1.0 Title Page

Statistical Analysis Plan

Study M16-009 (1311.13)

An open label extension trial assessing the safety and Efficacy of Risankizumab administered subcutaneously in patients with moderate to severe chronic plaque psoriasis.

Date: 19 Sep 2018

Version 1.0

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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 M16-009 Amendment 6 dated 30 January 2018.

This SAP will provide details to further elaborate statistical methods as outlined in the Protocol M16-009 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 objective of this study is to investigate long-term safety and efficacy of risankizumab during open-label treatment in patients with moderate to severe chronic plaque psoriasis.

4.2 Design Diagram

This open label extension trial (OLE), investigates the additional safety and efficacy of the 90 mg dose of risankizumab. Approximately 100 patients who meet the entry criteria are planned for inclusion in this trial, rolling over from the preceding Study 1311.2 trial. The treatment will be open label.

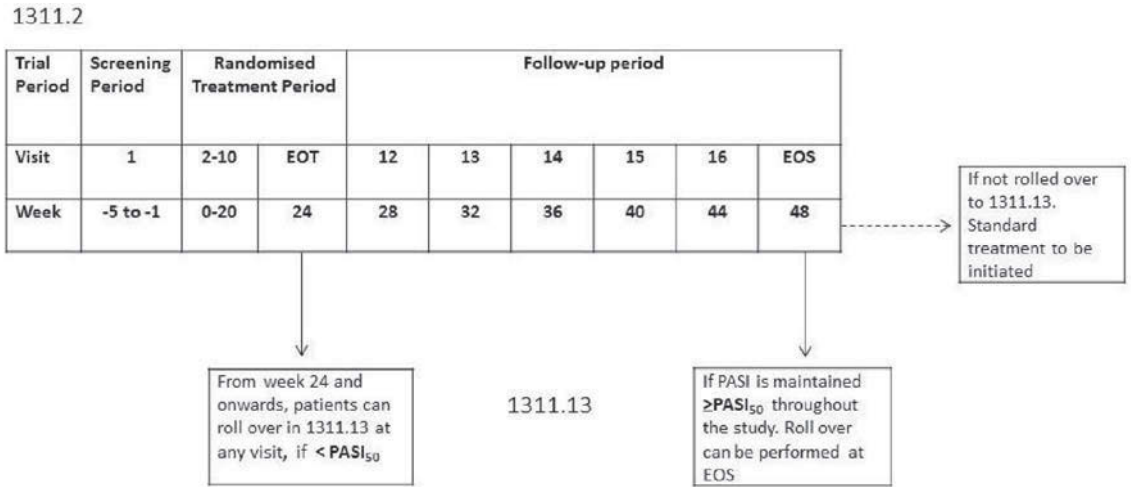
The treatment period will be approximately four years of administration starting with first administration of risankizumab in either Trial 1311.2 or this study, followed by a 12 week follow up period. After 01-May-2018 and approval of the protocol Amendment 6 in each respective country, the next study visit will be the Extended EOS visit and therewith the last visit in this study. Patients who have completed the study without early treatment discontinuation will be offered to roll over to Study M15-997

open label extension (OLE) trial if they fulfill the inclusion and exclusion criteria for the Study M15-997 trial.

Patients rolling over from the preceding Trial 1311.2 will have to complete the treatment period in that trial, or complete the entire trial including the follow up period, reaching end of study. If, during the follow up period of the preceding trial (at any visit from Week 24 and onwards in Trial 1311.2) loss of response is detected, the patient can roll over in this extension trial. For this, loss of response is defined as < PASI 50.

Extended Visit 1of this trial should preferably be performed as a combined visit the same day as End of Study visit of Study 1311.2, or within an interim period of maximum 6 weeks thereafter.

Figure 1. Guideline for roll over of patients from Study 1311.2 to this study

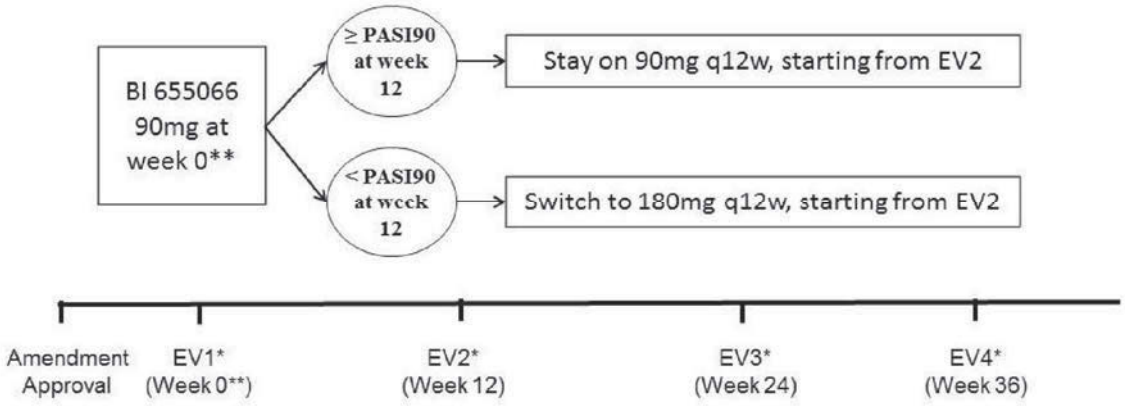


After the approval of protocol Amendment 6 in each respective country, all patients will follow Flow Chart (Extended Dosing Period) in the protocol and receive 90 mg risankizumab subcutaneously at their Extended Visit 1 (EV1). From EV1 onwards, risankizumab will be administered subcutaneously every 12 weeks during the trial. At EV2, if there is a lack of response, defined as < PASI 90, the dose should be increased to 180 mg for the remainder of the trial (see Figure 2).

For ongoing patients under the previous protocol amendment (Pre-Extended Dosing Period, see Figure 3), EV1 should be conducted at the following time points:

1. For ongoing patients with ≥ 12 weeks since the EOT visit: Conduct EV1 as soon as Possible.
2. For ongoing patients still undergoing treatment or with < 12 weeks since the EOT visit: Conduct EV1 at the time of the next scheduled treatment or follow up visit (note: EV1 should not be conducted at the time point of Visit 2 under the previous protocol, patients with Visit 2 as their next scheduled visit should have their EV1 replacing their Visit 3 instead)

Figure 2. Guideline for assessment of dose adjustment



* EV stands for extended visit
** Week 0 is the first scheduled visit after amendment approval.

Figure 3. Visit schedule Pre-Extended Dosing Period

Trial periods	Treatment period							Follow Up period			
Visit	1[1]	2	3	Interim Contact	4	5	EOT	FU 1	FU 2	FU 3	EOS visit
Day	1	42	84	126, 210, 294, etc…	168	252	336		EOT +168	EOT +252	EOT +336
Week	0	6	12	18, 30, 42, etc…	24	36	48	EOT +12	EOT +24	EOT +36	EOT +48
Visit window (days)	+7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7

If there are any tolerability issues, as assessed by the investigator, the patient will be discontinued.

The plaque psoriasis will be evaluated by PASI score at each visit. The standard clinical endpoints of PASI 50, PASI 75, PASI 90 and PASI 100 will be assessed at each visit based on the baseline PASI from Study 1311.2.

The end of study is defined as the date the last subject completes the Extended End-of-study visit.

4.3 Sample Size

The sample size is determined by the completion of Study 1311.2 and the consenting for the extension.

Eligible subjects from Study 1311.2 will be offered participation in this OLE study at their respective or referring sites. The check for subject eligibility will be based upon a successful completion of the Study 1311.2, signing the informed consent for this study, and the other inclusion and exclusion criteria.

4.4 Interim Analysis

Data will be reviewed periodically during the study by an independent Data Monitoring Committee (DMC).

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Intent to Treat (ITT) Populations:

The ITT Population is defined as all subjects who receive at least one dose of study drug in the study.

Safety Population:

Safety Population is the same as ITT Population for this study. This population will be used to provide a comprehensive summary of safety.

5.2 Variables Used for Stratification of Randomization

For this open-label study, no randomization of subjects into different treatment groups or stratification of randomization is required.

6.0 Analysis Conventions

Since this is a single arm open-label continuation study, no statistical test will be conducted. Summary statistics will be provided.

Definition of Baseline

1. Baseline is defined as the last non-missing value on or before the date of the first dose of study drug in Study 1311.2. The efficacy analyses will use these baseline values. These baseline values will be referred to as "BL" in this document.
2. RZB baseline is defined as the last non-missing value on or before the date of the first dose of risankizumab either in Study 1311.2 or this study. For vital sign assessments, only assessments prior to first dose time will be considered, since vital signs are to be assessed both pre- and post-dose in some visits. These values

will be referred to as BL_RZB in this document. BL_RZB will be used for safety analyses.

Definition of Final Observation (Applicable to Safety Analyses)

Final observation in the entire study is defined as the last non-missing observation collected within 105 days after the last dose of risakizumab.

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 risakizumab in this study. They are defined as the number of days between the day of the first dose of risakizumab and the specific time point. Rx days are negative values when the time point of interest is prior to the first risakizumab dose day. Rx days are positive values when the time point of interest is on or after the first risakizumab dose day. The day of the first dose of risakizumab is defined as Rx Day 1, while the day prior to the first risakizumab 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, study drug injections, 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 29).
- In order to include all post baseline data, the first post-baseline interval starts on the first day after the first dose of risakizumab (Rx Day 2).
- Determine the window around a specific nominal Rx day by adding or subtracting half of the interval between adjacent visits (e.g., days between Week 2 and Week 4 is 14). The threshold between adjacent visits is determined by splitting the interval evenly between the visits. If the resulting

split is between Rx days, then the threshold is determined as the midpoint between the adjacent visits. If the resulting split is on an Rx day, then the threshold is determined as being between that Rx day and the Rx day prior to it (e.g., the split between Week 2 and Week 4 would be between Rx Days 22 and 23).

- 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, study drug injections, local tolerability, clinical laboratory tests, and vital sign variables, are presented in the following Table 1.

Table 1. Visit Windows for Analysis of PASI, sPGA, Pain Vas, DLQI, Study Drug Injections, Local Tolerability Assessment, Clinical Laboratory Tests, and Vital Signs

Window label	Target day	Interval
Entry of this study[a]	1	≤ 1[b]
Week 12	85	[2, 127]
Week 24	169	[128, 211]
Week 36	253	[212, 295]
…	…	…
Week K	K × 7 + 1	[K × 7 – 40, K × 7 + 43]

a. There is no local tolerability measurements at entry of this study (Extended Visit 1).

b. If time is collected in vital signs, restrict to records prior to the first dose of RZB.

Note: Rx Day calculated relative to first dose date of risakizumab in this study.

Definition of Missing Data Imputation

No global imputation is taking place at the database level. Efficacy related imputations are outlined in Section 10.0. There is no imputation for missing values in the safety analyses.

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. 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, Multiple)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Body weight (kg)
- Body weight category (≤ 100 kg, > 100 kg)
- Height (cm)
- BMI (kg/m^2)
- BMI category (< 25, ≥ 25 – < 30, ≥ 30)
- Prior exposure to TNF antagonists (0 versus ≥ 1)

General Baseline Characteristics

- PASI (Psoriasis Area and Severity Index)
- BSA (Body Surface Area)
- sPGA (Static Physician Global Assessment)
- NAPSI (Nail Psoriasis Severity Index)
- PSSI (Psoriasis Scalp Severity Index)
- PPASI (Palmoplantar Psoriasis Area Severity Index)
- Dermatology Life Quality Index (DLQI)

Psoriasis and Cardiovascular History

- Psoriatic arthritis (diagnosed, suspected, no)
- Cardiovascular Diseases (angina pectoris, atherosclerosis, cerebrovascular accident, congestive heart failure, coronary artery disease, myocardial infarction, peripheral arterial disease, stroke, transient ischemic attack)
- Cardiovascular Risk Factors (hypertension, hyperlipidemia, diabetes mellitus (includes both type 1 and type 2))

General Use

- Smoking status (Never-smoked, Ex-smoker, Currently smokes)
- Alcohol status (Non-drinker, drinks – no interference, drinks – possible interference)

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

7.2 Medical History

Medical history (at the time of enrollment in the Study 1311.2) will be summarized using body systems and condition/diagnosis as captured on the eCRF. 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. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Previous Treatment and Concomitant Medications

Number of prior and concomitant medications per subject, and by generic name will be summarized.

A prior medication is defined as any medication taken at the time of entry into Study 1311.2 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 in Study 1311.2 or Study 1311.13 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 risankizumab + 21 days. 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.

- 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 and percentage of subjects for each of the following categories will be summarized by investigator:

- Number of subjects treated
- Subjects completed
- Subjects who discontinued study drug (by reason)
- Subjects who discontinued study (by reason)

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 as follows:

Risankizumab Exposure (in Days):

The Risankizumab Exposure (total duration during Study 1311.2 and this study) will be defined as follows:

The Risankizumab Exposure = Last risankizumab dose date – First risankizumab dose date (either in this study or Study 1311.2) + 84.

Compliance

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 who have not prematurely discontinued the study drug prior to the scheduled study drug injection. Subjects who have prematurely discontinued the study drug but have not prematurely discontinued the study are not used in the denominator.

10.0 Efficacy Analysis

10.1 General Considerations

The efficacy analysis will be performed for ITT population. The efficacy analysis will use the data from this study with baseline from Study 1311.2 and will be summarized by treatment groups in Study 1311.2.

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.

No missing data imputation will be applied. All efficacy analyses will be based on Observed Cases (OC) analysis, and thus a subject who does not have an evaluation at the analysis time point will not be included.

All endpoints will be analyzed up to the last visit at least one subject has observed measurements of that variable.

10.2 Key Efficacy Variables

The following key efficacy variables will be summarized at Week 48:

- Proportion of subjects achieving ≥ 90% reduction in Psoriasis Area and Severity Index (PASI) score (PASI 90)
- Proportion of subjects achieving the Static Physician Global Assessment (sPGA) score of clear or almost clear
- Proportion of subjects achieving ≥ 50% reduction in PASI score (PASI 50)
- Proportion of subjects achieving ≥ 75% reduction in PASI score (PASI 75)
- Proportion of subjects achieving 100% reduction in PASI score (PASI 100)
- Proportion of subjects achieving the sPGA score of clear

10.3 Additional Efficacy Analyses

The following additional efficacy variables will be summarized at all Extended dosing period visits:

- Proportion of subjects achieving PASI 50/75/90/100
- Proportion of subjects achieving the sPGA score of clear or almost clear
- Change from baseline in Pain-VAS (in subgroup of patients with diagnosed and suspected psoriatic arthritis)
- Change from baseline in DLQI.

- Proportion of subjects achieving DLQI score of 0 and 0/1;

11.0 Safety Analysis

11.1 General Considerations

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

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 in this study and with an onset date within 105 days after the last dose of study drug in the analysis period.

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

Considering the fact that some subjects had dose escalation due to lack of efficacy at EV2, selected safety tables will be generated breaking down by the group of subjects who remained at 90 mg throughout the study, the group of subjects who received 180 mg at EV2, and total.

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 TEAE
- Any TEAE with reasonable possibility of being related to study drug
- Any treatment emergent severe adverse event
- Any treatment emergent serious adverse event (SAE)
- Any SAE with reasonable possibility of being related to study drug
- Any TEAE leading to discontinuation of study drug.
- Any TEAE results in death.
- All death

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.

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.

The following summaries of TEAEs by SOC and PT will be generated:

- Any TEAE
- Any TEAE with causal relationship to study drug
- TEAE by maximum severity

In addition, summary of AEs by PT and by decreasing frequency of risankizumab total will be generated.

3. Areas of Safety Interest (ASI):

ASIs will be summarized and presented using ASI Grouping and PT. ASI groupings are listed in Table 2. These events are of interest due to a higer rate in the moderate to severe Ps 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.

Table 2. 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 2. Areas of Safety Interest (Continued)

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Serious infections, TB, fungal and opportunistic infections (including herpes zoster)	Serious infections	Serious PTs of the CMQ (company MedDRA query) Infections (CMQ 80000018)	PTs	Y
	TB	Tuberculosis (including Investigations) CMQ (code 80000033)	PTs	Y
	Opportunistic infections	Opportunistic infections CMQ (code 80000073)	PTs	N
	Fungal infections	Fungal infections CMQ (code 80000063)	PTs	N
	Herpes Zoster	Herpes zoster CMQ (code 80000175)	PTs	N
Malignancies	All possible malignancies	Narrow - Malignancies (SMQ 20000090)	PTs	N
	Malignant Tumours	Narrow - Malignant tumours (SMQ 20000194)	PTs	Y
	Non-melanoma skin cancer (NMSC)	Broad - Skin malignant tumours (SMQ 20000204) excluding terms identified by the Melanoma CMQ (code 80000119)	PTs	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.	PTs	Y

Table 2. Areas of Safety Interest (Continued)

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Hypersensitivity Reaction	Hypersensitivity	Narrow - Hypersensitivity (SMQ 20000214)	PTs	Y – serious events only
	Anaphylactic Reaction	Narrow - Anaphylactic reaction (SMQ 20000021)	PTs	N
Hepatic Events	Hepatic Events	Broad - Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ 20000013) Broad - Hepatitis, non-infectious (SMQ 20000010) Broad - Cholestasis and jaundice of hepatic origin (SMQ 20000009) Broad - Liver related investigations, signs and symptoms (SMQ 20000008) Narrow - Liver-related coagulation and bleeding disturbances (SMQ 20000015)	PTs	N

4. 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.

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.

The following summaries of AEs per 100 patient-years of exposure will be generated:

- Adverse event overview
- TEAE by SOC and PT
- SAE
- Treatment emergent adjudicated CV events
- Treatment emergent malignancies
- Serious treatment emergent malignancies

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

Deaths, AE leading to study drug discontinuation, and all SAEs will be presented in listing format. A listing of all pretreatment (i.e., events start prior to the first study drug injection) serious adverse events will be provided.

The following summaries of AEs by SOC and PT will be generated:

- Any SAE
- Any SAE with causal relationship to study drug
- Any TEAE leading to discontinuation of study drug
- Any TEAE leading to discontinuation of study drug with causal relationship to study drug

11.3 Analysis of Laboratory Data

Listing and descriptive statistics of laboratory values over time and extreme abnormal value on treatment will be provided. Baseline is the last non-missing values on or before the date of the first dose of risankizumab either in Study 1311.2 or this study. Extreme abnormal value on treatment is 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 3.

Table 3. Clinical Laboratory Tests

Category	Test name
Haematology	Hematocrit (Hct) Hemoglobin (Hb) Red Blood Cell Count/Erythrocytes Reticulocyte Count Glycosylated Hbc (HbA1c) White Blood Cells/Leukocytes Platelet Count/Thrombocytes
Diff. Automatic	Neutrophils (relative and absolute count) Eosinophils (relative and absolute count) Lymphocytes (relative and absolute count) Basophils (relative and absolute count) Monocytes (relative and absolute count)
Diff Manual (if Diff Automatic is abnormal)	Neutrophils, Bands (Stabs) Neutrophils, Polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Enzymes	Aspartate Aminotransferase/Glutamate-Oxaloacetate Transaminase (AST/GOT) Alanine transaminase (Glutamic Pyruvate Transaminase (ALT/GPT) Alkaline Phosphatase (AP/ALP) Creatine Kinase (CK) CK-MB if CK is elevated Lactic Dehydrogenase (LDH)
Coagulation	Partial Thromboplastin Time (= aPTT) Prothrombin Time (Quick and International normalised ratio (INR))
Electrolytes	Calcium Sodium Potassium

Table 3. Clinical Laboratory Tests (Continued)

Category	Test name
Substrates	Glucose Creatinine Blood urea nitrogen Bilirubin Total Bilirubin Direct Protein, Total C-Reactive Protein (CRP) Uric Acid Cholesterol, total High density lipoprotein (HDL) Cholesterol Calculated low density lipoprotein (LDL) Cholesterol Triglycerides
Urinalysis (Stix)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/Erythrocyte Urine WBC/Leukocytes Urine pH Urine albumin (microalbumin urine test) (roll-over visit only)
Urine-Sediment (microscopic examination) (if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epith Cells Urine Sediment Crystals, Unspecified Urine Sediment red blood cell count (RBC)/Erythrocytes Urine Sediment white blood cell count (WBC)/Leucocytes

11.3.2 Statistical Methods

Analysis of Quantitative Laboratory Parameters

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 sponsor will present the lab analyses based on the NCI CTCAE scale. Observed values at each scheduled visit in continuous laboratory

parameters will be summarized with the mean, standard deviation, median, minimum and maximum. If there are multiple post-baseline measurements on the same day, average value will be used.

Shift Tables

Shift tables will be provided for each hematology, clinical chemistry parameter. Shifts from Baseline to the following endpoints will be considered: post-Baseline value and final value. This analysis will be performed only for category of "low or normal" at Baseline which shift to 'high' and category of "high or normal" at Baseline which shift to category of 'low.' 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 4 and Table 5 will be summarized. Of note, a post baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table 4. Criteria for Potentially Clinically Important Chemistry Values

Chemistry Variables	Units	Definition of Potentially Clinically Important Current (Version 4) NCI CTCAE Grade 3 or greater	
		Very Low	Very High
Bilirubin Total	mcmol/L		> 3.0 × ULN
AST (GOT)	U/L		> 5.0 × ULN
ALT (GPT)	U/L		> 5.0 × ULN
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
CK	U/L		> 5.0 × ULN
Cholesterol, total	mmol/L		> 10.34
ALP			> 5.0 × ULN

Table 5. Criteria for Potentially Clinically Important Hematology Values

Hematology Variables	Units	Definition of Potentially Clinically Important Current (Version 4) Grade 3 or greater
		Very Low
Hemoglobin	g/dL	< 8.0
Platelets count	10^9/L	< 50.0
White Blood Cells	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

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 6 presents the Criteria for Potentially Clinically Significant Vital Sign Findings. Of note, a post baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table 6. 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 and decrease ≥ 20 mmHg from Baseline
	High Value	≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic Blood Pressure	Low Value	≤ 50 mmHg and decrease ≥ 15 mmHg from Baseline
	High Value	≥ 105 mmHg and increase ≥ 15 mmHg from Baseline
Pulse	Low Value	≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High Value	≥ 120 bpm and increase ≥ 15 bpm from Baseline

11.4.2 Statistical Methods

Observed values at each scheduled visit in vital sign parameters will be summarized with the mean, standard deviation, median, minimum and maximum. 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 vital sign parameter.

11.5 Local Tolerability

Local tolerability of the subcutaneous injection will be assessed by the investigator according to 6 items: swelling, induration, heat, redness, pain, and other findings. Number and proportion of subjects reporting each condition will be summarized.

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. This is the first version of the SAP.

15.0 Appendix

None.

16.0 References

Not applicable.

Document Approval

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