Statistical Analysis Plan for Study M23-702

A Phase 4 Multicenter, Randomized, Double-Blind Study of Risankizumab for the Treatment of Adult Subjects with Moderate to Severe Genital Psoriasis or Moderate to Severe Scalp Psoriasis

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Version 4.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for risankizumab Study M23-702, Genital or Scalp Psoriasis: A Phase 4 Multicenter, Randomized, Double-Blind Study of Risankizumab for the Treatment of Adult Subjects with Moderate to Severe Genital Psoriasis or Moderate to Severe Scalp Psoriasis.

Study M23-702 examines the efficacy and safety of risankizumab in adult individuals, at least 18 years old with moderate to severe genital psoriasis (Study-G) or moderate to severe scalp psoriasis (Study-S).

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

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

2.0 Study Objectives and Design

2.1 Study Objectives

Primary Objective

The primary objective of the study is to evaluate the efficacy and safety of risankizumab (RZB) for the treatment of moderate to severe genital psoriasis (Study-G) or moderate to severe scalp psoriasis (Study-S) in adults who are candidates for systemic therapy.

Primary Efficacy Endpoints

The primary efficacy endpoints are achievement of sPGA-G of 0 or 1 at Week 16 for subjects in Study-G, and achievement of scalp IGA of 0 or 1 at Week 16 for subjects in Study-S.

The hypotheses corresponding to the primary efficacy endpoints are:

- The proportion of subjects achieving sPGA-G of 0 or 1 in adult subjects with moderate to severe genital psoriasis at Week 16 in subjects randomized to RZB is greater than those randomized to placebo in Study-G.
- The proportion of subjects achieving scalp IGA of 0 or 1 in adult subjects with moderate to severe scalp psoriasis at Week 16 in subjects randomized to RZB is greater than those randomized to placebo in Study-S.

The estimands corresponding to the primary endpoints in Study-G and Study-S are defined as follows:

- Study-G: Difference in the proportion of subjects achieving sPGA-G of 0 or 1 in adult subjects with moderate to severe genital psoriasis at Week 16, regardless of premature discontinuation of study drug, in the RZB group compared with the placebo group.
- Study-S: Difference in the proportion of subjects achieving scalp IGA of 0 or 1 in adult subjects with moderate to severe scalp psoriasis at Week 16, regardless of premature discontinuation of study drug, in the RZB group compared with the placebo group.

Intercurrent events handling: No intercurrent event is considered.

Ranked Secondary Endpoints

The list of ranked secondary endpoints can be found in Section 3.2.

The hypotheses corresponding to the secondary endpoints are:

- Binary endpoints: The proportion of subjects achieving each endpoint in subjects treated with risankizumab is greater than those treated with placebo, in Study-G or Study-S.

- Continuous endpoint (change from Baseline in PSS for Study-S): The mean reduction from Baseline in PSS at Week 16 in subjects treated with risankizumab is greater than those treated with placebo in Study-S.

The estimands corresponding to the ranked secondary efficacy endpoints are:

- Binary endpoints: The estimand is defined as the difference in the proportion of subjects achieving each endpoint, regardless of premature discontinuation of study drug, in the RZB group versus the placebo group in adult subjects with moderate to severe genital (in Study-G) or scalp (in Study-S) psoriasis.
- Continuous endpoint (change from Baseline in PSS for Study-S): The estimand is defined as the difference in mean change from Baseline in PSS at Week 16, regardless of premature discontinuation of study drug, in the RZB group versus the placebo group in adult subjects with moderate to severe scalp psoriasis in Study-S.

Intercurrent events handling: No intercurrent event is considered.

2.2 Study Design Overview

This is a Phase 4, multicenter, randomized, double-blind, placebo-controlled study examining the effect of RZB in adult subjects with moderate to severe genital psoriasis (Study-G) or moderate to severe scalp psoriasis (Study-S).

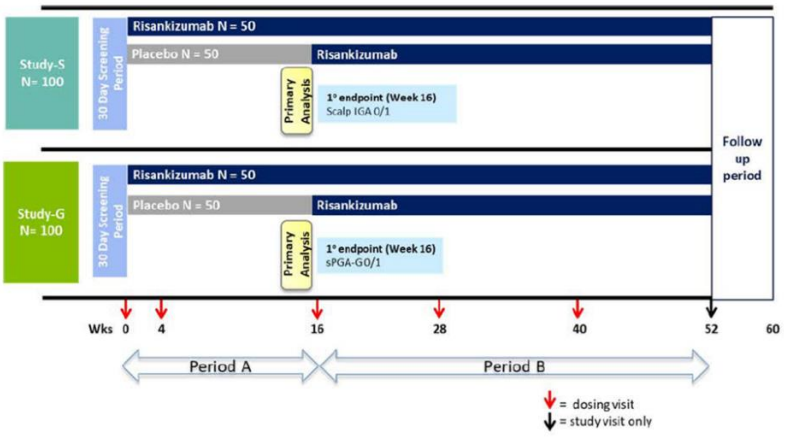
Participants will receive 150 mg of RZB (for those randomized to risankizumab) or matching placebo (for those randomized to placebo) subcutaneously at Baseline and Week 4. Starting at Week 16, all subjects will receive 150 mg of RZB every 12 weeks until the last dose at Week 40.

The duration of the studies will be approximately 64 weeks. Each study comprises a 30-day Screening Period, a 16-week double-blind placebo-controlled treatment period (Period A), a 36-week open-label treatment period (Period B), and an 8-week Follow-up Period. The follow-up phone call (20 weeks following the last dose of study drug) during the trial will not be required for any subject who initiates commercial RZB or continues

under another AbbVie protocol for the purposes of continued treatment (i.e., CTE or CTTP OLE).

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



2.3 Treatment Assignment and Blinding

All subjects will be assigned a unique identification number by the interactive response technology (IRT) at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule.

Subjects who satisfy eligibility criteria for Study-G only or Study-S only will be assigned to Study-G or Study-S, respectively. Subjects who meet the criteria for both Study-G and Study-S will first be randomized to either Study-G or Study-S with equal probability and then will be randomized to receive either RZB or placebo in a 1:1 ratio. After one of the two studies reaches 40 subjects in the BSA < 10% group, subjects with BSA < 10% who are eligible for both studies will be automatically assigned to the other study until both studies reach 40 subjects in this BSA < 10% group.

Randomization within each study will be in a 1:1 ratio to receive risankizumab or placebo, stratified by weight (≤ 100 kg vs. > 100 kg) and number of prior biologic therapies for psoriasis (0 vs. ≥ 1).

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Clinical Drug Supply Management Team) will remain blinded until the Primary Analysis at Week 16 is available. The investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the RZB pre-filled syringe (PFS) and matching placebo PFS provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

2.4 Sample Size Determination

This study is designed to randomize approximately 200 subjects, with approximately 100 subjects in Study-G (50 subjects/arm) and 100 subjects in Study-S (50 subjects/arm).

This will provide sufficient power to detect the treatment difference between RZB and placebo with respect to the primary endpoints within each study.

- In Study-G, assuming the treatment difference of 53% for RZB versus placebo (13%) in sPGA-G 0/1 at Week 16, a total sample size of N 100 subjects (RZB: 50; placebo: 50) will provide more than 90% power to detect the treatment difference between RZB and placebo, using a Chi-square test with a 2-sided significance level of 0.05.
- In Study-S, assuming the treatment difference of 37% for RZB versus placebo (11%) in Scalp IGA 0/1 at Week 16, a total sample size of N 100 subjects (RZB: 50; placebo: 50) will provide more than 90% power to detect the treatment difference between RZB and placebo, using a Chi-square test with a 2-sided significance level of 0.05.

3.0 Endpoints

3.1 Primary Endpoints

The primary endpoints are:

- Study-G: Achievement of sPGA-G of 0 or 1 at Week 16, among subjects in the ITT G population.
- Study-S: Achievement of scalp IGA of 0 or 1 at Week 16, among subjects in the ITT S population.

3.2 Secondary Endpoints

Ranked secondary endpoints are:

Study-G

1. Achievement of sPGA-G of 0 at Week 16, among subjects in the ITT G population.
2. Achievement of DLQI of 0 or 1 at Week 16, among subjects in the ITT G population.
3. Achievement of clinically meaningful (≥ 4-point) improvement from baseline on the Genital Psoriasis Itch NRS at Week 16 among subjects with a baseline score ≥ 4, among subjects in the ITT G population.
4. Achievement of GenPs-SFQ item 2 score of 0 or 1 at Week 16 among subjects with a baseline score ≥ 2, among subjects in the ITT_G population.

Study-S

1. Achievement of ≥ 90% improvement from baseline in PSSI (PSSI 90) at Week 16, among subjects in the ITT S population.

2. Achievement of PSSI 75 response at Week 16, among subjects in the ITT S population.
3. Change from baseline in PSS at Week 16, among subjects in the ITT S population.
4. Achievement of PSSI 100 response at Week 16, among subjects in the ITT S population.
5. Achievement of PSS of 0 at Week 16, among subjects in the ITT S population.

3.3 Additional Efficacy Endpoints

All variables listed above as primary or secondary endpoints will be evaluated at all scheduled visits during which the assessments are measured, unless otherwise noted.

The following endpoints will be evaluated at all scheduled visits during which the assessments are measured, unless otherwise noted.

Study-G

- Achievement of sPGA of 0 or 1
- Achievement of sPGA of 0
- Change from Baseline in the GPSS (itch, pain, discomfort, stinging, burning, redness, scaling, cracking and total) scores
- Achievement of at least 2-point reduction on PatGA-Genital among subjects with a baseline score ≥ 2
- Change from Baseline in DLQI
- Change from Baseline in HADS D-Score
- Change from Baseline in HADS A-Score

Study-S

- Achievement of sPGA of 0 or 1
- Achievement of sPGA of 0

- Achievement of scalp IGA of 0
- Achievement of ≥ 4-point improvement (reduction) from baseline on the Scalp Itch NRS among subjects with baseline scores ≥ 4
- Achievement of DLQI of 0 or 1
- Achievement of PSS of 0 or 1
- Change from Baseline in HADS D-Score
- Change from Baseline in HADS A-Score
- Change from Baseline on the Scalp Itch NRS
- Change from Baseline in PSSI

3.4 Safety Endpoints

The following safety evaluations will be performed throughout the study as measures of safety and tolerability:

- Adverse events (AEs)
- Vital signs
- Physical examinations
- ECGs
- Clinical laboratory assessments (hematology, chemistry, and urinalysis)

3.5 Other Endpoints

Not applicable.

4.0 Analysis Populations

The following population will be used for the analyses.

The **Intent-to-Treat (ITT) Populations** include:

- ITT G, includes all subjects randomized in Study-G.
- ITT S, includes all subjects randomized in Study-S.

- ITT_B_G, includes all subjects randomized in Study-G and enter Period B.
- ITT_B_S, include all subjects randomized in Study-S and enter Period B.

The ITT_G/ITT_B_G and ITT_S/ITT_B_S Populations will be used for all efficacy analyses in Study-G and Study-S respectively. Subjects will be included in the analysis according to the treatment group to which they were randomized (as randomized).

The **Safety Populations** include:

- Safety_G includes all subjects randomized to Study-G and received at least 1 dose of study drug.
- Safety_S includes all subjects randomized to Study-S and received at least 1 dose of study drug.
- Safety_B_G includes all subjects randomized to Study-G and received at least 1 dose of study drug in Period B.
- Safety_B_S includes all subjects randomized to Study-S and received at least 1 dose of study drug in Period B.

For the Safety_G/Safety_B_G and Safety_S/Safety_B_S Populations, subjects will be analyzed according to treatment actually received (as treated), regardless of the treatment randomized. The treatment actually received is determined by the first dose of study drug that the subject received during the specific analysis period.

The **All Risankizumab Treated Populations** include:

- ALL_RZB_G: all subjects who receive at least 1 dose of RZB as the study drug in Study-G.
- ALL_RZB_S: all subjects who receive at least 1 dose of RZB as the study drug in Study-S.

All RZB treated populations will be utilized for a comprehensive safety summary of RZB.

5.0 Subject Disposition

A summary of subject accountability by investigators will be provided among the ITT Populations where the number of subjects in each of the following categories will be tabulated for each study for each treatment groups:

- Subjects in each analysis population (ITT, safety);
- Subjects who discontinued study treatment;
- Subjects who completed Period A;
- Subjects who completed the study.

A summary of subject disposition in Period A will be provided based on ITT Populations where the number and percentage of subjects in each of the following categories will be tabulated for each study for each treatment group:

- Subjects who were randomized in the study;
- Subjects who took at least one dose of study treatment in Period A;
- Subjects who completed study treatment in Period A;
- Subjects who discontinued study treatment in Period A (overall and by reasons);
- Subjects who discontinued study in Period A (overall and by reasons);
- Subjects who completed Period A.

Summaries of subject disposition in Period B will be provided based on ITT B Populations where the number of subjects in each of the following categories will be summarized for each study for each treatment group:

- Subjects who entered into Period B;
- Subjects who took at least one dose of study treatment in Period B;
- Subjects who completed protocol-specified treatment in Period B;
- Subjects who prematurely discontinued study treatment in Period B (overall and by reason);

- Subjects who prematurely discontinued study in Period B (overall and by reason);
- Subjects who completed the study in Period B.

6.0 Study Treatment Duration and Compliance

For the Safety Populations, duration of treatment will be summarized by descriptive statistics of mean, standard deviation, median, minimum and maximum for each study for each period for each treatment group, as well as ALL RZB Population for each study.

Duration of each treatment for each period is defined as following:

Study Treatment Duration in Period A for ITT Populations:

- For subjects who do not continue into Period B:
  - minimum of (the last dose date in Period A + 84, the end of study date (if not missing) + 1 day, [and the Primary Analysis cutoff date for Period A + 1 day]) minus the first dose date in Period A
- For subjects who continue into Period B:
  - minimum of (the last dose date in Period A + 84, first dose date in Period B, the end of study date (if not missing) + 1, [and the Primary Analysis cutoff date for Period A + 1 day]) minus the first dose date in Period A

Study Treatment Duration in Period B for ITT B Populations:

- For subjects who continue into Period B:
  - minimum of (the last dose date in Period B + 84 days, and the end of study date + 1, [and the Primary Analysis cutoff date for Period A + 1 day]) minus the first dose date in Period B

Study Treatment Duration under the Administration of RZB (Applicable for ALL RZB Populations Only):

- minimum of (the last date of RZB + 84 days, the end of study date + 1) minus the first dose date of RZB.

Treatment compliance will be summarized by treatment groups for each period for each study based on the Safety G and Safety S Populations, by visit and overall.

Compliance in Period A for Safety Populations:

- For Period A, the possible subcutaneous injections can happen at Baseline and Week 4.

  The compliance for RZB and placebo will be summarized by the percentage of planned subcutaneous injections which are administered at each dosing visit and overall during Period A.

Compliance in Period B for Safety B Populations:

- For Period B, the possible subcutaneous injections can happen at Weeks 16, 28, and 40.

  The compliance for subjects continued RZB and switched from placebo to RZB will be summarized by the percentage of planned subcutaneous injections which are administered at each dosing visit and overall during Period B.

When computing the compliance for each treatment group at a visit, the denominator will include all subjects who reached the visit. For subjects who prematurely discontinued before the dosing visit, the subject will not be counted for the planned injections.

7.0 Subject Characteristics

Categorical variables will be summarized with the number and percentage of subjects. Continuous variables will be summarized with descriptive statistics (number of

non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Demographics and baseline disease characteristics will be summarized descriptively, overall and by treatment group for the ITT Populations. Unless otherwise specified, baseline is defined as the last non-missing value prior to the first administration of study treatment (or randomization date if no study treatment was administered).

Continuous demographic variables include age, weight, height, and body mass index (BMI).

Categorical demographic variables include: sex, ethnicity (Hispanic or Latino, Not Hispanic or Latino), race, Age (< 40, ≥ 40 to < 65, ≥ 65 years), weight (≤ 100 kg, > 100 kg), BMI (normal: < 25; overweight: ≥ 25 to < 30; obese: ≥ 30 kg/m^2), Nicotine user (current, former, never, unknown), alcohol user (current, former, never, unknown).

Baseline disease characteristics include BSA ($< 10\%$, $\geq 10\%$), prior biologic therapies for psoriasis (0, ≥ 1), sPGA (3,4), sPGA-G (3,4) for Study-G only, scalp IGA (3,4) for Study-S only, PSSI (by median) for Study-S only.

Patient Reported Outcomes (PROs) analyzed at baseline include:

- Study-G: GPSS, GenPs-SFQ, PatGA-Genital, DLQI (Dermatology Life Quality Index), and HADS
- Study-S: PSS, Scalp Itch NRS (Numerical Rating Scale), DLQI, and HADS

In addition to the analysis of Itch NRS as a continuous variable, Itch NRS ≥ 4 will be summarized as a categorical baseline variable.

7.2 Medical History and Prior and Concomitant Medications

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class (SOC) and preferred term (PT)) will be summarized overall and by treatment group for each study for the ITT Populations. The SOC will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

Prior and concomitant medications will be summarized separately. The number and percentage of subjects taking prior and concomitant medications will be summarized by generic drug name, based on the World Health Organization (WHO) Drug Dictionary. The actual version of the WHO Drug Dictionary will be noted in the statistical tables and clinical study report.

A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the last dose of study drug plus 140 days.

A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug in each period or any medication that started on or after the date of the first dose of study drug in each period, but not after:

For ITT Populations in Period A:

- For subjects who do not continue into Period B:
  - minimum of (the last dose date in Period A + 140, the end of study date (if not missing) + 1 day, [and the Primary Analysis cutoff date for Period A + 1 day])
- For subjects who continue into Period B:
  - minimum of (the last dose date in Period A + 140, first dose date in Period B, the end of study date (if not missing) + 1, [and the Primary Analysis cutoff date for Period A + 1 day])

For ITT_B Populations in Period B:

- For subjects who continue into Period B:
  - minimum of (the last dose date in Period B + 140 days, and the end of study date + 1)

Prior medications will be summarized among the ITT Populations. Concomitant medications will be summarized for Period A among the ITT Populations, and for Period B among ITT_B Populations.

7.3 Protocol Deviations

Protocol deviations include eligibility criteria violations, receipt of wrong treatment or incorrect dose of study treatment, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications.

For each of the following protocol deviation categories and across all categories, the number and percentage of randomized subjects with at least one protocol deviation will be summarized overall and by treatment group:

- Subject entered into the study even though s/he did not satisfy entry criteria;
- Subject developed withdrawal criteria during the study but was not withdrawn;

- Subject received wrong treatment or incorrect dose of study treatment;
- Subject took prohibited concomitant medication.

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

The efficacy endpoints (defined in Section 3.1, Section 3.2, and Section 3.3) will be analyzed based on the ITT populations. No intercurrent events will be considered in this study.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted on the ITT Population separately for each study.

The primary analysis will be performed when all ongoing subjects complete Week 16 of Study-G and Study-S and all data pertaining to Period A are cleaned. The Week 16 analysis is the only and final analysis for efficacy in Period A.

The final analysis will be conducted upon study completion.

For categorical variables, the number and proportion of subjects, and the 95% confidence interval (CI) of the proportion will be provided by each treatment group among ITT Populations.

In addition, comparisons between RZB and placebo will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for the actual values of stratification factors weight (≤ 100 kg, > 100 kg) and number of prior biologic therapies for psoriasis (0, ≥ 1), with a 2-sided significance level of 0.05 for each study. The CMH test will use weights proposed by Greenland & Robins, which is calculated as follows:

$\hat{\delta}_{MH} = \frac{\sum_{i=1}^{4} w_i \cdot \hat{\delta}_i}{\sum_{i=1}^{4} w_i}$, where

- $\hat{\delta}_i = \frac{x_i}{n_i} - \frac{y_i}{m_i}$ denotes the risk difference in stratum $i, i = 1, \cdots, 4$.
- $w_i = \frac{n_i \cdot m_i}{n_i + m_i}$ denotes the weight of stratum $i, i = 1, \cdots, 4$.
- x_i denotes the number of subjects with event in RZB in stratum $i, i = 1, \cdots, 4$.
- y_i denotes the number of subjects with event in PBO in stratum $i, i = 1, \cdots, 4$.
- n_i denotes the number of subjects in RZB in stratum $i, i = 1, \cdots, 4$.
- m_i denotes the number of subjects in PBO in stratum $i, i = 1, \cdots, 4$.

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

$$\widehat{var}\left(\hat{\delta}_{MH}\right) = \frac{\sum_{i=1}^{4} L_i}{\left(\sum_{i=1}^{4} w_i\right)^2}$$

where $L_i = \frac{x_i(n_i - x_i)\, m_i^3 + y_i(m_i - y_i)\, n_i^3}{n_i \cdot m_i \cdot (n_i + m_i)^2}$, $i = 1, \cdots, 4$

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 $N(0, 1)$:

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

The approximate p-value can be calculated using the following:

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

If there is a stratum with zero subjects in either treatment group, the 0 count will be replaced by 0.1 in order to prevent dividing by 0 in the above equations, as suggested in Greenland & Robins. In case of any stratum with zero subjects in both treatment groups, the corresponding stratification factor will not be controlled.

For continuous variables, the Baseline mean, visit mean, as well as the Least Square (LS) mean, 95% confidence interval (CI) and Standard Error (SE) of the mean, will be reported for each ITT Population. The comparisons between RZB and placebo will be analyzed using Mixed-Effect Model Repeated Measurement (MMRM) method, adjusting for the fixed effects of treatment, actual values of stratification factors at Baseline, Baseline value, visit and treatment by visit interaction as covariates.

"Baseline" refers to the last non-missing observation on or before the date of the first administration of study drug, or the date of randomization if no study drug is administered.

For analyses by stratification factors used for randomization, any subject who is randomized within an incorrect stratum will be analyzed according to the actual stratum to which the subject belongs.

9.2 Handling of Missing Data

Handling of missing data for the efficacy analyses is described below.

9.2.1 Categorical Endpoints

Non-Responder Imputation (NRI): The NRI approach will categorize any subject who has a missing value at a specific visit as a non-responder for that visit. The only exception will be if 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. The NRI will be the primary approach in the analysis of categorical variables.

Of note, during the Primary Analysis for Period A upon completion of Week 16, the NRI approach will only be performed at all visits up to Week 16.

9.2.2 Continuous Endpoints

Mixed-Effect Model Repeat Measurement (MMRM) will be the primary and only approach to handle missing data for continuous endpoints among all ITT Populations. The MMRM will be conducted using mixed model including observed measurements at all visits, using all available data even if a subject has missing data at some (but not all) post-baseline visits during the analysis period. An unstructured variance covariance matrix (UN) will be used. If the model cannot converge, an appropriate covariance structure matrix (e.g., autoregressive (1) or compound symmetry) will be used. The parameter estimations are based on the method of restrictive maximum likelihood (REML). The fixed effects will be used to report model-based means at corresponding visits.

Of note, during the Primary Analysis for Period A upon completion of Week 16, the MMRM analysis will only be performed at all visits up to Week 16.

9.3 Primary Efficacy Endpoints and Analyses

9.3.1 Primary Efficacy Endpoints

The primary endpoints are:

- Study-G: Achievement of sPGA-G of 0 or 1 at Week 16, among subjects in the ITT G population.
- Study-S: Achievement of scalp IGA of 0 or 1 at Week 16, among subjects in the ITT S population.

9.3.2 Analysis of Primary Efficacy Endpoints

The attributes of the estimand corresponding to the primary efficacy objective are summarized in Table 1.

Table 1. Summary of the Estimand Attributes Corresponding to the Primary Efficacy Objective(s)

Estimand Label	Attributes of the Estimand				
	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Study-G: sPGA-G 0/1 at Week 16	RZB and placebo	Study-G: Achievement of sPGA-G of 0 or 1 at Week 16	Adult subjects with moderate to severe genital psoriasis	No intercurrent event is considered	Difference in the proportion of subjects achieving sPGA-G of 0 or 1 at Week 16, regardless of premature discontinuation of study drug, in the RZB group compared with the placebo group
Study-S: scalp IGA 0/1 at Week 16		Study-S: Achievement of scalp IGA of 0 or 1 at Week 16	Adult subjects with moderate to severe scalp psoriasis	No intercurrent event is considered	Difference in the proportion of subjects achieving scalp IGA of 0 or 1 at Week 16, regardless of premature discontinuation of study drug, in the RZB group in compared with the placebo group

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoints

A sensitivity analysis for the primary endpoint, using MI to handle missing data:

To assess the robustness of the primary analysis, a CMH analysis with missing data handled by MI will be conducted on the primary endpoints sPGA-G 0/1 at Week 16 in the ITT G Population for Study-G and scalp IGA 0/1 at Week 16 in the ITT S Population for Study-S. Markov Chain Monte Carlo (MCMC) will be first applied to augment continuous variables (which are dichotomized to derive the primary endpoints) into monotonic missing pattern and PROC MI will be used to generate 30 datasets using the regression method. The variables to be included in the imputation model for each study are: treatment group, actual value of stratification factors (weight and number of prior biologic therapies for psoriasis), Baseline value, and measurements at each visit in

Period A. The random seeds for MCMC and the random seeds for PROC MI are specified in Appendix D. The imputed post-baseline measurements will be rounded to the same precision as the observed data before the determination of responder status. Subjects will be characterized as responders or non-responders based on MI imputed datasets. Using the Cochran-Mantel-Haenszel (CMH) model adjusted by actual value of stratification factors (weight and number of prior biologic therapies for psoriasis), the imputed endpoints will be analyzed using each of the 30 datasets. SAS PROC MIANALYZE will be used to generate the final inferences of the response rate difference between RZB group and placebo.

Tipping Point Analysis, a sensitivity analysis for the primary endpoints: To assess the robustness of the primary analysis, a tipping point analysis will be conducted on the primary endpoints sPGA-G 0/1 at Week 16 in the ITT G Population for Study-G and scalp IGA 0/1 at Week 16 in the ITT S Population for Study-S.

Details of the tipping point analysis are described below using proportion of subjects achieving sPGA-G 0/1 at Week 16 among ITT G Population for RZB vs. placebo as an example.

M1	Total number of subjects with missing sPGA-G 0/1 status at Week 16 among ITT G Population in the placebo group
M2	Total number of subjects with missing sPGA-G 0/1 status at Week 16 among ITT G Population in the RZB group
X1	Number of subjects who are imputed as responders, among the M1 subjects with missing sPGA-G 0/1 status at Week 16 among ITT G Population in the placebo group. X1 = 0, ..., M1
X2	Number of subjects who are imputed as responders among the M2 subjects with missing sPGA-G 0/1 status at Week 16 among ITT G Population in the RZB group. X1 = 0, ..., M2

1. For each pair of (X1, X2), simulations will be used to randomly draw X1 subjects from the M1 subjects with missing values in placebo group and X2 subjects from the M2 subjects with missing values in RZB group. These randomly selected X1 subjects in placebo and X2 subjects in RZB group with missing sPGA-G 0/1 status at Week 16 will be imputed as responders. The remaining subjects missing

sPGA-G 0/1 status at Week 16 will be imputed as non-responders. Analysis of RZB vs. placebo will be conducted using the combined observed data and imputed data for each treatment group. A p-value will be calculated using the CMH test adjusted by actual value of stratification factors.

2. The simulation will be repeated 50 times for each pair of (X1, X2) and the median p-value will be used for the conclusion. The random seed for simulation will be preset as specified in Appendix D. If one pair of parameters is found to just reverse the study conclusion (i.e., median p-value > 0.05 [tipping point analysis will be performed only if the primary analysis reached p-value ≤ 0.05]), then these parameters will be the tipping points.
3. Of note, an extreme case analysis will be checked first, where all missing data in placebo are imputed as responders and all missing data in the RZB group are imputed as non-responders. If the extreme case analysis does not reverse the conclusion based on the NRI approach, complete tipping point analysis will not be performed.

Similar tipping point analysis procedure as that for the sPGA-G 0/1 at Week 16 will be conducted on scalp IGA 0/1 at Week 16 among ITT S Population for RZB vs. placebo.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Ranked Secondary Efficacy Endpoints

The ranked secondary endpoints are as defined in Section 3.2.

9.4.2 Analyses of Ranked Secondary Efficacy Endpoints

The attributes of the estimands corresponding to the ranked secondary efficacy objectives are summarized in Table 2.

Table 2. Summary of the Estimand Attributes Corresponding to the Ranked Secondary Efficacy Objectives

Estimand Label	Attributes of the Estimand				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Study-G					
sPGA-G 0/1 at Week 16	RZB and placebo	Achievement of sPGA-G of 0 or 1 at Week 16	adult subjects with moderate to severe genital psoriasis	No intercurrent event is considered	The difference in the proportion of subjects achieving each endpoint, regardless of premature discontinuation of study drug, in the RZB group versus the placebo group
DLQI 0/1 at Week 16		Achievement of DLQI of 0 or 1 at Week 16			
Genital Psoriasis Itch NRS improvement ≥ 4 at Week 16		Achievement of clinically meaningful (≥ 4-point) improvement from baseline on the Genital Psoriasis Itch NRS at Week 16 among subjects with a baseline score ≥ 4			
GenPs-SFQ item 2 score of 0/1 at Week 16		Achievement of GenPs-SFQ item 2 score of 0 or 1 at Week 16 among subjects with a baseline score ≥ 2			

Estimand Label	Attributes of the Estimand				
	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Study-S					
PSSI 90 response at Week 16	RZB and placebo	Achievement of ≥ 90% improvement from baseline in PSSI response at Week 16	Adult subjects with moderate to severe scalp psoriasis	No intercurrent event is considered.	Difference in the proportion of subjects achieving each endpoint, regardless of premature discontinuation of study drug, in the RZB group versus the placebo group
PSSI 75 response at Week 16		Achievement of PSSI 75 (≥ 75% improvement from baseline in PSSI) response at Week 16			
PSSI 100 response at Week 16		Achievement of PSSI 100 (100% improvement from baseline in PSSI) response at Week 16			
PSS of 0 at Week 16		Achievement of PSS of 0 at Week 16			
PSS change from Baseline at Week 16	RZB and placebo	Change from baseline in PSS at Week 16	Adult subjects with moderate to severe scalp psoriasis	No intercurrent event is considered.	Difference in mean change from Baseline in PSS at Week 16, regardless of premature discontinuation of study drug, in the RZB group versus the placebo group

9.4.3 Sensitivity and Supplementary Analyses for Ranked Secondary Efficacy Endpoints

There will be no sensitivity analysis for ranked secondary efficacy endpoints.

9.5 Additional Efficacy Endpoints and Analyses

All additional efficacy endpoints are as defined in Section 3.3.

Analyses of additional efficacy endpoints will be conducted as specified in Section 9.1 by providing descriptive statistics and comparisons as needed.

9.6 Efficacy Subgroup Analyses

Subgroup analyses of the primary endpoints will be summarized descriptively based on following subgroups:

- Sex (male, female)
- Race (white, non-white)
- Age group (< 40, ≥ 40 to < 65, ≥ 65)
- Ethnicity (Hispanic or Latino vs. Not Hispanic or Latino)
- BMI (normal: < 25; overweight: ≥ 25 to < 30; obese: ≥ 30)
- BSA (< 10%, ≥ 10%)
- Prior biologic therapies for psoriasis (0, ≥ 1)
- Weight (≤ 100 kg, > 100 kg)
- Baseline sPGA (3, 4)
- Baseline sPGA-G (3, ≥ 4) for Study-G only
- Baseline scalp IGA (3, 4) for Study-S only
- Baseline PSSI (by median) for Study-S only

Age ≥ 65 years or BMI ≥ 30 subgroups will be combined with the adjacent subgroup when having fewer than 10% subjects.

The Breslow-Day test will be performed to assess the homogeneity of treatment effect across subgroups.

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Safety Populations. Safety summaries will be presented by the treatment group. Subjects are analyzed based on the treatment actually received, determined by the first dose of study drug received during the analysis period.

The overview of treatment-emergent adverse events (TEAEs) and Potentially Clinically Significant (PCS) findings in laboratory variables and vital sign variables will also be summarized among the Safety Populations.

10.2 Adverse Events

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

Unless specified otherwise, all the adverse event tables and listings will be provided for Period A (for subjects in Safety S and Safety G Populations) and Period B (for Safety B Populations). Adverse event tables will also be provided for ALL RZB Populations.

10.2.1 Treatment-Emergent Adverse Events

A treatment-emergent adverse events (TEAEs) in Period A for both Study-G and Study-S is defined as any AE worsened or newly occurred on or after the first dose of study drug in Period A and within the minimum of (140 days after the last dose of study drug in

Period A, one day before the first dose date in Period B if not missing [and the cutoff date during the Primary Analysis for Period A]).

A TEAE in Period B for both Study-G and Study-S is defined as any AE worsened or newly occurred on or after the first dose of study drug in Period B and within 140 days after the last dose of RZB in Period B.

A TEAE during the administration of RZB (i.e., among the ALL RZB G and ALL RZB S Population) is defined as any AE worsened or newly occurred on or after the first dose of RZB and within 140 days after the last dose of RZB [and the cutoff date during the Primary Analysis for Period A].

10.2.2 Adverse Event Overview

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

- Any treatment-emergent AE
- Any treatment-emergent AE related to study treatment according to the investigator
- Any severe treatment-emergent AE
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to discontinuation of study treatment
- Any treatment-emergent AE leading to death
- Any treatment-emergent Area of Safety Interest, as defined in Appendix B.
- All deaths will be summarized:
  - Deaths occurring ≤ 140 days after last dose of study treatment
  - Deaths occurring > 140 days after last dose of study treatment

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

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

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency for the RZB group in Period A for Safety G and Safety S Populations, for the RZB/RZB group in Period B for Safety B G and Safety B S Populations, and for RZB group in ALL RZB Populations.

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

Exposure-adjusted TEAEs per 100 patient-years will be provided, where TEAEs per 100 patient-years of exposure are defined as the number of TEAEs 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 TEAEs (i.e., a preferred term will not be counted twice on the same day for the same subject). The exposure-adjusted TEAE rate per 100 patient-years is calculated as:

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

where total patient years in each period are defined below.

Total Patient Years in Period A:

Sum of study drug exposure in Period A, defined as:

- For subjects who do not continue into Period B:
  - minimum of (the last dose date in Period A + 140, the end of study date (if not missing) + 1 day, [and the Primary Analysis cutoff date for Period A + 1 day]) minus the first dose date in Period A
- For subjects who continue into Period B:
  - minimum of (the last dose date in Period A + 140, first dose date in Period B, the end of study date (if not missing) + 1, [and the Primary Analysis cutoff date for Period A + 1 day]) minus the first dose date in Period A

normalized by 365.25 and rounded to one decimal place.

Total Patient Years in Period B:

Sum of study drug exposure in Period B, defined as: the minimum of (the last dose date in Period B + 140 days, and the end of study date + 1 day) minus the first dose date in Period B, normalized by 365.25 and rounded to one decimal place.

Total Patient Years in the All-Risankizumab Treated Period:

Sum of study drug of RZB exposure, defined as the minimum of (the last RZB dose date + 140 days, and the end of study date + 1 day) minus the first RZB dose date, normalized by 365.25 and rounded to one decimal place.

10.2.5 Deaths, Serious Adverse Events, and Adverse Events Leading to Study Treatment Discontinuation

Treatment-emergent serious adverse events (SAEs), TEAEs leading to premature discontinuation of study treatment, and TEAEs leading to death will be summarized by SOC and PT and in listing format.

A listing of pre-treatment SAEs with onset dates prior to the first dose of study drug (or prior to randomization date if not dosed), and a listing of all deaths will be provided for all subjects.

10.2.6 Area of Safety Interest

Area of safety interest (ASI) will be summarized by categories. Detailed information about the search criteria is provided in Appendix B.

The final list will be based on the most updated final version of RZB product Safety Statistical Analysis Plan, which is consistent with the most updated RZB Risk management plan.

10.3 Analysis of Laboratory Data

The clinical laboratory tests defined in the protocol operations manual (e.g., hematology, clinical chemistry, and urinalysis) will be summarized.

Each laboratory variable will be summarized for all time points (starting with Baseline) in Period A and B, with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for selected laboratory variables, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group and difference between treatment groups.

Laboratory parameters will be tabulated using shift tables either by National Cancer Institute (NCI) Common Terminology Criteria (CTC) or categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline either to the worse value (based on NCI-CTC) during treatment or to minimum and maximum value (based on normal range), will be created in Period A and B. A similar shift table will be provided to summarize shifts from baseline to the final post-baseline value in Period A and B.

Laboratory abnormalities meeting NCI-CTC Grade 3 and 4 will be summarized in Period A (Safety Populations), B (Safety B Populations) and during the administration of risankizumab (ALL RZB Populations).

Laboratory abnormalities will be evaluated based on Potentially Clinically Significant (PCS) criteria (Appendix C), in Period A (Safety Populations), B (Safety B Populations) and during the administration of risankizumab (ALL RZB Populations). For each laboratory PCS criterion, the number and percentage of subjects who have a laboratory value meeting the criteria will be summarized. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCS criteria.

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

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

A listing will include all subjects who met any of the following four criteria:

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

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

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

Urinalysis and pregnancy testing results will be provided in listings only.

10.4 Analysis of Vital Signs

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

Each vital sign variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum, in Period A (Safety Populations) and B (Safety B Populations). Mean change from baseline to each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group and difference between RZB vs. placebo.

Vital sign variables will be evaluated based on Potentially Clinically Significant (PCS) criteria (Appendix C). For each vital sign PCS criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized in Period A (Safety Populations), B (Safety B Populations) and during the administration of risankizumab (ALL RZB Populations). Listings will be provided to summarize subject-level vital sign data for subjects meeting PCS.

10.5 Other Safety Analyses

There will be no other safety analyses for this study.

10.6 Safety Subgroup Analyses

There will be no safety subgroup analyses for this study.

11.0 Assessment of Endpoints

11.1 Patient-Reported Outcomes

The patient-reported outcomes (PROs) are being collected to assess the multiplicity-controlled secondary endpoints and additional efficacy endpoints. Summary and analysis of pre-specified endpoints are described in Section 9.4 and Section 9.5. Below is a brief summary of the PRO endpoints.

11.1.1 Genital Psoriasis Symptoms Scale (GPSS)

The GPSS is a patient-administered assessment of 8 symptoms: itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. Respondents are asked to answer the questions based on their psoriasis symptoms in the genital area. Genital area is defined as the labia majora (outer lip), labia minora (inner lip), and perineum (area between vagina and anus) for females; penis, scrotum, and perineum (area between the penis and anus) for males. The self-reported overall severity of each of the 8 symptoms individually in the genital area is assessed on an 11-point horizontal NRS anchored at 0 (no) and 10 (worst imaginable), using a recall period of 1 day. If values from 4 or more days of the 7 day period are missing, then the rolling weekly average for that particular 7 day period will be set to missing.

11.1.2 Genital Psoriasis Sexual Frequency Questionnaire (GenPs-SFQ)

The GenPs-SFQ is a PRO measure to evaluate the impact of genital psoriasis symptoms on sexual frequency, using a 1-week recall period. It consists of 2 items that assess the impact of genital psoriasis symptoms on the frequency of sexual activity. Each item uses a Likert scale. Respondents are asked to answer the questions based on their psoriasis symptoms in the genital area. Genital area is defined as the labia majora (outer lip), labia

minora (inner lip), and perineum (area between vagina and anus) for females; penis, scrotum, and perineum (area between the penis and anus) for males. The definition of sexual activity is not limited to intercourse and includes activities such as masturbation.

Item 1 asks how many times a patient engaged in sexual activity in the past week with response options of none/zero (2), once (1), and two or more (0). Item 2 assesses how often genital psoriasis symptoms limited the frequency of sexual activity with response options ranging from 0 (never) to 4 (always). The individual item scores of the SFQ are reported separately. No total score is calculated for SFQ. The instructions for completion are embedded within the SFQ questionnaire for patients to read before responding to items. SFQ individual item scores at Week 16 are the scores collected at Week 16 on site.

11.1.3 Patient's Global Assessment of Genital Psoriasis (PatGA-Genital)

The PatGA-Genital is a patient-administered, single-item scale on which patients are asked to rank, by circling a number on a 0 to 5 NRS, the severity of their genital psoriasis "today" from 0 (clear), no genital psoriasis; to 5 (severe).

11.1.4 Psoriasis Symptoms Scale (PSS)

The PSS is a 4-item PRO instrument that assesses the severity of psoriasis symptoms in patients with moderate to severe psoriasis, using a recall period of 1 day. The symptoms include pain, redness, itching and burning from psoriasis. Current symptom severity is assessed using a 5-point Likert-type scale ranging from 0 (none) to 4 (very severe). Until Week 16, the weekly average score is calculated based on the 7 available daily scores from the days within each visit window that were closest to the nominal. If values from 4 or more days of the 7 day period are missing, then the rolling weekly average for that particular 7 day period will be set to missing.

The PSS was developed based on published evidence supporting the development of two similar, proprietary PRO instruments: the Psoriasis Symptom Inventory and the Psoriasis Symptom Diary.

11.1.5 Scalp Psoriasis Itch Numeric Rating Scale (Scalp Itch NRS)

The Scalp Itch NRS is a self-administered NRS that asks the patients to assess their scalp itch on a scale from 0 to 10 where 0 represents no itch and 10 represents worst imaginable itch. Scalp Itch NRS has been used in previous trials assessing the efficacy of apremilast among patients with scalp psoriasis.

11.2 Physician-Assessed Endpoints

The physician assessments included sPGA-G, scalp IGA, sPGA and PSSI. Summary and analysis of pre-specified endpoint are described in Section 9.3, Section 9.4 and Section 9.5.

11.2.1 Static Physician Global Assessment of Genitalia (sPGA-G)

The sPGA-G is a 6-point score ranging from 0 to 5. The sPGA-G score should be selected using the descriptors below that best describe the overall appearance of the subject's psoriasis lesions in genital area at a given time point. It is not necessary that all three criteria be fulfilled. The sPGA of Genitalia score should be based on a combination of erythema and the secondary features (plaque elevation and/or scale). Since erythema is the most robust finding, it should be the dominant feature influencing the sPGA of Genitalia rating in the majority of cases.

Score	Category	Category Description
0	Clear	Erythema = 0 (residual post-inflammatory hyperpigmentation or hypopigmentation may be present) Plaque elevation = 0 (no elevation over normal skin) Scaling = 0 (no scale)
1	Minimal	Erythema = faint (light pink coloration) Plaque elevation = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) Scaling = ± (surface dryness with some white coloration)
2	Mild	Erythema = mild (pink to light red coloration) Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped) Scaling = fine (fine scale partially or mostly covering lesions)
3	Moderate	Erythema = moderate (definite red coloration) Plaque elevation = moderate (moderate elevation with rough or sloped edges) Scaling = coarser (coarse scale covering most of all of the lesions)
4	Severe	Erythema = severe (bright red coloration) Plaque elevation = marked (marked elevation typically with hard or sharp edges) Scaling = coarse (coarse, non-tenacious scale predominates covering most or all of the lesions)
5	Very Severe	Erythema = very severe (extreme red coloration; dusky to deep red coloration) Plaque elevation = very marked (very marked elevation typically with hard sharp edges) Scaling = very coarse (coarse, thick tenacious scale over most of all of the lesions; rough surface)

11.2.2 Scalp Investigator Global Assessment (Scalp IGA)

The scalp IGA is a measurement of overall scalp involvement by the investigator at the time of evaluation. The scalp IGA is a 5-point scale ranging from 0 (clear) to 4 (severe) incorporating an assessment of the severity of the 3 primary signs of the disease: erythema, scaling, and plaque elevation. When making the assessment of overall scalp severity, the investigator should factor in areas that have already been cleared (i.e., have

scores of 0) and not just evaluate remaining lesions for severity, i.e., the severity of each sign is averaged across all areas of involvement, including cleared lesions.

11.2.3 Static Physician Global Assessment (sPGA)

The sPGA is a 5 point score ranging from 0 to 4 (where 0 clear), based on the physician's or representative's assessment of the average thickness, erythema, and scaling of all psoriatic lesions. The assessment is considered "static" which refers to the subject's disease state at the time of the assessments, without comparison to any of the subject's previous disease states, whether at baseline or at a previous visit. A lower score indicates less body coverage, with 0 being clear and 1 being almost clear.

11.2.4 Psoriasis Scalp Severity Index (PSSI)

The physician will assess the severity of scalp psoriasis using the PSSI, which consists of an assessment of erythema, induration, and desquamation on a scale from 0 (none) to 4 (very severe) and the percentage of scalp involved on a scale from 1 (< 10% of scalp involved) to 6 (90 to 100% of scalp involved). The composite score is calculated as the sum of the scores for erythema, induration and desquamation multiplied by the score recorded for the extent of scalp area involved. The PSSI ranges from 0 to 72. A negative change from baseline indicates improvement.

12.0 Interim Analyses

No interim analysis is planned for this study.

12.1 Data Monitoring Committee

No data monitoring committee is planned in the study.

13.0 Overall Type-I Error Control

For Study-G and Study-S, overall type-I error will be controlled under a two-sided significance level of 0.05 respectively for each study by testing the primary endpoint,

followed by the ranked secondary endpoints, in a hierarchical order as described in Section 3.1 and Section 3.2.

14.0 Version History

Table 3. SAP Version History Summary

Version	Date	Summary
1.0	04 October 2023	Initial version
2.0	01 November 2024	Updated to incorporate agency feedback, including: • Specify the analysis method for categorical variables in Section 9.1 • Add sensitivity analysis: MI and tipping points for primary endpoints in Section 9.3.3 • Update subgroup analysis in Section 9.6 • Add scale description of Patient-Reported Outcome and Physician-Assessed Endpoints in Section 11.0 Add some details regarding the final list of ASI in Section 10.2.6 for clarification purpose Clarify MMRM method for continuous variable in Section 9.1
3.0	07 February 2025	• In the subgroup analysis of sPGA-G 0/1 in Section 9.6, updated the Baseline sPGA-G (3, 4) subgroup to (3, ≥ 4), which is an error in the protocol. • In Section 7.2, deleted the sentence 'In addition, a subject's prior biologic use will be summarized by the reason for discontinuation' because the corresponding CRF page was not collected. • Clarified the Period B exposure duration definition in Section 6.0 and ALL RZB TEAE definition in Section 10.2.1.
4.0	18 February 2025	• In Section 11.2.4, the scale of percentage of scalp involved is updated to 1 – 6 from 0 – 6 according to protocol admin change.

14.1 Changes to Planned Analyses in the Protocol

- Add Sex, Race, Age, Ethnicity to efficacy subgroup analysis in Section 9.6.

- In the Protocol Section 7.4, subgroup of Baseline sPGA-G was defined as (3, 4). In the SAP Section 9.6, subgroup of Baseline sPGA-G was corrected as (3, ≥ 4).

15.0 References

Not applicable.

Appendix A. List of SAP Signatories

Name	Title	Role/Functional Area
[redacted]	[redacted]	Author
		Clinical Statistics
		Clinical Statistics
		Statistical Programming
		Clinical Development

Appendix B. Definition of Area of Safety Interest

Area of Safety Interest (ASI) will be identified using the following search criteria (Note: for each database lock, the categories of ASIs will follow the latest approved version of PSSAP for RZB):

Area of Safety Interest	Search Criteria[#]	
MACE	Adjudicated terms will be identified as described in PSSAP Table 4a using CECAT and CETERM from the CE SDTM dataset.	
Serious Infections	Serious AEs in the Infections and Infestations SOC	
Malignancies	Narrow	Malignant tumours (SMQ 20000194)
Serious hypersensitivity reactions	Serious AEs in the Hypersensitivity (SMQ 20000214)	
Extended MACE	Adjudicated terms will be identified as described in PSSAP Table 4a (for MACE +) using CECAT and CETERM from the CE SDTM dataset.	
Active Tuberculosis	Active Tuberculosis CMQ (code 80000188)	
Opportunistic Infection excluding tuberculosis and herpes zoster	Opportunistic infection excluding tuberculosis and herpes zoster CMQ (code 80000189)	
Herpes Zoster	Herpes Zoster CMQ (code80000175)	
Non melanoma Skin Cancer (NMSC)	Broad	Skin malignant tumours (SMQ 20000204) excluding terms identified by the Melanoma CMQ (code 80000119)
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.	
Hypersensitivity	Narrow	Hypersensitivity (SMQ 20000214)
Adjudicated Anaphylactic Reaction*	Adjudicated terms will be identified using SDTM data (e.g., CE and PR domains).	
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)

Area of Safety Interest	Search Criteria[#]	
Injection Site Reactions	Injection site reaction HLT of Injection Site Reactions (10022097) or HLT of Infusion Site Reactions (10068753)	
Suicidal Ideation and Behavior (SIB)	Narrow	Suicide/self injury (SMQ 20000037)
Depression	Narrow	Depression (excl suicide and self injury) (SMQ 20000167)

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

\# At the time of the DB lock, the searching criteria will be based on the most updated MedDRA version.

Appendix C. Potentially Clinically Significant Criteria for Safety Endpoints

The criteria for Potentially Clinically Significant (PCS) laboratory findings are described in Table C-1 and Table C-2, and the PCS criteria for vital sign findings are described in Table C-3.

Table C-1. Criteria for Potentially Clinically Significant Hematology Values

Hematology Variables	Units	Definition of Potentially Clinically Significant Current (Version 4.03) NCI CTCAE Grade 3 or Greater	
		Very Low	Very High
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 significant finding.

Table C-2. Criteria for Potentially Clinically Significant Chemistry Values

		Definition of Potentially Clinically Significant Current (Version 4.03) NCI CTCAE Grade 3 or Greater	
Chemistry Variables	**Units**	**Very Low**	**Very High**
TBL	mcmol/L		> 3.0 × ULN
ALP	U/L		> 5.0 × ULN
SGOT/AST	U/L		> 5.0 × ULN
SGPT/ALT	U/L		> 5.0 × ULN
Albumin	g/L	< 20	
Glucose	mmol/L	< 2.2	> 13.9
Triglycerides	mmol/L		> 5.7
Creatinine	mcmol/L		> 3.0 × ULN (> 3.0 × BL)
Sodium	mmol/L	< 130	> 155
Potassium	mmol/L	< 3.0	> 6.0
Calcium	mmol/L	< 1.75	> 3.1
CPK	U/L		> 5.0 × ULN
Total Cholesterol	mmol/L		> 10.34
GGT			> 5.0 × ULN

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

Table C-3. Criteria for Potentially Clinically Significant Vital Sign Values

Vital Signs Variables	**Criterion**	**Definition of Potentially Clinically Significant**
Systolic Blood Pressure (mmHg)	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic Blood Pressure (mmHg)	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from Baseline
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from Baseline

Appendix D. Random Seeds

Table D-1. Random Seeds for MI and Tipping Point Analysis

Endpoints	Random Seed
sPGA-G 0/1 at Week 16 (MCMC/MI)	12345/12346
scalp IGA 0/1 at Week 16 (MCMC/MI)	12347/12348
sPGA-G 0/1 at Week 16 (Tipping Point Analysis)	12349
scalp IGA 0/1 at Week 16 (Tipping Point Analysis)	12350