, 30 ≤ – < 60 ms, ≥ 60 ms, or missing. For the scheduled visits, the number and percentage of subjects within each category will be presented. Additionally, for each category, the number and percentage of subjects with a maximum change from baseline in the QTcF interval falling into the category will be presented; a similar summary will be presented for QTcB intervals.

Analyses will be conducted in the Safety_A1 Population, the Safety_B_R Population, and the ALL_RZB Population.

11.6 Local Tolerability

Local tolerability of the subcutaneous injection will be assessed by the investigator according to 6 items: swelling, induration, heat, redness, pain, and other findings. Proportion of subjects reporting each condition will be summarized.

Local tolerability will be summarized in the Safety_A1 Population and the Safety_B_R Population. In addition, the overall rate (with at least one occurrence) during the study will also be presented in the ALL_RZB Population.

12.0 Pharmacokinetic Analysis

Pharmacokinetic analysis is not covered in this SAP.

13.0 Biomarkers Analysis

Biomarker Analysis is not covered in this SAP.

14.0 Summary of Changes

14.1 Summary of Changes Between the Latest Version of Protocol and the Current SAP

- Defined analysis populations (including the Per-protocol population) in detail.
- Clarified independent null hypothesis test hierarchy in the ITT Population in Part B consisting re-randomized subjects.
- Added additional ranked secondary endpoint to the ITT Population in Part B consisting re-randomized subjects: achievement of sPGA of clear or almost clear (0 or 1) at Week 104.
- Pre-specified Areas of Safety Interest.

14.2 Summary of Changes Between the Previous Version and the Current Version of the SAP

Updated Table 25, Table 27, and Table 28 based on Integrated Summary of Safety SAP.

Updated the end day for inclusion concomitant medications, based on Integrated Summary of Safety SAP.

15.0 Appendix

None.

16.0 References

None.

17.0 List of Tables, Figures and Data Listings That are to Be Programmed

To be provided in a separate document.