# Statistical Analysis Plan for Study M19-164

# A Phase 3b, Multicenter, Interventional, Open-Label Study of Adult Subjects with Moderate to Severe Plaque Psoriasis Who Have a Suboptimal Response to Secukinumab or Ixekizumab and Are Switched to Risankizumab

## Date: 31 July 2023

## Version 4.0

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# 1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for risankizumab Study M19-164.

Study M19-164 examines the efficacy and safety of risankizumab in adult subjects with moderate to severe plaque psoriasis who have a suboptimal response to secukinumab or ixekizumab and are switched to risankizumab.

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 14.0.

# 2.0 Study Design and Objectives

## 2.1 Objectives, Hypotheses and Estimands

The objective of this study is to evaluate the efficacy and safety of switching to risankizumab in subjects with moderate to severe plaque psoriasis, who have been treated with labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a suboptimal response. Suboptimal response is defined as a static Physician's Global Assessment (sPGA) 2 or 3, and a Body Surface Area (BSA) 3% - < 10% after at least 6 months treatment with secukinumab or ixekizumab.

The study assesses whether Risankizumab improves skin symptoms and quality of life in subjects with moderate-to-severe plaque psoriasis who had a suboptimal response to secukinumab or ixekizumab.

The estimand for the primary endpoint is achievement of sPGA 0/1 at Week 16. The estimands for the secondary endpoints are achievement of sPGA 0 at Week 16, achievement of Dermatology Life Quality Index (DLQI) 0/1 at Week 16, achievement of Psoriasis Symptoms Scale (PSS) 0 at Week 16, achievement of sPGA 0/1 at Week 52, achievement of sPGA 0 at Week 52, achievement of DLQI 0/1 at Week 52, achievement of PSS 0 at Week 52, time to achieve sPGA 0/1 and time to achieve sPGA 0. Please refer to Section 9.3.2 and Section 9.4.2 for the detailed description of estimands.

## 2.2 Study Design Overview

This is a Phase 3b, global, interventional, multicenter, open-label, single-arm study examining the effect of risankizumab 150 mg administered at Week 0, Week 4, and then every 12 weeks (q12w) thereafter for 52 weeks in adult subjects with moderate to severe plaque psoriasis who have been treated with labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a suboptimal response. The patient population must be on the labeled secukinumab or ixekizumab for at least 6 months and are switched to risankizumab at Baseline (Week 0) (within ± 1 week of next scheduled dose for secukinumab or ixekizumab). Suboptimal response is defined as an sPGA 2 or 3 and a BSA 3% - < 10%.

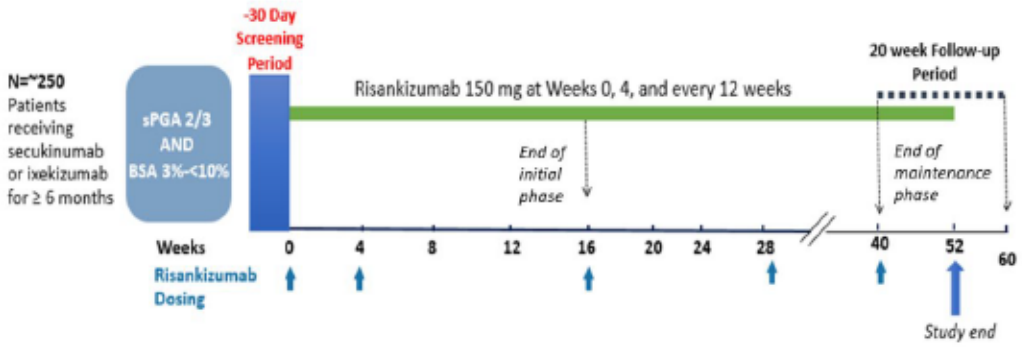
The study is designed to enroll 250 subjects.

Eligible subjects will receive 2 injections of active risankizumab 75 mg (150 mg total dosage) subcutaneously (SC) at Weeks 0 and 4, and then every 12 weeks (q12w) until the last dose at Week 40.

The study duration will be up to 64 weeks. The study comprises a 30-day Screening Period, a 52-week open-label study period, and a 20-week follow-up period after the last dose at Week 40. The 52-week open label period consists of an initial phase (Weeks 0-16) and a maintenance phase (Weeks 16-52). The follow-up period consists of a follow-up phone call 20 weeks after the last injection of study drug (at Week 40).

The schematic of the study is shown in Figure 1. Further details regarding study procedures are in the Operations Manual.

**Figure 1. Study Schematic**




## 2.3 Treatment Assignment and Blinding

No randomization. All subjects will receive open-label risankizumab.

## 2.4 Sample Size Determination

There is no published literature or clinical trial data to accurately estimate the primary endpoint sPGA 0/1 response rate at Week 16 for this study population – suboptimal response of subjects treated with secukinumab or ixekizumab. The assumption for risankizumab sPGA 0/1 response rate is expected to be between [redacted] based on the subjects who self-reported prior IL-17 failure from Phase 3 trials ULTIMMA 1& 2 and IMMhance.

The statistical precision measured by half-width of 95% confidence interval (CI) is the main criteria for sample size determination. By examining it over varying sample size, a choice of 250 subjects is associated with a half-width of no more than [redacted] which

corresponds to a response rate of 50% when variation is the greatest across all possible response rates (Figure 2).

From historical data of enrollment of the psoriasis studies conducted by AbbVie, the projected screen failure (SF) rate is [redacted]. Thus, [redacted] subjects will be needed to be screened to enroll 250 subjects.

# 3.0 Endpoints

## 3.1 Primary Endpoint

The primary endpoint is the proportion of subjects achieving sPGA 0/1 at Week 16.

## 3.2 Secondary Endpoints

The order of the secondary endpoints does not reflect a ranking.

The following secondary endpoints will be evaluated:

- The proportion of subjects achieving an sPGA clear response (sPGA 0) at Week 16;
- The proportion of subjects achieving a Dermatology Life Quality Index (DLQI) 0 or 1 at Week 16;
- The proportion of subjects achieving a Psoriasis Symptoms Scale (PSS) 0 at Week 16;
- The proportion of subjects achieving an sPGA 0/1 at Week 52;
- The proportion of subjects achieving an sPGA 0 at Week 52;
- The proportion of subjects achieving a DLQI 0/1 at Week 52;
- The proportion of subjects achieving a PSS 0 at Week 52;
- Time to achieve sPGA 0/1;
- Time to achieve sPGA 0.

## 3.3 Other Efficacy Endpoints

The exploratory efficacy endpoints are:

- The change from baseline in DLQI by visit;
- Treatment satisfaction as measured by the Treatment Satisfaction Questionnaire for Medication Version 9 (TSQM-9) at Baseline (Week 0) and at each visit;
- The proportion of subjects achieving absolute Psoriasis Area Severity Index (PASI) at thresholds (e.g., PASI $\leq$1, $\leq$3) by visit;
- The change from baseline in PASI by visit;
- The proportion of subjects achieving BSA $\leq$1%, $\leq$3%, by visit;
- The change from baseline in BSA by visit;
- The change from baseline in BSA x sPGA by visit;

- The proportion of subjects achieving sPGA 0/1 at Week 16 and maintained sPGA 0/1 response at Week 52.

### 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 Additional Endpoints

Not applicable.

## 4.0 Analysis Populations

Significant non-compliance was identified at a site. As a result of this finding, subjects enrolled in this site will not be included in any analysis population and data collected from this site will not be included in any analysis.

The following population sets will be used for the analyses.

The intent-to-Treat (ITT) Population, which is defined as all subjects who have at least one dose of study drug in Study M19-164, will be used for the efficacy analyses.

The Safety Analysis set, which is defined as all subjects who received at least one dose of study drug in Study M19-164, will be used for all safety analyses. In this study, the safety Analysis Set is the same as the ITT population.

## 5.0 Subject Disposition

The total number of subjects who were screened, enrolled, 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:

- Subjects enrolled in the study;
- Subjects who took at least one dose of study drug;
- Subjects who completed protocol-specified treatment;
- Subjects who prematurely discontinued study drug (all reasons and primary reason).

For end of study participation, the number and percentage of subjects who completed the protocol defined follow-up period (or did not with associated reasons) will be summarized.

## 6.0 Study Drug Duration and Compliance

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 ITT population for the entire treatment period. Treatment compliance is defined as the number of injections actually taken divided by the number of injections that should have been taken. Percent compliance will be summarized.

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

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the ITT Population. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

## 7.1 Demographics and Baseline Characteristics

Continuous demographic variables include:

- Age (years), defined as the number of years from date of birth to date of first drug
- Weight (kg)
- Height (cm)
- Body mass index (BMI, $kg/m^2$).

Categorical demographic variables include:

- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multi Race)
- Age categories (<40, 40 – 65, ≥ 65 years)
- Weight categories (≤ 100 or > 100 kg)
- BMI categories (< 25, ≥ 25 - < 30, ≥ 30 $kg/m^2$)

- Region (United States, Germany, Italy, Spain, United Kingdom, Israel, Australia, and Taiwan)
- Tobacco user (Current, Former, Never, Unknown)
- Alcohol user (Current, Former, Never, Unknown).

Disease characteristics include:

- General baseline characteristics: PASI (Psoriasis Area Severity Index), BSA (Body Surface Area), sPGA (static Physician's Global Assessment) categories, DLQI (Dermatology Life Quality Index), PSS (Psoriasis Symptoms Scale), treatment satisfaction as measured by TSQM-9 (Treatment Satisfaction Questionnaire for Medication Version 9)
- Duration of plaque psoriasis (in years)
- Cardiovascular diseases (myocardial infarction, angina pectoris, transient ischemic attack, stroke)
- Cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, obesity, family history of CV disease)
- Immediate prior treatment (secukinumab or ixekizumab).

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

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 140 days. The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

In addition, 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 Handling of Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The primary efficacy endpoint, proportion of subjects achieving sPGA 0/1 at Week 16 (defined in Section 3.1) will be analyzed based on the ITT population and the following methods will be used to address potential intercurrent events:

- Subjects who prematurely discontinued study drug before Week 16 due to lack of efficacy and/or treatment-emergent adverse events will be considered not achieving the primary endpoint.
- Subjects who die before assessment of the primary endpoint will count as failures to achieve the primary endpoint.

The secondary efficacy endpoints, proportion of subjects achieving sPGA 0 at Week 16, proportion of subjects achieving DLQI 0/1 at Week 16, and proportion of subjects achieving PSS 0 at Week 16 (defined in Section 3.2) will be analyzed based on the ITT

population and the following methods will be used to address the potential intercurrent events:

- Subjects who prematurely discontinued study drug before Week 16 due to lack of efficacy and/or treatment-emergent adverse events will be considered not achieving the above secondary endpoints.
- Subjects who die before assessment of the above secondary endpoints will count as failures to achieve the above secondary endpoints.

The secondary efficacy endpoints, proportion of subjects achieving sPGA 0/1 at Week 52, proportion of subjects achieving sPGA 0 at Week 52, proportion of subjects achieving DLQI 0/1 at Week 52, and proportion of subjects achieving PSS 0 at Week 52 (defined in Section 3.2) will be analyzed based on the ITT population and the following methods will be used to address the potential intercurrent events:

- Subjects who prematurely discontinued study drug before Week 52 due to lack of efficacy and/or treatment-emergent adverse events will be considered not achieving the above secondary endpoints.
- Subjects who die before assessment of the above secondary endpoints will count as failures to achieve the above secondary endpoints.

The secondary efficacy endpoints on time to achieve sPGA 0/1 and time to achieve sPGA 0 (defined in Section 3.2) will be analyzed based on the ITT population and the following methods will be used to address the potential intercurrent events:

- Subjects who prematurely discontinued study drug or early withdrew from the study due to lack of efficacy and/or treatment-emergent adverse events and never attained endpoints by the time of the last visit where sPGA was measured prior to discontinuation will have all data for the above secondary endpoints be considered as censored at the time of discontinuation of study drug or study due to lack of efficacy and/or treatment-emergent adverse events, whichever occurs first.

# 9.0 Efficacy Analyses

## 9.1 General Considerations

All efficacy analyses will be conducted in the ITT Population.

The primary analysis for all efficacy endpoints pertaining to the initial phase (Weeks 0-16) 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 and when a database lock will occur to enable the analysis. This will be the only and final efficacy analysis for the initial phase.

Categorical endpoints will be summarized by frequencies, percentages, and associated 95% confidence intervals (CIs). Continuous endpoints will be summarized by means, standard deviations as well as model based least square means, standard errors, and the 95% CIs after accounting for relevant baseline characteristics. Time to event endpoints will be analyzed using Kaplan-Meier estimates and Cox regression models with baseline sPGA and BSA measurements as covariates and hazard ratio between baseline sPGA 2 and baseline sPGA 3 and its 95% confidence interval will be reported. Time to event endpoints will be calculated as:

- Time to first achievement (with observed event) = [date of first achievement] - [date of first dose] + 1
- Subjects without sPGA measurements will not be included in the analysis.
- If a subject never attains the endpoint by the end of the evaluation period, that subject's time to first achievement will be censored at the last visit before the end of the evaluation period where sPGA was measured except the scenario described in Section 8.0.

"Baseline" refers to the last non-missing observation on or before the first administration of study drug. For variables where assessment time is collected, the baseline measurement must be prior to the time of the first administration of study drug.

## 9.2 Handling of Missing Data

Missing data could occur due to various reasons, including missing visits/assessments, early withdrawal from the study, or missing due to COVID-19 infection or logistic restriction.

The COVID-19 pandemic is interfering with the conduct of many ongoing trials, with potential impacts on treatment duration and the collection, analysis and the interpretation of clinical trial data. Some protocol-specified visits in the clinical trials may be impacted due to COVID-19 infection or logistical restrictions during the pandemic. For example, some scheduled visits may be missed due to self-quarantine or local government restrictions on travel; some visits may also be delayed or canceled due to healthcare resource constraints during the pandemic. Impacted visits due to COVID-19 will be recorded in the database. The probability of having missed visits and missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic can be reasonably assumed to be unrelated to the unobserved values. Therefore, for the purpose of statistical analysis, it is reasonable to assume that these missing data are missing at random (MAR) and the statistical models that require MAR assumption are appropriate.

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

- Non-Responder Imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C): the NRI-C analysis will categorize any subject who does not have evaluation during a specific visit window as a non-responder for that visit. The exceptions are: (1) 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; (2) missing data due to a COVID-19 infection or logistical restrictions related to the COVID-19 pandemic will be handled through Multiple Imputation (MI). The NRI-C will be the primary missing data imputation approach in the analyses of categorical variables.
- As-observed: The as-observed analysis will include all available assessments on a scheduled visit. No missing assessments will be imputed. And there will

be no overwriting for visits after subjects discontinue study drug due to lack of efficacy and/or treatment emergent adverse events. The as-observed analysis will be the sensitivity approach to handle missing data in the analysis of the primary and secondary categorical efficacy endpoints specified in Section 3.1 and Section 3.2.

- 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. The mixed model includes the categorical fixed effects of visits and the fixed covariates of baseline measurements. 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.

## 9.3 Primary Efficacy Endpoint and Analyses

### 9.3.1 Primary Efficacy Endpoint

The primary endpoint is the proportion of subjects achieving sPGA 0/1 at Week 16.

### 9.3.2 Main Analysis of Primary Efficacy Endpoint

The categorical variables will be summarized by frequencies, percentages, and associated 95% confidence intervals (CIs). Missing data will be handled using the NRI-C method.

The attributes of the estimand corresponding to the primary efficacy endpoint is summarized in Table 1.

**Table 1. Summary of the Estimand Attributes of the Primary Efficacy Endpoint**

| | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| **Estimand Label** | **Treatment** | **Endpoint** | **Population** | **Handling of Intercurrent Events** | **Statistical Summary** |
| Primary efficacy endpoint of sPGA 0/1 at Week 16 | Risankizumab 150 mg | Achievement of sPGA 0/1 at Week 16 | Subjects with moderate to severe plaque psoriasis, who have been treated with labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a suboptimal response | Subjects who prematurely discontinued study drug before Week 16 due to lack of efficacy and/or treatment-emergent adverse events will be considered not achieving the primary endpoint; Subjects who die before assessment of the primary endpoint will count as failures to achieve the primary endpoint. | Frequencies, percentages, and associated 95% confidence intervals |

### 9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

As-observed analysis will also be performed to handle missing data as sensitivity analysis.

## 9.4 Secondary Efficacy Endpoints and Analyses

### 9.4.1 Secondary Efficacy Endpoints

The secondary endpoints are as defined in Section 3.2.

### 9.4.2 Main Analyses of Secondary Efficacy Endpoints

Categorical endpoints will be summarized by frequencies, percentages, and associated 95% confidence intervals (CIs). Missing data will be handled using the NRI-C method.

Time to event endpoints will be analyzed using Kaplan-Meier estimates and Cox regression models with baseline sPGA and BSA measurements as covariates and hazard ratio between baseline sPGA 2 and baseline sPGA 3 and its 95% confidence interval will be reported.

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

| | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| **Estimand Label** | **Treatment** | **Endpoint** | **Population** | **Handling of Intercurrent Events** | **Statistical Summary** |
| Secondary efficacy endpoint of sPGA 0 at Week 16 | Risankizumab 150 mg | Achievement of sPGA 0 at Week 16 | Subjects with moderate to severe plaque psoriasis, who have been treated with labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a suboptimal response | Subjects who prematurely discontinued study drug before Week 16 due to lack of efficacy and/or treatment-emergent adverse events will be considered not achieving the endpoints; Subjects who die before assessment of the endpoint will count as failures to achieve the endpoints. | Frequencies, percentages, and associated 95% confidence intervals |
| Secondary efficacy endpoint of DLQI 0/1 at Week 16 | | Achievement of DLQI 0/1 at Week 16 | | | |
| Secondary efficacy endpoint of PSS 0 at Week 16 | | Achievement of PSS 0 at Week 16 | | | |

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

| | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| **Estimand Label** | **Treatment** | **Endpoint** | **Population** | **Handling of Intercurrent Events** | **Statistical Summary** |
| Secondary efficacy endpoint of sPGA 0/1 at Week 52 | Risankizumab 150 mg | Achievement of sPGA 0/1 at Week 52 | Subjects with moderate to severe plaque psoriasis, who have been treated with labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a suboptimal response | Subjects who prematurely discontinued study drug before Week 52 due to lack of efficacy and/or treatment-emergent adverse events will be considered not achieving the endpoints; Subjects who die before assessment of the endpoint will count as failures to achieve the endpoints. | Frequencies, percentages, and associated 95% confidence intervals |
| Secondary efficacy endpoint of sPGA 0 at Week 52 | | Achievement of sPGA 0 at Week 52 | | | |
| Secondary efficacy endpoint of DLQI 0/1 at Week 52 | | Achievement of DLQI 0/1 at Week 52 | | | |
| Secondary efficacy endpoint of PSS 0 at Week 52 | | Achievement of PSS 0 at Week 52 | | | |

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

| | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| **Estimand Label** | **Treatment** | **Endpoint** | **Population** | **Handling of Intercurrent Events** | **Statistical Summary** |
| Secondary efficacy endpoint of time to achieve sPGA 0/1 | Risankizumab 150 mg | Time to achieve sPGA 0/1 | Subjects with moderate to severe plaque psoriasis, who have been treated with labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a suboptimal response | Subjects who prematurely discontinued study drug or early withdrew from the study due to lack of efficacy and/or treatment-emergent adverse events and never attained endpoints by the time of last visit where sPGA was measured prior to discontinuation will have all data for the endpoints be considered as censored at the time of discontinuation of study drug or study due to lack of efficacy or treatment-emergent adverse events, whichever occurs first. | Kaplan-Meier estimates and Cox regression models with baseline sPGA and BSA measurements as covariates; hazard ratio between baseline sPGA 2 and baseline sPGA 3 and its 95% confidence interval will be reported. |
| Secondary efficacy endpoint of time to achieve sPGA 0 | | Time to achieve sPGA 0 | | | |

### 9.4.3 Sensitivity and Supplementary Analyses for Secondary Efficacy Endpoints

As-observed analysis will also be performed to handle missing data for categorical endpoints as sensitivity analysis.

## 9.5 Additional Efficacy Analyses

Categorical exploratory efficacy endpoints will be summarized by frequencies, percentages, and associated 95% confidence intervals (CIs). Missing data will be handled using the NRI-C method.

Continuous exploratory efficacy endpoints will be summarized by means, standard deviations as well model based least square means, standard errors, and the 95% CIs after accounting for relevant baseline characteristics. Missing data will be handled using the MMRM method.

## 9.6 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 endpoint if data allows.

- Age group ($< 40$ years, $\geq 40 - < 65$ years, $\geq 65$ years)
- Sex (male, female)
- Smoking (current, ex, never)
- BMI (normal: $< 25$, overweight: $\geq 25 - < 30$, obese: $\geq 30$)
- Baseline Weight ($\leq 100$ kg, $> 100$ kg)
- Baseline Weight (by quartiles)
- Baseline PASI (by median)
- Baseline BSA (by median)
- Baseline sPGA (2, 3)
- Immediate prior treatment (secukinumab or ixekizumab)

In addition, for the secondary efficacy endpoints time to achieve sPGA 0/1 and time to achieve sPGA 0, Kaplan-Meier estimates will be performed for the following subgroups:

- Baseline sPGA (2, 3)

# 10.0 Safety Analyses

## 10.1 General Considerations

Safety data will be summarized for the Safety Analysis Set. Safety analyses will include adverse events, laboratory, and vital sign measurements.

Missing safety data will not be imputed.

## 10.2 Adverse Events

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

### 10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AE with the onset that is after the first dose of study drug and within 20 weeks (140 days) after the last dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment emergent. All treatment-emergent AEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of subjects experiencing treatment-emergent AEs will be summarized.

### 10.2.2 Adverse Event Overview

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

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

All deaths will also be summarized:

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

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

Treatment-emergent adverse events will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and 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.

### 10.2.4 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.

### 10.2.5 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.

A listing of pre-treatment SAEs with onset dates prior to the first dose of study drug will be provided.

### 10.2.6 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.

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

## 10.3 Analysis of Laboratory Data

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

Each laboratory variable will be summarized for all applicable time points (starting with Baseline) 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.

Changes in laboratory parameters will be tabulated using shift tables based on the toxicity grades according to NCI CTCAE Version 4.03[1] of the laboratory used for each sample. A shift table from baseline to minimum and maximum value (based on toxicity grades), 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:

- $< 1.5 \times$ ULN
- $\geq 1.5 \times$ ULN – $< 3.0 \times$ ULN
- $\geq 3.0 \times$ ULN – $< 5.0 \times$ ULN
- $\geq 5.0 \times$ ULN – $< 10.0 \times$ ULN
- $\geq 10.0 \times$ ULN – $< 20.0 \times$ ULN
- $\geq 20.0 \times$ ULN

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

- ALT $\geq 3 \times$ ULN, or
- AST $\geq 3 \times$ ULN, or
- Alkaline Phosphatase $\geq 1.5 \times$ 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 $> 3 \times$ ULN or AST $> 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN.

## 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. 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.

Vital sign variables will be evaluated based on potentially clinically important (PCI) criteria (Appendix C). 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.

### 10.5 Safety Subgroup Analyses

No subgroup for safety analyses.

### 10.6 Other Safety Analyses

No other safety analyses.

## 11.0 Other Analyses

No other analyses.

## 12.0 Interim Analyses

An interim analysis for efficacy and safety data of the initial phase (Week 0 –16) will be conducted after 50% of all continuing subjects complete Week 16 and when an interim database lock will occur to enable the analysis. That is, the interim analysis will be conducted 16 weeks after 125 subjects complete study enrollment.

The primary analysis for the initial phase (Week 0-16) 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 and when a database lock will occur to enable the analysis.

### 12.1 Data Monitoring Committee

Not applicable.

## 13.0 Overall Type-I Error Control

Not applicable.

# 14.0 Version History

**Table 3. SAP Version History Summary**

| Version | Date | Summary |
|---|---|---|
| 1.0 | 05 December 2019 | Original version |
| 2.0 | 02 February 2021 | Clarified weight and BMI categories in demographics.<br>Removed France from the categories for Region in demographics.<br>Clarified items to be summarized for disposition to align with the new standard table.<br>Updated the definition of concomitant medication to align with the most updated risankizumab PSSAP.<br>Clarified PCI for safety analysis to align with the most updated risankizumab PSSAP.<br>Updated the definition of Hy's Law to align with the most updated risankizumab PSSAP.<br>Added details about how to handle missing data due to COVID-19.<br>Added as-observed analysis to handle missing data for the primary and secondary efficacy endpoints as sensitivity analysis.<br>Added primary endpoint subgroup analysis for baseline weight by quartiles.<br>Added subgroup analysis for the secondary efficacy endpoints time to achieve sPGA 0/1 and time to achieve sPGA 0.<br>Clarified statistical analysis to be performed for secondary efficacy endpoints time to achieve sPGA 0/1 and time to achieve sPGA 0.<br>Updated SAP according to the most updated SAP template; added estimands and their attributes for the primary and secondary endpoints in Section 2.1, Section 8.0, Section 9.3, and Section 9.4. |
| 3.0 | 13 May 2021 | Added more details for the analysis of time to event endpoints in Section 8.0, Section 9.1, and Section 9.4.2.<br>Clarified that there will be no overwriting due to intercurrent events for as-observed analysis.<br>Updated the subgroup analysis of smoking.<br>Updated that changes in laboratory parameters will be tabulated using shift tables based on toxicity grades instead of normal ranges. |
| 4.0 | 31 July 2023 | Section 4.0: Added statement about excluding a site from all analyses due to non-compliance. |

# 15.0 References

1. Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. 2010.

## 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 |

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

* 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, and the PCI criteria for vital sign findings are described in Table C-3.

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

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

Note: A post-baseline 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**

| | | Definition of Potentially Clinically Important NCI CTCAE (Version 4) 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 or > 3.0 × baseline |
| 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 grade must be more extreme than the baseline grade to be considered a potentially clinically important finding.

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

| Vital Signs Variables | Criterion | Definition of Potentially Clinically Important |
|---|---|---|
| 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 |