1.0 Title Page

Statistical Analysis Plan

Study 1311.30

Risankizumab Versus Adalimumab in a Randomized, Double Blind, Parallel Group Trial in Moderate to Severe Plaque Psoriasis to Assess Safety and Efficacy After 16 Weeks of Treatment and After Inadequate Adalimumab Treatment Response (IMMvent)

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 1311.30 dated 10 December 2015.

This SAP will provide details to further elaborate statistical methods as outlined in the Protocol 1311.30 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 main objectives of this study are to assess the efficacy and safety of risankizumab compared to adalimumab in subjects with moderate to severe chronic plaque psoriasis. The primary efficacy evaluation will be performed at Week 16. The study will also evaluate the efficacy of a 28-week treatment with risankizumab in subjects who were initially treated with adalimumab for 16 weeks, achieving insufficient or only partial response with adalimumab, and then switched to risankizumab treatment from Week 16 to Week 44.

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, exploratory biomarker analyses, and metabolic risk factor analyses, will not be included in this SAP.

4.2 Design Diagram

This confirmatory multi-national, randomized, double-blind, double dummy, active controlled, parallel design study compares risankizumab with adalimumab. In total, approximately 600 subjects with moderate to severe chronic plaque psoriasis will be randomized in this trial.

Subjects are included in the study once they have signed the informed consent. Subjects suitable after screening will be eligible to participate in the 44 week treatment period shown in Figure 1.

Subjects will be blinded to treatment. Subjects in each dose group will receive the same injections at each designated time point, in order to maintain blinding.

Part A:

Part A is a 16-week, double-blinded, active-controlled treatment period during which subjects will be randomized at a 1:1 ratio to risankizumab or adalimumab. The randomization will be stratified by weight (≤ 100 kg vs. > 100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1). Subjects randomized to risankizumab will receive 2 syringes of risankizumab active drug (2 × 75 mg) at randomization and at Week 4, and adalimumab placebo at randomization (2 syringes) and 1 adalimumab placebo syringe at Weeks 1, 3, 5, 7, 9, etc. up to Week 15. Subjects randomized to adalimumab will receive 2 syringes adalimumab at randomization (2 × 40 mg) followed by 1 syringe adalimumab (40 mg) at Weeks 1, 3, 5, 7, 9, 11, 13 and 15. These subjects will also receive 2 syringes of risankizumab placebo at randomization and at Week 4.

Part B:

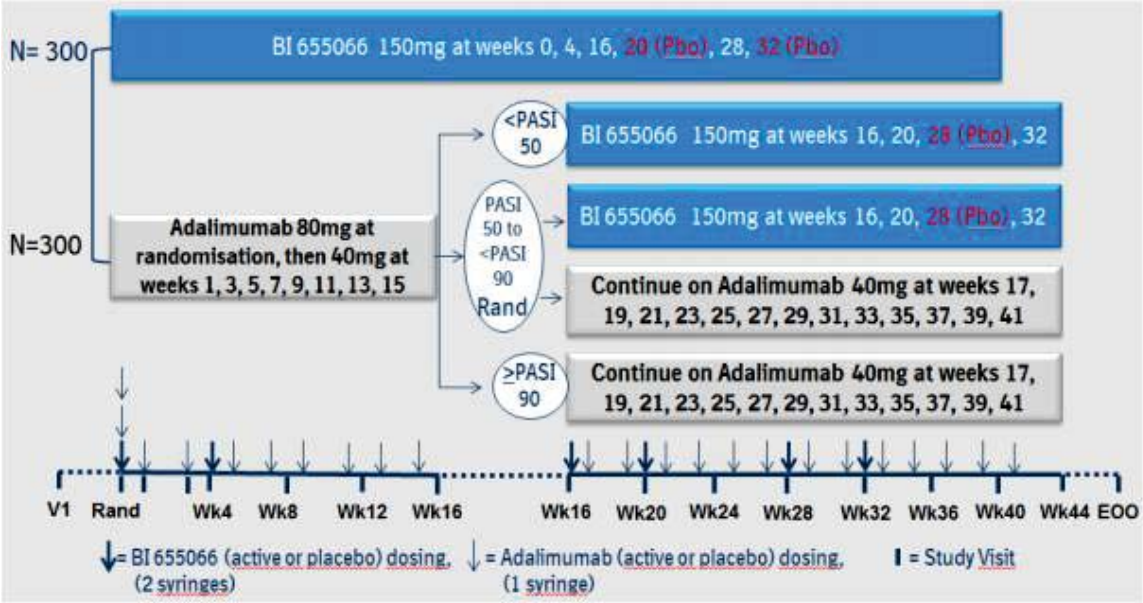
At Week 16, subjects initially on risankizumab will stay on risankizumab. These subjects will receive 2 syringes of risankizumab (2 × 75 mg) at Week 16 and 28, and 2 syringes of risankizumab placebo at Week 20 and 32. They will also receive 1 syringe of adalimumab placebo at Weeks 17, 19, 21, 23, etc. up to Week 41.

At Week 16, subjects initially on adalimumab and have < PASI 50 response (< 50% reduction in Psoriasis Area and Severity Index (PASI)) will be switched to risankizumab. These subjects will receive 2 syringes of risankizumab (2 × 75 mg) at Week 16, 20, and 32, and 2 syringes of risankizumab placebo at Week 28. They will also receive 1 syringe of adalimumab placebo at Weeks 17, 19, 21, 23, etc. up to Week 41.

At Week 16, subjects initially on adalimumab and ≥ PASI 90 will be stay on adalimumab. These subjects will receive 2 syringes of risankizumab placebo at Week 16, 20, 28 and 32. They will also receive 1 syringe of adalimumab at Weeks 17, 19, 21, 23, etc. up to Week 41.

At Week 16, subjects initially on adalimumab and ≥ PASI 50 and < PASI 90 will be re-randomized at a 1:1 ratio to risankizumab or adalimumab. Subjects re-randomized to risankizumab will receive 2 syringes of risankizumab (2 × 75 mg) at Week 16, 20 and 32, and 2 syringes of risankizumab placebo at Week 28. They will also receive 1 syringe of adalimumab placebo at Weeks 17, 19, 21, 23, etc. up to Week 41. Subjects re-randomized to adalimumab will receive 2 syringes of risankizumab placebo at Week 16, 20, 28 and 32. They will also receive 1 syringe of adalimumab at Weeks 17, 19, 21, 23, etc. up to Week 41.

Figure 1. Trial Design



BI 655066 is risankizumab.

4.3 Sample Size

This study is designed to show a benefit of risankizumab over adalimumab in terms of PASI 90 response and static Physician Global Assessment (sPGA) of clear or almost clear (sPGA of 0 or 1) at Week 16. This study is also powered to show a benefit in PASI 90 response at Week 44 between the subjects re-randomized to continue on adalimumab vs. subjects randomized to risankizumab at Week 16.

Based on the assumption that the Week 44 PASI 90 rate will be approximate 40% for adalimumab and 70% for risankizumab for the subjects who are re-randomized at Week 16, a total of 120 subjects will result in > 90% power for the primary efficacy analysis in Part B using a type-I error rate at 5%. See Table 1 sample size calculations for different scenarios. Assuming for those subjects originally randomized to adalimumab the response rate at Week 16 for PASI 90 and PASI 50 are 45% and 85%, respectively, then this leaves approximately 40% of subjects expected to fall in the more than or equal

to PASI 50 and less than PASI 90 range and thus be eligible for re-randomization. This requires that 300 (40% of 300 = 120) subjects be randomized to adalimumab at randomization.

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. For the primary analysis comparing risankizumab to adalimumab, sample sizes of 300 per arm will allow for > 90% power assuming 70% and 50% PASI 90 response rates for risankizumab and adalimumab, respectively. See Table 2 for more sample size calculations.

Table 1. Sample Sizes for 90% Power for Testing Against Adalimumab Using PASI 90 at Re-Randomization

Risankizumab	Adalimumab	Delta	Re-Randomization Ratio Risankizumab:Adalimumab = Total N
65%	40%	25%	82:82 = 164
70%	45%	25%	80:80 = 160
70%	40%	30%	56:56 = 112
75%	45%	30%	54:54 = 108
80%	50%	30%	51:51 = 102

Table 2. Sample Sizes for 90% Power for Testing Against Adalimumab Using PASI 90

Risankizumab	Adalimumab	Delta	Randomization Ratio Risankizumab:Adalimumab = Total N
65%	50%	15%	226:226 = 452
70%	55%	15%	217:217 = 434
70%	50%	20%	124:124 = 248
75%	55%	20%	118:118 = 236
70%	45%	25%	80:80 = 160
75%	50%	25%	77:77 = 154

Based on the outcome from Trials 1311.1 and 1311.2, the achievement of sPGA clear or almost clear rate at Week 16 is assumed to be at least 85% in the risankizumab arm.

Assuming 70% rate for the adalimumab arm, by using the PASI 90 required sample sizes, 300 subjects per treatment arm will provide at least 90% power for sPGA endpoint. See Table 3 for more sample size calculation.

As PASI 90 and sPGA are highly correlated, this trial will have > 90% power for comparing risankizumab arm to adalimumab arm on both of these endpoints.

Table 3. Sample Sizes for 90% Power for Testing Against Adalimumab Using sPGA Clear or Almost Clear

Risankizumab	Adalimumab	Delta	Randomization Ratio Risankizumab:Adalimumab = Total N
85%	72.5%	12.5%	223:223 = 446
85%	70%	15%	161:161 = 322
87.5%	72.5%	15%	148:148 = 296
87.5%	70%	17.5%	113:113 = 226

Calculations were performed using ADDPLAN Version 6.0.4.

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.

No other interim analyses are planned.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Efficacy Population:

Intent to Treat (ITT) Populations: The ITT Population in each period will be used for efficacy analyses.

- The ITT Population in Part A (ITT_A) is defined as all subjects who are randomized at Baseline.
- The ITT Population in Part B who are re-randomized (ITT_B_RR) is defined as all subjects who start with adalimumab at Baseline and are re-randomized at Week 16.
- The ITT Population for PASI 90 responders at the entry of Part B (ITT_B_R) is defined as all subjects who start with adalimumab at Baseline and achieve PASI 90 at Week 16 and receive at least one dose of active adalimumab on or after Week 16.
- The ITT Population for PASI 50 non-responders at the entry of Part B (ITT_B_NR) is defined as all subjects who start with adalimumab at Baseline and fail to achieve PASI 50 at Week 16 and receive at least one dose of active risankizumab on or after Week 16.
- The ITT Population in Part B continuously receiving risankizumab (ITT_B_RZB) is defined as all subjects who start with risankizumab at Baseline and receive at least one dose of active risankizumab on or after Week 16.

The ITT Population will be analyzed by the treatment group as randomized and as re-randomized where applicable.

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 determined via classification prior to database lock for data pertaining to the DB period. The PP population at Part A (PP_A) is defined as all ITT_A subjects meeting all the following criteria:

- Subjects must receive at least 75% of planned risankizumab injections, as well as at least 75% of planned adalimumab injections, including dummy placebo injections, per randomized, in Part A.
- Subjects must have either a PASI or sPGA assessment post-baseline in Part A.
- Inclusion Criterion 4: Subjects must have stable moderate to severe chronic plaque psoriasis baseline:
  - Have an BSA ≥ 10% and
  - Have a PASI ≥ 12 and
  - Have an sPGA ≥ 3.

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

The PP Population at Part B for re-randomized subjects (PP_B_RR) is defined as all subjects from the ITT_B_RR Population who meet all the following criteria:

- Subjects must receive at least 75% of planned risankizumab injections, as well as at least 75% of planned adalimumab injections, including dummy placebo injections, per re-randomized, in Part B.
- Subjects must have at least one PASI assessment post re-randomization in Part B.
- Subjects must have a response of PASI 50 – < 90 at re-randomization.

The primary and ranked secondary efficacy endpoint at Part B at Week 44 will be analyzed on the PP_B_RR Population.

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

Safety Populations (Safety):

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

Each ITT Population will have a corresponding safety population (Safety) defined which require subjects to have at least one dose of active study drug during the analysis period.

Complete safety tables will be provided for the Safety_A Population and the Safety_B_RR population. 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 (Safety_A) and at the re-randomization visit (Safety_B_RR).

In addition, an All Risankizumab Treated Population (ALL_RZB) is defined as all subjects who receive at least one dose of risankizumab 150 mg in the study. The ALL_RZB Population will be used for safety analyses. Complete safety tables will be provided in the ALL_RZB Population.

Notations for Treatment Groups:

Part A:

- ADA: Subjects randomized to adalimumab
- RZB: Subjects randomized to risankizumab 150 mg

Part B:

- RZB/RZB: Subjects randomized to risankizumab and continue with risankizumab
- ADA/ADA: Subjects randomized to adalimumab and stay with adalimumab at Week 16
- ADA/RZB: Subjects randomized to adalimumab and switched to risankizumab at Week 16

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 treatments, stratified by weight (≤ 100 kg vs. > 100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1). Subjects will be randomized to risankizumab or adalimumab in a ratio of 1:1 within each level of stratification.

Subjects patients initially on adalimumab and ≥ PASI 50 and < PASI 90 will be re-randomized at Week 16 in a 1:1 ratio to receive either risankizumab or adalimumab. Re-randomization will also be stratified by 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 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 A is defined as:

- The last non-missing observation collected within 105 days following the last dose of study drug in Part A for subjects who were not dosed in Part B.
- 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 A 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 A.

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

Definition of Analysis Windows

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

For efficacy analyses, local tolerability, 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 tables.

Table 4. Visit Windows for PASI/sPGA and Vital Signs for Part A (ITT_A/PP_A/Safety_A Populations)

Window Label	Target Day	Time Window
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 the first dose of study drug. For subjects randomized but not dosed, Rx Day calculated relative to randomization.

a. 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 5. Visit Windows for Laboratory and ECG Parameters for Part A (Safety_A Population)

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

Rx Day calculated relative to the 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 (and within 105 days of last dose for safety analyses).

Table 6. Visit Windows for Other Efficacy Endpoints Only Collected at Week 16 in Part A (ITT_A Population)

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

Rx Day calculated relative to the 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 7. Visit Windows for Local Tolerability for Part A (Safety_A Population)

Window Label	Target Day	Time Window
Week 1	8	[2,15]
Week 3	22	[16, 25]
Week 4	29	[26, 71]
Week 16	113	[72, 155[a]]

Rx Day calculated relative to the first dose 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) (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 8. Visit Windows for Analysis of PASI and sPGA in Part B (ITT_B_RR/ITT_B_R/ITT_B_NR/ITT_B_RZB/PP_B_RR Populations)

Window Label	Target Day	Time Window
Entry of B	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]

Rx Day calculated relative to the first dose 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.

Table 9. Visit Windows for Laboratory and ECG Parameters for Part B (Safety_B_RR Population)

Window Label	Target Day	Time Window
Entry of B	1	≤ 1
Week 28	85	[2, 141]
Week 44	197	[142, 211]
Week 48 (EOT + 4 Weeks)	225	[212, 239[a]]

Rx Day calculated relative to the first dose 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. The minimum of upper bound and 105 days of last dose for safety analyses.

Table 10. Visit Windows for Vital Signs for Part B (Safety_B_RR Population)

Window Label	Target Day	Time Window
Entry of B	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 (EOT + 4 Weeks)	225	[212, 239[a]]

Rx Day calculated relative to the first dose 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.

a. The minimum of upper bound and 105 days of last dose for safety analyses.

Table 11. Visit Windows for Other Efficacy Endpoints Only Collected at Week 44 in Part B (ITT_B_RR/ITT_B_R/ITT_B_NR/ITT_B_RZB/PP_B_RR Populations)

Window Label	Target Day	Time Window
Entry of B	1	≤ 1
Week 44	197	[2, 393]

Rx Day calculated relative to the first dose 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.

Table 12. Visit Windows for Local Tolerability for Part B (Safety_B_RR Population)

Window Label	Target Day	Time Window
Week 28	85	[2, 141]
Week 44	197	[142, 253[a]]

Rx Day calculated relative to the first dose 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.

a. The minimum of upper bound and 105 days of last dose for safety analyses.

Note. There is no local tolerability at re-randomization and after EOT.

Table 13. Visit Windows for Laboratory and ECG Parameters for ALL_RZB Population

Window Label	Target Day	Time Window
Baseline	1	≤ 1
Week 4	29	[2, 71]
Week 16	113	[72, 155]
Week 28	197	[156, 253]
Week 44	309	[254, 323]
Week 48 (EOT + 4 Weeks)	337	[324, 351[a]]

Rx Day calculated relative to the first dose of risankizumab.

a. The minimum of upper bound and 105 days of last dose of risankizumab for safety analyses.

Table 14. Visit Windows for Vital Signs for ALL_RZB Population

Window Label	Target Day	Time Window
Baseline	1	≤ 1[a]
Week 4	29	[2, 43]
Week 8	57	[44, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 127]
Week 20	141	[128, 155]
Week 24	169	[156, 183]
Week 28	197	[184, 211]
Week 32	225	[212, 239]
Week 36	253	[240, 267]
Week 40	281	[268, 295]
Week 44	309	[296, 323]
Week 48 (EOT + 4 Weeks)	337	[324, 351[b]]

Rx Day calculated relative to the first dose of risankizumab.

a. If time is collected in vital signs, restrict to records prior to the first dose of risankizumab.

b. The minimum of upper bound and 105 days of last dose of risankizumab for safety analyses.

Table 15. Visit Windows for Local Tolerability Parameters for ALL_RZB Population

Window Label	Target Day	Time Window
Week 1	8	[2, 15]
Week 3	22	[16, 25]
Week 4	29	[26, 71]
Week 16	113	[72, 155]
Week 28	197	[156, 253]
Week 44	309	[254, 323[a]]

Rx Day calculated relative to the first dose of risankizumab.

a. The minimum of upper bound and 105 days of last dose of risankizumab for safety analyses.

The time windows specified below will be used for the summary of study drug injections of each period.

Table 16. Visit Windows for Summary of RZB Injections for Part A

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

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

a. Before the first dose on or after Week 16.

Table 17. Visit Windows for Summary of RZB Self-Administration Questionnaire in Part A

Window Label	Target Day	Time Window
Week 4	29	[2, 57[a]]

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

a. Before the first dose on or after Week 16.

Table 18. Visit Windows for Summary of RZB Injections for Part B and RZB Self-Administration Questionnaire

Window Label	Target Day	Time Window
Week 16	1	≤ 1
Week 20	29	[2, 57]
Week 28	85	[58, 99]
Week 32	113	[100, 127]

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

Table 19. Visit Windows for Summary of ADA Injections for Part A

Window Label	Target Day	Time Window
Week 0	1	≤ 1
Week 1	8	[2, 15]
Week 3	22	[16, 29]
Week 5	36	[30, 43]
Week 7	50	[44, 57]
Week 9	64	[58, 71]
Week 11	78	[72, 85]
Week 13	92	[86, 99]
Week 15	106	[100, 113]

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

Table 20. Visit Windows for Summary of ADA Injections for Part B

Window Label	Target Day	Time Window
Week 17	8	[1, 15]
Week 19	22	[16, 29]
Week 21	36	[30, 43]
Week 23	50	[44, 57]
Week 25	64	[58, 71]
Week 27	78	[72, 85]
Week 29	92	[86, 99]
Week 31	106	[100, 113]
Week 33	120	[114, 127]
Week 35	134	[128, 141]
Week 37	148	[142, 155]
Week 39	162	[156, 169]
Week 41	176	[170, 183]

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

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_A and at Re-Randomization on ITT_B_RR. 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 (Static Physician Global Assessment)

- NAPSI (Nail Psoriasis Severity Index)
- PSSI (Psoriasis Scalp Severity Index)
- PPASI (Palmoplantar Psoriasis Area Severity Index)
- Dermatology Life Quality Index (DLQI)
- WLQ (Work Limitations Questionnaire)

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, drinks – possible interference)

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_A population:

- Number of subjects randomized

- Number of subjects treated during Part A
- Number of subjects who completed Part A
- Number of subjects who discontinued study drug during Part A
- Number of subjects who prematurely discontinued from the Part A

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

- Number of subjects re-randomized
- Number of subjects treated during Part B
- Number of subjects who completed Part B
- 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_B_R, ITT_B_NR, and ITT_B_RZB 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 in each treatment part in the corresponding ITT populations. Study drug compliance will be summarized in ITT_A, ITT_B_RR 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 Part:

Part A:

- For subjects who did not continue into Part B:
  - Date of last injection in Part A – Date of first injection in Part A + 14 days (ADA)
  - Date of last injection in Part A – Date of first injection in Part A + 84 days (RZB)
- For subjects who continued into Part B: the minimum of
  - Date of first injection in Part B – Date of first injection in Part A.
  - Date of last injection in Part A – Date of first injection in Part A + 14 days (ADA)
  - Date of last injection in Part A – Date of first injection in Part A + 84 days (RZB)

Part B:

- Date of last injection in Part B – Date of first injection in Part B + 14 days (ADA)
- Date of last injection in Part B – Date of first injection in Part B + 84 days (RZB)

ALL_RZB:

For study drug exposure during the administration of risankizumab in the ALL_RZB Population:

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

Compliance

There will be a summary of the number of subjects receiving study drug and dose at each scheduled study drug administration time point for adalimumab and for risankizumab, separately. 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 (or prematurely discontinued from study) prior to the scheduled study drug injection.

Self-Administration of Risankizumab Questionnaire

There will be a summary of the self-administration of risankizumab questionnaire completed by supervising nurse/health care professional.

The following items will be summarized as-observed at each visit:

- Patient able to inject all of the liquid (Yes/No)
- Reason for unable to inject all of the liquid (Unable to remove the needle cap; Unable to fully push down the plunger; Unable to empty the syringe; More than a drop of medication remained on their skin; Other)
- Injection site (Left lower abdomen; Right lower abdomen; Left thigh; Right thigh)
- Helped by supervising personnel (Yes/No)

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).

Efficacy variables will be summarized in all ITT populations. The efficacy analysis will be conducted in the ITT_A and the ITT_B_RR 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. The treatment groups will be compared 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:

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

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

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

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_A Populations 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 the first dose] + 1

- If a subject never attains Endpoint in Part A, that subject's time to first achievement will be censored at the last visit where PASI (or sPGA) was measured

Time to loss-of-response (and time to relapse) endpoints will only be performed in ITT_B_RR 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 – "Worsening of disease under study."
- Time to failure events = [date of failure] – [date of the first dose in Part B] + 1.
- Subjects who maintain Endpoint throughout the study, or discontinued from the study due to reasons other than AE – "Worsening of disease under study," 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_A and ITT_B_RR 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 has a missing value at a specific visit as a non-responder for that visit. The only exception is when the subject is a responder both before and after this specific visit window, within the same analysis period, then the subject will be categorized as a responder for the visit. The NRI will be the primary approach in the analyses of categorical variables.
- Last Observation Carried Forward (LOCF): The LOCF analyses will use the completed evaluation from the previous visit within the particular analysis period for efficacy measures assessed to impute missing data at later visits in the same analysis period. Baseline efficacy evaluations will not be carried forward. Of note, post-baseline observations from Part A can be carried

forward to the ITT_B_RZB subjects since treatment is the same. LOCF will be the primary approach in the analyses of continuous variables, and the secondary approach in the analyses 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 analysis 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, treatment group, prior TNF 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 – "Worsening of disease under study" 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 carried forward in the LOCF analyses.

10.2 Primary Efficacy Analysis

Primary Efficacy Analysis in Part A:

There are co-primary endpoints to assess the efficacy of risankizumab for the treatment of moderate to severe plaque psoriasis. 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 is not different from adalimumab in achieving ≥ 90% reduction from baseline in the Psoriasis Area and Severity Index score (PASI 90) and sPGA of clear (0) or almost clear (1) at Week 16.

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

The achievement of a sPGA of clear or almost clear at Week 16 is the second co primary endpoint and is a binary variable with values of 0 or 1. The analysis of 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 compared to ADA will be tested using a two-sided test with a type I error of 0.05.

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

Primary Efficacy Analysis in Part B:

The primary endpoint in Part B is the achievement of PASI 90 at Week 44 for those subjects who are re-randomized at Week 16. This endpoint will be tested independently with a type I error rate of 0.05, for the ITT_B_RR Population. A sensitivity analysis will also be performed on the same endpoint for the PP_B_RR Population.

10.3 Secondary Efficacy Analyses

10.3.1 Ranked Secondary Efficacy Analyses

10.3.1.1 Ranked Secondary Efficacy Analysis in Part A

The ranked secondary endpoints in Part A are 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

Ranked secondary endpoints above will be analyzed in the ITT_A 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 has been rejected:

1. Risankizumab is not different from adalimumab with respect to PASI 75 response at Week 16
2. Risankizumab is not different from adalimumab with respect to PASI 100 response 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 100% reduction from baseline PASI score (PASI 100) at Week 44.

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

The null hypotheses below 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 primary endpoint in Part B has been rejected:

1. Continuation of risankizumab is not different from switching to risankizumab with respect to PASI 100 response at Week 44.

10.3.2 Other Secondary Efficacy Analysis

The other secondary endpoints are as follows:

- Achievement of an sPGA of clear or almost clear at Week 44
- Achievement of sPGA of clear at Week 44

Other secondary endpoints will be analyzed for the ITT_B_RR Population.

10.3.3 Further Endpoint Analyses

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 until the first achievement of PASI 50, PASI 75, PASI 90, PASI 100 and sPGA of clear or almost clear

- Time until loss of PASI 75, and sPGA of clear or almost clear
- Change and percent change from baseline in PASI at all visits collected
- Achievement of an sPGA of clear or almost clear at all visits collected
- Achievement of an sPGA of clear at all visits collected
- 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 WLQ at all visits collected
- 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 variables 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 in the following 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: $\geq 25 - < 30$, 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 adalimumab group will be performed in the Safety Population in Safety_A and Safety_B_RR populations. Continuous variables will be analyzed using one-way ANOVA and categorical variables will be analyzed using Fisher's exact test. For the 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. 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_A:

For subjects who do not enter Part B, 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 B, TEAEs are defined as any event with an onset after the first dose of study drug in Part A and before the first dose of study drug in Part B.

TEAEs of Safety_B_RR, Safety_B_R, 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.

TEAE of ALL_RZB:

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

The number and percent of subjects experiencing treatment-emergent TEAEs will be tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class and preferred term.

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 also be summarized and presented using primary Medical Dictionary for Regulatory Activities (MedDRA version 16.1 or later version) 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 21. 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 (DILI).

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 21. 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 21. 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 21. 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
Hypersensitivity Reaction	Hypersensitivity	Narrow – Hypersensitivity (SMQ 20000214)	PTs	Y – serious events only

Table 21. Areas of Safety Interest (Continued)

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Hypersensitivity Reaction (continued)	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, 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_A and Safety_B_RR 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_A Population, the Safety_B_RR Population, and the ALL_RZB Population.

11.3.1 Variables and Criteria Defining Abnormality

Clinical laboratory tests performed are listed below.

Table 22. Clinical Laboratory Tests

Category	Test Name
Haematology	Hematocrit (Hct) Hemoglobin (Hb) Glycosylated Hbc (HbA1c) White Blood Cells/Leukocytes Platelet Count/Thrombocytes
Diff. Automatic	Neutrophils (relative count) Eosinophils (relative count) Lymphocytes (relative 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 (blood urea nitrogen) Uric acid Creatinine eGFR (estimated by CKD-EPI formula) Bilirubin Total Albumin C-Reactive Protein (high sensitive) Cholesterol, total Triglycerides LDL-Cholesterol 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 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 23. 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 24. 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 25 below:

Table 25. 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 five 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_A Population, the Safety_B_RR Population, and 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 26. 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 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, $30 \leq - < 60$ 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_A Population, the Safety_B_RR 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 analyzed.

Analyses will be conducted in the Safety_A Population and the Safety_B_RR 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 will not be covered in this SAP.

13.0 Biomarkers Analysis

Biomarker Analysis is not covered in this SAP.

14.0 Summary of Changes

Not applicable. This is the first version of the SAP.

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 100% reduction from baseline PASI score (PASI 100) at Week 44.
- Pre-specified Areas of Safety Interest.

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

Updated Table 23, Table 25, and Table 26 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.

Document Approval

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