1.0 Title Page

Statistical Analysis Plan

Study M16-766

A Multicenter, Randomized, Open Label, Efficacy Assessor-Blinded Study of Risankizumab Compared to Secukinumab for the Treatment of Adult Subjects with Moderate to Severe Plaque-type Psoriasis who are Candidates for Systemic Therapy

Date: 22 Oct 2019

Version 4.0

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3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analysis for risankizumab study Protocol M16-766. Further details and analysis conventions to guide the statistical programming work will be in a supplement document.

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

SAP will not be updated in case of future administrative or minor amendments to the protocol unless the changes have an impact on the analysis of the study data.

4.0 Study Background

4.1 Objective

The objective of this study is to evaluate the efficacy and safety of risankizumab compared with secukinumab for the treatment of adult subjects with moderate to severe plaque-type psoriasis who are candidates for systemic therapy.

4.2 Study Design

4.2.1 Study Design and Design Diagram

This is a Phase 3, global, multicenter, randomized, open-label, efficacy assessor-blinded, active comparator study examining the effect of 150 mg risankizumab versus 300 mg secukinumab in patients with moderate to severe plaque psoriasis who are candidates for systemic therapy. The study is designed to randomize approximately 310 subjects (155 subjects/arm).

The study duration will be up to 88 weeks. The study comprises a 30-day Screening Period, a 52-week open-label study period and a 16-week follow-up period. The follow-up period consists of a follow-up phone call 20 weeks after the last dose of study drug. Subjects in France who were randomized to risankizumab will have two additional dosing

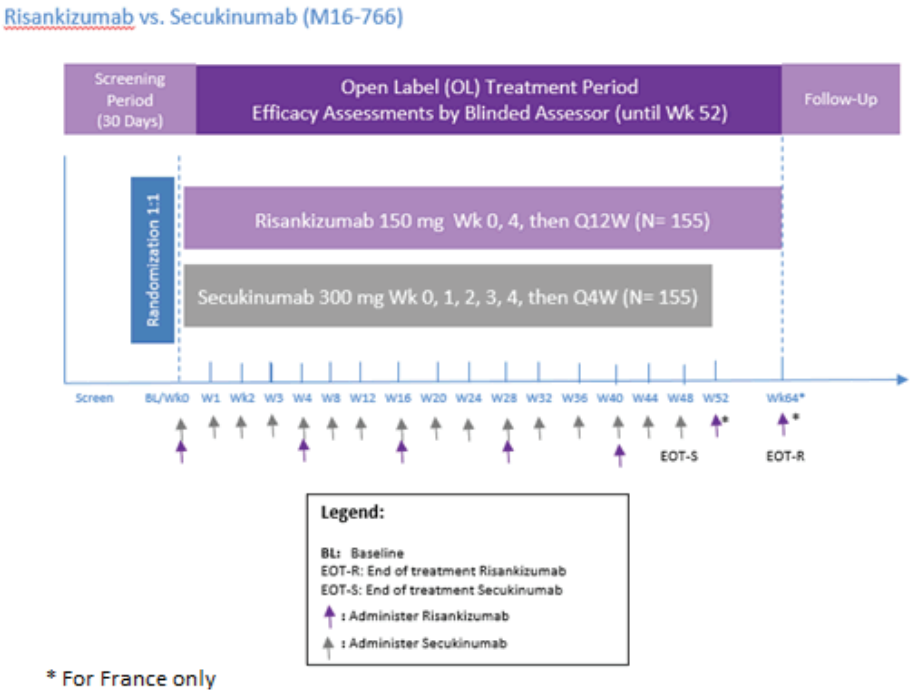
visits at Week 52 and Week 64 and a follow-up phone call 20 weeks after the last study drug dose.

For ease of description, Period A refers to Week 0 – 16, and Period B refers to the rest of the study.

Eligible subjects will be randomized to receive risankizumab or secukinumab in a 1:1 ratio as shown below in Figure 1:

- **Treatment A** (risankizumab SC injection): 2 injections of risankizumab 75 mg (150 mg total dosage) received subcutaneously at Weeks 0, 4, and every 12 weeks (q12w) thereafter until at Week 40. Subjects in France who were randomized to risankizumab will have two additional dosing visits at Week 52 and Week 64.
- **Treatment B** (secukinumab SC injection): 2 injections of secukinumab 150 mg (300 mg total dosage) received subcutaneously at Weeks 0, 1, 2, 3, 4, and every 4 weeks (q4w) thereafter until the last dose at Week 48.

Figure 1. Study Schematic



The primary analysis for Period A will be performed when the last subject completes the Week 16 visit. There will not be a modification to trial conduct based on the results of the analysis. Efficacy accessors will remain blinded for the duration of the study.

The Primary Analysis for all efficacy endpoints in Period B will be conducted after all continuing subjects have completed Week 52 and all data pertaining to Week 52 are cleaned and when a database lock will occur to enable the analysis.

4.2.2 Variables Used for Stratification at Randomization

The randomization will be stratified by weight (≤ 100 kg vs. > 100 kg) and prior systemic biologic for psoriasis (0 vs. ≥ 1).

4.3 Endpoint

4.3.1 Primary Efficacy Endpoint

The two primary endpoints are:

- Proportion of subjects achieving a Psoriasis Area Severity Index (PASI) 90 response at Week 52; superiority of risankizumab vs secukinumab.
- Proportion of subjects achieving a PASI 90 response at Week 16; non-inferiority of risankizumab vs. secukinumab with a non-inferiority margin of 12%.

4.3.2 Secondary Efficacy Endpoint

The multiplicity-controlled, ranked key secondary endpoints are:

- Proportion of subjects achieving a PASI 100 response at Week 52; superiority of risankizumab vs. secukinumab;
- Proportion of subjects achieving a static physician global assessment (sPGA) 0 or 1 at Week 52; superiority of risankizumab vs. secukinumab;
- Proportion of subjects achieving a PASI 75 response at Week 52; superiority of risankizumab vs. secukinumab.

4.3.3 Exploratory Efficacy Endpoint

The exploratory endpoints listed below will be analyzed for all visits in which the assessments are performed (other than those already included as primary or secondary endpoints):

- Proportion of subjects achieving ≥ 75%/90%/100% reduction from baseline in PASI score (PASI 75/90/100);
- Proportion of subjects achieving sPGA score of clear (0) or almost clear (0 or 1);

- Change and percent change from baseline in PASI and body surface area (BSA).

4.3.4 Safety Endpoint

Safety evaluations as a measure of safety and tolerability for the entire study duration include:

- Treatment emergent adverse events (TEAEs)
- Serious adverse events (SAEs)
- Areas of safety interest
- Adverse event (AE) leading to discontinuation
- Vital signs, laboratory tests, physical examination and electrocardiogram (ECG) findings

4.3.5 Pharmacokinetic Endpoint

The pharmacokinetic endpoints will be analyzed separately.

4.4 Sample Size Justification

There are two primary null hypotheses:

- Risankizumab is not different from secukinumab in achieving a PASI 90 response at Week 52.
- Risankizumab is inferior to secukinumab by 12% in achieving a PASI 90 response at Week 16.

The two null hypotheses will be tested in graphical procedures as illustrated in Section 4.6 with initial two-sided type I error 0.0125 and 0.0375, respectively.

The assumptions for the secukinumab Week 16 and Week 52 PASI 90 response rates of 69.7% and 60.6%, respectively, are based on weighted average from secukinumab studies SCULPTURE, ERASURE, FIXTURE, JUNCTURE, and CLEAR. The assumptions for

the risankizumab Week 16 and Week 52 PASI 90 response rates of 75.1% and 81.3%, respectively, are based on weighted average from UltiMMa-1 and UltiMMa-2 trials.

The calculation of sample size is based on ADDPLAN software using superiority test and non-inferiority test. The details of the formula can be found in: Wassmer, G (2003)[1] and Farrington, CP and Manning, G (1990).[2]

The non-inferiority margin was chosen based on the treatment effect of secukinumab versus placebo in PASI 90 response rate at Week 16. A 12% non-inferiority margin preserves 80% of the treatment effect of secukinumab over placebo.

Approximately 310 subjects (155 subjects per treatment group) will provide more than 90% power to detect the difference of risankizumab and secukinumab at Week 52 using a two-sided alpha level of 0.0125, and 90% power to determine the non-inferiority of risankizumab relative to secukinumab using a tolerance limit of 12% and a two-sided alpha level of 0.0375 at Week 16.

4.5 Interim Analysis

The primary analysis for Period A (Week 0 – 16) will be performed when the last subject completes the Week 16 visit. There will not be a modification to trial conduct based on the results of the analysis. Efficacy accessors will remain blinded for the duration of the study.

4.6 Multiplicity Testing Procedures for Type-I Error Control

The statistical comparisons for the two primary efficacy variables and the three ranked secondary variables will be carried out using graphical procedures as shown in Figure 2.

The 2 primary hypotheses are:

- H1: Risankizumab is not different from secukinumab in achieving a PASI 90 response at Week 52.

- H2: Risankizumab is inferior to secukinumab by 12% in achieving a PASI 90 response at Week 16.

The second null hypothesis (H2) will be tested with a two-sided type I error 0.0375. If the result is significant (p-value < 0.0375), then the 0.0375 will be passed to the first null hypothesis (H1), which will be tested with a two-sided type I error 0.05. On the other hand, if the result of H2 is not significant (p-value ≥ 0.0375), then H1 will be tested with a two-sided type I error 0.0125.

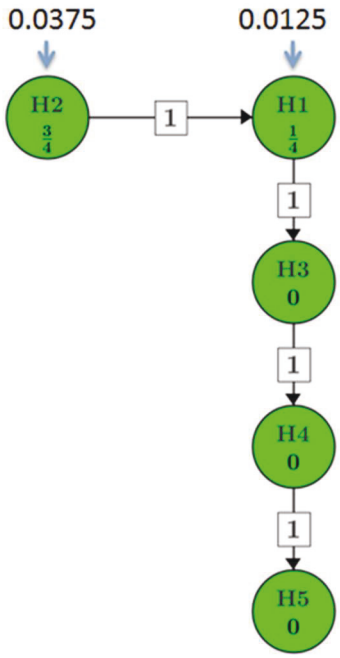
The multiplicity-controlled, ranked key secondary hypotheses are:

- H3: Risankizumab is not different from secukinumab in achieving a PASI 100 response at Week 52.
- H4: Risankizumab is not different from secukinumab in achieving an sPGA 0 or 1 at Week 52.
- H5: Risankizumab is not different from secukinumab in achieving a PASI 75 response at Week 52.

The three null hypotheses of secondary endpoints (H3, H4, and H5) will be tested in a sequential order with initial two-sided type I error of H3 same as that in H1, only when H1 is significant at its two-sided alpha level. The statistically significant results for the comparison in the higher rank of secondary endpoints are necessary to initiate the testing of the next comparison in the lower rank.

The details of using graphical procedures to control family wise type-I error could be found in Bretz, F, Maurer, W, Brannath, W, & Posch, M (2009).[3]

Figure 2. Graphical Approach for Type-I Error Control



4.7 Missing Data Imputation

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

- Non-Responder Imputation (NRI): The NRI analysis will categorize any subject who has missing value at a specific visit as non-responder for that visit. The only exception is when 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.
- Last Observation Carried Forward (LOCF): The LOCF analyses will use the completed evaluation from the previous visit within the particular period for efficacy measures assessed to impute missing data at later visits in the same period. LOCF will be the primary approach in the analysis of continuous variables, and a secondary approach for categorical variables.

- As-observed: The as-observed analysis will not impute values for missing evaluations. As-observed analysis will be the secondary approach in the analysis of continuous variables.
- Multiple Imputation (MI): The MI will be used as a sensitivity approach to impute missing data in primary endpoints.

5.0 Analysis Populations and Important Subgroups

5.1 Analysis Population

The Intent-to-Treat (ITT) Population will be used for the efficacy analyses. The ITT Population is defined as all subjects who are randomized at Baseline.

The following populations will be used for safety analysis:

- The Safety Population is defined as all subjects who are randomized at Baseline (ITT population) and received at least one dose of study drug. The Safety Population will be used to perform the 52-week head-to-head safety analysis between the two treatment groups.
- The All Risankizumab Treated (All_RZB) Population is defined as subjects who receive at least one dose of risankizumab in the study. The All_RZB Population will be used to perform a comprehensive safety summary for risankizumab.

In order to evaluate the impact of major protocol violations on the primary efficacy endpoints, additional sensitivity analyses will be performed on a Per-protocol Population, which excludes subjects with major protocol deviations that potentially affect the primary efficacy endpoints. The criteria for exclusion of subjects from the Per-protocol Population will be fully defined in the classification plan and the exclusion of subjects from the Per-protocol Population for the analysis will be finalized before the database lock.

5.2 Subgroup

Subgroup analyses will be performed for the primary endpoints by demographics and baseline characteristics as described in detail below (Section 6.5).

6.0 Efficacy Analysis

6.1 General Considerations

The Primary Analysis for all efficacy endpoints pertaining to Period A will be conducted after all continuing subjects have completed Week 16 and all data pertaining to Period A are cleaned and a database lock will occur to enable the analysis. This is the one and final efficacy analysis for Period A. The results will be included in an interim clinical study report (CSR) to support the efficacy and safety evaluation in the initial 16 weeks of treatment.

The Primary Analysis for all efficacy endpoints in Period B will be conducted after all continuing subjects have completed Week 52 and all data pertaining to Week 52 are cleaned and when a database lock will occur to enable the analysis.

The efficacy assessors will remain blinded for the duration of the entire study.

The efficacy analysis will be conducted in the ITT Population and Per-protocol Population. The ITT Population will be analyzed by treatment group as randomized. For the Per-protocol Population, subjects will be analyzed as randomized.

Comparison of the primary endpoints will be made between risankizumab group and secukinumab group using the Cochran-Mantel-Haenszel test adjusting for stratification by weight (≤ 100 kg vs. > 100 kg) and prior systemic biologic use for psoriasis. For the primary analysis, Non-Responder Imputation (NRI) will be used. The analysis will be repeated using last observation carried forward (LOCF) and Multiple Imputation (MI).

Categorical variables will be analyzed using Cochran-Mantel-Haenszel (CMH) test, stratified by weight (≤ 100 kg vs. > 100 kg) and prior systemic biologic use for psoriasis.

Continuous variables will be analyzed using ANCOVA method, with treatment, pooled center, and Baseline values in the model.

6.2 Primary Efficacy Analysis

The two primary endpoints are:

- Proportion of subjects achieving a PASI 90 response at Week 52; superiority of risankizumab vs secukinumab.
- Proportion of subjects achieving a PASI 90 response at Week 16; non-inferiority of risankizumab vs. secukinumab with non-inferiority margin of 12%.

6.3 Secondary Efficacy Analysis

The multiplicity-controlled, ranked key secondary endpoints are:

- Proportion of subjects achieving a PASI 100 response at Week 52; superiority of risankizumab vs. secukinumab;
- Proportion of subjects achieving an sPGA 0 or 1 at Week 52; superiority of risankizumab vs. secukinumab;
- Proportion of subjects achieving a PASI 75 response at Week 52; superiority of risankizumab vs. secukinumab.

6.4 Other Efficacy Analysis

Other efficacy endpoints include PASI 75/90/100, sPGA of clear or almost clear (0 or 1), change and percent change from baseline in PASI 75/90/100 and body surface area (BSA), except the ones that already included in the primary and secondary endpoints at all visits.

6.5 Efficacy Subgroup Analysis

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

Subgroup analyses will be performed on the primary endpoints using the following subgroups:

- Age group (< 40 years, ≥ 40);
- Sex (male, female);
- Race (white, non-white);
- Smoking (current, ex or never)
- BMI (normal: < 25, over weight: ≥ 25 – < 30, obese: ≥ 30);
- Baseline PASI score (by median);
- Baseline sPGA (3, 4)
- Psoriatic arthritis (yes, no)
- Prior biologic treatment (0, ≥ 1)

7.0 Safety Analysis

7.1 General Consideration

Safety analyses will include adverse events, laboratory, vital sign measurements and ECG parameter. Safety summaries will be provided using the safety populations.

The Safety Population will be analyzed as treated, based on the actual treatment received at the randomization visit.

Safety analysis in the All_RZB Population will be performed upon study completion.

7.2 Analysis of Adverse Events

A treatment-emergent AE (TEAE) among the Safety Population is defined as an event with onset or worsening on or after the first dose of study drug until the minimal of (i) 140 days following the last pre-Week 52 dose of risankizumab or secukinumab and (ii) the additional dose on or after Week 52.

A TEAE among the All_RZB Population is defined as an event with onset or worsening on or after the first dose of risankizumab until 140 days following the last dose of risankizumab throughout the study.

All safety analyses will be performed in the safety populations. Pre-treatment AEs will be summarized separately.

Safety summaries will also be provided among the All_RZB Population upon study completion.

All treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), AEs leading to discontinuation, and Areas of Safety Interest (ASI) will be analyzed during the study. The number and percentages of subjects experiencing TEAE will be tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class and preferred term. Summaries (including percentages and event per 100 patient-years) of SAEs, deaths, AEs leading to discontinuation, and Areas of Safety Interest will be provided as well.

7.3 Analysis of Laboratory Data

Mean change in laboratory and vital signs variables will be summarized among the Safety Population. For selected lab parameters, summaries of subjects with clinically significant laboratory abnormalities will be provided among the Safety Population and the All_RZB Population.

7.4 Analysis for Vital Signs and ECG Parameters

Mean change from baseline will be summarized among the Safety Population. Summaries of subjects with clinically significant vital sign determinations or ECG values will be provided among the Safety Population and the All_RZB Population.

8.0 Summary of Changes

Section 6.1. Corrected 'For the Per-protocol Population, subjects will be analyzed as treated' to 'For the Per-protocol Population, subjects will be analyzed as randomized' to be consistent with the protocol.

Section 7.1. Clarified 'The Safety Population will be analyzed as treated, based on the actual treatment received at the randomization visit. Safety analysis in the All_RZB Population will only be needed if at least one secukinumab subject (as treated) received risankizumab later in the study.'

Section 6.5. Corrected the subgroup of 'Psoriatic arthritis (yes [diagnosed or suspected], no)' to 'Psoriatic arthritis (yes, no).'

Section 6.5. Corrected the subgroup of 'Psoriasis Therapy History (Phototherapy or Photochemotherapy, TNF Antagonist, Other biologics, Non-biologic systemic therapy, All biologics, Naïve to all' with 'Prior biologic treatment (0, ≥ 1)).'

The following changes are made to align with the protocol amendment Version 1.1 in France:

- Section 4.2.1. Updated the study design.
- Section 5.1. Updated the definitions for the Safety Population and the All_RZB Population.
- Section 6.1. Updated the timing for the Primary Analysis for all efficacy endpoints in Period B
- Section 7. Updated the timing for safety summaries among the All_RZB Population. Clarified the TEAE definition among the All_RZB Population.

And clarified the safety summaries to be performed among the All_RZB Population.

9.0 References

1. Wassmer G. Data-driven analysis strategies for proportion studies in adaptive group sequential test designs. J Biopharm Stat. 2003;13(4):585-603.
2. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med. 1990;9(12):1447-54.
3. Bretz F, Maurer W, Brannath W. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28(4):586-604.