Statistical Analysis Plan for Sub-Study 2

Study M16-067

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Evaluate the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Ulcerative Colitis

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Version 2.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for Sub-Study 2 of risankizumab Study M16-067 "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Evaluate the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Ulcerative Colitis."

Study M16-067 comprises 2 sub-studies: Sub-Study 1, a Phase 2b dose-ranging induction sub-study and Sub-Study 2, a Phase 3 induction study. Sub-Study 1 (Phase 2b induction study) was to characterize the efficacy, safety, and pharmacokinetics of risankizumab as induction treatment in subjects with moderately to severely active UC and to identify the appropriate induction dose of risankizumab for further evaluation in Sub-Study 2 (Phase 3 induction study). Sub-Study 2 is to evaluate the efficacy and safety of risankizumab compared to placebo in inducing clinical remission in subjects with moderately to severely active UC.

The analyses of pharmacokinetic endpoints, pharmacodynamic biomarker endpoints and exploratory research and validation endpoints will not be covered in this SAP.

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

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

This SAP includes changes to analyses described in the protocol. Details are outlined in Section 14.0.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

The objective of Phase 3 induction study is to evaluate the efficacy and safety of risankizumab compared to placebo in inducing clinical remission (per Adapted Mayo score) in subjects with moderately to severely active UC.

Primary Efficacy Objective

The primary efficacy objective is to demonstrate a higher rate of clinical remission per Adapted Mayo score at Week 12 of treatment with risankizumab when compared to placebo based on Intent-to-Treat (ITT) population ITT2 as defined in Section 4.0.

The Hypothesis corresponding to the primary efficacy objective and endpoint is:

- The proportion of subjects achieving clinical remission per Adapted Mayo score treated with risankizumab 1200 mg intravenous (IV) is greater than those treated with placebo at Week 12.

The estimand corresponding to the primary efficacy objective is defined as follows:

- Difference in the proportion of subjects achieving clinical remission per Adapted Mayo score at Week 12 regardless of premature discontinuation of study drug, without initiation or dose escalation of UC-related corticosteroids and without UC-related surgery (ileostomy, colectomy, or proctocolectomy) (see Section 8.0) between risankizumab 1200 mg IV and placebo in the ITT2 population.

Secondary Efficacy Objective

The secondary efficacy objective is to demonstrate higher efficacy of treatment with risankizumab when compared to placebo with respect to the secondary endpoints as specified in Section 3.2. The secondary efficacy objectives will be assessed based on ITT2 population.

Hypotheses corresponding to the secondary efficacy objectives and endpoints are:

- For each binary secondary endpoint, greater proportion of subjects with improvement for the endpoint is achieved with risankizumab 1200 mg IV when compared to that of placebo.
- For each continuous secondary endpoint, greater mean change from baseline for the endpoint is achieved with risankizumab 1200 mg IV when compared to that of placebo.

The estimands corresponding to the secondary efficacy objectives are defined as follows:

- For each binary secondary endpoint except for UC-related hospitalization, the estimand is the difference in the proportion of subjects achieving the endpoint regardless of premature discontinuation of study drug and without initiation or dose escalation of UC-related corticosteroids and without UC-related surgery (ileostomy, colectomy, or proctocolectomy) (see Section 8.0) between risankizumab 1200 mg IV and placebo in the ITT2 population.
- For occurrence of UC-related hospitalization, the estimand is the difference in the proportion of subjects having UC-related hospitalization through Week 12 regardless of premature discontinuation of study drug and regardless of initiation or dose escalation of UC-related corticosteroids or UC-related surgery (ileostomy, colectomy, or proctocolectomy) (See Section 8.0) between risankizumab 1200 mg IV and placebo in the ITT2 population.
- For each continuous secondary endpoint, the estimand is the difference in the mean change from baseline of the endpoint regardless of premature discontinuation of study drug and without initiation or dose escalation of UC-related corticosteroids and without UC-related surgery (ileostomy, colectomy, or proctocolectomy) (See Section 8.0) between risankizumab 1200 mg IV and placebo in the ITT2 population.

2.2 Study Design Overview

Study M16-067 Sub-Study 2 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of risankizumab as

induction therapy in adult subjects with moderately to severely active UC, defined as Adapted Mayo score of 5 – 9 points (using the Mayo scoring system, excluding Physician's Global Assessment) with an endoscopic subscore of 2 or 3 on screening endoscopy, confirmed by central review.

Sub-Study 2 will enroll subjects who have had an intolerance or inadequate response (IR) to prior biologic therapy (bio-IR) and subjects who have not had an intolerance or inadequate response to prior biologic therapy (non-bio-IR). The bio-IR enrollment in Sub-Study 2 will be approximately 541 subjects and the non-bio-IR enrollment will be approximately 425 subjects.

The bio-IR population is defined as subjects with documented intolerance or inadequate response to one or more of the approved biologics for UC (infliximab, adalimumab, golimumab, and/or vedolizumab) or tofacitinib. The non-bio-IR population will include subjects who had an inadequate response or intolerance to conventional therapy. Conventional therapy is defined as one or more of the following: aminosalicylates, oral locally acting steroids (e.g., budesonide, beclomethasone), systemic corticosteroids (prednisone or equivalent), or immunomodulators. This population will also include subjects who have received biologic therapy or tofacitinib in the past but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease).

The study duration may be up to 45 weeks, including a Screening period of approximately 35 days, a 12-week Induction Period 1, a 12-week Induction Period 2 for those subjects who do not achieve clinical response at Week 12, and a 140-day follow-up period from the last dose of study drug.

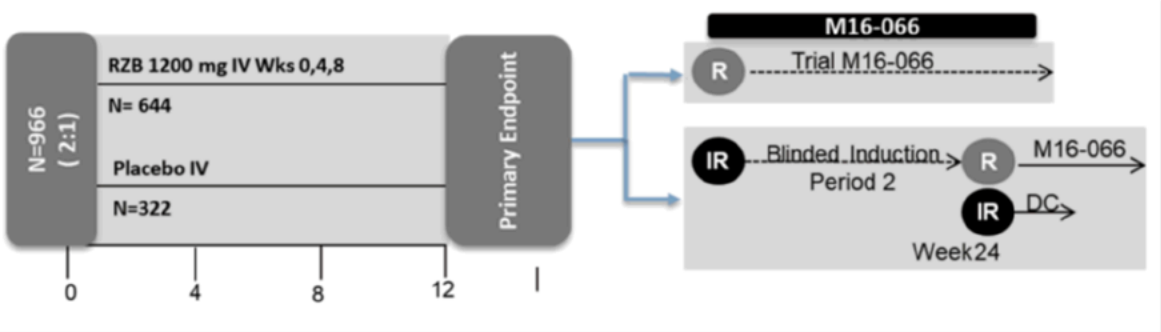
Sub-Study 2 Induction Period 1:

Subjects (n = 966) who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the double-blind 12-week study and randomized in a 2:1 ratio to one of the following treatment groups:

- Group 1: Risankizumab 1200 mg IV Weeks 0, 4, 8 (n = 644)
- Group 2: Placebo IV Weeks 0, 4, 8 (n = 322)

The schematic of the Induction Period 1 is shown in Figure 1.

Figure 1. Study Schematic of Induction Period 1



Endoscopy and efficacy evaluation will occur at Week 12. Subjects in Sub-Study 2 who achieve clinical response per Adapted Mayo score (locally read Mayo endoscopic sub score) after completion of the 12-week Induction Period 1 will be enrolled into maintenance Study M16-066. Subjects who do not achieve clinical response at Week 12, may be eligible to enter a blinded risankizumab treatment in Induction Period 2 as specified below.

Subjects are not eligible to enter Induction Period 2 until the Week 12 endoscopy has been completed, except in case of COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions:

If endoscopy cannot be performed at Week 12 due to COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions, clinical response will be calculated using the Partial Adapted Mayo score.

Subjects with missing endoscopy due to COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions and achieve clinical response per

Partial Adapted Mayo score at Week 12 may be eligible to enroll in Study M16-066 Sub-Study 3, which is an open-label long term extension study to evaluate long-term safety of risankizumab. Subjects who do not achieve clinical response at Week 12, may be eligible to enter a blinded risankizumab treatment in Induction Period 2 as specified below.

Sub-Study 2 Induction Period 2:

At Week 12, subjects who do not achieve clinical response will be randomized by Interactive Response Technologies (IRT) to Induction Period 2, a double-blind, double dummy 12-week treatment period to evaluate reinduction with risankizumab versus starting maintenance dosing on clinical response status.

Subjects who received IV risankizumab will be randomized 1:1:1 to:

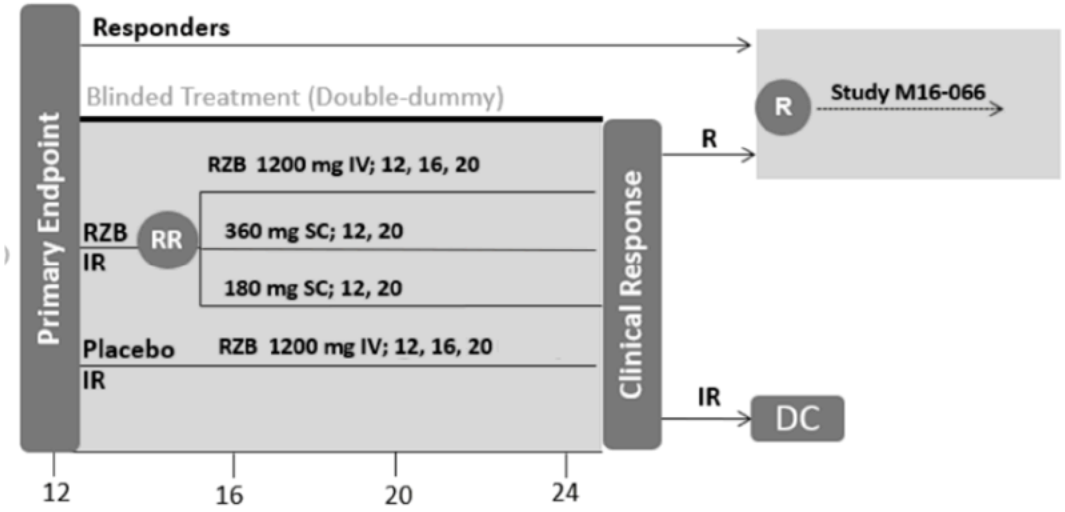
- Group 1: Risankizumab 1200 mg IV Weeks 12, 16, and 20
- Group 2: Risankizumab 360 mg SC Weeks 12, and 20
- Group 3: Risankizumab 180 mg SC Weeks 12, and 20

Subjects who received placebo induction treatment will receive:

- Group 4: Risankizumab 1200 mg IV Weeks 12, 16, and 20

The schematic of the Induction Period 2 is shown in Figure 2.

Figure 2. Study Schematic of Induction Period 2



Subjects randomized in Groups 1 and 4 will receive placebo SC and subjects randomized in Groups 2 and 3 will received placebo IV, in order to keep the blind. The IV risankizumab dose or matching IV placebo will be given at Weeks 12, 16, and 20. The SC risankizumab dose or matching SC placebo will be given at Weeks 12, and 20. At Week 24, subjects who receive blinded risankizumab during the Induction Period 2 will be reassessed and undergo a third endoscopy for evaluation of mucosal inflammation.

Subjects who achieve clinical response per Adapted Mayo score (locally read Mayo endoscopic sub score) at Week 24 may be eligible to enter into the maintenance Study M16-066.

If endoscopy cannot be performed at Week 24 due to COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions, clinical response will be calculated using the Partial Adapted Mayo score. Subjects with missing endoscopy due to COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions who achieve clinical response per Partial Adapted Mayo score at Week 24 may be eligible to enroll into maintenance Study M16-066 Sub-Study 3.

Subjects without clinical response at Week 24, as well as all subjects who terminate the study early (including subjects who are eligible for but do not receive blinded risankizumab therapy during Induction Period 2), will be discontinued and have a follow-up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs.

2.3 Treatment Assignment and Blinding

In Induction Period 1, approximately 966 subjects will be randomized in a 2:1 ratio to risankizumab 1200 mg IV dose or placebo. The randomization at baseline will be stratified by number of prior failed biologics (0, 1 vs > 1), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7).

In Induction Period 2, subjects who do not achieve clinical response and received IV risankizumab in Induction Period 1 will be randomized 1:1:1 to risankizumab 1200 mg IV, 360 mg SC and 180 mg SC groups. The randomization will be stratified by number of prior failed biologics (0, 1 vs > 1), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7). Subjects who do not achieve clinical response and received placebo in Induction Period 1 will receive risankizumab 1200 mg IV.

2.4 Sample Size Determination

In Induction Period 1, approximately 966 subjects will be randomized to the risankizumab 1200 mg IV dose or placebo in a randomization ratio of 2:1. The sample size for this study is based on the expected proportion of subjects who achieve clinical remission per Adapted Mayo Score at Week 12. The sample size has been re-assessed after analyzing combined PK, safety and efficacy results from Sub-Study 1. It is determined to provide adequate power for the primary endpoint and selected ranked secondary endpoints and adequate responders to meet the sample size requirement for Study M16-066. Assuming clinical remission rate of 6% in the placebo arm and 16% of the risankizumab treatment arm at Week 12, a sample size of 644:322 subjects in risankizumab 1200 mg IV dose and placebo group will provide at least 90% power to detect the 10% treatment difference in clinical remission rate between the risankizumab dose and placebo using two-sided

Miettinen and Nurminen test at a 0.05 significant level. The assumed remission rates were based on Sub-Study 1 for bio -IR population and on ustekinumab data for non-bio-IR population. The same sample size will also provide at least 90% power for ranked secondary endpoints, clinical remission per full mayo score at Week 12, endoscopic response at Week 12, endoscopic remission at Week 12, clinical response per adapted mayo score at Week 12 and clinical response per partial adapted mayo score at Week 4.

3.0 Endpoints

Below are the endpoint definitions for efficacy variables:

- Mayo Score
  - Full Mayo Score: composite score of UC disease activity based on the
    - stool frequency subscore [SFS] (0 – 3), rectal bleeding subscore [RBS] (0– 3), physician's global assessment [PGA] subscore (0 – 3) and endoscopic subscore (0 – 3). The endoscopic subscore will be based on central readings after adjudication (when applicable). The Full Mayo score ranges from 0 – 12 points with higher scores representing more severe disease.
  - Partial Mayo Score: Full Mayo score excluding the endoscopic subscore.
  - Adapted Mayo Score: Full Mayo score excluding the PGA subscore.
  - Partial Adapted Mayo Score: Adapted Mayo score excluding the endoscopic subscore.
- Clinical Remission per Adapted Mayo: stool frequency subscore (SFS) ≤ 1, and not greater than baseline, rectal bleeding subscore (RBS) = 0, and endoscopic subscore ≤ 1 without the evidence of friability
- Clinical Response per Adapted Mayo: decrease from Baseline ≥ 2 points and $\geq 30\%$, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1
- Clinical Response per Partial Adapted Mayo (without endoscopy): decrease from Baseline ≥ 1 points and $\geq 30\%$, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1
- Clinical Remission per Full Mayo: Full Mayo score ≤ 2 with no subscore > 1

- Endoscopic Improvement: endoscopy subscore of 0 or 1 without the evidence of friability
- Endoscopic Remission: endoscopic subscore = 0
- Histologic Remission: Geboes score of < 2.0
- Histologic Endoscopic Mucosal Improvement (HEMI): Endoscopic subscore of 0 or 1 without the evidence of friability and Geboes score ≤ 3.1.
- Histologic Endoscopic Mucosal Remission (HEMR): Endoscopy subscore of 0 and Geboes score < 2.0

Note: Evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity will confer an endoscopic subscore of 2.

3.1 Primary Endpoint(s)

The primary efficacy endpoint is the achievement of clinical remission per Adapted Mayo score at Week 12.

3.2 Secondary Endpoint(s)

Secondary endpoints are:

1. The achievement of clinical response per Adapted Mayo score at Week 12
2. The achievement of endoscopic improvement at Week 12
3. The achievement of histologic endoscopic mucosal improvement (HEMI) at Week 12
4. The achievement of endoscopic remission at Week 12
5. The achievement of clinical response per Partial Adapted Mayo score at Week 4
6. The achievement of no bowel urgency at Week 12
7. The achievement of no abdominal pain at Week 12
8. The achievement of histologic endoscopic mucosal remission (HEMR) at Week 12

9. Change from Baseline to Week 12 in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
10. Change from Baseline to Week 12 in Inflammatory Bowel Disease Questionnaire (IBDQ) total score
11. Occurrence of UC-related hospitalizations through Week 12
12. The achievement of no nocturnal bowel movements at Week 12
13. The achievement of no tenesmus at Week 12
14. Change from Baseline to Week 12 in number of fecal incontinence episodes per week
15. Change from Baseline to Week 12 in number of days per week with sleep interrupted due to UC symptoms

3.3 Additional Efficacy Endpoint(s)

The primary and secondary efficacy endpoints are listed in Section 3.1 and Section 3.2, respectively. The additional efficacy endpoints are:

Induction Period 1

- The achievement of SFS = 0, RBS = 0, and endoscopic subscore = 0 at Week 12
- The achievement of SFS $\leq$ 1 at Week 4, Week 8, Week 12 respectively
- The achievement of RBS = 0 at Week 4, Week 8, Week 12 respectively
- The achievement of clinical response per Partial Adapted Mayo score at Week 8, Week 12 respectively
- Change from Baseline in Partial Adapted Mayo score at Week 4, Week 8, Week 12 respectively
- Change from Baseline to Week 12 in Full Mayo score
- Change from Baseline in SFS at Week 4, Week 8, Week 12 respectively
- Change from Baseline in RBS at Week 4, Week 8, Week 12 respectively

- Change from Baseline in hs-CRP at Week 4, Week 8, Week 12 respectively
- Change from Baseline in FCP at Week 4, Week 12 respectively
- Change from Baseline to Week 12 in UCEIS
- The achievement of histologic remission at Week 12
- Change from Baseline to Week 12 in European Quality of Life 5 Dimensions (EQ-5D-5L)
- Change from Baseline to Week 12 in Work Productivity and Impairment Questionnaire – UC (WPAI-UC)
- Change from Baseline to Week 12 in UC-SQ
- The achievement of IBDQ remission (IBDQ total score $\geq$ 170) at Week 12
- The achievement of IBDQ response (increase of IBDQ $\geq$ 16 from Baseline) at Week 12
- Time to clinical response per Partial Adapted Mayo
- Change from baseline in PGIS at Week 4, Week 8, Week 12 respectively
- PGIC at Week 4, Week 8, Week 12 respectively
- Occurrence of UC-related surgeries through Week 12
- The achievement of clinical response per Adapted Mayo score at Week 12 in subjects with pancolitis at Baseline
- Change from Baseline to Week 12 in Short Form-36 (SF-36)
- The achievement of clinical remission per Full Mayo score at Week 12 in subjects with a Full Mayo score of 6 to 12 at Baseline

Induction Period 2

- The achievement of clinical remission per Adapted Mayo at Week 24
- The achievement of clinical remission per Full Mayo score at Week 24 in subjects with a Full Mayo score of 6 to 12 at Baseline
- The achievement of clinical response per Adapted Mayo score at Week 24
- The achievement of no abdominal pain at Week 24
- The achievement of no bowel urgency at Week 24
- The achievement of endoscopic remission at Week 24

- The achievement of endoscopic improvement at Week 24
- Change from Baseline to Week 24 in Inflammatory Bowel Disease Questionnaire (IBDQ) total score
- Change from Baseline to Week 24 in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
- The achievement of histologic endoscopic mucosal improvement at Week 24
- The achievement of no nocturnal bowel movements at Week 24
- The achievement of no tenesmus at Week 24
- Change from Baseline to Week 24 in number of fecal incontinence episodes per week
- Change from Baseline to Week 24 in number of days per week with sleep interrupted due to UC symptoms
- The achievement of clinical response per Adapted Mayo score at Week 24 in subjects with pancolitis at Baseline
- Occurrence of UC-related hospitalizations through Week 24
- Change from Baseline to Week 24 in Short Form-36 (SF-36)
- The achievement of SFS ≤ 1 at Week 16, Week 20, Week 24 respectively
- The achievement of RBS = 0 at Week 16, Week 20, Week 24 respectively
- Change from Baseline in Partial Adapted Mayo score at Week 16, Week 20, Week 24 respectively
- Change from Baseline in SFS at Week 16, Week 20, Week 24 respectively
- Change from Baseline in RBS at Week 16, Week 20, Week 24 respectively
- Change from Baseline in hs-CRP at Week 24
- Change from Baseline in FCP at Week 24
- Time to clinical response per Partial Adapted Mayo
- Change from baseline in PGIS at Week 16, Week 20, Week 24 respectively
- PGIC at Week 16, Week 20, Week 24 respectively

3.4 Safety Endpoint(s)

The following endpoints will be included in the safety analyses:

- Treatment emergent adverse events (TEAEs)
- Areas of Safety Interest (ASIs)
- Laboratory tests
- Vital signs.

4.0 Analysis Populations

The following population sets will be used for the statistical analyses:

Intent-to-Treat Population

Sub-Study 2 Induction Period 1:

ITT2 includes all randomized subjects who received at least one dose of study drug during Induction Period 1. The ITT2 will be used for all efficacy analysis, and demographic and baseline characteristics summary for Induction Period 1. Subjects will be included in the analysis according to the treatment groups that they are randomized to.

Sub-Study 2 Induction Period 2:

ITT2_P2 includes all subjects who received at least one dose of risankizumab during Induction Period 2 from Sub-Study 2. Subjects will be included in the analysis according to the treatment groups that they are re-randomized to the Induction Period 2 and the subjects who received placebo induction treatment during 12-Week Induction Period 1 and entered the Induction Period 2 will be also included (denoted as placebo/risankizumab). This analysis population will be used for efficacy analysis in Induction Period 2.

Safety Analysis Set

The safety analysis will be based on the corresponding safety analysis sets. Subjects will be analyzed in a treatment group based on the actual treatment received.

Sub-Study 2 – Induction Period 1

SA2 consists of all subjects who received at least one dose of study drug during Induction Period 1 in Sub-Study 2.

Sub-Study 2 Induction Period 2:

SA2_P2 consists of all subjects who received at least one dose of risankizumab during the Induction Period 2 after Week 12 in Sub-Study 2.

All Risankizumab:

SA2_ALL includes all subjects who received at least one dose of risankizumab any time during the Sub-Study 2.

5.0 Subject Disposition

The total number of subjects who were enrolled, randomized, and treated 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 for each treatment group:

- Subjects randomized in the study
- Subjects who took at least one dose of study drug (ITT2 for the Induction Period 1, ITT2_P2 for the Induction Period 2)
- Subjects who completed study drug (ITT2 for the Induction Period 1, ITT2_P2 for the Induction Period 2)
- Subjects who prematurely discontinued study drug (ITT2 for the Induction Period 1, ITT2_P2 for the Induction Period 2)
- Subjects who completed study (ITT2 for the Induction Period 1, ITT2_P2 for the Induction Period 2)
- Subjects who prematurely discontinued from study (ITT2 for the Induction Period 1, ITT2_P2 for the Induction Period 2)

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

In addition, the number and percentage of subjects who discontinued study drug or study will be summarized by reason (primary reason and all reasons) for each treatment group and overall within Induction Period 1 and Induction Period 2. The primary reason and all reasons for discontinuation of study or study drug will be summarized as recorded on the eCRF by the following categories:

- Adverse event (AE)
- Lost to follow-up
- Withdraw consent
- Lack of efficacy
- COVID-19 infection
- COVID-19 logistical restrictions
- Logistical problem (geo-political restrictions)
- Other

Subjects may have more than one reason for discontinuing study or study drug, but they will be counted once for the total number of discontinuations. Subjects have only one primary reason for discontinuing study drug or discontinuing from the study.

For subjects whose study participation were impacted by the geo-political conflicts in Ukraine or surrounding area, the detailed reason about how study participation was affected will be summarized.

6.0 Study Drug Duration and Compliance

6.1 Study Drug Duration

Induction Period 1

For the safety population SA2, duration of exposure to study drug will be summarized for each treatment group in Induction Period 1.

Duration of exposure in Induction Period 1:

- If the subjects enrolled into Study M16-066 after the Induction Period 1:
  - Duration of exposure = min (the first study drug dose date in Study M16-066 – the first study drug dose date in Induction Period 1, the last study drug dose date in the Induction Period 1– the first study drug dose date in the Induction Period 1 + 28 days),
- If the subject enrolled into Induction Period 2 after Induction Period 1:
  - Duration of exposure = min (the first study drug dose date in the Induction Period 2 – the first study drug dose date in Induction Period 1, the last study drug dose date in Induction Period 1 – the first study drug dose date in Induction Period 1 + 28 days),
- Otherwise:
  - Duration of exposure = the last study drug dose date in Induction Period 1 – the first study drug dose date in Induction Period 1 + 28 days.

For each treatment group and total in Induction Period 1, the duration of exposure will be summarized by the number of subjects treated, as well as the mean, standard deviation, median, minimum and maximum values. In addition, the number and percentage of subjects exposed to study drug will be summarized for the following exclusive duration intervals:

- 1 – 28 days
- 29 – 56 days
- 57 – 84 days

- 85 – 112 days
- > 112 days

Induction Period 2

For the safety population SA2_P2, the duration of exposure to study drug will be summarized for each treatment group in Induction Period 2.

Duration of exposure in Induction Period 2:

- If the subjects enrolled into Study M16-066 after Induction Period 2:
  - Duration of exposure = min (the first study drug dose date in Study M16-066 – the first study drug dose date in Induction Period 2, the last study drug dose date in Induction Period 2 – the first study drug dose date in Induction Period 2 + 28 days [for IV dose] or 56 days [for SC dose]),
- Otherwise:
  - Duration of exposure = the last study drug dose date in Induction Period 2 – the first study drug dose date in Induction Period 2 + 28 days [for IV dose] or 56 days [for SC dose].

For each treatment group and total in Induction Period 2, the duration of exposure will be summarized by the number of subjects treated, as well as the mean, standard deviation, median, minimum and maximum values. In addition, the number and percentage of subjects exposed to study drug will be summarized for the following exclusive duration intervals:

- 1 – 28 days
- 29 – 56 days
- 57 – 84 days
- 85 – 112 days
- > 112 days

All Risankizumab

For SA2_ALL, the duration of exposure to study drug will be summarized for all risankizumab treatment group over the whole course of the study.

Duration of exposure for all risankizumab:

- If the subjects enrolled into Study M16-066:
  - Duration of exposure = min (the first study drug dose date in Study M16-066 – the first risankizumab dose date in this study, the last risankizumab dose date in this study – the first risankizumab dose date in this study + 28 or 56 days [depending on that the last dose is IV or SC]),
- Otherwise:
  - Duration of exposure = the last risankizumab dose date in this study – the first risankizumab dose date in this study + 28 or 56 days [depending on that the last dose is IV or SC].

The duration of exposure will be summarized by the number of subjects treated, as well as the mean, standard deviation, median, minimum and maximum values. In addition, the number and percentage of subjects exposed to risankizumab will be summarized for the following exclusive duration intervals:

- 1 – 28 days
- 29 – 56 days
- 57 – 84 days
- 85 – 112 days
- 113 – 140 days
- 141 – 196 days
- > 196 days

6.2 Study Drug Compliance

Treatment compliance is calculated as follows:

$$TC = \frac{Total\ number\ of\ injections\ and/or\ infusions\ received}{Total\ number\ of\ injections\ and/or\ infustions\ planned} \times 100\%$$

Treatment compliance will be summarized by treatment group for Induction Period 1 and Induction Period 2 based on SA2 and SA2_P2, respectively. Descriptive summary including mean, median, standard deviation, minimum, and maximum, will be provided.

In addition, number and percentage of subjects who received full volume and average infusion duration (hours) will be provided for subjects who received intravenous therapy. Total number of injections received will also be provided for subjects who received subcutaneous therapy.

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

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized by treatment group and overall for the ITT2 and ITT2_P2 populations. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

The following demographic, as measured at baseline of the study, will be summarized.

Continuous variables:

- Age (years)
- Body weight (kg)
- Body weight – Female (kg)
- Body weight – Male (kg)
- Height (cm)
- Height – Female (cm)
- Height – Male (cm)
- Body Mass Index (kg/m^2)

Categorical variables:

- Sex (male, female)
- Age (18 - < 40, 40 - < 65, ≥ 65)
- Weight (< 60 kg, ≥ 60 kg)
- Race (American Indian/Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple)
- Race (White, Non-White)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Tobacco use (Never, current, former, unknown)
- Alcohol use (Never, current, former, unknown)
- Region (as defined in)
- BMI category
  - Underweight [< 18.5 kg/m^2]
  - Normal [≥ 18.5 and < 25 kg/m^2]
  - Overweight [≥ 25 and < 30 kg/m^2]
  - Obese [≥ 30 kg/m^2]

The following baseline characteristics, as measured at baseline of the study, will be summarized.

Continuous variables:

- Blood Pressure (systolic/diastolic) (mmHg)
- Pulse (bpm)
- Respiratory Rate (RPM)
- Temperature (°C)
- IBDQ total score and its components
- Full Mayo score and its components (stool frequency, rectal bleeding, PGA, and endoscopy subscores)
- Partial Adapted Mayo score
- Adapted Mayo score
- hs-CRP (mg/L)
- Fecal Calprotectin (mg/kg)
- Albumin (g/L)
- Short Form 36 Health Survey (SF-36) and its components
- European Quality of Life 5 Dimensions 5 Levels (EQ-5D-5L)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
- WPAI and its components
- Ulcerative Colitis Symptoms Questionnaire (UC-SQ)
- Disease duration (years)

Categorical variables (unless otherwise stated, the categorical variables regarding medication use are assumed to be UC-related):

- Advanced Therapy-IR status (yes, no),
  - The Advanced Therapy-IR is defined as documented intolerance or inadequate response to advanced therapy including one or more of the approved biologics for UC (infliximab, adalimumab, golimumab, ustekinumab, and/or vedolizumab) and/or approved JAK inhibitors for UC (tofacitinib, filgotinib, upadacitinib) and ozanimod.
- Number of prior failed advanced therapies (0, 1, 2, >2)

- Prior exposure to advanced therapy (yes, no) for non-Advanced Therapy-IR population
- Number of prior advanced therapies (≤ 1 or > 1) for Advanced Therapy -IR population
- Baseline corticosteroid use (yes, no)
- Baseline immunosuppressant use (yes, no)
- Baseline aminosalicylates use (yes, no)
- Prior exposure to anti-TNF for UC for non-Advanced Therapy-IR population (yes, no)
- Number of prior failed anti-TNF for UC (0, 1, 2, > 2) for Advanced Therapy-IR population
- Number of prior failed biologics for UC (0, 1, 2, > 2) for Advanced Therapy-IR population
- Mayo endoscopic subscore (2, 3)
- Baseline Adapted Mayo score (≤ 7 vs > 7)
- Baseline Partial Adapted Mayo score (≤ 4 vs > 4)
- Baseline Full Mayo score (≤ 9 vs > 9)
- Baseline hs-CRP (≤ 5 mg/L, > 5 mg/L)
- Baseline hs-CRP (≤ median, > median)
- Disease duration (≤ 3 years, > 3 years)
- Disease duration (≤ median, > median)
- Baseline Albumin (≤ median, > median)
- Baseline Fecal Calprotectin (≤ median, > median)
- Baseline Fecal Calprotectin (≤ 250 mg/kg, > 250 mg/kg)
- Baseline presence of pancolitis (yes, no)
- Disease extent (left-sided, extensive/pancolitis, limited to rectum)

In addition, some clinical tests at baseline such as TB test and electrocardiogram assessment will be summarized.

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 and by treatment group based on the ITT2 and ITT2_P2 populations. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term). In addition, any subject with the UC disease extent record "left-sided," "extensive/pancolitis" or "limited to rectum" will be counted as having "colitis ulcerative" (preferred term) within gastrointestinal disorders (SOC).

7.3 Prior and Concomitant Medications

Prior and concomitant medications including UC specific medications (biologics, corticosteroids, aminosalicylates, immunosuppressant agents, and antibiotics) 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. This includes medications with a start date before the first study drug administration date, regardless of the end date of these medications. Medications taken on the day of the first dose of study drug are not counted as prior medications. Summary on prior medication will be provided for ITT2.

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 after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug plus 140 days. The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

Summary on concomitant medication will be provided for Induction Period 1 and Induction Period 2 based on ITT2 and ITT2_P2 respectively.

8.0 Handling of Potential Intercurrent Events

The primary efficacy endpoint of clinical remission per Adapted Mayo score at Week 12 (defined in Section 3.1) and the secondary efficacy endpoints (defined in Section 3.2) will be analyzed based on the ITT2 population. The following methods will be used to address potential intercurrent events (IEs):

- IE1. Premature discontinue from the study drug:
  - Data collected will be used regardless of premature discontinuation of study drug.
- IE2. Initiation or dose escalation of UC-related corticosteroid event defined as:
  - Subjects not on UC-related corticosteroids (systemic or locally acting corticosteroids for UC) at baseline who then initiated UC-related corticosteroids during the Induction study.
  - Subjects on UC-related systemic corticosteroids at baseline who have dosages increased to greater than the prednisone equivalent dose of corticosteroid taken at baseline, or initiation of any rectal corticosteroids during the Induction study regardless of rectal corticosteroid dose.
  - Subjects on UC-related rectal corticosteroids at baseline who have dosages increased to greater than the dose taken at baseline, or initiation of any new type of rectal or any systemic corticosteroids during the Induction study.

    The time point of the UC-related corticosteroids intercurrent event is defined as the date when one of the scenarios above occurs for a subject. As such, subjects will be considered as "non-responder" for binary endpoints on or after the date of the UC-related corticosteroids intercurrent event through the end of the Induction study in the primary analysis (except for the occurrence of UC-related hospitalization and UC-related surgeries). For continuous endpoints, all measurements on or after the date of the UC-related corticosteroids intercurrent event through the end of the Induction study will not be used in the primary analysis.

- IE3. UC-Related Surgery (ileostomy, colectomy, or proctocolectomy):

  The time point of the UC-related surgery (ileostomy, colectomy, or proctocolectomy) intercurrent event is defined as the date of the first UC-related surgery. All measurements on or after the date of the UC-related surgery (ileostomy, colectomy, or proctocolectomy) will be handled similarly as UC-related corticosteroid intercurrent events.

For the additional Period 1 efficacy endpoints and Induction Period 2 efficacy endpoints similar methods to address potential intercurrent events will be applied.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted based on ITT2 for Induction Period 1. The overall type I error rate of the primary and secondary endpoints will be strongly controlled using a graphical multiple-testing procedure[1] as described in Section 13.0. Analyses for the efficacy endpoints in Induction Period 2 will be performed based on ITT2_P2.

The primary analysis will be performed after all ongoing subjects have completed the Sub-Study 2 activities up to Week 24 and the Sub-Study 2 database has been locked. This will be the only and final analysis for the primary and secondary efficacy endpoints as well as all additional efficacy endpoints in Sub-Study 2. Treatment assignments will be unblinded to AbbVie for statistical analyses.

Unless otherwise specified, categorical variables will be analyzed using Cochran-Mantel-Haenszel (CMH) test for common risk difference, stratified by Advanced Therapies-IR status (yes vs no), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7). If there is a stratum for a treatment group that has no subject in it, a value of 0.1 will be added to all cells in the corresponding table in order to prevent dividing by 0, as suggested in Greenland and Robins (1985).[3] Greenland and Robins (1985)[3] variance estimator is used for the common risk difference. For all stratification factors (including the randomization stratification factors) used for CMH analyses, their values will be based

on actual values. Continuous variables collected longitudinally (more than one post baseline visits) will be analyzed using Mixed-Effect Model Repeat Measurement (MMRM) method. Continuous variables collected with only one post baseline visit will be analyzed using Analysis of Covariance (ANCOVA) model. For multi-level categorical endpoints PGIC, percentage of each outcome category will be reported descriptively, and no statistical comparison will be performed. For time to event analysis, Kaplan-Meier method will be used. For all stratification factors (including the randomization stratification factors) used for analyses, their values will be based on actual values.

Baseline refers to the last non-missing observation on or before the first administration of study drug in Induction Period 1 or randomization if no study drug is given.

9.2 Handling of Missing Data

Missing data could occur due to various reasons, including missing visits/assessments, early withdrawal from the clinical trials, missing due to Coronavirus disease 2019 (COVID-19) infection or logistic restriction, or missing due to geo-political conflict in Ukraine or surrounding area.

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

missing data are missing at random (MAR) and the statistical models that require MAR assumption are appropriate. The intent is to provide reliable estimates of the treatment effects under the scenario without the impact of COVID-19 pandemic or without the impact of geo-political conflict in Ukraine or surrounding area.

Missing data for the efficacy analyses will be handled using the methods described below.

9.2.1 Categorical Endpoints

For binary efficacy endpoints, missing data will be handled using the following approaches:

- The primary approach for handling missing data in the analysis of binary endpoints except for occurrence of hospitalization and the occurrence of UC-related surgeries will use Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 or due to geo-political conflict in Ukraine or surrounding area (NRI-MI).

  The NRI-MI will categorize any subject who does not have an evaluation during a pre-specified visit window (either due to missing assessment or due to early withdrawal from the study) as a non-responder for the visit. The only exception is that missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic or due to geo-political conflict in Ukraine or surrounding area will be handled by Multiple Imputation (MI). At each visit, subjects will be characterized as responders or non-responders based on MI imputed values if missing due to COVID-19 or due to geo-political conflict in Ukraine or surrounding area; otherwise, subjects will be considered as non-responders for missing due to other reasons in the NRI-MI approach. In addition, on or after the date of the UC-related corticosteroids intercurrent event or the occurrence of the UC-related surgery (see Section 8.0), subjects will be counted as non-responders.

  - Multiple Imputation (MI) for NRI-MI: Markov Chain Monte Carlo (MCMC) will be first applied to augment data into monotonic missing pattern, where applicable, and PROC MI will be used to generate 30 datasets using the regression method. The variables to be included in

the imputation model are: treatment group, Advanced Therapies-IR status (yes vs no), baseline corticosteroid use (yes vs. no), baseline Adapted Mayo score (≤ 7 vs. > 7)), baseline measurement, and if applicable, post-baseline measurements at each visit up to the end of the analysis period. The imputed post-baseline measurements will be rounded to the same precision as the observed data before the determination of responder status.

- When a dichotomized variable is derived from a continuous scale, for example, IBDQ remission (IBDQ total score ≥ 170), the multiple imputation will be applied to the original scale, IBDQ (ranges from 32 – 224) assuming multivariate normal distribution. Then the dichotomized variable will be derived from the imputed value.
- When a dichotomized variable is derived from sub-scales, for example, clinical remission per Adapted Mayo score (SFS ≤ 1 and not greater than Baseline, RBS of 0, and endoscopic subscore ≤ 1), the multiple imputation will be applied to the original sub-scales, SFS, RBS, and endoscopic subscore (all range from 0 – 3). Then the dichotomized variable will be derived from the imputed values.
- For endpoints that are not derived from continuous variables, for example, no bowel urgency, the multiple imputation will be applied to the binary variable directly.

The MI procedure assumes that the data are missing at random (MAR). That is, for an outcome variable Y, the probability that an observation is missing depends only on the observed values of other variables, not on the unobserved values of the outcome variable Y. Statistical inference from the MI procedure is valid under the MAR assumption.

The multiple imputation scenarios are described below:

Scenarios	Argumentation Step	Multiple Imputation Step	PROC MI model
Endpoints that are derived from continuous scale or sub-scales and planned to have multiple post-baseline visits	Markov Chain Monte Carlo (MCMC) will be first applied to augment data into monotonic missing pattern.	For each monotone missing dataset, using SAS PROC MI with MONOTONE REG model statement, the outcome variable at each post-baseline visit with missing values will be imputed sequentially with covariates constructed from their corresponding sets of preceding variables	The imputation model for the missing data is a regression model, which controls for treatment group, Advanced Therapy-IR status (yes vs no), baseline corticosteroid use (yes vs. no) and baseline Adapted Mayo score (≤ 7 vs. > 7 (per central read after adjudication, when applicable), baseline measurement, and if applicable, post-baseline measurements at each visit up to the end of the analysis period.
Endpoints that are derived from continuous scale or sub-scales and have only single post-baseline	N.A.	PROC MI with FCS REG will be used	
Endpoint that are not derived from continuous variable	N.A.	PROC MI with FCS LOGISTIC will be used	

A 'complete' dataset with imputed values for the missing data is generated after the augmentation and imputation steps are completed.

- Subjects will then be characterized as responders or non-responders based on MI imputed datasets. Using the CMH model adjusted by stratification factors (Advanced Therapies-IR status (yes vs no), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7)), the imputed endpoints will be analyzed using each of the 30 datasets. SAS PROC MIANALYZE will be used to generate the final inferences of the risk difference between risankizumab treatment group and placebo group, using Rubin's rule. Note that measurements will be set to missing on or after the date of the UC-related corticosteroids intercurrent event or the occurrence of the UC-related surgery before applying MI. After the MI imputation, an NRI override will be implemented for missing values 1) due to reasons other than COVID-19 infection or logistic reasons or geo-political conflict in Ukraine or surrounding area, or 2) on or after the date of the UC-related corticosteroids intercurrent event, or 3) on or after or the date of the

UC-related surgery intercurrent event. That is, regardless of MI imputed values, subjects satisfying 1) or 2) will be considered as "non-responder" for binary efficacy endpoints.

- For binary efficacy endpoints of occurrence of hospitalization and the occurrence of UC-related surgeries, As Observed (AO) analysis will be used.
  - As Observed: The AO 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 AO analysis for that visit. AO will include all values collected in the study regardless of intercurrent events.
- Tipping Point Analysis for Binary Endpoints
  - The tipping point analyses are two-dimensional, i.e., assumptions about the missing outcomes on each of the risankizumab group and the placebo group can vary independently. The response rate among those subjects with missing response is assumed to be p0 for placebo group and p1 for risankizumab group, and the response rate p0 and p1 systematically vary from 0% to 100% by every 10% respectively. Given a set of (p0, p1), the subjects with missing response will be randomly assigned as responders or non-responders using binomial distribution to generate 30 imputed datasets, and the same CMH method used for the primary analysis will be performed on each of the imputed datasets to obtain the results for each comparison between the risankizumab group versus the placebo group. SAS PROC MIANALYZE will be used to generate the final inferences of the risk difference between risankizumab group and placebo group, using Rubin's rule.[4]
  - If one pair of (p0, p1) is found to reverse the study result interpretation in terms of p-value larger than 0.05, then the (p0, p1) is identified as the tipping point. The results for a grid of (p0, p1) combinations are provided in tabular format. Note that missing data on or after the date of the UC-related corticosteroids intercurrent event or on or after or the date of the UC-related surgery will be considered as non-responders and will not be imputed in the tipping point analysis.

9.2.2 Continuous Endpoints

- The primary approach for handling missing data in the analysis of continuous endpoints will use Multiple Imputation incorporating Return-to-Baseline (RTB-MI) to handle visits on or after the date of UC-related corticosteroids intercurrent event (IE2) or on or after the date of the UC-related surgery (IE3). To handle the potential departures from the missing-at-random (MAR) assumption for visits on or after the date of IE2 or IE3(see Section 8.0), the Return-to-Baseline (RTB)[5,6] approach which assumes subjects with initiation or dose escalation of UC-related corticosteroids or with UC-related surgery (ileostomy, colectomy, or proctocolectomy) will have a washout "return to baseline" of any potential treatment effect, will be performed as following:
- Step 1: after setting data on or after the date of IE2 or IE3 as missing.
- Step 2: subject's efficacy assessments on or after the date of IE2 or IE3will be assumed to have returned to baseline. For each imputed dataset, missing change from baseline data on or after IE2 or IE3 will be replaced by a value randomly drawn from a normal distribution $N(0, V_c)$, where V_c is the variance of change from baseline estimated from all other observed values without IE2 or IE3 at the corresponding visit, regardless of treatment groups, excluding those on or after the date of IE2 or IE3. A total of 30 datasets will be imputed.
- Step 3: For each imputed dataset, the MMRM or ANCOVA model described below will be applied to each completed set and the inference will be drawn using Rubin's combination rules (SAS proc MIANALYZE).
    - MMRM: The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, stratification factors (Advanced Therapies-IR status (yes vs no), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7)), and the continuous fixed covariates of Baseline measurements. An unstructured variance covariance matrix (UN) will be used. If the model cannot converge, an autoregressive (1) covariance structure matrix will be used. The parameter estimations are based on the method of restrictive maximum likelihood (REML). The fixed effects will be used to report model-based means at corresponding visits.

- ANCOVA: For continuous efficacy variables that are collected at only one post-baseline visit, ANCOVA will be used. The model includes the categorical fixed effects of treatment, stratification factors, and the continuous fixed covariates of baseline and measurement.

9.3 Primary Efficacy Endpoint and Analyses

9.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the achievement of clinical remission per Adapted Mayo score at Week 12.

9.3.2 Main Analysis of Primary Efficacy Endpoint(s)

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

Table 1. Summary of the Estimand Attributes of the Primary Efficacy Endpoint(s)

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Primary	Risankizumab 1200 mg IV vs. placebo	Achievement of clinical remission per Adapted Mayo score at Week 12	ITT2	IE1: premature discontinuation of study drug. IE2: initiation or dose escalation of UC-related corticosteroids. IE3: occurrence of the UC-related surgery (ileostomy, colectomy, or proctocolectomy) All data after IE1 will be used. All subjects will be considered as non-responder on or after the date of IE2 or IE3.	Proportion of subjects achieving clinical remission per Adapted Mayo score

The primary analysis of the primary endpoint will be conducted on ITT2 population based on randomized treatment groups (risankizumab 1200 mg IV vs placebo) using NRI-MI for missing data handling. Point estimate and 95% CI using normal approximation will be provided for the response rate for each randomized treatment group. The difference between the treatment groups (risankizumab 1200 mg IV vs placebo) in the primary efficacy endpoint will be assessed using the CMH test and will be stratified by Advanced Therapies-IR status (yes vs no), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7). Point estimate, 95% CI and nominal p-value for the treatment comparison will be presented.

The following rules are used to calculate the stool frequency subscore (SFS) and rectal bleeding subscore (RBS) (ePRO specification document, Appendix F) in the primary analysis:

- Daily RBS is captured directly in the eDiary 'STOOL1-How often saw Blood in Stool'.
- Daily SFS is calculated by subtracting subject's normal number of bowel movements from the absolute daily stool frequency and assigning the following scores:
  - 0 = Equal to or less than Normal
  - 1 = 1-2/day more than normal
  - 2 = 3-4/day more than normal
  - 3 = >4 stools/day more than normal

    Note: The stool frequency subscore during days which the subject received anti-diarrheal medication will be scored as a 3.
- Define a 10-day period during which daily subscores are collected before the partial adapted Mayo score at each visit.
- Subscores will be calculated by averaging the 3 most recent valid Daily SFS & RBS within the 10-day period, excluding the day before endoscopy (due to bowel preparation), day of endoscopy and 2 days following the endoscopy (for visits that include an endoscopy). The calculated scores following these above rules will be recorded to an eCRF page by study sites that will used in the primary analysis.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

Tipping point analyses will be conducted as sensitivity analyses for the primary endpoint.

The above described CMH analysis will be repeated with the ITT2 population using AO data as a supplementary analysis.

In addition, the following sensitivity analysis will be conducted for the primary endpoint:

- The conflict in Ukraine may impact the treatment or follow-up of subjects in Ukraine and the surrounding region. Moreover, the conflict may also impact the quality of the data or the ability to verify the data. The above described

CMH analysis based on NRI-MI will be conducted with a subgroup of ITT2; ITT2 population excluding subjects who were impacted by the geo-political conflict in Ukraine or surrounding area.

- The above described CMH analysis based on NRI-MI will be conducted with the ITT2 population applying the following rules to calculate the stool frequency subscore and rectal bleeding subscore for the primary endpoint:
  - Define a 7-day period during which daily subscores are collected before the partial adapted Mayo score at each visit.

    Note: The stool frequency subscore during days which the subject received anti-diarrheal medication will be scored as a 3.
  - The subscores should be calculated by averaging the daily subscores from within this 7-day period, excluding the before endoscopy (due to bowel preparation) and day of endoscopy (for visits that include an endoscopy).
  - A minimum of 3 consecutive days of completed diary entries or 4 nonconsecutive days are necessary (otherwise the score should be considered missing).

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints are defined in Section 3.2.

9.4.2 Main Analyses of Secondary Efficacy Endpoints

The attributes of the estimands corresponding to the secondary efficacy endpoints are summarized in Table 2.

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

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Categorical Secondary	Risankizumab 1200 mg IV vs. placebo	Achievement of: • clinical response per Adapted Mayo score at Week 12 • endoscopic improvement at Week 12 • histologic endoscopic mucosal improvement at Week 12 • endoscopic remission at Week 12 • clinical response per Partial Adapted Mayo score at Week 4 • no bowel urgency at Week 12 • no abdominal pain at Week 12 • histologic endoscopic mucosal remission at Week 12 • no nocturnal bowel movements at Week 12 • no tenesmus at Week 12	ITT2	IE1: premature discontinuation of study drug. IE2: initiation or dose escalation of UC-related corticosteroids. IE3: occurrence of the UC-related surgery (ileostomy, colectomy, or proctocolectomy) All data after IE1 will be used. All subjects will be considered as non-responder on or after the date of IE2 and IE3.	Proportion of subjects achieving each categorical secondary endpoint

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Continuous Secondary	Risankizumab 1200 mg IV vs. placebo	Change from Baseline to Week 12 in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)/in Inflammatory Bowel Disease Questionnaire (IBDQ) total score/ in number of fecal incontinence episodes per week/in number of days per week with sleep interrupted due to UC symptoms	ITT2	IE1: premature discontinuation of study drug. IE2: initiation or dose escalation of UC-related corticosteroids. IE3: occurrence of the UC-related surgery (ileostomy, colectomy, or proctocolectomy) All data after IE1 will be used. All data on or after the date of IE2 and IE3 will not be used for continuous endpoints.	Mean change from Baseline in each continuous endpoint
UC-related hospitalizations through Week 12	Risankizumab 1200 mg IV vs. placebo	Occurrence of UC-related hospitalization through Week 12	ITT2	IE1: premature discontinuation of study drug IE2: initiation or dose escalation of UC-related corticosteroids IE3: occurrence of the UC-related surgery (ileostomy, colectomy, or proctocolectomy) All data after IE1will be used. All data after IE2 or IE3 will be used.	Proportion of subjects having at least one UC-related hospitalization through Week 12

The binary secondary endpoints will be analyzed based on ITT2 using the same approach as that for primary endpoint as specified in Section 9.3.2. Specifically, CMH adjusting for stratification factors will be used to construct the treatment difference, the associated

95% CI and p-value between risankizumab 1200 mg IV group and placebo group. The NRI-MI will be the primary approach for missing data handling in the analyses of binary secondary efficacy endpoints except for Occurrence of UC-related hospitalization, of which AO data will be used.

For UC-related hospitalizations through Week 12, to consider Missing-Not-At-Random (MNAR) assumption due to different dropout rates between treatment groups, a supplementary analysis will be performed based on exposure adjusted occurrence of UC-related hospitalizations through Week 12. Exposure adjusted occurrence of UC-related hospitalization will be analyzed based on incidence rates. Incidence rates for hospitalization will be calculated as the number of patients with the respective event divided by the time at risk. For patients with an event during the study period, time at risk is the patient-years (PYs) from the first dose date to the first event before Week 12. For patients without an event during Period 1, time at risk is PYs from first dose date to the end of study follow-up period, where the follow-up period starts from the first dose date to the last dose date in Period 1+ 140 days if prematurely discontinues the study drug without entering Period 2 or M16-066, or the first dose date of Period 2 or M16-066 if enters Period 2 or M16-066, whichever occurs earlier. The event date is defined as the date of admission to the hospital for hospitalizations. The incidence rate difference, 95% CI and p-value are calculated to evaluate the statistical significance of the difference between risankizumab 1200 mg IV group and placebo group using normal approximation to Poisson distribution. The analysis will be based on the AO data.

The continuous secondary endpoints will be analyzed based on ITT2 by RTB-MI with MMRM (for endpoints with more than one post-baseline visits) or with ANCOVA (for endpoints with one post-baseline visit) and the corresponding analyses are specified in Section 9.2.2. The least square (LS) mean and 95% CI for each randomized treatment group and the LS mean treatment difference, the associated 95% CI and the p-value between risankizumab 1200 mg IV group and the placebo group will be provided. Considering unequal variances due to the unequal sample size in the two treatment groups (2:1 randomization), a sensitivity analysis will be performed for continuous secondary

endpoints with only a single post-baseline measure using an ANCOVA model that estimates variance by treatment group.

9.5 Additional Efficacy Endpoints and Analyses

9.5.1 Additional Analyses

All additional binary efficacy endpoints specified in Section 3.3 will be analyzed based on ITT2 using the same approach as the primary approach for primary endpoint as specified in Section 9.3.2. Specifically, CMH adjusting for stratification factors will be used to construct the treatment difference, the associated 95% CI and p-value between risankizumab 1200 mg IV group and placebo group. The NRI-MI will be the primary approach for missing data handling in the analyses of binary secondary efficacy endpoints except for the occurrence of UC-related hospitalization.

All additional continuous endpoints will be analyzed based on ITT2 by RTB-MI and the corresponding analyses are specified in Section 9.2.2. The least square (LS) mean and 95% CI for each randomized treatment group and the LS mean treatment difference, the associated 95% CI and the p-value between risankizumab 1200 mg IV group and the placebo group will be provided. For time to clinical response per Partial Adapted Mayo score in Period 1, the distribution of time to clinical response including median will be estimated for each treatment group using Kaplan-Meier method and compared between the two treatment groups using stratified Log-rank test. The hazard ratio and corresponding 95% CI between the two treatment groups will also be obtained using the Cox Proportional Hazard Model. Subjects who have experienced IE2 or IE3 prior to experiencing the event (clinical response per Partial Adapted Mayo) are censored at the time of the earliest intercurrent event of IE2 or IE3. Subjects who are not experiencing the event (clinical response per Partial Adapted Mayo) are censored at the date of study discontinuation (if discontinued in Period 1) or last non-missing measurement of partial adapted Mayo score in Period 1 (if not discontinued in Period 1).

9.5.2 Induction Period 2 Efficacy Analysis

For all endpoints specified in Section 3.3, descriptive summary including point estimate (% or mean) and 95% CI will be provided for ITT2_P2 population by treatment sequence. The NRI-MI and RTB-MI will be used in the analyses of binary and continuous efficacy endpoints, respectively, as specified in Section 9.3.2. For time to clinical response per Partial Adapted Mayo score in Period 2, the distribution of time to clinical response including median time with will be descriptively summarized for each treatment group using Kaplan-Meier method.

9.6 Efficacy Subgroup Analyses

Subgroup analysis will be performed for the primary efficacy endpoint for the subgroups listed in Table 3 below using ITT2. Point estimate and 95% CI for each treatment group as well as point estimate and 95% CI for treatment differences between risankizumab 1200 mg IV and placebo groups will be presented. The NRI-MI approach will be used for missing data handling. No p-value will be provided. If any of the resulting subgroups except for age, sex and race has fewer than 10% of the planned study size, the subgroup analyses for that category will not be presented.

Table 3. Subgroups for Efficacy Analysis

Subgroup Factor	Categories
Age	[18, 40), [40, 65), ≥ 65
Sex	Male or Female
Baseline weight	< 60 kg or ≥ 60 kg
Race	White or non-White
Geographic Region	North America, South/Central America, Western Europe, Eastern Europe, Asia, Other
Baseline corticosteroid use	Yes or No
Baseline immunosuppressant use	Yes or No
Baseline Adapted Mayo Score	≤ 7 or > 7
Baseline Partial Adapted Mayo Score	≤ 4 or > 4
Prior exposure to anti-TNF for UC for non-Advanced Therapy-IR population	Yes or No
Number of prior failed anti-TNF for UC for Advanced Therapy -IR population	0, 1, 2, > 2
Prior exposure to advanced therapy	0, 1, > 1
Number of prior failed advanced therapies	0 (Non-Advanced Therapy -IR population), ≥ 1 (Advanced Therapy -IR population) (Then analyze 1, 2, > 2 within Advanced Therapy -IR population
Presence of pancolitis at Baseline	Yes or No
Disease Duration at Baseline	≤ median or > median
Disease Duration at Baseline	≤ 3 years or > 3 years
Baseline hs-CRP	≤ median or > median
Baseline hs-CRP	≤ 5 mg/L or > 5 mg/L
Baseline Albumin	≤ median or > median
Baseline Calprotectin	≤ median or > median
Baseline Calprotectin	≤ 250 mg/kg or > 250 mg/kg

All the secondary efficacy endpoints will be analyzed in the Advanced Therapy-IR and non-Advanced Therapy -IR subgroups in the ITT2 population.

In addition, point estimate of response rate will be summarized for primary endpoint for the following subgroups based on ITT2 population using NRI-MI for risankizumab treatment group (risankizumab 1200 mg IV):

- Treatment Emergent Anti-Drug Antibodies (ADA+, ADA-)
- Treatment Emergent NAb status (NAb+, NAb-)

10.0 Safety Analyses

10.1 General Considerations

Safety analysis will be performed on the safety populations in Induction Period 1 (SA2 population) and Induction Period 2 (SA2_P2 population) in Sub-Study 2. Safety summaries will be presented by treatment group, including a total group for all subjects on active study drug for SA2_P2. In addition, safety analysis will be provided for all Risankizumab treated safety population (SA2_ALL population) combined as one group.

For the safety analysis, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

The standard safety analyses will include reporting of adverse events (AEs), Areas of Safety Interest (ASIs), laboratory, and vital signs measurements. Frequency tables of subjects with treatment-emergent adverse events (TEAEs) by system organ class (SOC) and by preferred term (PT) as in the Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be provided by treatment group. All continuous laboratory parameters and vital signs variables at each visit will also be summarized by actual treatment group. Frequency tables of subjects meeting criteria for potentially clinically significant vital sign values and for potentially clinically significant laboratory values will be provided by treatment group.

Missing safety data will not be imputed.

Baseline for laboratory and vital signs

For SA2 population, the baseline value is defined as the last available measurement before study drug administration for each subject. For SA2_P2 and SA2_ALL populations, the baseline value is defined as the last available measurement on or before first dose of risankizumab.

10.2 Adverse Events

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

Summaries of AEs discussed in this section will be provided for SA2 and SA2_P2 population. For SA2_ALL population, exposure-adjusted AEs per 100 patient-years will be provided as described in Section 10.2.4. For exposure-adjusted event rate (EAER) calculation, the numerator will be the total number of AEs reported for the event (i.e., a subject can contribute more than one event to the numerator) and the denominator will be the total exposure time among subjects under the treatment group. The number of AEs reported (numerator), the total number of years of study drug exposure (denominator, calculated as total number of days exposed to study drug (i.e., last dose date – first dose date + 140 days) for all treated subjects divided by 365.25), and the exposure-adjusted AE event rate per 100 patient-years calculated as ([numerator (number of AEs)/denominator]) × 100 will be presented for each treatment group.

10.2.1 Treatment-Emergent Adverse Events

The Treatment-Emergent Adverse Events (TEAEs) for SA2, SA2_P2 and the SA2_ALL populations are defined as follows:

Induction Period 1 (SA2 population):

TEAEs for Induction Period 1 are defined as events that begin either on or after the first dose of the study drug in Induction Period 1 and

- before first dose of study drug in Induction Period 2 if the subject is enrolled into Induction Period 2 or
- before first dose of study drug in the Maintenance Study (M16-066) if the subject is enrolled into the Maintenance Study (M16-066) or
- within 140 days after the last dose administration of the study drug for subjects who are not enrolled in Induction Period 2 and do not participate in the Maintenance Study (M16-066); or for subjects who are responders in Induction Period 1 but do not participate in the Maintenance Study (M16-066).

Induction Period 2 (SA2_P2 population):

TEAEs for Induction Period 2 are defined as events that begin either on or after the first dose of risankizumab in Induction Period 2 and

- before first dose of study drug in the Maintenance Study if the subject is enrolled into the Maintenance Study (M16-066) or
- within 140 days after the last dose administration of the study drug for subjects who do not participate in the Maintenance Study (M16-066).

SA2_ALL population:

TEAEs are defined as events that begin either on or after the first dose of risankizumab in either Induction Period 1 or Induction Period 2 and

- before first dose of study drug in the Maintenance Study (M16-066) if the subject is enrolled into the Maintenance Study (M16-066) or
- within 140 days after the last dose of risankizumab in this study for subjects who do not participate in the Maintenance Study (M16-066).

Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless the study drug start time and the adverse event start time are collected and the adverse event start time is prior to the study drug start time. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

All treatment-emergent AEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

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

10.2.2 Adverse Event Overview

For SA2 and SA2_P2 populations, an overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any TEAE
- Any COVID-19 related TEAE
- Any TEAE related to study drug according to the investigator
- Any severe TEAE
- Any serious TEAE
- Any TEAE leading to discontinuation of study drug
- Any TEAE leading to death
- TEAE of Safety Interest (as defined in)

- All deaths
  - COVID-19 related deaths
  - Deaths occurring ≤ 140 days after last dose of study drug
  - Deaths occurring > 140 days after last dose of study drug.

Additional AEs may be considered for tabulation/summary based on recommendations from Clinical and Safety as deemed appropriate.

The point estimate and 95% CI (using normal approximation and separate group variance) will also be provided for the treatment difference in AE percentage between risankizumab group and the placebo group for analyses performed on SA2 population.

For SA2 and SA2_P2 populations, an overview of the ASI will be provided similarly and the categories of ASI are defined in Appendix B.

In addition, for SA2 and SA2_P2 populations, an overview of AEs per 100 patient-years of study exposure and an overview of ASI per 100 patient-years of study exposure will be presented. The number of TEAEs reported, the total number of years of study drug exposure, and the TEAE rate per 100 patient-years will be presented. The point estimate and 95% CI will be provided for the treatment difference between risankizumab group and the placebo group.

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

The following summary of treatment-emergent adverse events will be summarized by SOC and PT:

- All TEAE
- Serious TEAEs
- Severe TEAEs
- TEAEs related to study drug according to the investigator
- TEAEs leading to discontinuation of study drug
- TEAE leading to death

- COVID-19 related TEAE

TEAE will also be summarized by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency for the total active group.

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

For SA2 and SA2_P2 populations, an overview of AEs per 100 patient-years of study exposure and an overview of ASI per 100 patient-years of study exposure will be presented.

Exposure-adjusted AEs per 100 patient-years will be provided for SA2_ALL for the following categories:

- AE overview
- ASI overview
- All TEAEs by SOC and PT
- All serious TEAEs by SOC and PT
- All Severe TEAEs by SOC and PT
- TEAEs related to study drug according to the investigator by SOC and PT
- TEAEs leading to discontinuation of study drug by SOC and PT
- TEAE leading to death by SOC and PT
- COVID-19 related TEAE by SOC and PT

- TEAE by PT and sorted by decreasing frequency for the total active group
- SAEs (including deaths) and AEs leading to study drug discontinuation by SOC and PT and in listing format.
- ASI by SOC and PT (or by Adjudicated Terms)

Calculation of EAER is defined in Section 10.2.

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

SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and in listing format. Calculation of EAER is defined in Section 10.2.

10.2.6 Areas of Safety Interest

Areas of Safety Interest will be summarized by SOC and PT and will be based on standardized or company MedDRA queries (SMQs or CMQs). Adjudicated cardiovascular events will be summarized and presented by treatment group using the CAC adjudicated categories. Areas of Safety Interest are categorized as follows:

- Adjudicated MACE
- Adjudicated extended MACE
- Serious infections
- Active Tuberculosis
- Opportunistic infections excluding tuberculosis and herpes zoster
- Herpes zoster
- Malignancies (Malignant tumours, NMSC and Malignancies excluding NMSC)
- Hypersensitivity
- Serious hypersensitivity
- Adjudicated Anaphylactic reactions
- Hepatic events

- Injection site reactions

Detailed information about the search criteria is provided in Appendix C.

In addition, an overview of ASI per 100 patient-years of study exposure will be presented. The number of TEAEs reported, the total number of years of study drug exposure, and the TEAE rate per 100 patient-years will be presented.

The exposure adjusted incidence rate (censored at the time of first event) may be conducted for deaths and selected Areas of Safety Interest categories including adjudicated cardiovascular events, malignant tumors, non-melanoma skin cancer (NMSC), and malignant tumors excluding NMSC, as appropriate.

Tabular listings of ASI listed above will also be provided.

10.3 Analysis of Laboratory Data

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

Analysis of Quantitative Laboratory Parameters

For SA2 and SA2_P2 populations, each laboratory variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for 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 within each treatment group. In addition, for SA2_P2 populations, each laboratory variable will be summarized for all time points (starting with Induction

Period 2 baseline referring to the last available measurement before first dose in Induction Period 2) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from Induction Period 2 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 Induction Period 2 baseline mean, standard error, and 95% confidence interval will be presented for the mean change from Induction Period 2 baseline within each treatment group.

For SA2 population, treatment group differences between Risankizumab 1200 mg IV treatment group and placebo group for changes from Baseline will be analyzed using a one-way Analysis of Variance (ANOVA) model with treatment as a fixed factor and 95% CI for treatment difference will be presented for selected laboratory parameters.

Shift Table Analyses

For SA2 and SA2_P2 populations, changes in laboratory parameters will be tabulated using shift tables either by NCI CTC criteria or categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline either to the worse value (based on NCI CTC criteria) during treatment or 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.

Potentially Clinically Significant Laboratory Values

For SA2, SA2_P2 and SA2_ALL populations, laboratory abnormalities meeting CTC criteria grade 3, grade 4 and ≥ Grade 3 will be summarized, with a grade worsening compared to baseline.

Laboratory abnormalities will be evaluated based on Potentially Clinically Significant (PCS) criteria (). For each laboratory PCS 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 PCS criteria.

Assessment of Liver Elevations

For SA2, SA2_P2 and SA2_ALL populations, the liver-specific laboratory tests include the serum glutamic pyruvic transaminase (SGPT/ALT), serum glutamic-oxaloacetic transaminase (SGOT/AST), alkaline phosphatase (ALP), and total bilirubin (TBL). The frequencies and percentages of subjects with post baseline liver specific function test values that meet the following criteria of potential clinical interest will be summarized by treatment group:

- ALT $\geq 3 \times$ ULN
- ALT $\geq 5 \times$ ULN
- ALT $\geq 10 \times$ ULN
- ALT $\geq 20 \times$ ULN
- AST $\geq 3 \times$ ULN
- AST $\geq 5 \times$ ULN
- AST $\geq 10 \times$ ULN
- AST $\geq 20 \times$ ULN
- TBL $\geq 2 \times$ ULN
- Alkaline phosphatase $\geq 1.5 \times$ ULN
- (ALT and/or AST $\geq 3 \times$ ULN) and (TBL $\geq 1.5 \times$ ULN)
- (ALT and/or AST $\geq 3 \times$ ULN) and (TBL $\geq 2 \times$ ULN)

where ULN is the upper limit of normal.

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 4 criteria:

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

A listing of possible Hy's Law cases, defined as those who meet all of the following conditions at any post-baseline visit will be provided:

- ALT of > 3 × ULN or AST of > 3 × ULN,
- Total bilirubin ≥ 2 × ULN.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, pulse rate, body weight and body temperature will be summarized.

For SA2 and SA2_P2 populations, each vital sign variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group. In addition, for SA2_P2 populations, each vital sign variable will be summarized for all time points (starting with Induction Period 2 baseline referring to the last available measurement before first dose in Induction Period 2) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from Induction Period 2 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 Induction Period 2 baseline mean, standard error, and 95% confidence interval will be presented for the mean change from Induction Period 2 baseline within each treatment group.

For SA2 population, treatment group differences between Risankizumab 1200 mg IV treatment group and placebo group for changes from Baseline will be analyzed using a one-way Analysis of Variance (ANOVA) with treatment as a fixed factor and 95% CI for treatment difference will be presented for each vital sign variable.

For SA2, SA2_P2 and SA2_ALL populations, vital sign variables will be evaluated based on potentially clinically significant (PCS) criteria (). For each vital sign PCS 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 PCS criteria.

10.5 Safety Subgroup Analyses

No safety subgroup analyses are planned.

10.6 Other Safety Analyses

No other analyses are planned.

11.0 Other Analyses

No other analyses are planned.

12.0 Interim Analyses

There will be no formal interim efficacy analyses planned before the Primary Analysis for the Induction Study.

12.1 Data Monitoring Committee

An external data monitoring committee (DMC) composed of persons independent of AbbVie and with relevant expertise in their field will review unblinded 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.

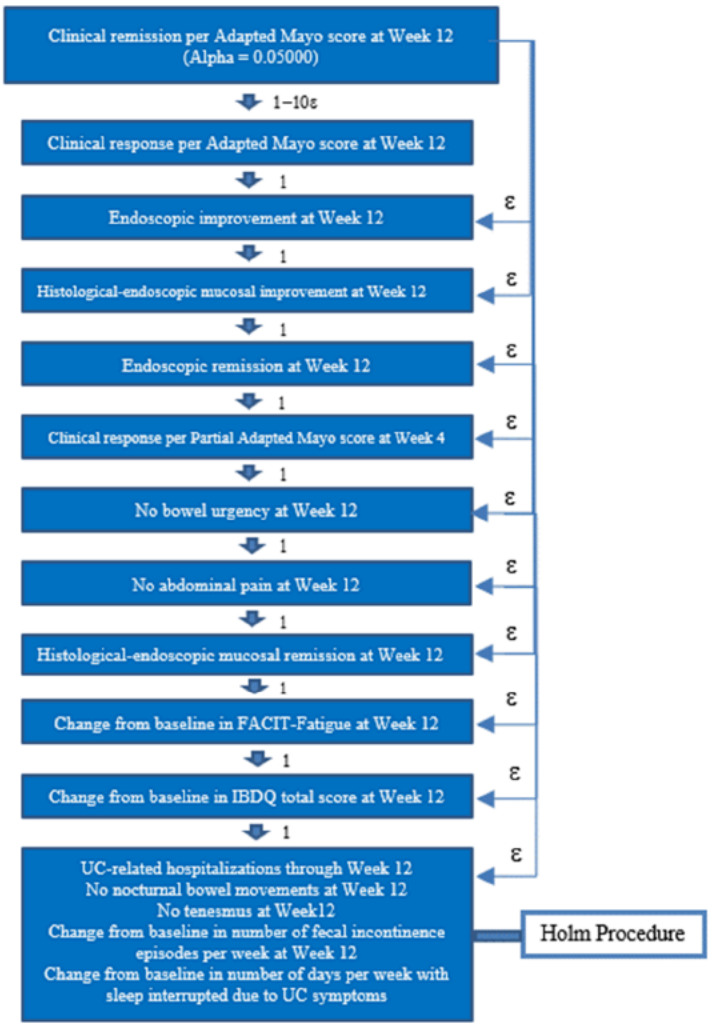
Since there are no efficacy analyses for early stopping, no alpha adjustment is needed.

13.0 Overall Type-I Error Control

The overall type I error rate of the primary and secondary endpoints will be strongly controlled using a graphical multiple-testing procedure[1] as described below. The primary endpoint will be tested at the pre-specified significance level of 0.05 (2-sided). The secondary efficacy endpoints are divided into two groups. The first group includes the first ten secondary endpoints. The second group includes all the remaining five secondary endpoints which will be tested using the Holm procedure.[2] If the primary endpoint achieves statistical significance, continued testing will follow a pre-specified weight of α allocation specified in Figure 3. In the graph, the arrows specify the weight of α allocation between nodes. Once a hypothesis is rejected (i.e., deemed the endpoint is significant) at its assigned significance level, its significance level will be allocated to the subsequent node. If more than one arrow originates from a node, the significance level will be split between multiple subsequent nodes following the pre-specified weight. The numbers on the arrows denote the weights. For example, the weight 1 denotes 100% transfer of significance level to the next node, and the weight ε denotes 0.02% of the overall significance level (corresponding to α of 0.02%*0.05=of 0.00001) to be transferred.

Overall Type I control will not be applied to additional efficacy endpoints listed in Section 3.3.

Figure 3. Graphical Multiple Testing Procedure for Primary and Secondary Efficacy Endpoints



Note that ε = 0.0002 corresponding to α of 0.00001.

14.0 Version History

Table 4. SAP Version History Summary

Version	Date	Summary
1.0	19 Jan 2021	Original version
2.0 Draft	25 Aug 2022	1. Updated the ranking in secondary endpoints and multiple testing procedure considering agency's comments and recent available trial data. 2. Replaced NRI-C by NRI-MI as primary approach to handle both missing due to Covid and missing due to geo-political conflict. Updated CMH test as primary method for binary endpoints instead of M-N test due to agency's request. 3. Removed NRI-NC as the sensitivity analysis. Added tipping point analyses as the sensitivity analyses for the primary endpoint. 4. For continuous endpoints, replaced MMRM by RTB-MI as primary approach. 5. Removed AO as a supplementary analysis for secondary or additional endpoints. 6. Updated analysis population terminology to follow protocol 7. Updated Bio-IR and non-Bio-IR as Bio/JAK-IR and non-Bio/JAK-IR, respectively and added the definition for clarity.

Version	Date	Summary
2.0	10 Feb 2023	1. Updates per agency feedback: a. Added UC-related surgeries (ileostomy, colectomy, or proctocolectomy) as an additional intercurrent event in Section 8.0 and Section 9.0. b. Added disposition summary analysis for subjects whose study participation were impacted by the geo-political conflicts in Ukraine or surrounding area in Section 5.0. c. Added more details in Section 9.0 to clarify the statistical approaches for the efficacy analysis. d. Specified a sensitivity analysis for continuous secondary endpoints with only a single post-baseline measure using an ANCOVA model that estimates variance by treatment group to consider unequal variances in Section 9.0. 2. Details added to clarify: a. In Section 3.0, added definitions of endpoints related to mayo score and clarified that endoscopic subscore in the analysis will be based on central readings after adjudication, when applicable. b. In Section 7.0, added some demographics and baseline characteristics to make sure characteristics used in efficacy subgroup analysis will be included in baseline summary. 3. Other updates: a. Updated 'bio/JAK-IR' in study design/enrollment section (Section 2.2) to 'bio-IR' to be consistent with protocol. b. Updated 'bio/JAK-IR' in statistical analysis section (Section 9.0) to 'Advanced Therapy-IR' to be consistent with protocol. c. Updated Appendix B Definition of Areas of Safety Interest

15.0 References

1. Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28(4):586-604.
2. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat. 1979(6):65-70.
3. Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics. 1985;41(1):55-68.

4. Rubin DB. Multiple imputation for nonresponse in surveys. 1987.
5. Kim Y, Wang Y, et al. Statistical Review and Evaluations (NDA 209210). FDA. Reference ID 4153028. 2017.
6. Zhang Y, Zimmer Z, Xu L, et al. Missing data imputation with baseline information in longitudinal clinical trials. Stat Biopharm Res. 2020;2(14):242-8.

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 Areas of Safety Interest

Areas of Safety Interest (ASI) will be identified using the following search criteria:

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Adjudicated CV Events	MACE	Adjudicated terms will be identified using CECAT and CETERM from the CE SDTM dataset.	Display underlined terms defined by the following adjudicated terms: • CV Death which includes all CETERM values with CEDECOD= "Cardiovascular death" or "Death due to stroke" • Non-fatal Myocardial infarction • Non-fatal Stroke	Y
	Extended MACE	Adjudicated terms will be identified (for MACE +) using CECAT and CETERM from the CE SDTM dataset.	Display underlined terms from MACE and underlined terms below: • Hospitalization for Unstable Angina • Coronary Revascularization Procedures	Y

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Serious Infections, TB, and Opportunistic Infections (including Herpes Zoster)	Serious Infections	Serious PTs of the SOC Infections and Infestations	PTs	Y
	Active TB	Active Tuberculosis CMQ (code 10000002)	PTs	Y
	Opportunistic Infections Excluding Tuberculosis and Herpes Zoster	Opportunistic infections CMQ excluding Tuberculosis and Herpes Zoster (code 10000105)	PTs	Y
	Herpes Zoster	Herpes zoster CMQ (code 10000079)	PTs	Y
Malignancies	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 10000100)	PTs	Y
	Malignancies excluding NMSC	'Malignancies excluding NMSC' is identified by the 'Malignant Tumours' search excluding terms identified by the 'Non-melanoma skin cancer' (NMSC) search.	PTs	Y
Hypersensitivity Reaction	Hypersensitivity	Narrow Hypersensitivity (SMQ 20000214)	PTs	Y – serious events separately summarized

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Anaphylactic Reaction	Adjudicated Anaphylactic Reaction	Adjudicated terms will be identified using SDTM data (e.g., CE and PR domains).	Adjudicated term defined in the charter	Y
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	Y
Injection site reactions		Injection site reaction CMQ (code 10000091)	PTs	Y
		Injection site reaction assessment and infusion site reaction assessment CRFs	Terms on the CRF	N

Appendix C. Potentially Clinically Significant Criteria for Safety Endpoints

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

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

		Definition of Potentially Clinically Significant Current (Version 4.03) CTCAE Grade 3 or Greater
Hematology Variables	**Units**	**Very Low**
Hemoglobin	g/L	< 80.0
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 value must be more extreme than the baseline value (higher CTC grade than baseline) to be considered a potentially clinically significant finding.

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

		Definition of Potentially Clinically Significant Current (Version 4.03) 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
GGT	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 (> 3.0 × BL)
Sodium	mmol/L	< 130	> 155
Potassium	mmol/L	< 3.0	> 6.0
Calcium[&]	mmol/L	< 1.75	> 3.1
Total Cholesterol	mmol/L		> 10.34

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

[&] For Calcium, the Calcium corrected for Albumin will be used in the safety analysis.

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

Vital Sign	Category	Criteria for Potential Clinically Significant Vital Signs
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

Appendix D. Common Toxicity Criteria (CTC) Grade for Laboratory Data

Test	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry Variables				
SGPT/ALT increased	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
SGOT/AST increased	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
GGT increased	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
ALP increased	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
TBL increased	> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 10.0 × ULN	> 10.0 × ULN
Creatinine* increased	> 1 – 1.5 × baseline (BL); > ULN – 1.5 × ULN	> 1.5 – 3.0 × BL; > 1.5 – 3.0 × ULN	> 3.0 × BL; > 3.0 – 6.0 × ULN	> 6.0 × ULN
Total Cholesterol increased	> ULN - 7.75	> 7.75 - 10.34	> 10.34 - 12.92	> 12.92
Albumin decreased	< LLN - 30	< 30 - 20	< 20	N/A
Triglycerides increased	1.71 - 3.42	> 3.42 - 5.7	> 5.7 - 11.4	> 11.4
Glucose	< LLN - 3.0 or > ULN - 8.9	< 3.0 - 2.2 or > 8.9 - 13.9	< 2.2 - 1.7 or > 13.9 - 27.8	< 1.7 or > 27.8
Sodium	< LLN – 130 or > ULN - 150	> 150 – 155	< 130 – 120 or > 155 - 160	< 120 or > 160
Potassium	< LLN - 3.0 or > ULN - 5.5	< LLN - 3.0 or > 5.5 - 6.0	< 3.0 - 2.5 or > 6.0 - 7.0	< 2.5 or > 7.0
Calcium&	< LLN - 2.0 or > ULN - 2.9	< 2.0 - 1.75 or > 2.9 - 3.1	< 1.75 - 1.5 or > 3.1 - 3.4	< 1.5 or > 3.4
Hematology Variables				
Hemoglobin decreased	< LLN – 100.0 g/L	< 100.0 – 80.0 g/L	< 80.0 g/L	N/A
Neutrophil count decreased	< LLN – 1.5 × 10^9/L	< 1.5 – 1.0 × 10^9/L	< 1.0 – 0.5 × 10^9/L	< 0.5 × 10^9/L
WBC decreased	< LLN – 3.0 × 10^9/L	< 3.0 – 2.0 × 10^9/L	< 2.0 – 1.0 × 10^9/L	< 1.0 × 10^9/L
Lymphocyte count decreased	< LLN – 0.8 × 10^9/L	< 0.8 – 0.5 × 10^9/L	< 0.5 – 0.2 × 10^9/L	< 0.2 × 10^9/L
Platelets count decreased	< LLN - 75.0 × 10^9/L	< 75.0 - 50.0 × 10^9/L	< 50.0 - 25.0 × 10^9/L	< 25.0 × 10^9/L

* If the calculation based on BL results in a different grade than the calculation based on ULN, use the higher grade.

& For Calcium, the Calcium corrected for Albumin will be used in the safety analysis.

Appendix E. Geographic Region

Below table lists the countries/regions considered for each geographic region.

Geographic Region	Countries/Regions
Asia	Japan (JPN), China (CHN), Hong Kong (HKG), Malaysia (MYS), Singapore (SGP), South Korea (KOR), Taiwan (TWN)
Eastern Europe	Belarus (BLR), Bosnia and Herzegovina (BIH), Bulgaria (BGR), Croatia (HRV), Czech Republic (CZE), Estonia (EST), Hungary (HUN), Kazakhstan (KAZ), Latvia (LVA), Lithuania (LTU), Poland (POL), Romania (ROU), Russia (RUS), Serbia (SRB), Slovakia (SVK), Slovenia (SVN), Turkey (TUR), Ukraine (UKR)
North America	Canada (CAN), United States (USA), Puerto Rico (PRI)
Other	Australia (AUS), Egypt (EGY), Israel (ISR), New Zealand (NZL), South Africa (ZAF), Tunisia (TUN)
South/Central America	Argentina (ARG), Brazil (BRA), Chile (CHL), Colombia (COL), Mexico (MEX), Guatemala (GTM)
Western Europe	Austria (AUT), Belgium (BEL), Denmark (DNK), Finland (FIN), France (FRA), Germany (DEU), Greece (GRC), Ireland (IRL), Italy (ITA), Netherlands (NLD), Norway (NOR), Portugal (PRT), Spain (ESP), Switzerland (CHE), Sweden (SWE), United Kingdom (GBR)

Appendix F. Risankizumab M16-067 Electronic Patient Reported Outcomes Specification: Daily Mayo Sub-Scores Calculation and Average SFS&RBS Calculation Risankizumab

Daily Mayo Sub scores calculation

Daily Stool Frequency sub-score is calculated comparing** the below two questions

1. "How many stools did you have in the last 24 hours? - Stools Tab/Number of Stools"
2. "Please enter subject's normal number of bowel movements, in a 24 hour period, when his/her ulcerative colitis is **not** active?"

and assigning the following scores:
0=Equal to or less than Normal
1=1-2/day more than normal
2=3-4/day more than normal
3= >4 stools/day more than normal

**Subtracting value of question #2 from #1

Daily Rectal Bleeding sub-score is calculated using the following:
("How often did you see blood in your stool in the last 24 hours?" - Stools Tab/Bloody Stool)
And assigning the following score
0=none
1=Visible blood in stool less than half the time
2=visible blood in stool half of the time or more
3=passing blood alone (At least 1 entered in "How many times did you see ONLY blood without any stool in the last 24 hours?")

Rules:

1. Provide the scores for the last 10 days **starting with current day -1**
2. If anti-diarrheal taken (Diarrhea Tab/Diarrhea Meds), 'Stool Frequency' will be given a value of 3.
3. If Endoscopy Prep was indicated in the Daily Diary (Endoscopy Prep Tab/Endoscopy Meds), the scores will be highlighted in red for that day.

Mayo Calculation (Average Stool Frequency & Rectal Bleeding sub-score)
Add the following questions (To be answered by investigator at every visit):

1. Did the subject have an endoscopy within the last 10 calendar days (excluding today)?
   Options:
   Yes
   No
   (If yes for above)
2. What was the date of the endoscopy?

The system will show the last 10 daily Stool Frequency & Rectal Bleeding sub-scores and highlight in red, "the Date the subject took endoscopy prep. Med," "the day the endoscopy was done and 2 days following the endoscopy."

Calculate the average of the 3 most recent valid Daily stool frequency &rectal bleeding sub-score starting the date prior the study visit and show the scores.
Rules:
The following dates should not be included to calculate the average (not valid dates):

1. Day the subject took the end, prep medication
2. Day the endoscopy was performed and 2 days later

In case a date is missing or not valid, the system will use earlier diary entries to provide the most recent data for 3 days prior the study visit

Document Approval

Study Report Appendix - m16067-sap-v2-substudy2 - 14-Feb-2023

Version: 1.0 **Date:** 14-Feb-2023 **Company ID:** 20230214-0900f9f6860359f7-1.0-en

Signed by:	Date:	Meaning of Signature:
[redacted]	14-Feb-2023 21:00 UTC	Approver
	13-Feb-2023 13:10 UTC	Approver
	11-Feb-2023 22:23 UTC	Author
	10-Feb-2023 22:25 UTC	Approver - Statistics
	10-Feb-2023 22:22 UTC	Approver

Statistical Analysis Plan Sub-Study 1 of Study M16-067

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Evaluate the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Ulcerative Colitis Who Have Failed Prior Biologic Therapy

Date: 18 November 2020

Version 6.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for Sub-study 1 of Study M16-067 only, A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Evaluate the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Ulcerative Colitis Who Have Failed Prior Biologic Therapy.

M16-067 comprises 2 sub-studies: a Phase 2b dose-ranging induction sub-study (Sub-study 1) and a Phase 3 induction sub-study (Sub-study 2). Sub-study 1 (Phase 2b induction) is to characterize the efficacy, safety, and pharmacokinetics of risankizumab as induction treatment in subjects with moderately to severely active UC and to identify the appropriate induction dose of risankizumab for further evaluation in Sub-study 2 (Phase 3 induction). Sub-study 2 (Phase 3 induction) is to evaluate the efficacy and safety of risankizumab compared to placebo in inducing clinical remission in subjects with moderately to severely active UC.

The analyses of pharmacokinetic and biomarker analyses will not be covered in this SAP.

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 or later (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

This SAP includes changes to analyses described in the protocol amendment 2 dated February 14, 2018. Details are outlined in Section 13.0.

2.0 Study Design and Objectives

2.1 Objectives and Hypotheses

- The objectives of Sub-Study 1 (Phase 2b induction) are to characterize the efficacy, safety, and pharmacokinetics of risankizumab as induction treatment

in subjects with moderately to severely active Ulcerative Colitis (UC) and to identify the appropriate induction dose of risankizumab for further evaluation in Sub-Study 2 (Phase 3 induction)

2.2 Study Design Overview

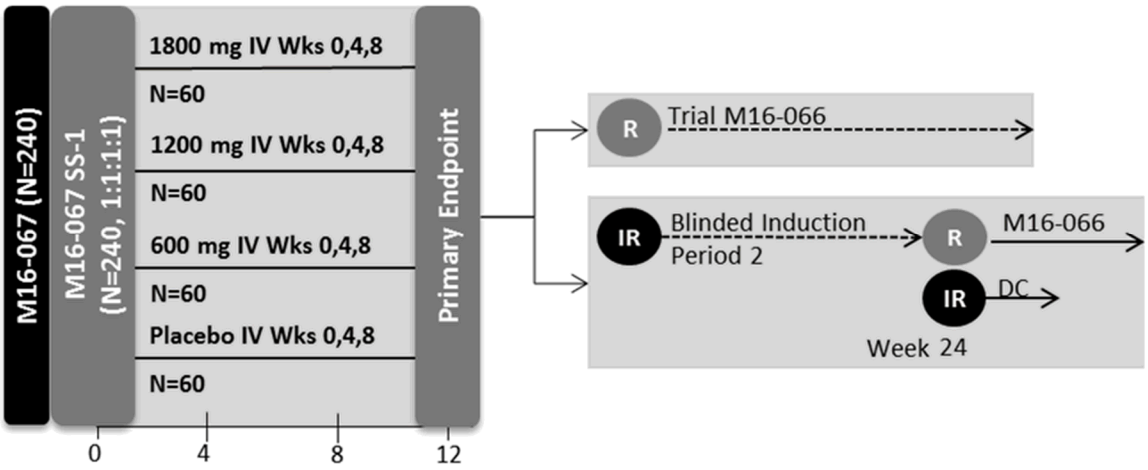
Sub-study 1 is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled study. The study will enroll patients who have had intolerance or inadequate response (IR) to prior biologic therapy (bio-IR).

In Induction Period 1, approximately 240 subjects will be randomized in a 1:1:1:1 ratio as shown in Figure 1. Once all 240 randomized subjects have completed the 12-week Induction Period 1, dose response and exposure response analysis for the key efficacy and safety variables will be performed. During the analysis, Sub-Study 1 will continue to enroll additional subjects in the 1800 mg dosing group, on an open-label basis, to avoid interrupting the study activities during the analysis period and to generate a sufficient number of subjects with clinical response to be enrolled into the maintenance Study M16-066.

At Week 12, subjects who do not achieve clinical response will be randomized by Interactive Response Technologies (IRT) to Induction Period 2 (see schematics in Figure 2), a double-blind, double-dummy 12-week treatment period to evaluate reinduction with risankizumab versus starting maintenance dosing on clinical response status.

For details of the study design, visits and variables collected at each visits, refer to the protocol.

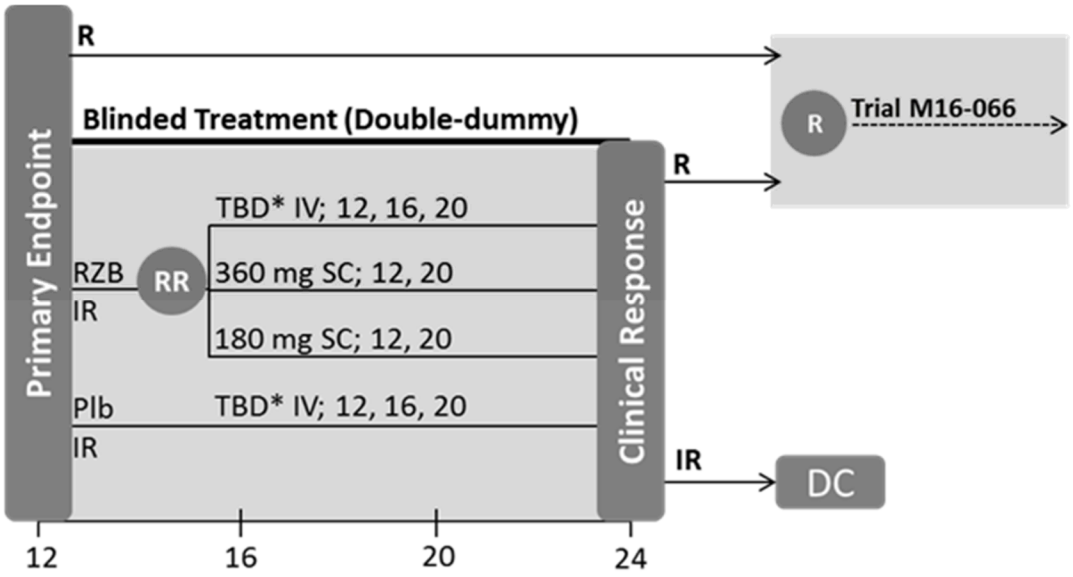
Figure 1. Induction Period 1 of Study M16-067 Sub-Study 1* (Phase 2b)



DC = discontinue; IR = subjects with inadequate clinical response; IV = intravenous; R = subjects with clinical response; SS-1 = Sub-Study 1

* DBL for Study M16-067 Sub-Study 1 occurs after first randomized 240 subjects complete 12 weeks assessment. After 240 subjects have been enrolled and before the dose has been selected for Sub-Study 2, additional subjects will continue to be enrolled into Sub-Study 1, where they will be assigned to the risankizumab 1800 mg IV Wks 0, 4 and 8 dosing group.

Figure 2. Induction Period 2 of Study M16-067 (Sub-Study 1)



DC = discontinue; RZB = risankizumab; IR = subjects with inadequate response; IV = intravenous; Plb = placebo; R = subjects with clinical response; RR = re-randomize; SC = subcutaneous; TBD = to be determined

* Subjects who enter from Study M16-067 Sub-Study 1 will receive risankizumab 1800 mg IV.

2.3 Treatment Assignment and Blinding

Sub-Study 1 (Phase 2b Induction):

Induction Period 1:

Subjects (n = 240) who meet all of the inclusion criteria and none of the exclusion criteria will be randomized into the study in a 1:1:1:1 ratio to one of the following treatment groups:

- Group 1: Risankizumab 1800 mg IV Weeks 0, 4, 8 (n = 60)
- Group 2: Risankizumab 1200 mg IV Weeks 0, 4, 8 (n = 60)
- Group 3: Risankizumab 600 mg IV Weeks 0, 4, 8 (n = 60)

- Group 4: Placebo IV Weeks 0, 4, 8 (n = 60)

The randomization at baseline will be stratified by baseline steroid use (yes vs no) and baseline Adapted Mayo score (≤ 7 vs > 7). Endoscopy and evaluation of clinical response and remission will occur at Week 12.

Induction Period 2:

At Week 12, subjects who do not achieve clinical response will be randomized by Interactive Response Technologies (IRT) to Induction Period 2, a double-blind, double-dummy 12-week treatment period to evaluate reinduction with risankizumab versus starting maintenance dosing on clinical response status.

Subjects who received IV risankizumab induction will be randomized 1:1:1 to:

- Group 1: 1800 mg IV risankizumab Weeks 12, 16, 20
- Group 2: 360 mg SC risankizumab Weeks 12, 20
- Group 3: 180 mg SC risankizumab Weeks 12, 20

Subjects who received IV placebo induction treatment will receive:

- Group 4: 1800 mg IV risankizumab Weeks 12, 16, 20

Subjects randomized in Groups 1 and 4 will receive placebo SC and subjects randomized in Groups 2 and 3 will received placebo IV, in order to keep the blind. The IV risankizumab dose or matching IV placebo will be given at Weeks 12, 16, and 20. The SC risankizumab dose or matching SC placebo will be given at Weeks 12, and 20.

Dose Selection Analysis:

During this analysis, Sub-Study 1 will continue to enroll additional subjects in the 1800 mg dosing group, on an open-label basis, to avoid interrupting the study activities

during the analysis period and to generate a sufficient number of subjects with clinical response to be enrolled into the maintenance Study M16-066.

2.4 Sample Size Determination

Sub-Study 1 (Phase 2b):

For Sub-Study 1 (Phase 2b portion of the study), approximately 240 subjects in the Bio-IR population will be equally randomized using a 1:1:1:1 ratio to three risankizumab treatment groups (600 mg, 1200 mg and 1800 mg IV Q4W) and the placebo group. The sample size for this study is based on the expected proportion of subjects who achieve clinical remission per Adapted Mayo Score at Week 12. Assuming clinical remission rate of 7% in the placebo arm and maximum of 25% in at least one of the risankizumab treatment groups at Week 12, a sample size of 60 subjects per treatment group is sufficient to test for the presence of a dose response signal, to select the best dose response model for the observed data out of a pre-specified set of candidate models, and to estimate target doses of interest (e.g., MED) via modeling using MCP-Mod (Multiple comparison procedure and modeling) approach.[1,2] The assumptions for the rates of clinical remission were estimated based on the meta-analysis of Phase 3 induction studies of the marketed drugs for patient population who have had intolerance or inadequate response to prior biologic therapy. This approach provides an average power of approximately 87% to detect a dose effect at 5% level of significance (one-sided) with the linear, E_{max} (ED_{50} = 600 per dosing visit), exponential (δ = 600 per dosing visit), logistic (ED_{50} = 600 per dosing visit and δ = 160) and sigE_{max} (ED_{50} = 600 per dosing visit and h = 3) models pre-specified as likely candidates to characterize the dose response for risankizumab for the primary endpoint of clinical remission at Week 12 per Adapted Mayo Score.

A minimum of 240 subjects will be enrolled into Study M16-067 Sub-Study 1 for dose selection analysis. The additional subjects enrolled during the dose selection analysis period will not be part of the dose selection analysis, but will be evaluated separately as exploratory in the final CSR.

3.0 Endpoints

Endpoint definitions (Sub-Study 1):

- **Clinical Remission per Adapted Mayo:** stool frequency subscore (SFS) ≤ 1, and not greater than baseline, rectal bleeding subscore (RBS) = 0, and endoscopic subscore ≤ 1
- **Clinical Response per Adapted Mayo:** decrease from Baseline ≥ 2 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1
- **Clinical Response per Partial Adapted Mayo (without endoscopy):** decrease from Baseline ≥ 1 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1
- **Clinical Remission per Full Mayo:** Full Mayo score ≤ 2 with no subscore > 1
- **Endoscopic Improvement:** endoscopy subscore of 0 or 1
- **Endoscopic Remission:** endoscopic subscore = 0
- **Histologic Remission:** Geboes score < 2.0
- **Mucosal Healing:** endoscopic and histologic remission

Note: Evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity will confer an endoscopic subscore of 2.

3.1 Primary Endpoint(s)

The primary endpoint for Phase 2b induction (Sub-Study 1) is the proportion of subjects who achieve clinical remission per Adapted Mayo score at Week 12.

3.2 Secondary Endpoint(s)

The secondary endpoints for Sub-Study 1 are:

Ranked Secondary Endpoints:

1. The achievement of endoscopic improvement at Week 12
2. The achievement of clinical remission per Full Mayo score at Week 12 in subjects with a Full Mayo score of 6 to 12 at Baseline
3. The achievement of clinical response per Adapted Mayo score at Week 12
4. The achievement of clinical response per Partial Adapted Mayo score at Week 4
5. The achievement of endoscopic remission at Week 12
6. Occurrence of hospitalizations through Week 12
7. The achievement of mucosal healing at Week 12
8. Change from Baseline in UC-Symptom Questionnaire (UC-SQ) at Week 12
9. Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) at Week 12
10. Change from Baseline in Short Form-36 at Week 12
11. Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) at Week 12
12. UC-related surgeries through Week 12

<u>Non-Ranked Secondary Efficacy Endpoints:</u>

- The achievement of SFS = 0, RBS = 0, and endoscopic subscore = 0 at Week 12
- The achievement of SFS ≤ 1 over time
- The achievement of RBS = 0 over time
- Change from Baseline in Partial Adapted Mayo score over time
- Change from Baseline in Full Mayo score at Week 12
- Change from Baseline in SFS over time
- Change from Baseline in RBS over time
- Change from Baseline in hs-CRP over time

- Change from Baseline in FCP over time
- Change from Baseline in Ulcerative Colitis Endoscopic Index of Severity (UCEIS) at Week 12
- The achievement of histologic remission at Week 12
- Change from Baseline in European Quality of Life 5 Dimensions (EQ-5D-5L) over time
- Change in Work Productivity and Impairment Questionnaire – UC (WPAI-UC) over time
- Time to clinical response per partial adapted Mayo score
- Change from baseline in Patient Global Impression of Severity (PGIS) over time
- Patient Global Impression of Change (PGIC) over time
- The achievement of clinical remission per Adapted Mayo over time
- The achievement of endoscopic improvement over time
- The achievement of endoscopic remission over time
- The achievement of no bowel urgency at Week 12
- The achievement of no abdominal pain at Week 12
- Achieving response in IBDQ bowel symptom domain (increase of IBDQ bowel symptom domain score ≥ 6 from baseline) at Week 12
- Change from Baseline in subject-reported stool frequency (absolute values)
- Change from Baseline in percentage of colonic segments with an endoscopic subscore ≤ 1 (local read)

3.3 Other Efficacy Endpoints

The primary and/or secondary efficacy endpoints are listed in Section 3.1 and/or Section 3.2, respectively. All the efficacy endpoints listed in Section 3.1 and Section 3.2 during Induction Period 2 are exploratory endpoints.

3.4 Safety Endpoint(s)

Adverse events, vital signs, physical examination results, and clinical laboratory data will be assessed throughout the study.

4.0 Analysis Populations

The following population sets will be used for the analyses.

Intent-to-Treat Analysis Set

Sub-Study 1 – Induction Period 1:

The Intent-to-Treat (ITT) Analysis Set for Induction Period 1 in Sub-Study 1 includes all randomized subjects who received at least one dose of study drug during Sub-Study 1 (denoted as ITT1A) at the time of dose-selection analysis. The set of all the additional subjects who received at least one dose of risankizumab 1800 mg IV treatment group after 240 subjects were randomized during the dose-selection period is denoted as ITT1B. The ITT for Induction Period 1 in Sub-Study 1 will be denoted ITT1 and will be the combination of ITT1A and ITT1B.

Sub-Study 1 Induction Period 2:

Subjects who received at least one dose of risankizumab during Induction Period 2 in Sub-Study 1 (denoted as ITT1_P2) will be analyzed separately for exploratory purposes.

Safety Analysis Set

For the safety analysis set in each sub-study, subjects will be analyzed in a treatment group based on the treatment actually received, not randomized. The safety analysis in each sub-study will be based on the corresponding safety analysis set.

Sub-Study 1 – Induction Period 1

The Safety Analysis Set for Induction Period 1 in Sub-Study 1 includes all subjects who received at least one dose of study drug during Induction Period 1 in Sub-Study 1 (denoted as SAS1A) at the time of dose-selection analysis. The set of all the additional subjects who received at least one dose of risankizumab 1800 mg IV treatment group after 240 subjects were randomized during the dose-selection period is denoted as SAS1B. The Safety Analysis Set for Induction Period 1 in Sub-Study 1 in Period 1 will be denoted SAS1 and will be the combination of SAS1A and SAS1B.

Sub-Study 1 Induction Period 2:

Subjects who received at least one dose of risankizumab during the Induction Period 2 after Week 12 in Sub-Study 1 (denoted as SAS1_P2) will be analyzed separately for exploratory purposes.

5.0 Subject Disposition

The number of subjects will be tabulated by country, investigator site and overall for the following sets: Induction Period 1 ITT1A, ITT1B and Induction Period 2 ITT1_P2 populations, Safety populations, subjects who completed study by period, and subjects who prematurely discontinued for study drug or study by period, for each treatment group and overall, as appropriate.

In addition, the number and percentage of subjects who discontinued study drug or study will be summarized by reason for each treatment group and overall. All reasons and primary reasons for discontinuation of study drug will be summarized as recorded on the eCRF by the following categories:

- Adverse event (AE)
- Lost to follow-up
- Withdraw consent
- Lack of efficacy

- COVID-19 infection
- COVID-19 logistical restrictions
- Other

Subjects may have more than one reason for discontinuing study drug, but they will be counted once for the total number of discontinuations. Subjects have only one primary reason for discontinuing study drug or discontinuing from the study.

6.0 Study Drug Duration and Compliance

Induction Period:

For the safety populations SAS1A and SAS1B, the duration of exposure to study drug will be summarized for each treatment group in the induction Period 1.

- Duration of exposure in the induction Period 1:
  - If the subjects went to Study M16-066 after the induction Period 1:
    - Duration of exposure = min (the first study drug dose date in Study M16-066 – the first study drug dose date in induction Period 1, the last study drug dose date in the induction period – the first study drug dose date in the induction period + 28 days),
  - If the subject went to the induction Period 2 after induction Period 1:
    - Duration of exposure = min (the first study drug dose date in the induction Period 2 – the first study drug dose date in induction Period 1, the last study drug dose date in induction Period 1 – the first study drug dose date in induction Period 1 + 28 days),
  - Otherwise:
    - Duration of exposure = the last study drug dose date in induction Period 1 – the first study drug dose date in induction Period 1 + 28 days,

Where study drug dose date refers to recorded dates of injections of study drug.

For each treatment group and total in the induction period, the duration of exposure will be summarized by the number of subjects treated, as well as the mean, standard deviation, median, minimum and maximum values. In addition, the number and percentage of subjects exposed to study drug will be summarized for the following exclusive duration intervals:

- 1 – 28 days
- 29 – 56 days
- 57 – 84 days
- 85 – 112 days
- > 112 days

Induction Period 2:

For the safety population SAS1_P2, the duration of exposure to study drug will be summarized for each treatment group in induction Period 2.

- Duration of exposure in induction Period 2:
  - If the subjects went to Study M16-066 after induction Period 2:
    - Duration of exposure = min (the first study drug dose date in Study M16-066 – the first study drug dose date in induction Period 2, the last study drug dose date in induction Period 2 – the first study drug dose date in induction Period 2 + 28 days),
  - Otherwise:
    - Duration of exposure = the last study drug dose date in induction Period 2 – the first study drug dose date in induction Period 2 + 28 days,

Where study drug dose date refers to recorded dates of injections of study drug.

For each treatment group and total in induction Period 2, the duration of exposure will be summarized by the number of subjects treated, as well as the mean, standard deviation,

median, minimum and maximum values. In addition, the number and percentage of subjects exposed to study drug will be summarized for the following exclusive duration intervals:

- 1 – 28 days
- 29 – 56 days
- 57 – 84 days
- 85 – 112 days
- > 112 days

Treatment compliance is calculated as follows:

$$TC = \frac{Total\ number\ of\ injections\ and/or\ infusions\ received}{Total\ number\ of\ injections\ and/or\ infustions\ planned} \times 100\%$$

Number of subjects receiving study drug and dose will be summarized for both periods in Sub-Study 1 and 2 based on safety analysis set using descriptive statistics. Subjects with missing data for the number of injections returned will be excluded from the summary.

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

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the ITT1A and ITT1B populations overall and by treatment group. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

The following demographic, as measured at baseline of the study, will be summarized.

Continuous variables:

- Age (years)
- Body weight (kg)
- Body weight – Female (kg)
- Body weight – Male (kg)
- Height (cm)
- Height – Female (cm)
- Height – Male (cm)
- Body Mass Index (kg/m^2)

Categorical variables:

- Sex (male, female)
- Age (< 18, 18 - < 40, 40 - < 65, ≥ 65)
- Race (American Indian/Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple)
- Race (White, Non-White)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Tobacco use (Never, current, former, unknown)
- Alcohol use (Never, current, former, unknown)
- Body Mass Index (kg/m^2):
    - Underweight [< 18.5 kg/m2]
    - Normal [≥ 18.5 and < 25 kg/m2]
    - Overweight [≥ 25 and < 30 kg/m2]
    - Obese [≥ 30 kg/m2]

The following baseline characteristics, as measured at baseline of the study, will be summarized.

Continuous variables:

- Blood Pressure (systolic/diastolic) (mmHg)
- Pulse (bpm)
- Respiratory Rate (RPM)
- Temperature (°C)
- IBDQ total score and its components
- Full Mayo score and its components (stool frequency, rectal bleeding, PGA, and endoscopy subscores)
- Partial Mayo score
- Adapted Mayo score
- hs-CRP (mg/L)
- Fecal Calprotectin (mg/kg)
- Albumin (g/L)
- Short Form 36 Health Survey (SF-36) and its components
- European Quality of Life 5 Dimensions 5 Levels (EQ-5D-5L)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
- WPAI and its components
- Ulcerative Colitis Symptoms Questionnaire (UC-SQ)
- Disease duration

Categorical variables:

- Baseline corticosteroid use (yes, no)
- Baseline immunosuppressant use (yes, no)
- Baseline aminosalicylates use (yes, no)
- Baseline anti TNF use (yes, no)
- Baseline biologics use (yes, no)
- Baseline hs-CRP (≤ 5 mg/L, > 5 mg/L)
- Disease duration (≤ 3 years, > 3 years)

- Disease extent (left-sided, extensive/pancolitis, limited to rectum)
- Region (US, ex-US)

In addition, clinical tests including TB test and electrocardiogram assessment at screening will be summarized.

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 and by treatment group for the Induction Period 1 ITT1A, ITT1B and the Induction Period 2 ITT1_P2 Populations. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

7.3 Prior and Concomitant Medications

Prior and concomitant medications including UC specific medications (corticosteroids, aminosalicylates, immunosuppressant agents, and UC-related antibiotics) that the subject has received within 90 days of baseline 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. This includes medications with a start date before the first study drug administration date, regardless of the end date of these medications. Medications taken on the day of the first dose of study drug are not counted as prior medications.

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 after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug plus 140 days. The number and percentage of subjects

taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

8.0 Efficacy Analyses

8.1 General Considerations

The primary and secondary efficacy endpoints will be analyzed based on ITT1A in Induction Period 1 of Sub-Study 1 as the primary analysis.

The primary and ranked secondary efficacy endpoints will be analyzed based on ITT1B in Induction Period 1 of Sub-study 1 as the exploratory analysis.

All analyses for the efficacy endpoints in Induction Period 2 will also be performed based on ITT1_P2 for Sub-Study 1 for exploratory purpose.

For all efficacy endpoints, the descriptive statistics will be provided by treatment group for each induction period in each sub-study. The statistics include number of observations, mean, standard deviation, minimum, median, and maximum for continuous variables; and number and percentage of subjects for categorical variables.

8.2 Handling of Missing Data

UC-related corticosteroids Censoring

For both Periods 1 and 2, the following subjects will be censored for efficacy assessments from that point through the end of the study.

- subjects not on UC-related corticosteroids (systemic or locally acting corticosteroids for UC) at Baseline who then initiated during the study or
- subjects on UC-related corticosteroids who have dosages increased to greater than the dose taken at Baseline.

I.e., these subjects will be considered as 'Not Achieved' for binary endpoints (Y/N) and any non-missing continuous assessments after censoring will not be used in the analysis

For composite endpoint, censoring will be applied on each component before calculating the composite endpoint. If any component is censored, the composite endpoint will be considered as censored. These subjects will continue to be evaluated in the safety population. In addition, hospitalizations and UC-related surgeries will not be censored.

Handling of Missing Data

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

- Observed Cases (OC): The OC 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 OC analysis for that visit. All the other imputations will be performed after OC.
- Non-Responder Imputation (NRI): The NRI approach is used for binary efficacy variables. These variables can take values of 'Achieved' or 'Not Achieved' or may be. According to the NRI approach, all missing values will be considered as 'Not Achieved.'
- Last Observation Carried Forward (LOCF): The LOCF analyses will use the completed evaluation from the previous visit for efficacy measures assessed to impute missing data at later visits. Baseline and Pre-Baseline value will not be used for the imputation. If there are no non-missing values after the Baseline, then the LOCF value also will be missing.
- Mixed-Effect Model Repeat Measurement (MMRM): The repeated measures analysis will be conducted using a mixed model including OC at all visits. The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, main stratification factors at randomization, and the continuous fixed covariates of baseline measurement. 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).
- Hybrid Multiple Imputation Method. Primary endpoint of clinical remission will be analyzed using hybrid multiple imputation (MI) method. Subjects who discontinue study prior to Week 12 due to lack of efficacy or AEs will be considered as "not achieved" for clinical remission. Subjects who discontinue

for other reasons will be categorized according to multiple imputations. MI approach will be used as a sensitivity analysis for the primary endpoint. For the primary endpoint, 20 'complete' datasets will be generated using SAS PROC MI. The seed will be 12345. The imputed post-baseline measurements will be rounded to the same precision as the observed data before the determination of responder status. Using the Cochran-Mantel-Haenszel (CMH) model adjusted by main stratification factors, the imputed endpoints will be analyzed using each of the 20 datasets. SAS PROC MIANALYZE will be used to generate the final inferences of the risk difference between treatment groups.

8.3 Primary Efficacy Endpoint(s) and Analyses

8.3.1 Primary Efficacy Endpoint(s)

The primary endpoint of this study is the proportion of subjects who achieve clinical remission per Adapted Mayo score (defined as stool frequency subscore ≤ 1 and not greater than baseline, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1) at Week 12.

8.3.2 Handling of Missing Data for the Primary Efficacy Endpoint(s)

Subjects with missing primary endpoint data at Week 12 will be classified as "not achieved" (non-responder imputation [NRI] method) for the primary analysis.

8.3.3 Primary Efficacy Analysis

For Sub-Study 1 – Induction Period 1:

The dose-response relationships among the three risankizumab dose groups (600 mg, 1200 mg and 1800 mg) and placebo group will be characterized for the primary endpoint at Week 12 using Multiple Comparison Procedure - Modeling (MCP-Mod)[1,2] approach based on ITT1A population. The response based on the primary analysis approach NRI will be used, and ADDPLAN DF software will be used to perform the MCP-Mod analyses.

A set of 5 pre-specified standardized candidate dose-response models (including log-linear, E_{max}, exponential, logistic and sigE_{max}) will be utilized to examine the dose-response relationship. A statistically significant dose response relationship will be declared if at least one model is identified by the MCP-Mod method to be statistically significant at $\alpha = 0.05$ (one-sided). The fitted dose response curves will be presented graphically for all statistically significant models along with confidence bands. The minimum effective dose (MED) will be identified for each statistically significant model based on the pre-specified clinical meaningful target. The weighted MED across all significant models will be calculated, with weight being inverse of model AIC.

The pairwise comparison between the treatment groups will also be performed using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline corticosteroid use and baseline Adapted Mayo score (≤ 7 and > 7) with one-sided alpha level of 0.05. A two-sided 90% confidence interval for the difference between treatment groups and placebo will be constructed. There will be no multiplicity adjustment for the pairwise comparison. The goal of the CMH test is to provide an estimation of the effect size for each dose to inform the dose selection for Phase 3, not for statistical inference purposes.

Descriptive statistics based on ITT1B will be provided as an exploratory analysis. NRI will be used as imputation method.

8.3.4 Additional Analyses of the Primary Efficacy Endpoint(s)

The following sensitivity analyses for the primary endpoint of clinical remission will be conducted:

- The primary analysis will be repeated using a hybrid multiple imputation method. Subjects who discontinue study drug prior to Week 12 due to lack of efficacy or adverse events will be considered as "not achieved" for the clinical remission. Subjects who discontinue for other reasons will be categorized according to multiple imputations.
- An analysis of observed cases, which excludes those subjects with missing data at scheduled assessment visits.

8.4 Secondary Efficacy Analyses

Sub-Study 1 – Induction Period 1:

For Induction Period 1 in Sub-Study 1, the ranked secondary and non-ranked secondary efficacy variables listed in Section 3.2 will be analyzed by treatment group for ITT1A as the primary analysis at the nominal α level of 0.05 (one-sided).

Continuous secondary efficacy variables will be analyzed using a Mixed-Effect Model Repeated Measures (MMRM) method. It will be used for primary inference purpose. Analysis of Covariance (ANCOVA) model using LOCF imputation method will be applied as sensitivity analysis.

Categorical secondary efficacy variables will be analyzed using the CMH test controlling for stratification variables. NRI imputation will be used for primary inference purpose and observed case analyses will be used for sensitivity analysis.

Additional exploratory analysis based on ITT1B will be provided for all ranked secondary efficacy variables: continuous secondary efficacy variables will be analyzed using MMRM method and descriptive statistics will be provided for categorical secondary efficacy variables with NRI imputation method.

8.5 Additional Efficacy Analyses

The efficacy analysis for subjects who were randomized and received at least one dose of risankizumab during the Induction Period 1 in Sub-study 1 (both ITT1A and ITT1B populations) and the Induction Period 2 in Sub-Study 1 (ITT1_P2 population) will be performed for exploratory purpose at the nominal α level of 0.05 (two-sided).

Definition of Time to Event (Clinical Response Per Partial Adapted Mayo Score)

Time to event is defined as number of days from the date of the first dosing to the date of the first occurrence of an event. It is calculated as (date of first occurrence of Event – date of the first dosing + 1). Subjects who discontinue from study prior to experiencing the

event are censored at the time of discontinuation. Subjects who are not experiencing the event are censored at the date of last non-missing measurement of partial adapted Mayo score. Pairwise comparison between each treatment group and placebo will be performed by log-rank test and Cox proportional hazards regression analysis including treatment and baseline stratification factors as covariates.

Time to event analysis will be based on OC data.

8.6 Efficacy Subgroup Analyses

Subgroup analysis for the primary endpoint, clinical remission per Adapted Mayo Score at Week 12, will be conducted by the subgroups specified listed below for ITT1A population. The difference in the primary efficacy endpoint between the treatment groups in each subgroup will be assessed using a Chi-squared test or Fisher's exact test if ≥ 20% of the cells have expected cell count < 5. Non-responder imputation (NRI) method, where subjects with missing data at scheduled assessment visits will be considered as "not achieved" for the clinical remission, will be used for primary analysis.

- Sex (male, female)
- Age (≤ median, > median)
- Race (white, non-white)
- Baseline corticosteroid use (yes, no)
- Baseline immunosuppressant use (yes, no)
- Baseline Adapted Mayo Score (≤ 7, > 7)
- Baseline Partial Adapted Mayo Score (≤ 4, > 4)
- Prior exposure to biologic therapy (1, > 1)
- Baseline weight (≤ median, > median)
- Presence of pancolitis at Baseline (yes, no)
- Disease duration at Baseline (≤ median, > median)
- Baseline hs-CRP (≤ 3 mg/L, > 3 mg/L)
- Baseline Albumin (≤ median, > median)

- Baseline Calprotectin (≤ median, > median)
- Region (US, ex-US)

9.0 Safety Analyses

9.1 General Considerations

Safety analysis in each sub-study will be carried out using the corresponding safety analysis set as defined in Section 4.0. Safety analyses performed on the SAS1A for Sub-Study 1 are considered as primary safety analysis in Sub-study 1. The separate safety analysis for SAS1B, SAS1_P2 will be performed for exploratory purpose. Adverse events (AEs), laboratory data and vital signs are the primary safety parameters and will be analyzed in each sub study.

The following summary statistics will be presented for subjects who have both baseline and post-baseline values for laboratory parameters and vital signs: the mean value at Baseline and at each respective protocol specified visit, and the mean, standard deviation and median for changes from Baseline. Categorical data will be summarized using frequencies and percentages. The number of non-missing values will be given. Missing safety data will not be imputed.

A subject's actual treatment will be determined by the most frequent dose regimen received.

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. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs

multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

9.2.1 Treatment-Emergent Adverse Events

Sub-Study 1 – Induction Period 1:

Treatment emergent AEs (TEAEs) for Induction Period 1 in Sub-Study 1 are defined as events that begin or worsen either on or after the first dose of the study drug in Induction Period 1 and within 140 days after the last dose administration of the study drug for subjects who do not participate in the maintenance Study M16-066, or until the first dose of study drug in the maintenance Study M16-066 if the subject is enrolled into Study M16-066, or until the first dose of study drug in Induction Period 2 if the subject is enrolled into Induction Period 2.

Sub-Study 1 – Induction Period 2:

TEAEs for Induction Period 2 in Sub-Study 1 are defined as events that begin or worsen either on or after the first dose of the study drug in Induction Period 2 and within 140 days after the last dose administration of the study drug for subjects who do not participate in the maintenance Study M16-066 or until first dose of study drug in the maintenance Study M16-066 if the subject is enrolled into Study M16-066.

Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless the study drug start time and the adverse event start time are collected and the adverse event start time is prior to the study drug start time. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

All analyses of AEs will be based on the number of patients with AEs (not the number of AEs). Treatment group differences in the overall incidence of TEAEs will be assessed with Fisher's exact test for each preferred term.

Treatment labels for the safety analyses in Sub-Study 1 will be assigned accounting for the two induction periods:

a. Induction Period 1 will consist of four treatment labels: Placebo, Risankizumab 1800 mg IV, Risankizumab 1200 mg IV, and Risankizumab 600 mg IV.
b. Induction Period 2 will consist of three treatment labels: Risankizumab 1800 mg IV, Risankizumab 360 mg SC, Risankizumab 180 mg SC.

9.2.2 Adverse Event Overview

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

- Any treatment-emergent AE
- Any treatment-emergent AE related to study drug according to the investigator
- Any severe treatment-emergent AE
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to discontinuation of study drug
- Any treatment-emergent AE leading to death
- Any treatment-emergent adverse event of safety interest.
- Any COVID-19 related TEAE
- All deaths
- Any COVID-19 related deaths

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

Treatment-emergent adverse events, including COVID-19 related TEAE, 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 SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific

adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency for the total active group.

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.

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

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

9.2.6 Adverse Events of Safety Interest

Adverse events of safety interest will be summarized by SOC and PT and will be based on standardized or company MedDRA queries (SMQs or CMQs), or based on adjudication results. Adverse events of special interest and detailed information about the search criteria are provided in Appendix B.

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 (e.g., hematology and clinical chemistry) will be summarized.

Each laboratory variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for 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 within each treatment group and difference between treatment groups (each active vs. placebo).

Changes in laboratory parameters will be tabulated using shift tables either by NCI CTC criteria or categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline either to the worse value (based on NCI CTC criteria) during treatment or 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

- ≥ 20.0 × ULN

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 4 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 of > 3 × ULN or AST of > 3 × ULN,
- associated with an increase in bilirubin ≥ 2 × ULN,

9.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, pulse rate, and body temperature will be summarized.

Each vital sign variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group and difference between treatment groups (active vs. placebo).

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

Not applicable.

9.6 Other Safety Analyses

Not applicable.

10.0 Other Analyses

Not applicable.

11.0 Interim Analyses

The first interim lock will take place when approximately 240 subjects in Sub-Study 1 have completed the Week 12 visit (including those who discontinue prior to the Week 12 visit).

The second interim lock will take place when all the subjects in Sub-Study 1 have completed the Week 24 visit (including those who discontinue prior to the Week 12 visit).

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 unblinded 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.

12.0 Overall Type-I Error Control

Sub-Study 1 (Phase 2b) – Induction Period 1:

Sub-Study 1 is the Phase 2b randomized, placebo-controlled dose ranging study. The primary, the ranked secondary and non-ranked secondary efficacy variables will be analyzed by treatment group for the Intent-to-Treat (ITT) analysis set for Sub-Study 1, defined in Section 4.0, at the nominal α level of 0.05 (one-sided). No multiplicity adjustment will be performed for the Phase 2b dose ranging study.

No multiplicity adjustment will be applied to non-ranked secondary efficacy endpoints listed in Section 3.2. The analysis for non-ranked secondary efficacy endpoints will be performed at the nominal α level of 0.05 (two-sided).

Sub-Study 1– Induction Period 2:

For Induction Period 2, no multiplicity adjustment will be performed for all efficacy endpoints listed in Section 3.3. The analysis for all efficacy endpoints will be performed at the nominal α level of 0.05 (two-sided) for exploratory purpose.

13.0 Version History

Table 1. SAP Version History Summary

Version	Date	Summary
1.0	10 May 2017	Original version
2.0	13 Nov 2017	The definition of clinical remission per adapted mayo score has expanded to include 'stool frequency subscore (SFS) ≤ 1 and not greater than baseline.' Efficacy endpoints have been updated to reflect changes in the protocol. CTCAE is now used for assessing AE severity.
3.0	19 Feb 2018	MCP-Mod section updated to address regulatory feedback. The 105-day follow up period has been updated to 140-day follow up period to reflect changes in protocol. Analysis methods for secondary continuous efficacy endpoints have been updated in Section 6.3. The placebo clinical remission rate was update from 10% to 7% to reflect the results of a more recent meta-analysis. For continuous secondary efficacy endpoints, MMRM method will be used for primary inference purpose and ANCOVA model using LOCF imputation method will be applied as sensitivity analysis. The Hochberg procedure for multiplicity adjustment has been changed to Holm procedure. The search criteria for Serious Infections in the Summary of Adverse Events of Safety Interest table has been updated to reflect a change in convention.
4.0	05 Mar 2019	Figure 4 in Section 4.6 was updated to reflect that the final group of endpoints will utilize the Holm procedure. Section 7.3 was updated per changes to the PSSAP.
5.0	25 Nov 2019	Section of subject disposition is added. Section of study drug duration and compliance is added. Section of demographics, baseline characteristics is added. More details on subgroups are provided in section of efficacy subgroup analyses. AESI and PCS criteria updated per PSSAP.
6.0	16 Nov 2020	Added Covid-19 related safety summary. Added BMI categorical summary. Updated Hy's Lawu, AESI and PCS criteria per PSSAP. Updated UC-related corticosteroids Censoring per immunology convention. Removing analyses on Sub-study 2 from this SAP since it will be described in a standalone SAP.

14.0 References

1. Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat. 2006;16(5):639-56.

2. Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics. 2005;61(3):738-48.
3. Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28(4):586-604.
4. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat. 1979:65-70.

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 Adverse Events of Safety Interest

Adverse Events of Safety Interest (AESI) will be identified using the following search criteria:

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Adjudicated CV Events	MACE	Adjudicated terms will be identified using CECAT and CETERM from the CE SDTM dataset.	Display underlined terms defined by the following adjudicated terms: • CV Death which includes adjudicated results of: Sudden Cardiac death, Death due to Acute MI, Death due to Heart Failure, Death due to CV Procedures, Death due to CV Hemorrhage, Death due to Other CV Causes (specify), Death due to stroke • Non-fatal Myocardial infarction • Non-fatal Stroke	Y
	Extended MACE	Adjudicated terms will be identified (for MACE +) using CECAT and CETERM from the CE SDTM dataset.	Display underlined terms from MACE and underlined terms below: • Hospitalization for Unstable Angina • Coronary Revascularization Procedures	N

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Serious Infections, TB, and Opportunistic Infections (including Herpes Zoster)	Serious Infections	Serious PTs of the SOC Infections and Infestations	PTs	Y
	Active TB	Active Tuberculosis CMQ (code 80000188)	PTs	Y
	Opportunistic Infections Excluding Tuberculosis and Herpes Zoster	Opportunistic infections CMQ excluding Tuberculosis and Herpes Zoster (code 800000189)	PTs	Y
	Herpes Zoster	Herpes zoster CMQ (code 80000175)	PTs	N
Malignancies	Malignant Tumours	Narrow Malignant tumours (SMQ 20000194)	Malignant Tumours	Y
	Non-Melanoma Skin Cancer (NMSC)	Broad Skin malignant tumours (SMQ 20000204) excluding terms identified by the Melanoma CMQ (code 80000119)	PTs	N
	Malignancies excluding NMSC	'Malignancies excluding NMSC' is identified by the 'Malignant Tumours' search excluding terms identified by the 'Non-melanoma skin cancer' (NMSC) search.	PTs	Y

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	Serious Anaphylactic Reactions	Narrow Serious AEs in the Anaphylactic Reaction SMQ (SMQ 20000021)	PTs	Y
	Adjudicated Anaphylactic Reaction	Adjudicated terms will be identified using SDTM data (e.g., CE and PR domains).	PTs	Y
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
Injection site reactions		Injection site reaction CMQ (code 80000019)	PTs	N

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 Significant Current (Version 4.03) CTCAE Grade 3 or Greater
Hematology Variables	**Units**	**Very Low**
Hemoglobin	g/L	< 80.0
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 value must be more extreme than the baseline value (higher CTC grade than baseline) to be considered a potentially clinically important finding.

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

		Definition of Potentially Clinically Significant Current (Version 4.03) 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(> 3.0 × BL)
Sodium	mmol/L	< 130	> 155
Potassium	mmol/L	< 3.0	> 6.0
Calcium	mmol/L	< 1.75	> 3.1
Total Cholesterol	mmol/L		> 10.34
GGT			> 5.0 × ULN

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

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

Vital Sign	**Category**	**Criteria for Potential Clinically Significant Vital Signs**
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

Appendix D. Common Toxicity Criteria (CTC) Grade for Laboratory Data

Test	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry Variables				
SGPT/ALT increased	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
SGOT/AST increased	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
GGT increased	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
ALP increased	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
TBL increased	> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 10.0 × ULN	> 10.0 × ULN
Creatinine* increased	> 1 – 1.5 × baseline (BL); > ULN – 1.5 × ULN	> 1.5 – 3.0 × BL; > 1.5 – 3.0 × ULN	> 3.0 × BL; > 3.0 – 6.0 × ULN	> 6.0 × ULN
CPK increased	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 10.0 × ULN	> 10.0 × ULN
Total Cholesterol increased	> ULN - 7.75	> 7.75 - 10.34	> 10.34 - 12.92	> 12.92
Albumin decreased	< LLN - 30	< 30 - 20	< 20	N/A
Triglycerides increased	1.71 - 3.42	> 3.42 - 5.7	> 5.7 - 11.4	> 11.4
Glucose	< LLN - 3.0 or > ULN - 8.9	< 3.0 - 2.2 or > 8.9 - 13.9	< 2.2 - 1.7 or > 13.9 - 27.8	< 1.7 or > 27.8
Sodium	< LLN – 130 or > ULN - 150	> 150 – 155	< 130 – 120 or > 155 - 160	< 120 or > 160
Potassium	< LLN - 3.0 or > ULN - 5.5	< LLN - 3.0 or > 5.5 - 6.0	< 3.0 - 2.5 or > 6.0 - 7.0	< 2.5 or > 7.0
Calcium	< LLN - 2.0 or > ULN - 2.9	< 2.0 - 1.75 or > 2.9 - 3.1	< 1.75 - 1.5 or > 3.1 - 3.4	< 1.5 or > 3.4
Hematology Variables				
Hemoglobin decreased	< LLN – 100.0 g/L	< 100.0 – 80.0 g/L	< 80.0 – 65.0 g/L	< 65.0 g/L
Neutrophil count decreased	< LLN – 1.5 × 10^9/L	< 1.5 – 1.0 × 10^9/L	< 1.0 – 0.5 × 10^9/L	< 0.5 × 10^9/L
WBC decreased	< LLN – 3.0 × 10^9/L	< 3.0 – 2.0 × 10^9/L	< 2.0 – 1.0 × 10^9/L	< 1.0 × 10^9/L
Lymphocyte count decreased	< LLN – 0.8 × 10^9/L	< 0.8 – 0.5 × 10^9/L	< 0.5 – 0.2 × 10^9/L	< 0.2 × 10^9/L
Platelets count decreased	< LLN - 75.0 × 10^9/L	< 75.0 - 50.0 × 10^9/L	< 50.0 - 25.0 × 10^9/L	< 25.0 × 10^9/L

* If the calculation based on BL results in a different grade than the calculation based on ULN, use the higher grade.

Document Approval

Study M16067 - Statistical Analysis Plan Version 6 - 18Nov2020 (E3 16.1.9)

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