Statistical Analysis Plan for Study M16-005

A Multicenter, Single-Arm, Open-Label Study to Assess the Usability of the Risankizumab Autoinjector Combination Product in Adult Patients with Moderate to Severe Plaque Psoriasis

Date: 22 April 2020

Version 5.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for risankizumab Study M16-005 A Multicenter, Single-Arm, Open-Label Study to Assess the Usability of the Risankizumab Autoinjector Combination Product in Adult Patients with Moderate to Severe Plaque Psoriasis. Study M16-005 evaluates the usability of the combination product of risankizumab in an AI and to evaluate the efficacy, safety, and tolerability of risankizumab 150 mg/mL administered by AI for the treatment of adult patients with moderate to severe plaque psoriasis.

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

There will be no analyses of pharmacokinetic endpoints in this study.

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

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

This SAP includes changes to analyses described in the protocol. Details are outlined in Section 13.0.

2.0 Study Design and Objectives

2.1 Objectives and Hypotheses

The objectives of this study are to evaluate the usability of the combination product of risankizumab in an AI and to evaluate the efficacy, safety, and tolerability of risankizumab 150 mg/mL administered by AI for the treatment of adult patients with moderate to severe plaque psoriasis.

The following key endpoints will be evaluated:

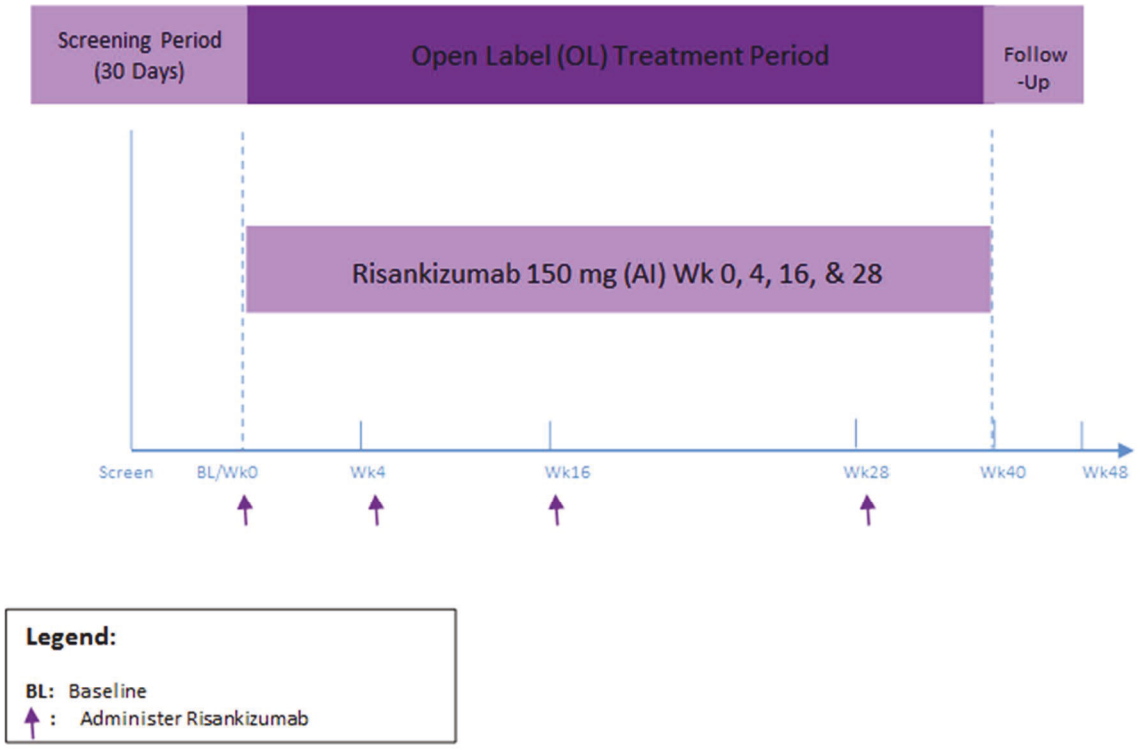
- Proportion of subjects with an Observer rating of successful subject self-administration, defined as any subjects who successfully completed the sequence of 4 critical steps in the Instructions for Use (IFU) without errors to administer study drug via the AI at Week 0 and Week 28
- Proportion of subjects achieving at least 90% improvement from baseline in the Psoriasis Area and Severity Index (PASI) (PASI 90) at Week 16
- Proportion of subjects achieving sPGA clear or almost clear at Week 16
- Proportion of subjects achieving 100% improvement from baseline in PASI (PASI 100) at Week 16
- Proportion of subjects achieving at least 75% improvement from baseline in PASI (PASI 75) at Week 16
- Proportion of subjects achieving sPGA of clear at Week 16.
- Proportion of subjects who had no potential hazards as measured by an Observer on the possible use-related hazards checklist for self-administration with AI at Week 0 and Week 28
- Subject rating of acceptability by the Self-Injection Assessment Questionnaire (SIAQ; Operations Manual Appendix B) at each visit collected.

2.2 Study Design Overview

This is a Phase 3 multicenter, single-arm, open-label study that will evaluate usability of the risankizumab-AI combination product. In addition, efficacy will be evaluated by an efficacy assessor. The study includes a 30-day screening period with study visits at Week 0, 4, 16, 28, and 40 with a subsequent follow-up telephone call at approximately 20 weeks after the last dose of study drug (Week 48). Study drug dosing will consist of four self-administered doses given subcutaneously on Weeks 0, 4, 16, and 28. Dosing on Week 4 and Week 16 will be self-administered at home. Efficacy assessments will be performed at each study visit (Weeks 0, 4, 16, 28, and 40).

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



2.3 Treatment Assignment and Blinding

All subjects will receive open-label risankizumab.

2.4 Sample Size Determination

This study is designed to enroll approximately 100 subjects who will self-administer the risankizumab-AI combination product at Weeks 0, 4, 16, and 28.

Assuming the point estimate is 90% for the proportion of subjects with an observer rating of successful subject self-administration at Week 28, the current sample size of 100 subjects will provide a 95% confidence interval of ± 5.9% around a point estimate.

In addition, assuming comparable response rates as the Phase 3 pivotal studies, with the current sample size of 100, the PASI 90 rate at Week 16 can be estimated with a 95% confidence interval of ± 8.6% when the point estimate is 74%; and the sPGA of clear or almost clear rate at Week 16 can be estimated with a 95% confidence interval of ± 7.0% when the point estimate is 85%.

3.0 Endpoints

3.1 Key Efficacy and Usability Endpoints

The following key endpoints will be evaluated:

- Proportion of subjects with an Observer rating of successful subject self-administration, defined as any subjects who successfully completed the sequence of 4 critical steps in the IFU without errors to administer study drug via the AI at Week 0 and 28
- Proportion of subjects achieving at least 90% improvement from baseline in PASI (PASI 90) at Week 16
- Proportion of subjects achieving sPGA clear or almost clear at Week 16
- Proportion of subjects achieving 100% improvement from baseline in PASI (PASI 100) at Week 16
- Proportion of subjects achieving at least 75% improvement from baseline in PASI (PASI 75) at Week 16
- Proportion of subjects achieving sPGA of clear at Week 16.
- Proportion of subjects who had no potential hazards as measured by an observer on the possible use-related hazards checklist for self-administration with AI at Week 0 and Week 28
- Subject rating of acceptability by the Self-Injection Assessment Questionnaire (SIAQ) at each visit collected.

3.2 Additional Efficacy Endpoints

All key efficacy endpoints will be analyzed at all other visits collected. Additional variables to be provided will include the proportion of subjects achieving PASI 50, as well as change and percent change from baseline in PASI, at each visit collected.

3.3 Safety Endpoints

The following endpoints will be included in the safety analyses:

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

3.4 Additional Endpoints

There are no additional endpoints planned other than those described above.

4.0 Analysis Populations

The following population sets will be used for the analyses.

The intent-to-treat (ITT) Population, which is defined as all subjects who have at least 1 dose of study drug in Study M16-005, will be used for the efficacy and usability analyses.

The Safety Analysis Population, which is defined as all subjects who received at least 1 dose of study drug in Study M16-005, will be used for all safety analyses. In this study, the safety population is the same as the ITT population.

5.0 Subject Disposition

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

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

- Subjects who received at least one study drug;
- Subjects who completed study;
- Subjects who discontinued study drug (all reasons and primary reason);
- Subjects who discontinued study (all reasons and primary reason)

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

6.0 Study Drug Duration and Compliance

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

Treatment compliance will be summarized for the entire treatment period and each study drug administration visit for the ITT population.

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

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

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

7.1 Demographics and Baseline Characteristics

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

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

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

7.2 Medical History

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

Medical history will be summarized among the ITT Population.

7.3 Prior and Concomitant Medications

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

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

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

8.0 Efficacy Analyses

8.1 General Considerations

All summary statistics for the efficacy and usability analysis will be conducted in the ITT Population. No statistical tests will be performed.

All efficacy endpoints will be summarized up to Week 28 during this analysis.

Categorical variables will be summarized by frequencies, percentages, and the 95% confidence intervals (CIs). Continuous variables will be summarized by least square mean, standard error, and the 95% CIs.

8.2 Handling of Missing Data

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

- Non-Responder Imputation (NRI): The NRI analysis will categorize any subject who does not have evaluation during a specific visit window as a non-responder for that visit. The exceptions are: (1) if the subject is a responder both before and after a specific visit window in the particular period, then the subject will be categorized as a responder for the visit; (2) when the subject missed a visit due to COVID-19 pandemic, the missing assessment from that visit will be imputed using Multiple Imputation (MI) to determine the corresponding response status. In present study, only Week 28 or later visits may be affected by the COVID-19 pandemic. The NRI will be the primary missing data imputation approach in the analyses of categorical variables.
- Modified-NRI: Patients who discontinue study drug due to lack of efficacy or due to AE of worsening of psoriasis and do not have Week 16 measurements will be counted as non-responders. Other patients will be summarized using as-observed data. The modified-NRI analysis will be the sensitivity approach to handle missing data in the analysis of key efficacy endpoints specified in Section 3.1.
- As-observed: The as-observed analysis will include all available assessments on a scheduled visit. No missing assessments will be imputed. The as-observed analysis will be the sensitivity approach to handle missing data in the analysis of the key efficacy endpoints specified in Section 3.1.
- Mixed-effect Model Repeat Measurement (MMRM): The repeated measures analysis will be conducted using a mixed model including baseline value and observed measurements at all post-baseline visits, using all available data even if a subject has missing data at some post-baseline visits. The mixed model includes visit as the covariate. An unstructured variance covariance matrix will be used. Parameter estimation is based on the assumption of data being missing at random and using the method of restrictive maximum likelihood (REML). MMRM will be the primary approach in the analysis of continuous variables.

The key usability endpoints will be summarized by as-observed cases.

8.3 Efficacy and Usability Analysis

8.3.1 Key Usability Analysis

The following key usability endpoints will be evaluated:

- Proportion of subjects with an Observer rating of successful subject self-administration, defined as any subjects who successfully completed the sequence of 4 critical steps in the Instructions for Use (IFU) without errors to administer study drug via the AI at Week 0 and Week 28
- Proportion of subjects who had no potential hazards as measured by an Observer on the possible use-related hazards checklist for self-administration with AI at Week 0 and Week 28
- Subject rating of acceptability by the Self-Injection Assessment Questionnaire (SIAQ) at each visit collected.

8.3.2 Handling of Missing Data for the Key Usability Analysis

The key usability endpoints will be summarized by as-observed cases.

8.4 Key Efficacy Analysis

The following key efficacy endpoints will be evaluated:

- Proportion of subjects achieving PASI 90 at Week 16
- Proportion of subjects achieving sPGA clear or almost clear at Week 16
- Proportion of subjects achieving PASI 100 at Week 16
- Proportion of subjects achieving PASI 75 at Week 16
- Proportion of subjects achieving sPGA of clear at Week 16.

Key efficacy endpoints at Week 16 will be analyzed using NRI method to handle missing data. Modified-NRI analysis and as-observed analysis will also be performed to handle missing data as sensitivity analyses.

8.4.1 Supportive Secondary Efficacy Analyses

There are no additional supportive secondary efficacy analyses planned other than those described above.

8.5 Additional Efficacy Analyses

All key efficacy endpoints will be analyzed at all other visits collected. Additional variables to be provided will include the proportion of subjects achieving PASI 50, as well as change and percent change from baseline in PASI, at each visit collected.

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

8.6 Efficacy Subgroup Analyses

No efficacy subgroup analyses are planned.

9.0 Safety Analyses

9.1 General Considerations

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

Missing safety data will not be imputed.

9.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same adverse event will be counted once, and only the

maximum severity level will be presented in the severity summaries, and the worst/highest relationship level in the relationship summaries.

9.2.1 Treatment-Emergent Adverse Events

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

9.2.2 Adverse Event Overview

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

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

All deaths will also be summarized:

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

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

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

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

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

Exposure-adjusted AEs per 100 patient-years will be provided, where AEs per 100 patient-years of exposure are defined as the number of AEs divided by the total exposure in 100 patient-years.

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

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

where total patient years is defined as the sum of the study drug exposure (defined as date of last dose – date of first dose + 140 days (5 half-lives)) of all subjects normalized by 365.25, and rounded to one decimal place.

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

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

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

9.2.6 Area of Safety Interest

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

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

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

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

9.3 Analysis of Laboratory Data

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

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

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

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

Laboratory abnormalities will be evaluated based on Potentially Clinically Important (PCI) criteria (Appendix C). For each laboratory PCI criterion, the number and percentage of subjects who have a laboratory value meeting the criteria will be summarized. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCI criteria.

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

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

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

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

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

- ALT of > 3 × ULN or AST of > 3 × ULN,
- Associated with an increase in total bilirubin ≥ 2 × ULN,
- Alkaline Phosphatase < 2 × ULN

9.4 Analysis of Vital Signs

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

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

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

9.5 Safety Subgroup Analyses

No safety subgroup analyses are planned.

9.6 Other Safety Analyses

No other safety analyses are planned.

10.0 Other Analyses

No other analyses are planned.

11.0 Interim Analyses

11.1 Data Monitoring Committee

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

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

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

11.2 Interim Analysis

An interim analysis will occur after all ongoing subjects complete the Week 28 Visit. All efficacy variables up to Week 28, as well as all observed safety and usability variables, will be summarized during this analysis.

12.0 Overall Type-I Error Control

No statistical tests will be performed in this single-arm, open-label study.

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

13.0 Version History

Table 1. SAP Version History Summary

Version	Date	Summary
1.0	28 Nov 2018	Original version
2.0	02 Jan 2019	Added more statistical analysis details to the document. Deleted the wording of "blinded efficacy assessor" to be consistent with the protocol admin change 1.
3.0	19 Jul 2019	Added more statistical analysis details to the document.
4.0	17 Apr 2020	Clarified weight and BMI categories in demographics. Clarified items to be summarized for disposition to align with the new standard table. Removed baseline BSA from MMRM model in efficacy analysis, as most BSA information is covered by the corresponding components in baseline PASI. Updated the definition of concomitant medication to align with the most updated risankizumab PSSAP. Clarified shift tables, PCI, and ASI definitions for safety analysis, to align with the most updated risankizumab PSSAP. Corrected the dates in version history. Added the AE summary of any injection site reactions, according to FDA suggestion. Added details about how to handle missing data due to COVID-19 in the NRI analysis. Added modified-NRI and as-observed sensitivity analyses for the key efficacy endpoints. Added sPGA clear at Week 16 to key efficacy endpoints.
5.0	22 Apr 2020	Corrected a typo at Section 8.3.1 that there are 4 critical steps in the Instructions for Use (IFU) of achieving an observer rating of successful subject self-administration.

14.0 References

Appendix A. Protocol Deviations

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

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

Appendix B. Definition of Area of Safety Interest

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

Area of Safety Interest	Search Criteria		Include in AE Overview (Y/N)
MACE	Adjudicated terms will be identified as described in PSSAP Table 3 using CECAT and CETERM from the CE SDTM dataset.		Y
Extended MACE	Adjudicated terms will be identified as described in PSSAP Table 3 (for MACE +) using CECAT and CETERM from the CE SDTM dataset.		N
Serious Infections	Serious AEs in the Infections and Infestations SOC		Y
Tuberculosis	Active Tuberculosis CMQ (code 80000188)		Y
Opportunistic Infections	Opportunistic infection excluding tuberculosis and herpes zoster CMQ (code 80000189)		N
Fungal Infections	Fungal infections CMQ (code 80000063)		N
Malignant Tumours	Narrow	Malignant tumours (SMQ 20000194)	Y
Non-melanoma Skin Cancer (NMSC)	Broad	Skin malignant tumours (SMQ 20000204) excluding terms identified by the Melanoma CMQ (code 80000119)	N
Malignant Tumours excluding NMSC	'Malignant Tumours excluding NMSC' is identified by the 'Malignant Tumours' search excluding terms identified by the 'Non-melanoma skin cancer (NMSC)' search.		Y
Hypersensitivity	Narrow	Hypersensitivity (SMQ 20000214)	Y – serious events only
Adjudicated Anaphylactic Reaction*	Adjudicated terms will be identified using SDTM data (e.g., CE and PR domains).		N
Hepatic Events	Broad	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ 20000013)	N
	Broad	Hepatitis, non-infectious (SMQ 20000010)	N
	Broad	Cholestasis and jaundice of hepatic origin (SMQ 20000009)	N
	Broad	Liver related investigations, signs and symptoms (SMQ 20000008)	N

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

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

Appendix C. Potentially Clinically Important Criteria for Safety Endpoints

The criteria for Potentially Clinically Important (PCI) laboratory findings are described in Table C-1 and Table C-2, and the PCI criteria for vital sign findings are described in Table C-3.

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

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

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

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

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

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

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

Vital Signs Variables	**Criterion**	**Definition of Potentially Clinically Important**
Systolic Blood Pressure (mmHg)	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic Blood Pressure (mmHg)	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from Baseline
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from Baseline