1.0 Title Page

Statistical Analysis Plan

Study M15-988

A Phase 3, Randomized, Open-Label Study to Assess Efficacy and Safety of Two Different Dose Regimens of Risankizumab Administered Subcutaneously in Japanese Subjects with Generalized Pustular Psoriasis or Erythrodermic Psoriasis

Date: 05 Jan 2018

Version 2.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analysis to be completed by the AbbVie Clinical Statistics Department for study Protocol M15-988 Amendment 1 dated 18 January 2017.

This SAP will provide details to further elaborate statistical methods as outlined in the Protocol M15-988 and will describe analysis conventions to guide the statistical programming work. The SAP will be signed off before the study database is locked.

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

4.0 Study Objectives, Design and Procedures

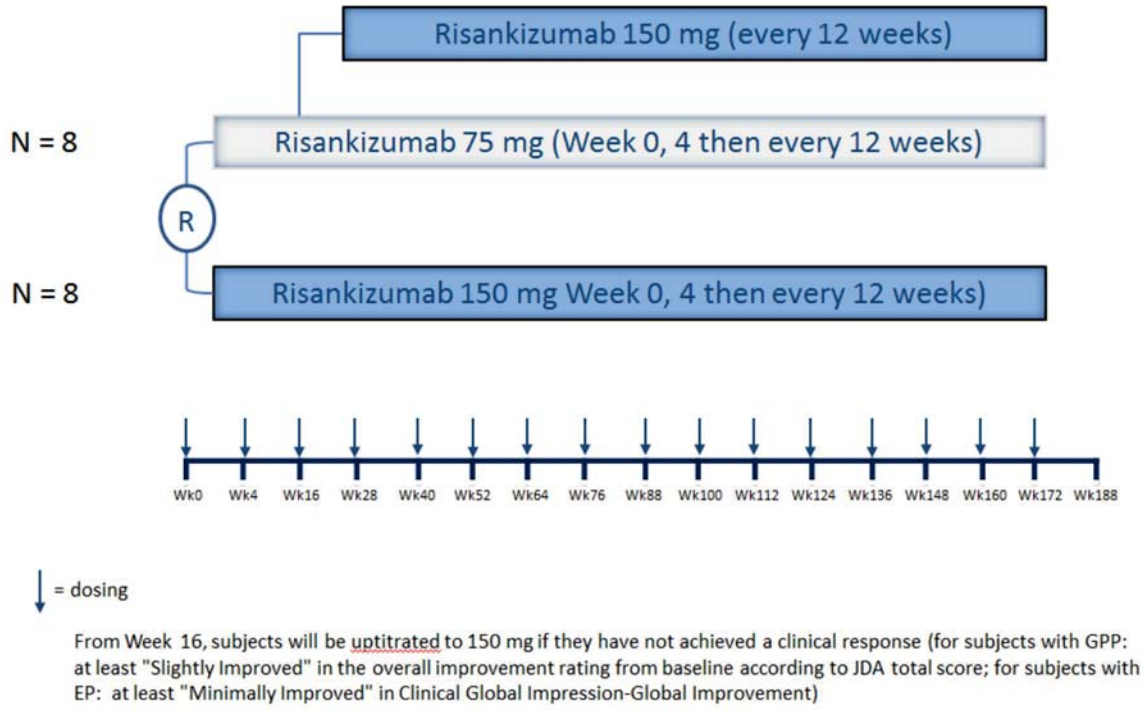
4.1 Primary Study Objective

The primary objectives of this study are to investigate the safety and efficacy of two different dose regimens of risankizumab for Japanese subjects with GPP or EP.

4.2 Design Diagram

This trial is a randomized, open-label study of two different dose regimens of risankizumab, 150 mg (2 syringes, 75 mg each) or 75 mg (1 syringe) at Week 0, 4 and every 12 weeks in two populations (subjects with GPP and with EP). Starting after the Week 16 visit, subjects on 75 mg may increase dosage to 150 mg. In total, at least 16 subjects, 8 with generalized pustular psoriasis and 8 with erythrodermic psoriasis will be randomized in this trial. From Week 16, subjects will be uptitrated to 150 mg if they have not achieved a clinical response (for subjects with GPP:at least "Slightly Improved" in the overall improvement rating from baseline according to JDA total score; for subjects EP: at least "Minimally Improved" in Clinical Global Impression-Global Improvement).

Figure 1. Trial Design



All subjects are to adhere to the visit schedule as specified in the Protocol Appendix C Each visit date (with its window) is to be counted from Day 1. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

4.3 Sample Size

The sample size is not estimated based on powering for any hypothesis testing. There are only approximately 1600 and 40000 Japanese subjects with generalized pustular psoriasis and erythrodermic psoriasis respectively, thus finding subjects to participate in the trial will be difficult. Therefore, the sample size is determined based on feasibility. In total, at least 16 subjects will be enrolled: at least 8 subjects for GPP and EP separately.

4.4 Interim Analysis

An interim analysis will be conducted when the last subject completes the Week 28 visit and all data pertaining to Week 28 and earlier are cleaned. For this analysis all Week 16 efficacy endpoints will be analysed, and all safety as well as pharmacokinetic and antiimmunogenicity data received by cut-off date will be analysed. Another interim analysis will be conducted when the last subject completes the Week 52 visit. The analyses will be performed for the efficacy endpoints until Week 52, as well as all safety and pharmacokinetic and immunogenicity data received by cut-off date.

Additional interim analysis may be performed if deemed necessary for regulatory purpose.

5.0 Analysis Populations

The Intent-to-Treat (ITT) subject population in each Substudy is defined as all randomized subjects with at least one dose of study drug. The Safety population is the same as the ITT population.

5.1 Variables Used for Stratification of Randomization

Subjects who are eligible based on inclusion and exclusion criteria and have had all pre randomization procedures performed will be randomized in a 1:1 fashion in each group to either 150 mg (2 syringes, 75 mg each) or 75 mg (1 syringe) at Week 0, 4 and every 12 weeks. Randomization will be done using an adequate block size.

6.0 Analysis Conventions

Since this is an open-label continuation study, no statistical test will be conducted. Summary statistics will be provided. Data from preceding studies will be integrated with data from this study in the summaries.

Definition of Baseline

For this study, baseline values are defined as the last non-missing values prior to the first dose of study drug in this study. These baseline values will be referred to as "BL" in this document. Unless otherwise specified, this will be the "baseline" for analysis.

Definition of Rx Days (Days Relative to the Date of First Dose of Study Drug)

Rx days are calculated for each time point relative to the date of first dose of this study. They are defined as the number of days between the day of the first dose of risankizumab and the specific time point. Rx days are negative values when the time point of interest is prior to the first risankizumab dose day. Rx days are positive values when the time point of interest is on or after the first risankizumab dose day. The day of the first dose of risankizumab is defined as Rx Day 1, while the day prior to the first risankizumab dose is defined as Rx Day –1 (there is no Rx Day 0).

Definition of Analysis Windows

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

For efficacy analyses, local tolerability, laboratory parameters, and vital sign variables, analysis windows are constructed using the following algorithm:

- Determine the nominal Rx day for each visit (e.g., Week 4 [4 weeks after Baseline visit] equals Rx Day 28).
- In order to include all post baseline data, the first post-baseline interval starts on the first day and the time after the first dose of risankizumab (Rx Day 1).
- Determine the window around a specific nominal Rx day, are presented in the Protocol Appendix C.
- If more than one assessment is included in a time window the assessment closest to the nominal day will be used. If there are two observations equidistant to the nominal day, the one after the nominal day will be used in analyses. If more than one post baseline assessment is included on the same

day, then the worst assessment on that day will be used in analyses, except those specified in Section 11.0.

The protocol specified visits and corresponding time windows used in the efficacy analyses, local tolerability, laboratory parameters, and vital sign variables, are presented in the following Table 1 – Table 32.

Table 1. Visit Windows for Analysis of Clinical Laboratory Tests, Vital Signs, Local Tolerability (WBC, CRP and ALB), and Efficacy Variables (PASI/JDA Score and Responder Rating/PGA-GPP/CGI-GI/BSA)

Window Label	Target Day	Interval
Screening	–	[–42, –1]
Baseline[a]	1	≤ 1[b]
Week 4	29	[2, 43]
Week 8	57	[44, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 134]
Week 22	155	[135, 176]
Week 28	197	[177, 218]
Week 34	239	[219, 260]
Week 40	281	[261, 302]
Week 46	323	[303, 344]
Week 52	365	[345, 407]
Week 64	449	[408, 491]
Week 76	533	[492, 575]
Week 88	617	[576, 659]
Week 100	701	[660, 743]
Week 112	785	[744, 827]
Week 124	869	[828, 911]
Week 136	953	[912, 995]
Week 148	1037	[996, 1079]
Week 160	1121	[1080, 1142]
Week 172	1163	[1143, 1205]
Week 184	1247	[1206, 1261]
Week 188	1275	[1262, 1282]

Rx Day calculated relative to first dose of risankizumab. For subjects randomized but not dosed, Rx Day calculated relative to Randomization.

a. There is no baseline for local tolerability measurements and CGI-GI.

b. If time is collected, restrict to records prior to the first dose of study drug.

Table 2. Visit Windows for Analysis of Clinical Laboratory Tests (excluding WBC, CRP and ALB)

Window Label	Target Day	Interval
Screening	–	[–42, –1]
Baseline[a]	1	≤ 1[a]
Week 8	57	[2, 85]
Week 16	113	[86, 155]
Week 28	197	[156, 239]
Week 40	281	[240, 323]
Week 52	365	[324, 533]
Week 100	701	[534, 869]
Week 148	1037	[870, 1100]
Week 172	1163	[1101, 1205]
Week 184	1247	[1206, 1261]
Week 188	1275	[1262, 1282]

Rx Day calculated relative to first dose of risankizumab. For subjects randomized but not dosed, Rx Day calculated relative to Randomization.

a. If time is collected, restrict to records prior to the first dose of study drug.

Table 32. Visit Windows for Analysis of Efficacy Variable (DLQI)

Window Label	Target Day	Interval
Baseline	1	≤ 1[a]
Week 12	85	[2, 99]
Week 16	113	[100, 239]
Week 52	365	[240, 407]
Week 64	449	[408, 491]
Week 76	533	[492, 575]
Week 88	617	[576, 659]
Week 100	701	[660, 743]
Week 112	785	[744, 827]
Week 124	869	[828, 911]
Week 136	953	[912, 995]
Week 148	1037	[996, 1079]
Week 160	1121	[1080, 1142]
Week 172	1163	[1143, 1205]
Week 184	1247	[1206, 1261]
Week 188	1275	[1262, 1282]

Rx Day calculated relative to first dose of risakizumab. For subjects randomized but not dosed, Rx Day calculated relative to Randomization.

a. If time is collected, restrict to records prior to the first dose of study drug.

Definition of Missing Data Imputation

The following rules will be used to impute for missing data. Data imputation will be used for missing values in the efficacy analysis, but not the safety analyses.

- For continuous endpoints, LOCF (Last Observation Carried Forward) will be used to impute missing values. The LOCF will use the last observed non-missing evaluation (last completed non-missing evaluation, from composite endpoint) from the previous visit within the particular period for efficacy measures assessed to impute missing data at later visits in the same period. Baseline efficacy evaluations will not be carried forward.
- For all binary endpoints (i.e., endpoints that are either 1 (subject responded) or 0 (subject did not respond):

1. If no assessment after that visit*, then impute as failure (NRI [No Response Imputation])
2. If there are assessments at visits* before and after, only impute as success if both visits are successes; else impute as failure

Subjects that take prohibited medications to treat Psoriasis will be treated the same as those that discontinued from the trial – i.e., subsequent visits following start of prohibited medication will be considered as failure for binary endpoints.

Rounding of Numeric Results

Rounding will be performed for presentation of results. No rounding will be performed before or during analyses. The ROUND function of SAS will be used to round results.

When dichotomizing continuous variables, associated continuous variables will be rounded to 9 decimal points before applying the cutoff point to determine the response status (for example, percent change from baseline in PASI score will be rounded to 9 decimal places before comparing to 90%).

The mean and median will be rounded for presentation to 1 decimal more than the data entered into the database. The standard deviation will be rounded to 2 decimal places more than the data entered into the database. The minimum and maximum values will be presented as entered into the database.

Probabilities will be rounded to 3 decimal places before assignment of statistical significance and will be presented in rounded format. Probabilities that round to zero or are reported by SAS as zero will be presented as "< 0.001." Probabilities that round to 1 or are reported by SAS as 1 will be presented as "> 0.999."

7.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications

7.1 Demographic and Baseline Characteristics

Demographics and Baseline characteristics will be summarized for ITT population, two different treatment arms (150 mg or 75 mg) and two diseases (GPP or EP). Continuous variables will be summarized with the number of non-missing observations by mean, standard deviation, median, minimum and maximum values. Categorical data will be summarized using frequencies and percentages. No Statistical tests will be performed for this study.

The following demographic and baseline parameters will be summarized.

Subject Demographics

- Sex (male, female)
- Age (years), defined as the number of years from date of birth to date of first drug
- Age categories (< 40 years, ≥ 40 – < 65 years, ≥ 65 years.)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multi Race)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Body weight (kg)
- Body weight category (≤ MEDIAN kg, > MEDIAN kg)
- Height (cm)
- BMI (kg/m^2)
- BMI category (< 25, ≥ 25 – < 30, ≥ 30)

General Baseline Characteristics

- PASI (Psoriasis Area and Severity Index)
- JDA (Japanese Dermatological Association) component scores (Mild, Moderate, Severe)

- PGA-GPP (Physician's Global Assessment of Generalized Pustular Psoriasis) (Cleared, except for residual, Minimal, Mild, Moderate, Severe, Very severe)
- DLQI (Dermatology Life Quality Index)
- BSA (Body surface area)
- C-Reactive Protein

Psoriatic Arthritis and Cardiovascular History

- Psoriatic arthritis (yes, no)
- Cardiovascular Diseases (myocardial infarction, angina pectoris, transient ischemic attack, stroke, deep vein thrombosis)
- Cardiovascular Risk Factors (hypertension, hyperlipidemia, diabetes mellitus, obesity)

General Use

- Smoking status (Current, Former, Never, Unknown)
- Alcohol status (Current, Former, Never, Unknown)

Prior Treatment

- Prior Biological Medication History (yes, no)
- Prior non-Biological Medication History (yes, no)
- Prior Psoriasis Therapy (yes, no)

Vital Signs at Baseline

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse (beats per minute)
- Respiratory rate (breaths per minute)
- Temperature (°C)

Clinical Tests at Screening

- Chest x-ray
- Tuberculin PPD skin test, QuantiFERON TB Gold test
- Hepatitis Testing
- Serum pregnancy test
- ECG

Immunization History

- BCG immunization
- Hepatitis B immunization

Also, Physical Exam and Pregnancy Test will be presented in listing format.

7.2 Medical History

Medical or surgical history other than psoriatic arthritis or cardiovascular diseases will be summarized using body systems and condition/diagnosis as captured on the eCRF for ITT population, two different treatment arms (150 mg or 75 mg) and two diseases (GPP or EP). The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized for each treatment arm and disease. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system. Tuberculosis history will be also summarized.

7.3 Previous Treatment and Concomitant Medications

Prior and concomitant medications will be summarized for ITT population, two different treatment arms (150 mg or 75 mg) and two diseases (GPP or EP) by generic name. A prior medication is defined as any medication taken at the time of entry into the study and prior to the first dose of risankizumab. A concomitant medication is defined as any medication that started prior to the first dose of risankizumab and continued to be

taken after the first dose of risankizumab or any medication that started after the first dose of risankizumab, but not after the last dose of study drug. The number and percentage of subjects who had taken medications will be summarized by generic drug name assigned by the World Health Organization (WHO) for both prior and concomitant medications.

7.4 Protocol Deviation

Number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided in the ITT population, two different treatment arms (150 mg or 75 mg) and two diseases (GPP or EP).

- Subject entered into the study even though she/he did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded or prohibited concomitant

8.0 Patient Disposition

The number of subjects will be tabulated by investigator site and overall. The number of subjects for each of the following categories will be summarized, for overall, two different treatment arms (150 mg or 75 mg) and two diseases (GPP or EP) in the ITT population.

- Number of subjects randomized
- Number of subjects that took at least one dose of study drug
- Number of subjects who completed at Week 28
- Number of subjects who prematurely discontinued from the study before Week 28

In addition, the number and percentage of subject who discontinued the study drug will be summarized by following categorized reason (primary and all) with frequencies and

percentages for overall, two different treatment arms (150 mg or 75 mg) and two diseases (GPP or EP) in the ITT population. Subjects with multiple reasons for premature discontinuation will be counted once in the calculation of the number and percentage of total discontinuations ("Premature Discontinuation").

- Adverse event
- Withdrew consent
- Lost to follow-up
- Others.

9.0 Study Drug Exposure and Compliance

Study drug exposure (days) will be summarized using the sample size, mean, standard deviation, minimum, median and maximum. Study drug exposure will be summarized for overall, two different treatment arms (150 mg or 75 mg) and two diseases (GPP or EP) in the ITT population as follows:

Risankizumab Exposure (in Days):

The Risankizumab Exposure (total duration) will be defined as follows:

The Risankizumab Exposure = Last risankizumab dose date – First risankizumab dose date + 1

10.0 Efficacy Analysis

10.1 General Considerations

The efficacy analysis will be performed for two different treatment arms (150 mg or 75 mg) and two diseases (GPP or EP) in the ITT population. The efficacy analysis will use the data from the study after subjects started to take Risankizumab. The BL values (baseline values) will be used to determine responses and changes in the efficacy variables.

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, maximum as well as the 95% confidence intervals (CIs) of the mean values. Categorical variables will be summarized by counts and percentages, as well as the 95% CIs of the percentages. No statistical tests will be performed in this study.

Missing data will be imputed using NRI and LOCF methods (see Section 6.0) for the efficacy analyses. And As-Observed Cases (OC) method also will be used for efficacy analyses.

- As-Observed Cases (OC): The as-observed analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the as-observed analysis for that visit. As-observed analysis will be the secondary approach in the analysis of continuous variables.

10.2 Primary Efficacy Endpoints

The following key efficacy variables will be summarized at all visits it the ITT population for each disease:

For GPP:

- Proportion of subjects achieving a GPP Clinical Response according to JDA total score, defined as at least "Slightly Improved" in the overall improvement rating from baseline, at Week 16.

For EP:

- Proportion of subjects achieving an EP Clinical Response, defined as at least "Minimally Improved" in Clinical Global Impression-Global Improvement (CGI-GI) at Week 16.

10.3 Secondary Efficacy Endpoints

The following additional efficacy variables will be summarized at all visits in the ITT population:

For GPP:

- Proportion of subjects achieving a GPP Clinical Response at Week 52
- Proportion of subjects achieving ≥ 90% reduction from baseline Psoriasis Area
- Severity Index (PASI) score (PASI 90) at Week 16
- Proportion of subjects achieving PASI 90 at Week 52

For EP

- Proportion of subjects achieving an EP Clinical Response at Week 52
- Proportion of subjects achieving PASI 90 at Week 16
- Proportion of subjects achieving PASI 90 at Week 52

10.4 Other Efficacy Endpoint(s)

The following endpoints will be summarized at each scheduled visit that the respective variable is collected:

For GPP

- Proportion of subjects achieving a GPP Clinical Response, defined at least "Slightly Improved" according to JDA total score in the overall improvement rating from baseline.
- Change from baseline in each of the JDA component scores
- Change and Percent change from baseline in JDA score
- Change and Percent change from baseline in PASI
- Change from baseline in BSA
- Proportion of subjects achieving PASI 50/75/90/100 response

- Proportion of subjects achieving Dermatology Life Quality Index (DLQI) of 0/0 or 1
- Change from baseline in DLQI
- Proportion of subjects achieving at least two grades of improvement in Physician's Global Assessment of Generalized Pustular Psoriasis (PGA-GPP).

For EP

- Proportion of subjects achieving an EP Clinical Response, defined at least "Minimally Improved" in CGI-GI for EP
- Proportion of subjects achieving at least "Much Improved" in CGI-GI for EP
- Percent change from baseline in PASI
- Change from baseline in PASI
- Proportion of subjects achieving PASI 50/75/90/100 response
- Change from baseline in BSA
- Proportion of subjects achieving DLQI of 0/0 or 1
- Change from baseline in DLQI

11.0 Safety Analysis

11.1 General Considerations

Safety analyses will include adverse events, laboratory, local tolerability, ECG, and vital sign measurements.

For the safety analyses, a baseline value (BL) is defined as the last non-missing observation on or prior to the date of the first dose of Risankizumab in this study. Safety summaries will be performed for two different treatment arms (150 mg or 75 mg) total arms, two diseases (GPP or EP) and overall in the safety population. The safety population is same as the ITT population.

11.2 Analysis of Adverse Events

11.2.1 Treatment-Emergent Adverse Events

Treatment emergent adverse events (TEAEs) are defined as any event with an onset that is after the first dose of risankizumab and with an onset date within 105 days after the last dose of study drug in the analysis period.

- **TEAE of Retreatment**: TEAE are defined as any event with an onset that is after the first dose of retreatment and no more than 105 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, unless the adverse event start time is prior to the study drug start time. If an incomplete onset date is collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event is not treatment-emergent (e.g., the event end date is prior to the study drug start date).

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

Summary tables will be presented as follows:

1. **Adverse Event Overview**

   The number and percentage of subjects experiencing treatment-emergent adverse events will be summarized for the following adverse event categories:

   - Any AE
   - Any AE that was assessed as related to study drug by the investigator
   - Any severe AE
   - Any serious AE
   - Any serious AE that was assessed as related to study drug by the investigator
   - Any AE leading to discontinuation of study drug

- Any AE leading to death
- Any deaths
- Areas of Safety Interest

2. **Adverse Events by System Organ Class and Preferred Term**

TEAEs will also be summarized and presented using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs). The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one type of adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one type of adverse event will be counted only once in the overall total.

In addition, the number and percentage of adverse events events with causal relationship between the events and the study drug will be summarized using the same conventions described above.

3. **Adverse Events by Maximum Severity**

The severity grading of AEs follows Rheumatology Common Toxicity Criteria (RCTC).

- Grade 1 – mild
- Grade 2 – moderate
- Grade 3 – severe
- Grade 4 – life threatening

Adverse events will also be summarized by maximum severity. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another

occurrence of the same adverse event with the most extreme severity – ("Life-threatening"). In this case, the subject will be counted under the "Life-threatening" category.

4. **Adverse Events by Maximum Relationship**

   Adverse events will be summarized by maximum relationship to study drug, as assessed by the investigator. Relationship of an AE to study drug is assessed by the investigator and collected in the CRF as 'Yes' or 'No.' If a subject has an adverse event with unknown relationship, the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship of "No." If the subject has another occurrence of the same adverse event with a relationship assessment of "Yes," the subject will be counted under the "yes" category.

A listing of all pretreatment (i.e., events start prior to the first study drug injection) serious adverse events will be provided.

The following tables are planned.

Treatment-emergent adverse events will be summarized as follows:

- Grouped by System Organ Class and Preferred Term
- Grouped by System Organ Class, Preferred Term and Relationship to Study Drug
- Grouped by System Organ Class, Preferred Term and Severity

Treatment-emergent serious adverse events will be summarized as follows:

- Grouped by System Organ Class and Preferred Term
- A by-subject listing will be provided

Pre-treatment serious adverse events will be summarized as follows:

- A by-subject listing will be provided

Treatment-emergent adverse events leading to death or premature discontinuation of study drug will be summarized as follows:

- Grouped by System Organ Class and Preferred Term
- Separate listings by subject for deaths and premature terminations of study drug due to adverse events will be provided.

Treatment-emergent areas of safety interest will be summarized as follows:

- Grouped by System Organ Class and Preferred Term
- A listing by subject will be provided.

Areas of Safety Interest:

Areas of Safety Interest groupings are listed in Table 43. These events are of interest due to a higher rate in the moderate to severe psoriasis population, or of interest for all Ig products or products in general (DILI).

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

Grouped Terms

Grouped terms will be summarized by grouped term or SMQ, including sub-SMQs and preferred term for any adverse event, adverse events leading to discontinuation, serious adverse events, moderate or severe adverse events and related adverse events.

Table 43. Areas of Safety Interest

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Adjudicated CV Events	Major adverse cardiovascular events (MACE)	Adjudicated events	Display underlined terms defined by the following adjudicated terms: • CV Death which includes CETERM values: Fatal CV, Fatal PE, Fatal Non-Cardiac/Non-Neuro Arterial Thrombosis/Thromboembolism, Undetermined Death, Not assessable death (cardiac/neuro/thrombotic), Fatal Stroke • Myocardial infarction • Stroke	Y
	Extended MACE	Adjudicated events	Display underlined terms from MACE and underlined terms below: • Hospitalization for Unstable Angina • Coronary Revascularization Procedures	N
	Other CV events	Adjudicated events	Display underlined terms defined by the following adjudicated terms: • Thrombotic events which includes CETERM values: Deep Vein Thrombosis, TIA, Pulmonary Embolism, Non-fatal Non-Cardiac/Non-Neurological Arterial Thrombosis/ Thromboembolism, Other Venous Thrombosis, specified (non-fatal) • Cardiac arrhythmia which includes CETERM of: Clinically Significant Arrhythmia • Congestive heart failure which includes CETERM of Heart Failure • Hypertensive emergency	N

Table 43. Areas of Safety Interest (Continued)

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Possible Drug induced liver injury (DILI)	Possible Drug induced liver injury (DILI)	Broad – Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ 20000013) Broad – Hepatitis, non-infectious (SMQ 20000010) Broad – Cholestasis and jaundice of hepatic origin (SMQ 20000009) Broad – Liver related investigations, signs and symptoms (SMQ 20000008) Narrow – Liver-related coagulation and bleeding disturbances (SMQ 20000015)	PTs	Y

Adverse Event per 100 Patient-Years of Exposure

Adverse events occurring during the entire study will be presented by event rate per 100 patient-year. These will be presented for any TEAEs, serious adverse events, Areas of Special Interest.

AEs per 100 patient-years of exposure is defined as the number of AEs divided by the total exposure in 100 patient-years. Note that one event per preferred term per day per

subject will be counted in the calculation of the number of AEs (i.e., a preferred term will not be counted twice on the same day for the same subject). See the calculation method below.

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

where total patient years is defined as the sum of the study drug exposure (defined as date of last dose – date of first dose + 105 days (5 half-lives)) of all subjects normalized by 365.25, and rounded to one decimal place.

11.2.2 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

Deaths and all SAEs will be presented in listing format. In addition, SAEs and AE leading to study drug discontinuation will be summarized by System Organ Class and MedDRA Preferred Term.

11.3 Analysis of Laboratory Data

Listing and descriptive statistics of laboratory values over time, changes from baseline, and extreme abnormal value on treatment will be provided. Baseline is understood as the last available measurement before study drug administration. Extreme abnormal value on treatment is understood as the on treatment laboratory value which is most significantly away from the reference range. Frequency of subjects with transitions relative to reference range and listing of subjects with significant abnormal laboratory values will be presented as well.

11.3.1 Variables and Criteria Defining Abnormality

Clinical laboratory tests performed are listed in Table 54.

Table 54. Clinical Laboratory Tests

Category	Test Name
Hematology	Hematocrit (Hct) Hemoglobin (Hb) Red Blood Cell Count/Erythrocytes White Blood Cells/Leukocytes Platelet Count/Thrombocytes
Diff. Automatic	Neutrophils (relative count) Eosinophils (relative count) Basophils (relative count) Monocytes (relative count) Lymphocytes (relative count)
Enzymes	AST (GOT) ALT (GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) Gamma-Glutamyl Transferase (GGT/γ-GT)
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Substrates	Glucose BUN (blood urea nitrogen) Creatinine eGFR (estimated by CKD-EPI formula) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Albumin C-Reactive Protein (CRP) (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol
Urinalysis (dipstick)	Urine pH

11.3.2 Statistical Methods

Analysis of Quantitative Laboratory Parameters (Hematology, Chemistry and Urinalysis)

Though the protocol indicates utilizing the Rheumatology Common Toxicity Criteria (RCTC) scale for grading laboratory values, given that the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) scale includes a more comprehensive list of laboratory values, the lab analyses based on the NCI CTCAE scale will be presented. Changes from Baseline to each scheduled visit and to the final value in continuous laboratory parameters will be summarized with the mean, standard deviation and median.

If there are multiple post-baseline measurements on the same day, average value will be used.

Shift Tables

Shift tables for changes from Baseline according to the normal range will be provided for each hematology, clinical chemistry and urinalysis (pH only) parameter. Shifts from Baseline to the following endpoints will be considered: minimum value, maximum value and final value. Categories of "low or normal" and "high or normal" will be included at Baseline in addition to the categories of "low," "normal," "high" and "missing." If there are multiple post-baseline measurements on the same day, last value will be used.

Potentially Clinically Significant Laboratory Values

Frequencies and percentages of subjects with post Baseline lab values met the following criteria in Table 65 and Table 76 will be summarized.

Table 65. Criteria for Potentially Clinically Important Chemistry Values

		Definition of Potentially Clinically Important Current (Version 4) NCI CTCAE Grade 3 or Greater	
Chemistry Variables	**Units**	**Very Low**	**Very High**
TBL	mcmol/L		> 3.0 × ULN
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
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

Table 76. Criteria for Potentially Clinically Important Hematology Values

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

A separate listing will be provided that presents all of the subjects and values that are NCI CTCAE toxicity grade 3 or above. For each of these subjects, the whole course of the respective parameter will be listed.

If there are multiple measurements on the same day, the worst value will be used.

Liver Function Tests

Additional summaries will be presented for liver function tests including ALT or serum glutamic-pyruvic transaminase (SGPT), AST or serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase, and total bilirubin. Each laboratory value will be categorized as follows:

- < 1.5 × ULN
- ≥ 1.5 × ULN – < 3.0 × ULN
- ≥ 3.0 × ULN – < 5.0 × ULN
- ≥ 5.0 × ULN – < 10.0 × ULN
- ≥ 10.0 × ULN – < 20.0 × ULN
- ≥ 20.0 × ULN

Shift tables of Baseline to the maximum (relative to the normal range, i.e., the largest multiple relative to the upper limit of normal) values, and from Baseline to final value will be presented using these five categories. A listing of potentially clinically significant liver function laboratory values will be provided. The listing will include all subjects who met any of the following four criteria:

- ALT ≥ 3 × ULN, or
- AST ≥ 3 × ULN, or
- Alkaline phosphatase ≥ 1.5 × ULN, or
- Total bilirubin ≥ 2 × ULN.

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

- ALT > 3 × ULN or AST > 3 × ULN
- Associated with an increase in bilirubin ≥ 2 × ULN

- Alkaline phosphatase < 2 × ULN

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality

The following vital sign parameters will be assessed: Systolic blood pressure [mmHg], Diastolic blood pressure [mmHg], Pulse [beats per minute], Respiratory rate [breaths per minute], Temperature [°C], Weight [kg]. The following Table 87 presents the Criteria for Potentially Clinically Significant Vital Sign Findings.

Table 87. Criteria for Potentially Clinically Significant Vital Sign Findings

Vital Sign	Category	Criteria for Potential Clinically Significant Vital Signs
Systolic Blood Pressure	Low Value	≤ 90 mmHg or decrease ≥ 20 mmHg from Baseline
	High Value	≥ 180 mmHg or increase ≥ 20mmHg from Baseline
Diastolic Blood Pressure	Low Value	≤ 50 mmHg or decrease ≥ 15 mmHg from Baseline
	High Value	≥ 105 mmHg or increase ≥ 15 mmHg from Baseline
Pulse	Low Value	≤ 50 bpm or decrease ≥ 15 bpm from Baseline
	High Value	≥ 120 bpm or increase ≥ 15 bpm from Baseline

11.4.2 Statistical Methods

Changes from Baseline to each visit and to the final value in vital sign parameters will be summarized with the mean, standard deviation and median. The Baseline and final value means will also be presented for subjects who have both the Baseline and final values.

If there are multiple post-baseline measurements on the same day, average value will be used.

For systolic blood pressure, diastolic blood pressure and pulse, a listing of all subjects with any vital sign value meeting criteria for potentially clinically important values will be provided. For each of these subjects, the whole course of the respective parameter will be listed. The number and percentage of subjects who have at least one value meeting

criteria for potentially clinically important values will be provided for each selected vital sign parameter.

12.0 Pharmacokinetic Analysis

Pharmacokinetic analysis will not be covered in this SAP.

13.0 Biomarkers Analysis

Biomarker Analysis is not covered in this SAP.

14.0 Summary of Changes

Not applicable.

14.1 Summary of Changes between the Latest Version of Protocol and the Current SAP

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

15.0 Appendix

Not applicable.

16.0 References

Not applicable.

17.0 List of Tables, Figures and Data Listings that Are to be Programmed

To be provided in a separate document.

Document Approval

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Signed by:	Date:	Meaning Of Signature:
[redacted]		Approver
		Approver