

## **Statistical Analysis Plan for Study M15-999**

### **A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Risankizumab Using a New Formulation for the Treatment of Adult Subjects with Moderate to Severe Plaque Psoriasis**

**Date: 05 March 2020**

**Version 4.0**

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## **1.0 Introduction**

This Statistical Analysis Plan (SAP) describes the statistical analyses for risankizumab Study M15-999 A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Risankizumab Using a New Formulation for the Treatment of Adult Subjects with Moderate to Severe Plaque Psoriasis. Study M15-999 evaluates the safety and efficacy of the 150 mg/mL formulation of risankizumab in a pre-filled syringe (PFS) compared with placebo for the treatment of adult subjects with moderate to severe plaque psoriasis.

This SAP provides summaries of the planned statistical analyses for safety and efficacy endpoints, interim analysis, and overall type-I error control strategies.

The analyses of pharmacokinetic endpoints will not be covered in this SAP.

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

This SAP includes changes to analyses described in the protocol. Details are outlined in Section [13.0](#).

## **2.0 Study Design and Objectives**

### **2.1 Objectives and Hypotheses**

The primary objective of this study is to evaluate the safety and efficacy of the 150 mg/mL formulation of risankizumab in a pre-filled syringe (PFS) compared with placebo for the treatment of adult subjects with moderate to severe plaque psoriasis.

The co-primary endpoints are:

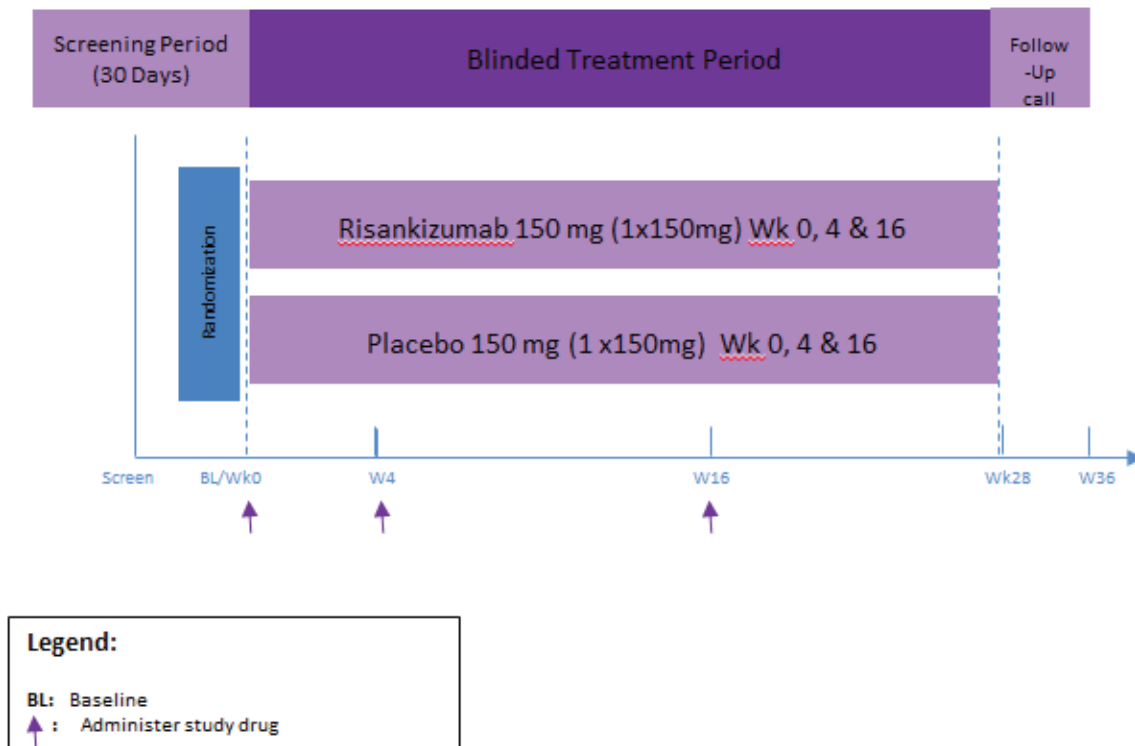
- The proportion of subjects achieving  $\geq 90\%$  reduction from Baseline in Psoriasis Area and Severity Index (PASI 90) response at Week 16.
- The proportion of subjects achieving a static physician global assessment (sPGA) clear or almost clear (0 or 1) at Week 16.

## 2.2 Study Design Overview

This is a multicenter, randomized, double-blind, placebo-controlled, parallel group study that will evaluate the safety and efficacy of risankizumab 150 mg/mL formulation in PFS in patients with moderate to severe plaque psoriasis. The study includes a 30-day screening period, a 28-week treatment period with study visits at Weeks 0, 4, 16 and 28, and a subsequent follow up telephone call at approximately 20 weeks after the last dose of study drug. Study drug dosing will consist of 3 self-administered doses given subcutaneously on Weeks 0, 4, and 16. Dosing on Week 4 will be self-administered at home. Efficacy assessments will be performed at each study visit (Weeks 0, 4, 16, and 28).

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 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 generated by the statistics department at AbbVie.

Subjects will be randomized in a 2:1 ratio to risankizumab 150 mg or placebo. Stratification is not planned for this study.

The investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the risankizumab PFS and placebo PFS provided for the study will be identical in appearance.

In the event of a medical emergency in which the investigator believes that knowledge of study drug treatment is required, reasonable efforts must be made to contact the AbbVie emergency contact prior to breaking the blind, as long as it does not compromise subject safety. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie emergency contact, the investigator can directly access the IRT system to break the blind without AbbVie agreement. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

## **2.4 Sample Size Determination**

This study is designed to enroll approximately 150 subjects, randomized in a 2:1 ratio to risankizumab or placebo. Assuming the response rates at Week 16 to be 74% for the risankizumab arm and 3% for the placebo arm for PASI 90, and 85% for the risankizumab arm and 7% for the placebo arm for sPGA of clear or almost clear, the study will provide more than 95% power for each of the two co-primary efficacy endpoints (an overall power of more than 90%) based on Pearson Chi-square test with 2-sided significance level of 0.05.

## **3.0 Endpoints**

### **3.1 Primary Efficacy Endpoints**

The co-primary endpoints of this study are:

1. Proportion of subjects achieving PASI 90 (defined as at least 90% improvement from baseline in PASI) at Week 16.
2. Proportion of subjects achieving sPGA of clear or almost clear at Week 16.

### 3.2 Secondary Efficacy Endpoints

**Key Secondary Endpoints:** The following ranked secondary endpoints will be tested between risankizumab and placebo in the hierarchical order only if the null hypotheses for both co-primary endpoints have been rejected:

1. Proportion of subjects achieving PASI 100 (defined as 100% improvement from baseline in PASI) at Week 16.
2. Proportion of subjects achieving sPGA of clear at Week 16.

### 3.3 Additional Endpoints

All primary and key secondary endpoints will be analyzed at all other visits collected. In addition, the following endpoints will be analyzed in all visits collected.

- Proportion of subjects achieving PASI 50/75
- Change and percent change from baseline in PASI

The following usability endpoints will also be summarized, for each treatment arm, at all visits collected.

- Proportion of subjects with an observer rating of successful subject self-administration, defined as any subjects who successfully completed the sequence of 3 critical steps in the Instructions for Use (IFU) without errors to administer study drug
- Proportion of subjects who experienced no potential hazards as measured by an observer
- Subject rating of acceptability using the Self-Injection Assessment Questionnaire (SIAQ)

### 3.4 Safety Endpoints

The following endpoints will be included in the safety analyses:

- Treatment emergent adverse events (TEAEs);
- Serious adverse events (SAEs);
- Areas of safety interest (ASI);
- Adverse events (AEs) leading to discontinuation;
- Vital signs and laboratory tests.

### **3.5 Pharmacokinetic Endpoints**

The pharmacokinetic endpoints will be analyzed separately.

## **4.0 Analysis Populations**

The intent-to-treat (ITT) Population includes all randomized subjects. The ITT Population will be used for all efficacy analyses. Subjects will be analyzed according to treatment as randomized.

The Safety Analysis Population consists of all randomized subjects who received at least 1 dose of study drug. For the safety analysis, subjects will be analyzed according to the first dose of study drug (risankizumab or placebo) that the subject received.

## **5.0 Subject Disposition**

The total number of subjects who were randomized, treated, completed, and discontinued will be summarized.

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

- Subjects randomized in the study;
- Subjects who received randomized study drug;
- Subjects who completed study;
- Subjects who discontinued study drug (all reasons and primary reason);

For end of study participation, the number and percentage of subjects who completed this study (or did not with associated reasons) will be summarized overall and by treatment group.

## **6.0 Study Drug Duration and Compliance**

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

Treatment compliance will be summarized for the entire treatment period by treatment group for the ITT population.

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

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

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

### **7.1 Demographics and Baseline Characteristics**

Continuous demographic variables include age, weight, height, and body mass index (BMI). Categorical demographic variables include sex, ethnicity, race, age (< 40, 40 – 65, ≥ 65 years), weight (≤ 100 or > 100 kg), BMI (< 25, ≥ 25 – < 30, ≥ 30 kg/m<sup>2</sup>), tobacco user (current, former, never, unknown), and alcohol user (current, former, never, unknown).

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

Demographics and baseline characteristics will be summarized among the ITT Population, overall and by treatment group. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

## **7.2 Medical History**

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

Medical history will be summarized among the ITT Population.

## **7.3 Prior and Concomitant Medications**

Prior and concomitant medications will be summarized by generic name. A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken on or after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug plus 28 days. The number and percentage of subjects taking medications will be summarized by generic drug name based on the

World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

In addition, subjects' prior biologic therapy for psoriasis will also be summarized by the reason for discontinuation.

Prior and concomitant medications will be summarized among the ITT Population.

## **8.0 Efficacy Analyses**

### **8.1 General Considerations**

All efficacy analyses will be conducted in the ITT Population. All tests will be 2-sided at an alpha level of 0.05.

The Primary Analysis will be performed after the last subject has completed the Week 16 visit or has discontinued from the study participation, and the data up to Week 16 have been cleaned. This will be the only and final primary efficacy analyses. All efficacy endpoints will be analyzed up to Week 16 during this analysis.

Categorical variables will be analyzed using Chi-square test. Continuous variables will be analyzed using MMRM with treatment as the fixed effect term, with treatment and Baseline values in the model.

Usability endpoints will be summarized by each treatment arm, by numbers and proportions for categorical variables; and by mean, standard deviation, median, minimal, and maximal values for continuous variables.

"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 given. For variables where assessment time is collected, the baseline measurement must be prior to the time of the first administration of study drug.

## 8.2 Handling of Missing Data

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

- **Non-Responder Imputation (NRI):** The NRI analysis will categorize any subject who does not have evaluation during a specific visit window as a non-responder for that visit. The only exception is when if the subject is a responder both before and after a specific visit window in the particular period, then the subject will be categorized as a responder for the visit. The NRI will be the primary approach to handle missing data in the analyses of categorical variables.
- **Modified-NRI:** Patients who discontinue study drug due to lack of efficacy or due to AE of worsening of psoriasis and do not have Week 16 measurements will be counted as non-responders. The only exception is when if the subject is a responder both before and after a specific visit window in the particular period, then the subject will be categorized as a responder for the visit. Other patients will be summarized using as-observed data. The modified-NRI analysis will be the sensitivity approach to handle missing data in the analysis of the co-primary and the ranked secondary endpoints.
- **As-observed:** The as-observed analysis will not impute values for missing assessments, thus subjects who do not have the assessments on a scheduled visit will be excluded from the analysis of that visit. The as-observed analysis will be the sensitivity approach to handle missing data in the analysis of the co-primary and the ranked secondary endpoints.
- **Mixed-effect Model Repeat Measurement (MMRM):** The repeated measures analysis will be conducted using a mixed model including baseline value and observed measurements at all post-baseline visits, using all available data even if a subject has missing data at some post-baseline visits. The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction as covariates. An unstructured variance covariance matrix will be used. Parameter estimation is based on the assumption of data being missing at random and using the method of restrictive maximum likelihood (REML). MMRM will be the primary approach in the analysis of continuous variables.

Usability endpoints will be analyzed by as-observed cases.

### **8.3 Primary Efficacy Endpoints and Analyses**

#### **8.3.1 Primary Efficacy Endpoints**

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

- Proportion of subjects achieving  $\geq 90\%$  improvement from baseline in PASI (PASI 90) at Week 16
- Proportion of subjects achieving an sPGA of clear or almost clear (0 or 1) at Week 16

The corresponding null hypotheses based on the Co-Primary Endpoints will be tested simultaneously:

- No difference in the proportion of subjects achieving PASI 90 at Week 16 between risankizumab 150 mg and placebo
- No difference in the proportion of subjects achieving sPGA clear or almost clear at Week 16 between risankizumab 150 mg and placebo

#### **8.3.2 Handling of Missing Data for the Primary Efficacy Endpoint(s)**

The co-primary endpoints will be analyzed using the NRI method to handle missing data. Modified-NRI and as-observed approaches will also be performed to handle missing data as sensitivity analyses.

#### **8.3.3 Primary Efficacy Analysis**

The two categorical variables will be analyzed using Chi-square test among the ITT Population. Both null hypotheses must be rejected simultaneously under a two-sided significance level of 0.05.

### **8.3.4 Additional Analyses of the Primary Efficacy Endpoints**

Not applicable.

## **8.4 Secondary Efficacy Analyses**

### **8.4.1 Key Secondary Efficacy Analyses**

The ranked secondary efficacy endpoints at Week 16 will be tested between the risankizumab and placebo treatment groups among the ITT Population in a hierarchical order only if the null hypotheses for both primary endpoints have been rejected.

Secondary efficacy endpoints will be analyzed using the NRI method to handle missing data. Modified NRI and as-observed approaches will also be performed to handle missing data as sensitivity analyses for these ranked secondary endpoints.

### **8.4.2 Supportive Secondary Efficacy Analyses**

Not applicable.

## **8.5 Other Efficacy Analyses**

Additional efficacy endpoints will be compared between the risankizumab and placebo treatment groups among the ITT Population.

Non-Responder Imputation (NRI) will be used for categorical efficacy endpoints to handle missing data. Mixed-effect Model Repeat Measurements (MMRM) will be used for continuous efficacy endpoints.

Usability endpoints will be analyzed by as-observed cases.

## **8.6 Efficacy Subgroup Analyses**

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

- Age group (< 40 years, ≥ 40 – < 65 years, ≥ 65 years)
- Sex (male, female)
- Smoking (current, ex or never)
- BMI (normal: < 25, over weight: ≥ 25 – < 30, obese: ≥ 30)
- Baseline Weight (≤ 100 kg, > 100 kg)
- Baseline PASI (by median)
- Baseline BSA (by median)
- Baseline sPGA (3, 4)
- Psoriatic arthritis (yes, no)
- Prior systemic biologic for psoriasis (naïve to biologics, experienced to biologics, biologic failures)

## **9.0 Safety Analyses**

### **9.1 General Considerations**

Safety data will be summarized for the Safety Analysis Population. Safety summaries will be presented by treatment group. For the safety analysis, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized. Safety analyses will include adverse events, laboratory, and vital sign measurements.

A subject's actual treatment will be determined by the first dose of study drug that the subject received.

Missing safety data will not be imputed.

### **9.2 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. When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same adverse event will be counted once, and only the maximum severity level will be presented in the severity summaries, and the worst/highest relationship level in the relationship summaries.

### **9.2.1 Treatment-Emergent Adverse Events**

Treatment-emergent adverse events (TEAEs) are defined as any event newly developed on or after the first dosing of study drug to 20 weeks (140) days after the last dose of study drug.

### **9.2.2 Adverse Event Overview**

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

- Any treatment-emergent AE
- Any treatment-emergent AE related to study drug according to the investigator
- Any severe treatment-emergent AE
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to discontinuation of study drug
- Any adjudicated MACE
- Any infection
- Any serious infection
- Any tuberculosis
- Any malignant tumor
- Any malignant tumor excluding NMSC
- Any serious hypersensitivity
- Any treatment-emergent AE leading to death

All deaths will also be summarized:

- Deaths occurring  $\leq$  140 days after last dose of study drug

- Deaths occurring > 140 days after last dose of study drug.

### **9.2.3 Treatment-Emergent Adverse Events by SOC and/or PT**

Treatment-emergent adverse events will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and by SOC and PT; by maximum severity and by SOC and PT; and by SOC and PT listing associated subject number. When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same adverse event will be counted once, and only the maximum severity level will be presented in the severity summaries, and the worst/highest relationship level in the relationship summaries.

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

### **9.2.4 Treatment-Emergent Adverse Events per Patient-Years of Exposure**

Exposure-adjusted AEs per 100 patient-years will be provided, where AEs per 100 patient-years of exposure are 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 + 140 days (5 half-lives)) of all subjects normalized by 365.25, and rounded to one decimal place.

### **9.2.5 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation**

Treatment-emergent SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and in listing format.

Pre-treatment AEs with onset dates prior to the first dose of study drug will be summarized separately.

### **9.2.6 Area of Safety Interest**

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

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

In addition, any injection site reactions by CMQ (code 80000019) will also be summarized by preferred terms in this study.

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

## **9.3 Analysis of Laboratory Data**

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

Mean change from baseline to each applicable post-baseline visit will be summarized for selected laboratory variables, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will

be presented for the mean change from baseline within each treatment group and difference between treatment groups.

Changes in laboratory parameters will be tabulated using shift tables categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline to minimum and maximum value (based on normal range), will be created. A similar shift table will be provided to summarize shifts from baseline to the final post-baseline value.

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

Laboratory abnormalities will be evaluated based on Potentially Clinically Important (PCI) criteria ([Appendix C](#)). For each laboratory PCI 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 PCI criteria.

In addition, ALT/SGPT, AST/SGOT, alkaline phosphatase, and total bilirubin will be categorized as follows:

- $< 1.5 \times \text{ULN}$
- $\geq 1.5 \times \text{ULN} - < 3.0 \times \text{ULN}$
- $\geq 3.0 \times \text{ULN} - < 5.0 \times \text{ULN}$
- $\geq 5.0 \times \text{ULN} - < 10.0 \times \text{ULN}$
- $\geq 10.0 \times \text{ULN} - < 20.0 \times \text{ULN}$
- $\geq 20.0 \times \text{ULN}$

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

- $\text{ALT} \geq 3 \times \text{ULN}$ , or
- $\text{AST} \geq 3 \times \text{ULN}$ , or

- $ALP \geq 1.5 \times ULN$ , or
- Total bilirubin  $\geq 2 \times ULN$ .

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

- ALT of  $> 3 \times ULN$  or AST of  $> 3 \times ULN$ ,
- Associated with an increase in total bilirubin  $\geq 2 \times ULN$ ,
- $ALP < 2 \times ULN$

#### **9.4 Analysis of Vital Signs**

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

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 treatment groups.

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

#### **9.5 Safety Subgroup Analyses**

No subgroup for safety analyses.

#### **9.6 Other Safety Analyses**

No other safety analyses.

## **10.0 Other Analyses**

No other analyses.

## **11.0 Interim Analyses**

### **11.1 Data Monitoring Committee**

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

A separate DMC charter describes the roles and responsibilities of the DMC members, frequency of data reviews, relevant data to be assessed, and general operations.

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

## **12.0 Overall Type-I Error Control**

The Primary Analysis will be the only and final analysis for the co-primary efficacy endpoints. Both primary endpoints need to be achieved simultaneously under a two-sided significance level of 0.05.

Overall type-I error will be controlled by testing the co-primary endpoints, followed by the ranked secondary endpoints, in a hierarchical order as described in [Section 8.3](#) and [Section 8.4](#).

Since there are no efficacy analyses for early stopping planned for the DMC review, no alpha spending is needed due to the DMC review.

## 13.0 Version History

**Table 1. SAP Version History Summary**

Version	Date	Summary
1.0	28 Nov 2018	Original version
2.0	20 Dec 2018	Updated study title to be consistent with Protocol Amendment 1
3.0	12 Jul 2019	Added baseline weight by 100 kg to the efficacy subgroup analysis. Added more statistical analysis details to the document.
4.0	05 Mar 2020	<p>Clarified weight and BMI categories in demographics.</p> <p>Clarified items to be summarized for disposition to align with the new standard table.</p> <p>Removed baseline BSA from MMRM model in efficacy analysis, as most BSA information is covered by the corresponding components in baseline PASI.</p> <p>Updated key secondary and other efficacy endpoints and analyses, as well as type-I error control, to align with Protocol Amendment (protocol version 4)</p> <p>Updated the definition of concomitant medication to align with the most updated risankizumab PSSAP.</p> <p>Clarified shift tables, PCI, and ASI definitions for safety analysis, to align with the most updated risankizumab PSSAP.</p> <p>Added the AE summary of any injection site reactions, according to FDA suggestion.</p> <p>Clarified that all efficacy endpoints will be analyzed up to Week 16 during the Primary Analysis.</p> <p>Added modified-NRI and as-observed sensitivity analyses to handle missing data for the co-primary and ranked secondary endpoints.</p>

## 14.0 References

## **Appendix A. Protocol Deviations**

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

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

## Appendix B. Definition of Area of Safety Interest

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

Area of Safety Interest	Search Criteria		Include in AE Overview (Y/N)
MACE	Adjudicated terms will be identified as described in PSSAP Table 3 using CECAT and CETERM from the CE SDTM dataset.		Y
Extended MACE	Adjudicated terms will be identified as described in PSSAP Table 3 (for MACE +) using CECAT and CETERM from the CE SDTM dataset.		N
Serious Infections	Serious AEs in the Infections and Infestations SOC		Y
Tuberculosis	Active Tuberculosis CMQ (code 80000188 )		Y
Opportunistic Infections	Opportunistic infection excluding tuberculosis and herpes zoster CMQ (code 80000189 )		N
Fungal Infections	Fungal infections CMQ (code 80000063)		N
Malignant Tumours	Narrow	Malignant tumours (SMQ 20000194)	Y
Non-melanoma Skin Cancer (NMSC)	Broad	Skin malignant tumours (SMQ 20000204) excluding terms identified by the Melanoma CMQ (code 80000119)	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.		Y
Hypersensitivity	Narrow	Hypersensitivity (SMQ 20000214)	Y – serious events only
Adjudicated Anaphylactic Reaction*	Adjudicated terms will be identified using SDTM data (e.g., CE and PR domains).		N
Hepatic Events	Broad	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ 20000013)	N
	Broad	Hepatitis, non-infectious (SMQ 20000010)	N
	Broad	Cholestasis and jaundice of hepatic origin (SMQ 20000009)	N

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Area of Safety Interest		Search Criteria	Include in AE Overview (Y/N)
	Broad	Liver related investigations, signs and symptoms (SMQ 20000008)	N
	Narrow	Liver-related coagulation and bleeding disturbances (SMQ 20000015)	N

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

## Appendix C. Potentially Clinically Important Criteria for Safety Endpoints

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

**Table C-1. Criteria for Potentially Clinically Important Hematology Values**

Hematology Variables	Units	Definition of Potentially Clinically Important: NCI CTCAE (Version 4) Grade 3 or Greater
		Very Low
Hemoglobin	g/dL	< 8.0
Platelets count	10 <sup>9</sup> /L	< 50.0
WBC count	10 <sup>9</sup> /L	< 2.0
Neutrophils	10 <sup>9</sup> /L	< 1.0
Lymphocytes	10 <sup>9</sup> /L	< 0.5

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

**Table C-2. Criteria for Potentially Clinically Important Chemistry Values**

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

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

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**Appendix D. Criteria for Potentially Clinically Important Vital Sign Values**

<b>Vital Signs Variables</b>	<b>Criterion</b>	<b>Definition of Potentially Clinically Important</b>
Systolic Blood Pressure (mmHg)	Low	Value $\leq 90$ mmHg and decrease $\geq 20$ mmHg from Baseline
	High	Value $\geq 160$ mmHg and increase $\geq 20$ mmHg from Baseline
Diastolic Blood Pressure (mmHg)	Low	Value $\leq 50$ mmHg and decrease $\geq 10$ mmHg from Baseline
	High	Value $\geq 100$ mmHg and increase $\geq 10$ mmHg from Baseline

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