Statistical Analysis Plan for Study M21-446

A Single-Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABBV-668 in Subjects with Moderate to Severe Ulcerative Colitis

Version 3.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for ABBV-668 Study M21-446, a single-arm, open-label study to evaluate the efficacy and safety of ABBV-668 in subjects with moderate to severe ulcerative colitis (UC).

Study M21-446 examines the efficacy and safety of ABBV-668 CCI mg orally twice a day (BID) as treatment in adult subjects with moderately to severely active UC.

The analyses of pharmacokinetic endpoints and biomarker research 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.

2.0 Study Objectives and Design

2.1 Study Objectives

The primary efficacy objective of the study is to demonstrate greater proportion of subjects achieving endoscopic improvement with ABBV-668 treatment in the Intent-to-Treat (ITT) Population, which consists of all enrolled subjects with at least one dose of study treatment, when compared with historical placebo group.

The hypothesis corresponding to the primary efficacy objective is that the proportion of subjects achieving endoscopic improvement with ABBV-668 treatment at Week 8 is greater than the historical placebo group. The estimand for the primary endpoint is defined as the difference in the proportion of subjects achieving endoscopic improvement at Week 8 without initiation or dose escalation of UC-related corticosteroids and without initiation of any targeted immunomodulators (TIM) therapy (including biologics and

non-biologics), regardless of premature discontinuation of study treatment, between the ABBV-668 treatment group in the ITT Population and the historical placebo group.

The secondary efficacy objectives are to evaluate the efficacy of ABBV-668 with respect to the secondary endpoints specified in Section 3.2.

The estimands corresponding to the secondary efficacy objectives are:

For each binary secondary endpoint specified in Section 3.2: The difference in the proportion of subjects achieving a response without initiation or dose escalation of UC-related corticosteroids and without initiation of any TIM therapy (including biologics and non-biologics), regardless of premature discontinuation of study treatment, between the ABBV-668 treatment group in the ITT Population and the historical placebo group.

2.2 Study Design Overview

Study M21-446 is a Phase 2a, multicenter, open-label proof of concept study to investigate the efficacy and safety of ABBV-668 in subjects with moderate to severe UC. The study contains a 30-day screening period, 16-week treatment period, and a 30-day follow up period from the last dose of study drug.

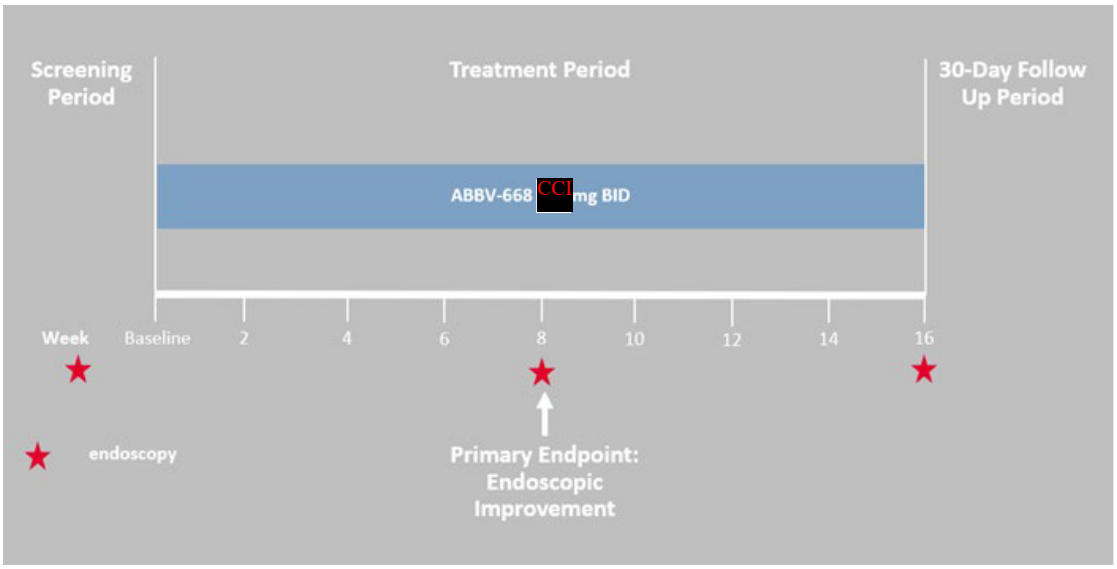
Approximately 40 subjects will be enrolled in this study.

An endoscopy is required at Screening, and at Week 8 to evaluate endoscopic improvement. In order to explore the time-course of ABBV-668 efficacy, subjects will continue through Week 16. An endoscopy will be performed at Week 16 for subjects:

- Who have an endoscopic sub-score ≥1 at the Week 8 endoscopy; or
- Who have an endoscopic sub-score of 0 at the Week 8 endoscopy AND have subsequent worsening of their disease (as assessed by the Investigator) after the Week 8 endoscopy.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



BID = twice a day

2.3 Treatment Assignment and Blinding

This is a single-arm, open-label study.

2.4 Sample Size Determination

The planned sample size is approximately 40 subjects.

A meta-analysis for historical placebo data from UC studies for tofacitinib (OCTAVE1/2), upadacitinib (Phase 2b and Phase 3; data on file), and ustekinumab (UNIFI) gives CCI [redacted] improvement rate at Week 8. A prior placebo distribution that matches this overall rate and has a variance close to the variance of the rate estimate from CCI [redacted] The prior distribution for the ABBV-668 treatment group is set to Jeffreys non-informative prior *Beta* (0.5, 0.5). Assuming a response rate increase of 30% in the ABBV-668 group compared to historical placebo, a sample size of 40 subjects will provide more than 90% probability to demonstrate that the posterior probability of rate difference (ABBV-668 vs. external

placebo) > 0 is larger than 90%. The external placebo response may be updated if new placebo data from similar trials become available before the Primary Analysis database lock.

3.0 Endpoints

Definitions of Efficacy Endpoints

Clinical Remission per Adapted Mayo Score: stool frequency subscore (SFS) ≤ 1, and not greater than Baseline, rectal bleeding subscore (RBS) = 0, and endoscopic subscore (ESS) ≤ 1

Clinical Response per Adapted Mayo Score: decrease from Baseline ≥ 2 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1

Clinical Response per Partial Adapted Mayo Score: decrease from Baseline ≥ 1 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1

Clinical Remission per Full Mayo Score: Full Mayo score ≤ 2 with no subscore > 1

Clinical Response per Full Mayo Score: decrease from Baseline ≥ 3 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1

Endoscopic Improvement: Mayo endoscopic subscore (ESS) of 0 or 1. Note that evidence of friability during endoscopy in subjects with a Mayo ESS of 0 or 1 will confer an endoscopic subscore of 2.

Endoscopic Remission: Mayo ESS = 0

Histologic remission: Geboes score of < 2.0

Histologic-endoscopic mucosal improvement: Mayo ESS ≤ 1 and Geboes score ≤ 3.1

Mucosal Healing: endoscopic (Mayo ESS = 0) and histologic remission (Geboes score of < 2.0).

3.1 Primary Endpoint

The primary endpoint is the achievement of endoscopic improvement (Mayo ESS of 0 or 1) at Week 8.

3.2 Secondary Endpoints

The secondary endpoints are as follows:

- Achievement of clinical remission per Adapted Mayo score at Week 8.
- Achievement of clinical response per Adapted Mayo score at Week 8.
- Achievement of clinical response per Partial Adapted Mayo score at Week 8.
- Achievement of endoscopic remission at Week 8.

3.3 Additional Efficacy Endpoints

In addition, the primary and secondary efficacy endpoints will be analyzed at all other scheduled visits during which the assessments are measured. The following endpoints will also be evaluated at scheduled visits during which the assessments are measured, unless otherwise specified:

- Achievement of clinical response per Full Mayo score over time in subjects with a Full Mayo score of 6 to 12 at Baseline.
- Achievement of clinical remission per Full Mayo score over time in subjects with a Full Mayo score of 6 to 12 at Baseline (at visits with endoscopy).
- Achievement of SFS = 0, RBS = 0, and ESS = 0 over time (at visits with endoscopy).
- Achievement of SFS = 0, RBS = 0, and ESS $\leq$ 1 over time (at visits with endoscopy).
- Time to clinical response per Partial Adapted Mayo.
- Achievement of SFS $\leq$ 1 over time.
- Achievement of RBS = 0 over time.
- Change from Baseline in RBS over time.

- Change from Baseline in SFS over time
- Achievement of histologic-endoscopic mucosal improvement over time (at visits with endoscopy).
- Achievement of histologic remission over time (at visits with endoscopy).
- Achievement of mucosal healing (endoscopic and histologic remission) over time (at visits with endoscopy).
- Change from Baseline in number of extraintestinal manifestations (EIM) over time (as captured in the EIM electronic case report form [eCRF]).
- Change from Baseline in fecal calprotectin (FCP) over time.
- Achievement of FCP below 150 mg/kg over time.
- Achievement of FCP below 250 mg/kg over time.
- Change from Baseline in high sensitivity C-reactive protein (hs-CRP) over time.
- Achievement of no nocturnal bowel movements at Week 8 as assessed by the UC symptom daily diary.
  Achievement of no nocturnal bowel movements at Week 16 as assessed by the UC symptom daily diary.
- Achievement of no tenesmus at Week 8 as assessed by the UC symptom daily diary.
  Achievement of no tenesmus at Week 16 as assessed by the UC symptom daily diary.
- Change from Baseline in number of fecal incontinence episodes per week at Week 8 as assessed by the UC symptom daily diary.
  Change from Baseline in number of fecal incontinence episodes per week at Week 16 as assessed by the UC symptom daily diary.
- Change from Baseline in number of days over a week with sleep interrupted due to UC symptoms at Week 8 as assessed by the UC symptom daily diary.
  Change from Baseline in number of days over a week with sleep interrupted due to UC symptoms at Week 16 as assessed by the UC symptom daily diary.
- Change from Baseline at Week 8 in Inflammatory Bowel Disease Questionnaire (IBDQ) total score.
  Change from Baseline at Week 16 in IBDQ total score.

- Achievement of no abdominal pain at Week 8 as assessed by the UC symptom daily diary.
  Achievement of no abdominal pain at Week 16 as assessed by the UC symptom daily diary.
- Achievement of no bowel urgency at Week 8 as assessed by the UC symptom daily diary.
  Achievement of no bowel urgency at Week 16 as assessed by the UC symptom daily diary.
- Change from Baseline at Week 8 in Functional Assessment of Chronic Illness (FACIT)-Fatigue.
  Change from Baseline at Week 16 in FACIT-Fatigue.

3.4 Safety Endpoints

Safety measures monitored in the study include the following:

- Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to discontinuation of study drug
- Safety topics of interest
- Potentially clinically significant laboratory and vital signs parameters
- Columbia-Suicide Severity Rating Scale (C-SSRS) parameters

4.0 Analysis Populations

The following populations will be used for the analyses.

The ITT Population consists of all subjects who received at least 1 dose of study drug. The ITT Population will be used for all efficacy and Baseline analyses.

The Safety Population consists of all subjects who received at least 1 dose of study drug. The Safety Population will be used for all safety analyses.

5.0 Subject Disposition

Enrollment failure subjects (i.e., subjects who consented to participate in the study but were not enrolled) and associated reasons for failure to enroll (e.g., screen failed [eligibility criteria not met], withdrawal by subject, etc.) will be tabulated for all screened subjects.

A summary of subject accountability by investigator will be provided where the number of subjects in each of the following categories will be tabulated for the treatment group:

- Subjects enrolled in the study;
- Subjects who took at least one dose of study treatment;
- Subjects who completed study treatment;
- Subjects who prematurely discontinued study treatment

The number and percentage of subjects in the ITT Population who prematurely discontinued study treatment will be summarized by primary reasons for not completing study treatment.

6.0 Study Treatment Duration and Compliance

For the Safety Population, duration of treatment will be summarized for ABBV-668 treatment group. Duration of treatment is defined for each subject as last dose date minus first dose date + 1 day. Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of subjects in each treatment duration interval (≥ 15 days, ≥ 30 days, ≥ 45 days, ≥ 60 days, ≥ 75 days, ≥ 90 days, ≥ 105 days) will be summarized.

Treatment compliance will be summarized for the entire treatment period for the Safety Population. Treatment compliance is defined as the number of capsules actually taken divided by the number of capsules that should have been taken. Percent compliance will be summarized.

7.0 Subject Characteristics

Categorical variables will be summarized with the number and percentage of subjects. 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

Demographics and Baseline or disease characteristics will be summarized descriptively for the ITT Population. Unless otherwise specified, Baseline is defined as the last non-missing value prior to the first administration of study treatment.

Continuous demographic variables include age, weight, height, and body mass index (BMI).

Categorical demographic variables include:

- Sex (Male, Female)
- Age Group 1 (< 40, 40 – 64, ≥ 65 years)
- Age Group 2 (≤ median, > median)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, Other)
- Region (US, ex-US)
- Tobacco user (current, former, never, unknown)
- Alcohol user (current, former, never, unknown).
- BMI (normal: < 25 kg/m^2, overweight: ≥ 25 – 30 kg/m^2, obese: ≥ 30 kg/m^2)

Continuous disease characteristics at Baseline include:

- UC disease duration (years)
- Full Mayo score and its components (stool frequency, rectal bleeding, Physician Global Assessment, and endoscopy subscores)

- Partial Mayo score
- Adapted Mayo score
- Partial Adapted Mayo score
- hs-CRP (mg/L)
- Fecal Calprotectin (µg/g)
- Geboes score
- Number of extraintestinal manifestations
- IBDQ total and domain score
- FACIT-Fatigue score

Categorical disease characteristics variables at Baseline include:

- Baseline corticosteroid use (yes, no)
- Baseline immunosuppressant use (yes, no)
- Baseline aminosalicylates use (yes, no)
- Prior exposure to TIM therapy (including biologic and non-biologic) for UC (1, > 1)
- Prior inadequate response/intolerance to TIM therapy (including biologic and non-biologic) for UC (1, > 1)
- Baseline fecal calprotectin (≥ 250 mcg/kg, < 250 mcg/kg)
- Baseline Adapted Mayo score (≤ 7, > 7)
- Baseline Full Mayo score (≤ 9, > 9)
- Mayo endoscopic subscore (2, 3)
- Baseline hs-CRP (≤ 5 mg/L, > 5 mg/L)
- Disease duration Group 1 (≤ 3 years, > 3 years)
- Disease duration Group 2 (≤ median, > median)
- Disease extent (rectosigmoid, left-sided, extensive/pancolitis)

7.2 Medical History and Prior and Concomitant Medications

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 (SOC) and preferred term) will be summarized for the ITT Population. The 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).

Prior and concomitant medications will be summarized separately. A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken 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 + 1 day. The number and percentage of subjects taking prior and concomitant medications will be summarized by generic drug name, based on the World Health Organization (WHO) Drug Dictionary. The actual version of the WHO Drug Dictionary will be noted in the statistical tables and clinical study report.

7.3 Protocol Deviations

For each of the following protocol deviation categories and across all categories, the number and percentage of dosed subjects with at least one protocol deviation will be summarized overall and by treatment group:

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

8.0 Handling of Potential Intercurrent Events for the Primary and Secondary Endpoints

The primary and secondary efficacy endpoints (defined in Section 3.1 and Section 3.2) will be analyzed based on the ITT Population and the following methods will be used to address potential intercurrent events.

Intercurrent events (ICE):

ICE1: Premature discontinuation of study treatment

A treatment policy strategy will be used to handle ICE1, namely, available data collected will be used regardless of premature discontinuation of study treatment.

ICE2: Initiation or dose escalation of UC-related corticosteroid (defined as below) or initiation of any TIM therapy (including biologics and non-biologics) for UC. A composite strategy will be used to handle ICE2, namely, subjects will be considered as not achieving response at or after ICE2.

UC-related corticosteroid ICE is defined as:

- Subjects who were not on UC-related corticosteroids (systemic or locally acting corticosteroids for UC) at Baseline initiate UC-related corticosteroids during the study.
- Subjects who were on UC-related systemic corticosteroids at Baseline who have dosage increased to greater than the prednisone equivalent dose of corticosteroid taken at Baseline, or initiation of any rectal corticosteroids during the study regardless of rectal corticosteroid dose.

The time of ICE2 is defined as the date when either of the two scenarios above first occurs for a subject. As such, the subject will be considered as a "non-responder" for the efficacy endpoint on or after the date of ICE2 through the end of the study. In the scenario when both ICE1 and ICE2 occur, data will be used on or after the date of ICE1 until ICE2, which the subject will be considered as a "non-responder" for the efficacy endpoint on or after the date of ICE2.

Same intercurrent events handling approaches will be used for additional efficacy endpoints, except for:

- For continuous endpoints, data collected on or after ICE2 will be excluded from the analysis (i.e., treated as missing data) handled by mixed effect model repeat measurement (MMRM).
- For time-to-event endpoint, subjects will be censored at ICE2.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted on the ITT Population.

The Primary Analysis will be performed after all subjects have completed the Week 8 assessment or withdrawn from the study.

The final analysis will be performed after all subjects have either withdrawn from the study or completed the Week 16 assessment, and completed safety follow-up.

9.2 Handling of Missing Data

9.2.1 Categorical Endpoints

For binary efficacy endpoints, the primary approach to handle missing data will be non-responder imputation (NRI). The NRI approach categorizes any subject who does not have an evaluation during a pre-specified visit window as a non-responder for the visit.

In cases data missing at random can be reasonably assumed (e.g., missing due to pandemic or geo-political reasons), NRI while incorporating multiple imputation (NRI-MI) may be performed as additional approach.

In addition, AO analysis will be performed. The AO analysis will not impute values for missing observations, and thus a subject who does not have an evaluation on a scheduled

visit will be excluded from the AO analysis for that visit. All observed data will be used in AO analysis.

9.2.2 Continuous Endpoints

MMRM will be the primary approach for the analysis of continuous variables with more than one post Baseline assessment. MMRM analysis will be conducted using mixed-effect model including observed measurements at all visits. For the MMRM analysis, data collected on or after the date of ICE2 will be excluded. The mixed model includes the categorical fixed effects of visit, Baseline corticosteroid use (yes vs no), Baseline Mayo endoscopic sub-score (2 vs 3), prior TIM therapy failure (Yes vs No) and the continuous fixed covariate of Baseline measurement, if applicable. An unstructured variance covariance matrix will be used. If there is a convergence issue, an autoregressive (1) or compound symmetric (CS) covariance structure matrix will be used. The parameter estimations are based on the assumptions of data being missing at random and using the method of restricted maximum likelihood (REML).

Additional approaches, such as Return-to-Baseline Multiple Imputation (RTB-MI), in which data collected on or after the date of ICE2 will be imputed by Baseline values generated from MI model may be conducted for selected continuous endpoints.

9.2.3 Time to Event Endpoints

For the time-to-event endpoint, i.e., time to clinical response per Partial Adapted Mayo score, no missing date will be imputed and subjects will be censored at the last available assessment time.

9.3 Primary Efficacy Endpoint(s) and Analyses

9.3.1 Primary Efficacy Endpoint(s)

The primary endpoint is the achievement of endoscopic improvement (Mayo ESS of 0 or 1) at Week 8.

9.3.2 Main Analysis of Primary Efficacy Endpoint(s)

Analysis of the primary efficacy endpoint will be conducted on the ITT Population. Comparison of the primary efficacy endpoint will be performed between the ABBV-668 treatment group and historical placebo group using Bayesian approach with prior distribution CCI [redacted] obtained from meta-analysis for the historical placebo data, and non-informative prior $Beta$ (0.5, 0.5) for the ABBV-668 treatment group. The posterior probability of rate difference > 0 given data will be calculated. The mean difference and the corresponding 95% credible interval will be provided. Point estimate and 95% CI using normal approximation will be provided for the response rate for the ABBV-668 group. Plots of prior and posterior distribution for the rate difference between ABBV-668 and historical placebo will also be provided.

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

Table 1. Summary of the Estimand Attributes Corresponding to the Primary Efficacy Endpoint

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Primary: Achievement of endoscopic improvement at Week 8	ABBV-668 vs. Historical Placebo	Achievement of endoscopic improvement at Week 8	Adult subjects with moderately to severely active UC	ICE1: Premature discontinuation of study treatment (treatment policy) ICE2: Initiation or dose escalation of UC-related corticosteroids or initiation of any TIM therapy (composite) All data will be used regardless of ICE1 occurrence. Subjects will be considered as non-responders on or after the date of ICE2.	Difference in proportion of subjects achieving response

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint(s)

The same Bayesian approach will be also conducted based on other analyses approaches as described in Section 9.2 as sensitivity analyses.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Secondary Efficacy Endpoints

- Achievement of clinical remission per Adapted Mayo score at Week 8.
- Achievement of clinical response per Adapted Mayo score at Week 8.
- Achievement of clinical response per Partial Adapted Mayo score at Week 8.
- Achievement of endoscopic remission at Week 8.

9.4.2 Analyses of Secondary Efficacy Endpoints

Point estimate and 95% CI using normal approximation will be provided for the response rate for ABBV-668 treatment group. The same Bayesian approach specified in Section 9.3.2 will be also conducted based on the ITT Population, if applicable.

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

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

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Binary Secondary Variable	ABBV-668 vs. Historical Placebo	Achievement of each binary secondary endpoint respectively	Adult subjects with moderately to severely active UC	ICE1: Premature discontinuation of study treatment (treatment policy) ICE2: Initiation or dose escalation of UC-related corticosteroids or initiation of any TIM therapy for UC (composite) All data will be used regardless of ICE1 occurrence. Subjects will be considered as non-responders on or after the date of ICE2.	Difference in proportion of subjects achieving response

9.4.3 Sensitivity and Supplementary Analyses for Secondary Efficacy Endpoints

Similar analysis will be performed based on AO data.

9.5 Additional Efficacy Endpoints and Analyses

Additional efficacy endpoints described in Section 3.3 will be summarized at scheduled timepoints.

For additional binary endpoints, point estimate and 95% CI using normal approximation will be provided for the response rate of the ABBV-668 group. For additional continuous endpoints, the LS-mean and 95% CI will be reported for the ABBV-668 group using MMRM model, which includes visit, Baseline corticosteroid use (yes vs. no), Baseline

Mayo endoscopic sub-score (2 vs 3), TIM (including biologic and non-biologic) failure (Yes vs No) and Baseline measurement, if applicable. For endpoints with a single post-baseline visit, analysis of covariance (ANCOVA) will be used. Same covariates except for visit will be used. Similar analysis using RTB-MI may be performed as sensitivity analysis.

9.6 Efficacy Subgroup Analyses

Subgroup analyses of the primary endpoint will include:

- Baseline corticosteroids use (Yes, No)
- Endoscopic subscore (2, 3)
- Prior TIM (biologic and non-biologic) failure (Yes, No)

Descriptive summaries will be provided for the subgroup analysis. Comparison may be performed if historical data is available. If any subgroup has fewer than 10 subjects, then the analysis for this subgroup will not be performed.

For the final analysis, additional summary for the following endpoints based on AO data will be provided for subjects who received Week 16 endoscopy.

- Achievement of histologic-endoscopic mucosal improvement over time (at visits with endoscopy).
- Achievement of histologic remission over time (at visits with endoscopy).
- Achievement of mucosal healing (endoscopic and histologic remission) over time (at visits with endoscopy).

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Safety Population. Safety summaries of adverse events, laboratory, vital sign measurements and C-SSRS evaluations will be presented.

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.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AE with an onset date that is after the first dose of study treatment and no more than 30 days after the last dose of study treatment. Events where the onset date is the same as the study treatment start date are assumed to be treatment-emergent. 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

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 treatment according to the investigator
- Any treatment-emergent AE with grade ≥ 3 (according to National Cancer Institute (NCI) CTCAE version 5.0)
- Any treatment-emergent serious AE (TESAE)

- Any treatment-emergent AE leading to discontinuation of study treatment
- Any treatment-emergent AE leading to death
- Any treatment-emergent AE related to COVID-19
- Any treatment-emergent serious infections
- All deaths
- Deaths occurring ≤ 30 days after last dose of study treatment
- Deaths occurring > 30 days after last dose of study treatment.

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

Treatment-emergent adverse events will be summarized by SOC and PT; by maximum relationship to study treatment as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum toxicity 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 toxicity 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 ABBV-668 treatment group.

10.2.4 Deaths, Serious Adverse Events, and Adverse Events Leading to Study Treatment Discontinuation

Treatment-emergent serious adverse events, TEAEs leading to premature discontinuation of study treatment, and TEAEs leading to death will be summarized by SOC and PT.

Tabular listings will be provided for all deaths, all SAEs, TESAEs, TEAEs leading to death and TEAEs leading to premature discontinuation of study treatment.

10.2.5 Safety Topic of Interest

Safety topics of interest will be summarized by SOC and PT and will be based on standardized or AbbVie-defined company MedDRA queries (SMQs or CMQs), or based on adjudication results. Safety topics of interest are categorized as follows:

- Serious infections
- Opportunistic infections excluding tuberculosis and herpes zoster
- Tuberculosis
- Herpes zoster
- Fungal infection
- Malignancies
- Malignancies excluding Non-Melanoma Skin Cancer
- Non-Melanoma Skin Cancer
- Hypersensitivity reactions
- Psychiatric adverse events: suicidal ideations or attempt, abnormal/vivid dreams, or nightmares
- Neurologic adverse events

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

Tabular listings of safety topics of interest will be provided.

10.3 Analysis of Laboratory Data

The selected clinical laboratory tests defined in the protocol operations manual (e.g., hematology, 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. The number of observations,

Baseline mean, visit mean, change from Baseline mean, standard deviation, median, minimum and maximum will be presented for ABBV-668 treatment group.

Changes in laboratory parameters will be tabulated using shift tables by NCI CTC criteria (v4.03). A shift table from Baseline to the worst value (based on NCI CTC criteria) during treatment will be created. A similar shift table will be provided to summarize shifts from Baseline to the final post-baseline value.

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:

- ALT > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- AST > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- TBL > 2 × ULN
- ALT and/or AST > 3 × ULN and TBL > 1.5 × ULN
- ALT and/or AST > 3 × ULN and TBL > 2 × ULN
- Alkaline phosphatase > 1.5 × ULN
- ALT and/or AST > 3 × ULN and TBL > 2 × ULN and alkaline phosphatase < 2 × ULN

A listing of ALT, AST, total bilirubin (and direct and indirect bilirubin, if available), and alkaline phosphatase values for subjects meeting the laboratory criteria specified above will be provided.

An Evaluation of Drug Induced Serious Hepatotoxicity (eDISH) plot of the maximum post-baseline ALT value (as a multiple of the ULN) vs. the maximum post-baseline total

bilirubin value (as a multiple of the ULN), will also be utilized to assess for potential hepatotoxicity. Reference lines will be included at 3 × ULN for ALT and at 2 × ULN for total bilirubin. A similar eDISH plot can be presented for AST vs. total bilirubin.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, weight, pulse rate, respiratory 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. The number of observations, Baseline mean, visit mean, change from Baseline mean, standard deviation, median, minimum and maximum will be presented for ABBV-668 treatment group.

Vital sign variables will be evaluated based on 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.

10.5 Other Safety Analyses

The C-SSRS is a systematically administered instrument developed to track suicidal adverse events across a treatment study. At Screening the C-SSRS will be administered to collect lifetime history as well as experience during the past year. At all other visits, the C-SSRS will collect experience since the last visit. Affirmative responses on the C-SSRS will be summarized for the Baseline and each subsequent visit for the treatment group. A listing will also be prepared that includes all subjects with 1 or more affirmative responses.

11.0 Interim Analyses

Interim analyses may be performed to provide information for future study decisions.

11.1 Data Monitoring Committee

No data monitoring committee (DMC) is planned for this study.

12.0 Overall Type-I Error Control

No multiplicity adjustment will be performed for this single-arm open-label proof of concept study.

13.0 Version History

Table 3. SAP Version History Summary

Version	Date	Summary
1.0	12 July 2023	Initial version

2.0	04 September 2024	• Removed "Ulcerative colitis symptoms daily diary" from the Section 7.1.
		• Added details of intercurrent events handling in Section 8.0
		• Added and clarified the analysis details in Section 9.0.
		• Updated the prior distribution for the historical placebo rate in Section 9.3.2:
		  o Removed the ustekinumab (UNIFI) study from the meta-analysis, due to different friability criteria.
		  o Updated the historical placebo rate using mixed population in the meta-analysis, as mixed population were enrolled in the study.
		• Revised interim analysis in Section 11.0.
		• Added NMSC and malignancies excluding NMSC in the list of safety topics of interest in Appendix B.
		• Added Appendix D

3.0	31 October 2024	• Corrected external rate from the meta-analysis and updated Figure 2 in Appendix D to align with the historical placebo population change in the previous version.

Appendix A. List of SAP Signatories

Name	Title	Role/Functional Area
PPD		Author
		Clinical Statistics
		Clinical Statistics
		Statistical Programming
		Clinical Development

Appendix B. Definition of Safety Topics of Interest

Safety topics of interest (STI) will be identified using the following search criteria:

Safety Topics of Interest	Search Criteria
Serious infections	Infections CMQ subset for SAEs
Opportunistic infections excluding tuberculosis and herpes zoster	Opportunistic Infections excluding TB and Herpes Zoster CMQ
Active Tuberculosis (TB)	Active Tuberculosis CMQ
Herpes zoster (HZ)	Herpes Zoster CMQ
Fungal infection	Fungal CMQ
Malignancies	Malignant Tumours SMQ (Narrow)
Malignancies: excluding Non-Melanoma Skin Cancer (NMSC)	Malignant Tumours SMQ Narrow EXCLUDING [Skin malignant tumors SMQ Broad excluding PTs identified by Melanoma CMQ
NMSC	Skin malignant tumors SMQ Broad excluding PTs identified by Melanoma CMQ
Hypersensitivity reactions	Hypersensitivity SMQ (Narrow)
Psychiatric adverse events: abnormal dreams and nightmares	Preferred Terms: Abnormal dreams; Nightmare
Psychiatric adverse events: suicidal ideation/suicidal events	Suicide/self-injury SMQ (Narrow)
Neurological events	Nervous System Disorder (SOC)

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

Hematology Variables	Units	Definition of Potentially Clinically Important	
		Very Low	Very High
Hemoglobin	g/dL	< 8.0	
Neutrophils	10^9/L	< 1.0	
Lymphocytes	10^9/L	< 0.5	> 20.0
WBC count	10^9/L	< 2.0	
Platelets count	10^9/L	< 50.0	

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

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

		Definition of Potentially Clinically Important	
Chemistry Variables	**Units**	**Very Low**	**Very High**
TBL	mcmol/L		> 3.0 × ULN
ALP	U/L		> 5.0 × ULN
SGOT/AST	U/L		> 5.0 × ULN
SGPT/ALT	U/L		> 5.0 × ULN
Albumin	g/L	< 20	
Glucose	mmol/L	< 2.2	> 13.9
Triglycerides	mmol/L		> 5.7
Creatinine	mcmol/L		> 3.0 × ULN
Sodium	mmol/L	< 130	> 155
Potassium	mmol/L	< 3.0	> 6.0
Corrected Calcium	mmol/L	< 1.75	> 3.1
Total Cholesterol	mmol/L		> 10.34
GGT	U/L		> 5.0 × ULN
Creatine Kinase	U/L		> 5.0 × ULN
Phosphate	mmol/L	< 0.6	

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

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

Vital Signs Variables	Criterion	Definition of Potentially Clinically Important
Systolic blood pressure (mmHg)	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic blood pressure (mmHg)	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from Baseline
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from Baseline
Pulse	Low	Value ≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High	Value ≥ 120 bpm and increase ≥ 15 bpm from Baseline
Respiratory Rate	Low	< 10 rpm
	High	> 24 rpm
Body temperature	High	> 39.0°C (102.3°F)
Weight	High	> 7% increase from Baseline
	Low	> 7% decrease from Baseline

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

Appendix D. Details for Historical Data

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

Table D-1 External Placebo Data for Secondary Endpoints at Week 8

Endpoints	External Data				External Rate	Prior Distribution
	OCTAVE-1	OCTAVE-2	M14-234	M14-675		
Clinical Remission per Adapted Mayo Score	NA	NA	7/154	7/174	4%	$Beta$ (14.0, 312.4)
Clinical Response per Adapted Mayo Score	NA	NA	42/154	44/174	26%	$Beta$ (85.7, 241.0)
Clinical Response per Partial Adapted Mayo Score	NA	NA	64/154	51/174	35%	$Beta$ (20.9, 38.4)
Endoscopic Remission	2/122	2/112	2/154	3/174	2%	$Beta$ (9.0, 547.8)

NA = data is not available