Statistical Analysis Plan for Study M20-371

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Moderately to Severely Active Crohn's Disease (CD): AIM-CD

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Version 2.0

Table of Contents

List of Tables

List of Figures

List of Appendices

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for ABBV-154 Study M20-371, "A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Moderately to Severely Active Crohn's Disease (CD): AIM-CD."

The pharmacokinetic/pharmacodynamic endpoints, pharmacogenetic endpoints, selected biomarkers, Patient Global Impression of Change –- Crohn's Disease+ (PGIC-CD+) and Change from Baseline in Patient Global Impression of Severity –- Crohn's Disease+ (PGIS-CD+) for variable validation purposes, and data collected in the Wearable Device Substudy will be analyzed separately and are not described 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.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

The objective of Study M20-371 is to assess the efficacy, safety, and tolerability of ABBV-154 in comparison with placebo in subjects with moderately to severely active Crohn's Disease (CD) who had inadequate response to or were intolerant of prior biologics.

Primary Efficacy Objective

The primary efficacy objective of Study M20-371 is to demonstrate a higher rate of endoscopic response after 12 weeks of treatment with ABBV-154 when compared to placebo in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics.

Hypothesis corresponding to the primary efficacy objective is:

- The proportion of subjects achieving endoscopic response (see Section 3.0) with ABBV-154 is greater than that with placebo at Week 12 in the Induction Period.

The estimand corresponding to the primary efficacy objectives are defined as follows:

- The difference in the proportion of subjects that achieve endoscopic response at Week 12 without use of concomitant medication that could confound the efficacy (see Section 8.1) and regardless of premature discontinuation of study drug (see Section 8.2), in each of the ABBV-154 dose groups compared with the placebo group in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics.

Secondary Efficacy Objectives

The secondary efficacy objectives of the Study M20-371 are to demonstrate greater efficacy with ABBV-154 treatment when compared with placebo treatment with respect to the secondary endpoints specified in Section 3.2, in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics.

Hypotheses corresponding to the ranked secondary efficacy objectives are: for each of the secondary endpoints specified in Section 3.2, greater proportion of subjects with improvement is achieved with ABBV-154 when compared to that of placebo.

The estimands corresponding to the secondary efficacy objectives are defined for each of the secondary endpoints as follows:

- For endpoints in the Induction Period: The difference in the proportion of subjects that achieve response/remission without use of concomitant medication that could confound the efficacy (see Section 8.1) and regardless of premature discontinuation of study drug (see Section 8.2), in each of the ABBV154 dose groups compared with the placebo group in subjects with

moderately to severely active CD who had inadequate response to or were intolerant of prior biologics.

- For endpoints in the Maintenance Period: The difference in the proportion of subjects that achieve response/remission without use concomitant medication that could confound the efficacy (see Section 8.1) and regardless of premature discontinuation of study drug (see Section 8.2), in each of the ABBV154 dose groups compared with the placebo group in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics and achieved response after the 12-week induction treatment with ABBV-154.

2.2 Study Design Overview

This is a randomized, double-blind, placebo-controlled Phase 2b study to assess the safety, tolerability, PK, PD, immunogenicity, and efficacy of ABBV-154 in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics. The enrollment for subjects with prior adalimumab use is capped at approximately 30% of the total enrolled subjects. The study comprises 3 periods: a 12-Week Double-Blind Placebo-Controlled Induction Period, a 12-Week Double-Blind Re-Induction Period (for subjects considered to be clinical non-responders and endoscopic non-responders), and a 40-Week Double-Blind Placebo-Controlled Maintenance Period.

At the Baseline Visit of the Induction Period, approximately 265 subjects will be randomized in a 1:1:1:1:1 ratio into 4 ABBV-154 treatment groups or placebo:

- Induction Group 1: Loading dose of 150 mg IV at Week 0, followed by 80 mg subcutaneous (SC) at Week 2 and every other week (EOW);
- Induction Group 2: Loading dose of 300 mg IV at Week 0, followed by 230 mg SC at Week 2 and EOW;
- Induction Group 3: Loading dose of 600 mg IV at Week 0, followed by 530 mg SC at Week 2 and EOW;
- Induction Group 4: Loading dose of 600 mg IV at Week 0, followed by 530 mg SC at Weeks 4 and 8, and placebo at Weeks 2, 6, and 10; and

- Induction Group 5: Matching placebo (IV and SC).

At Week 12 of the Induction Period, subjects achieving clinical response, defined as a decrease in Crohn's Disease Activity Index (CDAI) ≥ 100 points from Baseline (CR100) AND/OR endoscopic response defined as a decrease in SES-CD > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2-point reduction from Baseline) (per local read) will receive treatment in the 40-Week Maintenance Period as follows:

- Induction Group 1: Re-randomized in a 1:1 ratio to receive ABBV-154 80 mg SC EOW or matching placebo;
- Induction Groups 2 to 4: Re-randomized in a 1:1:1 ratio to receive ABBV-154 80 mg SC EOW, ABBV-154 230 mg SC EOW, or matching placebo;
- Induction Group 5: ABBV-154 80 mg SC EOW.

At Week 12 of the Induction Period, subjects who are categorized as clinical non-responders and endoscopic non-responders (per local read) will be re-randomized into the Re-Induction Period. Subjects who receive Rescue Therapy, fail to complete glucocorticoid tapering by Week 6, or increase doses of or initiate treatment with aminosalicylates or immunomodulators in the Induction Period will be considered non-responders, regardless of clinical response or endoscopic response (per local read) per the definitions above at Week 12 and will be re-randomized in a 1:1 ratio into 2 ABBV-154 treatment groups in the 12-Week Re-Induction Period as follows:

- Re-Induction Group 1: Loading dose of 300 mg IV at Week 0, followed by 230 mg SC at Week 2 and EOW;
- Re-Induction Group 2: Loading dose of 600 mg IV at Week 0, followed by 530 mg SC at Week 2 and EOW.

Subjects who achieve clinical response AND/OR endoscopic response (per local read) at Week 12 of the Re-Induction Period will be re-randomized into the Maintenance Period as described above for subjects achieving clinical response AND/OR endoscopic response

(per local read) after Week 12 of the Induction Period. Subjects who do not achieve either clinical response or endoscopic response (per local read) after the Re-Induction Period will be discontinued and will have a follow-up visit scheduled 70 days after last study drug administration.

To determine endoscopic response status for re-randomization into the Maintenance Period, the SES-CD score per local read at Week 12 of the Induction/Re-Induction Period and the SES-CD score per central read at Baseline will be used. In the case of missing data where either clinical response or endoscopic response cannot be determined, subjects will be considered non-responders for the re-randomization criteria evaluation.

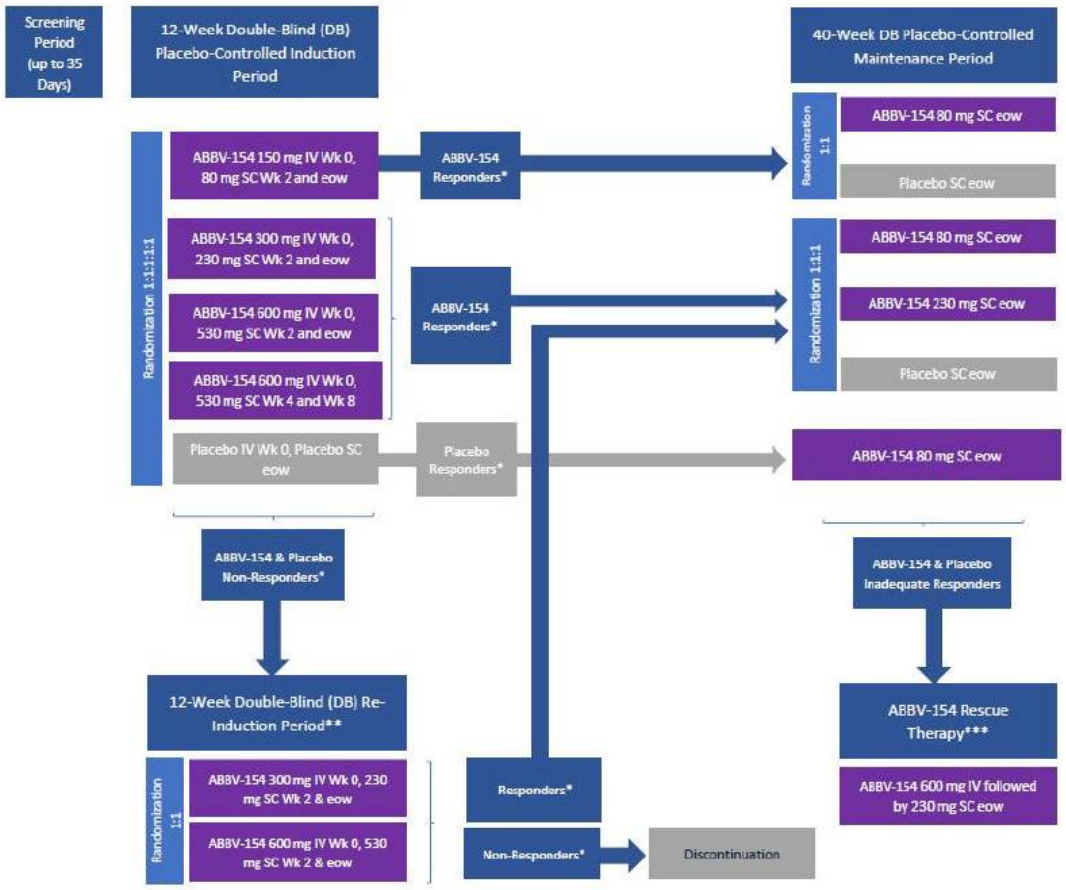
Subjects who have an inadequate response at or after Week 4 in the Maintenance Period will be eligible to receive Rescue Therapy with a single dose of ABBV-154 600 mg IV followed by ABBV-154 230 mg SC EOW. Subjects who have received rescue therapy with ABBV-154 for at least 4 weeks and who continue to demonstrate inadequate response may receive additional Rescue Therapy with oral glucocorticoids, aminosalicylates, or immunomodulators.

The last dose of study drug will be given at Week 38 of the Maintenance Period. A follow-up visit will be scheduled 70 days after the last study drug administration.

The Primary Analysis for the Induction Period and Re-Induction Period will be performed after all subjects have either completed Week 12 of the Induction Period and Re-Induction Period, respectively, or prematurely discontinued study participation. The final analysis will be conducted after all subjects have completed Week 40 of the Maintenance Period plus the 70-day Follow-up Visit or prematurely discontinued study participation. To ensure the integrity of the trial, the study sites and subjects will remain blinded until the final database lock is completed.

The schematics of the overall study design are shown in Figure 1.

Figure 1. Study M20-371 Study Schematic



DB = double-blind; EOW = every other week; IV = intravenous; SC = subcutaneous; Wk = week

* Responders are defined as clinical responders AND/OR endoscopic responders (per local read), and non-responders are defined as clinical non-responders AND endoscopic non-responders (per local read). Clinical responder is defined at Week 12 of the Induction Period or Re-Induction Period as a decrease in CDAI ≥ 100 points from Baseline (CR100). Endoscopic responder is defined at Week 12 of the Induction Period or Re-Induction Period as a decrease in SES-CD > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2-point reduction from Baseline) (per local read). In the case of missing data where clinical response and endoscopic response cannot be calculated, subjects will be considered as non-responders for the re-randomization criteria evaluation.

** Only subjects who are considered to be clinical non-responders and endoscopic non-responders (per local read) at Week 12 of the Induction Period will be re randomized into the Re-Induction Period.

*** Subjects with inadequate response at/after Week 4 of the Maintenance Period will be eligible to receive Rescue Therapy consisting of ABBV-154 600 mg IV followed by ABBV-154 230 mg SC EOW.

2.3 Treatment Assignment and Blinding

All subjects will be assigned a unique identification number by the Interactive response technology (IRT) at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule. Randomization into the 12-Week Double-Blind Induction Period, the 12-Week Double-Blind Re-Induction Period, and the 40-Week Double-Blind Maintenance Period is outlined in Section 2.2.

Randomization at Baseline (Week 0, Day 1) of the Induction Period will be stratified as follows:

- Baseline glucocorticoid use (yes/no);
- Endoscopic disease severity (SES-CD < 15; SES CD ≥ 15); and
- Inadequate response to adalimumab (yes/no).

Re-randomization at Baseline (Week 0, Day 1) of the Re-Induction Period will be stratified as follows:

- Treatment group in the Induction Period

Re-randomization at Baseline (Week 0, Day 1) of the Maintenance Period will be stratified as follows:

- Achievement of CR100 at entry of the Maintenance Period (Week 12 of the Induction/Re Induction Period)
- For subjects who enter from the Induction Period: ABBV-154 dose groups in the Induction Period
- For subjects who enter from Re-Induction Period:
  - ABBV-154 dose groups in the Re-Induction Period
  - Induction Period treatment: ABBV-154 (any dose group) versus placebo.

2.4 Sample Size Determination

Approximately 265 subjects will be randomized into 4 ABBV-154 treatment groups or placebo in a 1:1:1:1:1 ratio at Baseline of the Induction Period. There will be a cap of approximately 30% the total enrolled of subjects who had prior use of adalimumab treatment.

A total of 265 subjects (53 subjects per group) will provide more than 90% power to detect a 26% difference in endoscopic response rates at Week 12 of the Induction Period between an ABBV-154 group and the placebo group (assuming the response rate in the placebo group is 11%) using a Chi square test at α level of 0.1 (two-sided).

Under the response rate assumptions for ABBV-154 and placebo in the Induction Period, it is expected that at least 40 subjects per group will be available for the analysis of endoscopic response at Week 40 in the Maintenance Period. This sample size (40 subjects per group) will provide more than 80% power to detect a 26% difference between ABBV-154 and placebo (assuming the response rate in the placebo group at Week 40 of the Maintenance Period is 11%) using a Chi-square test at α level of 0.1 (two sided).

The total sample size (planned as 265 subjects) for the Induction Period may be adjusted to ensure at least 40 subjects per group for the analysis in the Maintenance Period.

3.0 Endpoints

In Section 3.0, please note

1. "Baseline" refers to the last available measurement on/before Baseline [Week 0, Day 1] of the Induction Period;
2. All endoscopic endpoints will be scored by central review;
3. Average daily liquid or very soft stool frequency (SF) and average daily abdominal pain (AP) score (SF/AP)-based efficacy endpoints will be analyzed in

the subset of subjects with an average daily liquid or very soft SF score ≥ 4 and/or average daily AP score ≥ 2 at Baseline.

The following endpoint definitions apply to the efficacy variables described below:

- **Endoscopic response:** decrease in Simple Endoscopic Score for Crohn's Disease (SES-CD) > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2-point reduction from Baseline)
- **Clinical remission per CDAI:** CDAI < 150
- **Clinical response (CR100):** a decrease of CDAI ≥ 100 points from Baseline
- **Clinical remission per SF/AP:** average daily very soft or liquid SF ≤ 2.8 and not worse than Baseline AND average daily AP score ≤ 1 and not worse than Baseline
- **Enhanced Clinical Response per SF/AP:** ≥ 60% decrease in average daily very soft or liquid SF and/or ≥ 35% decrease in average daily AP score and both not worse than baseline, and/or clinical remission per SF/AP
- **Clinical response per SF/AP:** ≥ 30% decrease in average daily liquid or very soft SF and/or ≥ 30% decrease in average daily AP score and both not worse than Baseline
- **Endoscopic remission:** SES-CD ≤ 4 and at least a 2-point reduction versus Baseline and no subscore > 1 in any individual variable
- **Ulcer-free endoscopy:** SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore ≥ 1 at Baseline

Details of CDAI, SES-CD and patient-reported outcome (PRO) questionnaires are provided in Appendix B, Appendix C and Appendix D respectively.

3.1 Primary Endpoint

The primary endpoint is:

- Achievement of endoscopic response at Week 12 in the Induction Period.

3.2 Secondary Endpoints

The following endpoints will be included as secondary endpoints:

- Achievement of:
  - clinical remission per CDAI at Week 12 in the Induction Period.
  - clinical remission per SF/AP at Week 12 in the Induction Period.
  - endoscopic response at Week 40 in the Maintenance Period.
  - clinical remission per CDAI at Week 40 in the Maintenance Period.
  - clinical remission per SF/AP at Week 40 in the Maintenance Period.

3.3 Other Efficacy Endpoints

In the Induction/Re-Induction/Maintenance Periods, the additional endpoints below will be analyzed at timepoints specified in the schedule of events table of the protocol, except for those specified as primary/secondary endpoints above.

- Achievement of clinical remission per CDAI.
- Achievement of clinical remission per SF/AP.
- Achievement of CR100.
- Achievement of clinical response per SF/AP.
- Achievement of enhanced clinical response per SF/AP.
- Achievement of endoscopic remission.
- Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) total score.
- Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).
- Change from Baseline in the Bowel Incontinence Scale.
- Change from Baseline in CDAI.
- Change from Baseline in individual IBDQ domain scores (bowel, emotional, social, systemic).

- Change from Baseline in individual IBDQ items under Bowel Symptom domain (for Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, and Q29).
- Achievement of IBDQ remission defined as IBDQ ≥ 170 points.
- Achievement of IBDQ response defined as increase in IBDQ ≥ 16 points from Baseline.
- Change from Baseline in 36-Item Short Form Health Survey (SF-36).
- Change from Baseline in fecal calprotectin (FCP).
- Change from Baseline in high-sensitivity C-Reactive Protein (hs-CRP).
- Change from Baseline in average daily AP score.
- Change from Baseline in average daily liquid or very soft SF.
- Change from Baseline in SES-CD.
- Achievement of SES-CD ulcerated surface subscore ≤ 1 in each segment with a SES-CD ulcerated surface subscore ≥ 2 at Baseline.
- Achievement of Ulcer-free endoscopy.
- Achievement of absence of bowel urgency.
- Change from Baseline in average daily bowel urgency frequency.
- Achievement of absence of rectal bleeding.

3.4 Safety Endpoints

The following endpoints will be included in the safety analyses:

- Treatment emergent adverse events (TEAEs), serious adverse events (SAEs), AEs leading to discontinuation of the study drug;
- Occurrence of possible glucocorticoid-related AEs;
- Potentially clinically significant laboratory, vital signs, and electrocardiogram (ECG) variables.

4.0 Analysis Populations

The following population sets will be used for the analyses.

ITT Populations

ITT population: The ITT Population includes all subjects who were randomized and received at least 1 dose of study drug.

ITT1 population: The subset of the ITT Population who were randomized and received at least 1 dose of study drug in the Induction Period. The ITT1 Population is the primary analysis population for efficacy analyses of the Induction Period.

ITT2 population: The subset of the ITT population who were randomized and received at least one dose of study drug in the Re-Induction Period. The ITT2 Population is the analysis population for efficacy analyses of the Re-Induction Period.

ITT3 population: The subset of the ITT population who received ABBV-154 for 12 weeks before entering the Maintenance Period (including subjects were randomized to ABBV-154 dose groups in the Induction Period and entered the Maintenance Period from the Induction Period OR were randomized to the placebo group in the Induction Period and entered the Maintenance Period from the Re-Induction Period) AND were randomized and received at least one dose of study drug in the Maintenance Period. The ITT3 Population is the primary analysis population for efficacy analyses of the Maintenance Period.

ITT3-RN population: The subset of the ITT population who were enrolled and received at least one dose of study drug in the randomized portion of the Maintenance Period.

ITT3-NRN population: The subset of the ITT population who were enrolled and received at least one dose of study drug in the non-randomized portion of the Maintenance Period.

ITT3-RES population: The subset of the ITT population who received at least one dose of ABBV-154 rescue therapy in the Maintenance Period.

The ITT Populations (including ITT1, ITT2, ITT3, ITT3-RN, ITT3-NRN populations) will be analyzed as randomized (i.e., according to the randomized/assigned treatment assignment).

Safety Populations

The safety population for the Induction Period (denoted by **SA1**) includes all subjects who received at least one dose of the study drug in the Induction Period.

The safety population for the Re-Induction Period (denoted by **SA2**) includes all subjects who received at least one dose of the study drug in the Re-Induction Period.

The safety population for the Maintenance Period (denoted by **SA3**) includes all subjects who received at least one dose of the study drug in the Maintenance Period.

The all ABBV-154 safety population (**SA-ALL154**) includes all subjects who received at least one dose of ABBV-154 in the Induction Period, or the Re-Induction Period, or the Maintenance Period.

The all ABBV-154 rescue safety population (**SA-RES**) includes all subjects who received at least one dose of ABBV-154 rescue therapy in the Maintenance Period.

The following safety populations are defined for safety analyses based on data from multiple study periods:

SA-IN2: all subjects who received at least one dose of ABBV-154 in both Induction Period and Re-Induction Period.

SA-INMN: all subjects who received at least one dose of ABBV-154 in either Induction Period or Re-Induction Period AND at least one dose of ABBV-154 in the Maintenance Period.

SA-IN2MN: all subjects who received at least one dose of ABBV-154 in the Induction Period AND at least one dose of ABBV-154 in the Re-Induction Period AND at least one dose of ABBV-154 in the Maintenance Period.

For the safety populations, subjects are assigned to a treatment group based on the "as treated" treatment group, regardless of the treatment randomized.

5.0 Subject Disposition

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized by treatment group for each period separately, among the corresponding ITT population:

- Subjects enrolled (randomized) in the study;
- Subjects who took at least one dose of study drug;
- Subjects who completed protocol-specified treatment;
- Subjects who prematurely discontinued study drug;
- Subjects who withdrew from study.

Number and percentage of subjects who discontinued study drug and who withdrew from the study will be summarized by reason (primary reason and all reasons) and by treatment group for each period separately. Subjects with multiple reasons for premature discontinuation will be counted once in the calculation of the number and percentage of total discontinuations.

In addition, subjects who reported at least one of the protocol deviation categories (Appendix A) will be summarized for each treatment group.

6.0 Study Drug Duration and Compliance

For the safety populations (SA1, SA2 and SA3), duration of treatment will be summarized by each treatment group for each period. Duration of treatment is defined for each subject as last dose date of blinded study drug minus first dose date + 14. Duration of treatment

will be summarized for each treatment group using the number of subjects treated, mean, standard deviation, median, minimum, and maximum. In addition, the number and percentage of subjects in the following treatment duration intervals will be summarized.

Induction/Re-Induction Period: < 2 weeks [14 days], ≥ 2 weeks [14 days], ≥ 4 weeks [28 days], ≥ 8 weeks [56 days], and ≥ 12 weeks [84 days]

Maintenance Period: < 2 weeks [14 days], ≥ 2 weeks [14 days], ≥ 4 weeks [28 days], ≥ 8 weeks [56 days], ≥ 12 weeks [84 days], ≥ 24 weeks [168 days], ≥ 36 weeks [252 days], and ≥ 40 weeks [280 days]

Treatment compliance will be summarized by treatment group for each period for the safety population. Treatment compliance is defined as the number of infusions/injections actually taken divided by the number of infusions/injections that should have been taken. Percent compliance will be summarized.

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 overall and by treatment group, and overall for each of the ITT1/ITT2/ITT3/ITT3-RN/ITT3-NRN population. 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, standard deviation, median, minimum, and maximum).

7.1 Demographics and Baseline Characteristics

Demographic/vital Signs

- Sex (Male, Female)
- Age (Years)
- Age Category (≥ 18 years - < 40 years, ≥ 40 years - < 65 years, ≥ 65 years)

- Ethnicity (Hispanic/Latino, Non-Hispanic/Latino)
- Race category (White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, Multiple)
- Geographic Region category (US, ex-US)
- Geographic Region category (Asia, Eastern Europe, Western Europe, North America, South/Central America, Other)
- Tobacco/Nicotine Use (currently smokes, ex-smoker, never smoked, unknown)
- Alcohol use (current drinker, former drinker, non-drinker, unknown)
- Body weight (kg) – overall and by sex
- Body Mass Index (BMI, kg/m^2)
- BMI category
  - [$< 18\ kg/m^2$]
  - [≥ 18 and $< 25\ kg/m^2$]
  - [≥ 25 and $< 30\ kg/m^2$]
  - [$\geq 30\ kg/m^2$]

Patient Reported Outcome Questionnaires at Baseline

- IBDQ total and domain scores
- FACIT-F total score
- SF-36 - 8 domain scores, PCS and MCS
- PGIS-CD+

Other Baseline Characteristics

- CDAI
- Average Daily very soft or liquid SF
- Average Daily AP score
- SES-CD
- SES-CD category (< 15, ≥ 15)

- Crohn's disease Duration (years)
- Crohn's disease Duration category (≤ 5 years, > 5 years)
- hs-CRP (mg/L)
- hs-CRP category (< 5, ≥ 5 mg/L)
- FCP (µg/g)
- FCP category (≤ 250 µg/g, > 250 µg/g)
- CD Location Per SES-CD (ileal, ileocolonic, colonic; Appendix F)

Prior and Concomitant Treatment use

- Baseline CD-related glucocorticoid use (yes, no)
- Baseline CD-related immunomodulator use (yes, no)
- Baseline CD-related aminosalicylates use (yes, no)
- Prior inadequate response and/or intolerance to biologics
  - Number of prior biologics with inadequate response and/or intolerance (≤ 1, 2, ≥ 3)
  - Prior inadequate response and/or intolerance to an anti-TNF agent (yes, no)
    - Inadequate response to an anti-TNF agent (yes, no)
    - Intolerance to an anti-TNF agent (yes, no)
    - Inadequate response to adalimumab (yes, no)
  - Prior inadequate response and/or intolerance to vedolizumab/natalizumab (yes, no)
  - Prior inadequate response and/or intolerance to ustekinumab (yes, no)

In addition, clinical tests at baseline such as TB test, pregnancy test and electrocardiogram assessment will be summarized. Crohn's disease history (Montreal classification) and Crohn's disease surgical history will be summarized separately as well.

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 (SOC) and preferred term (PT)] will be summarized overall and by treatment group. 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 PT).

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name (ITT1 population for prior medications; ITT1, ITT2 and ITT3/ITT3-RN/ITT3-NRN populations for concomitant medications). A prior medication is defined as any medication taken prior to the date of the first dose of study drug in the Induction Period.

A concomitant medication for the Induction Period is defined as any medication other than study drug that (1) was started prior to the first dose study drug in the Induction Period and continued to be taken after the first dose of study drug in the Induction Period, or (2) was started after the first dose of study drug in the Induction Period, but (i) prior to the first dose of study drug in the Re-Induction Period (if applicable), or (ii) prior to the first dose of study drug in the Maintenance Period (if applicable), or (iii) within the last dose in the Induction Period + 14 days, whichever is earlier.

A concomitant medication for the Re-Induction Period is defined as any medication other than study drug that (1) was started prior to the first dose study drug in the Re-Induction Period and continued to be taken after the first dose of study drug in the Re-Induction Period, or (2) was started after the first dose of study drug in the Re-Induction Period, but (i) prior to the first dose of study drug in the Maintenance Period (if applicable), or (iii) within the last dose in the Re-Induction Period + 14 days, whichever is earlier.

A concomitant medication for the Maintenance Period is defined as any medication other than study drug that (1) was started prior to the first dose study drug in the Maintenance Period and continued to be taken after the first dose of study drug in the Maintenance Period, or (2) was started after the first dose of study drug in the Maintenance Period, but (i) within the last dose in the Maintenance Period + 14 days, or (ii) prior to initiation of ABBV-154 rescue therapy, whichever is earlier.

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

Potential intercurrent events considered in the Study M20-371 include 1) premature discontinuation of study drug and 2) CD-related confounding medications defined in Section 8.1. As suggested by Qu et al. (2021), a mix of strategies will be used to handle different intercurrent events for the efficacy analysis.

8.1 Intercurrent Event 1 (IE1): CD-Related Confounding Medications

The CD-related confounding medications intercurrent event is defined as follows.

In the Induction Period:

1. Initiation of protocol-defined Rescue Therapy for the Induction Period;
2. Initiation of glucocorticoids after Baseline of the Induction Period;
3. Fail to complete glucocorticoid taper by Week 6 of the Induction Period;
4. Initiation/increasing doses of aminosalicylates or immunomodulators.

In the Maintenance Period:

- Initiation of protocol-defined Rescue Therapy for the Maintenance Period.

Within each period, the time point of the CD-related confounding medications intercurrent event is defined as the date when one of the scenarios above occurs for a subject.

Binary endpoints: A composite strategy will be used in the efficacy analysis: the subject will be considered as non-responders at all visits on/after the CD-related confounding medications intercurrent event.

Continuous endpoints: A hypothetical strategy will be used in the efficacy analysis. Data collected on/after the initiation of CD-related confounding medications will not be used in the analysis. Efficacy analysis will be handled by using corresponding statistical models (e.g., the Mixed-Effect Model Repeated Measurement [MMRM] model).

8.2 Intercurrent Event 2 (IE2): Premature Discontinuation of Study Drug

Following the intent-to-treat (ITT) principle, a treatment policy strategy will be used to handle the IE2. Data collected on/after premature discontinuation of study drug will be used for all efficacy endpoints.

The only exception is when data are collected on/after the date subjects switching to other treatments for CD, which will be handled as follows:

- **Binary endpoints:** A composite strategy will be used in the efficacy analysis: the subject will be considered as non-responder at all visits after the initiation of other CD-related treatments.
- **Continuous endpoints:** A hypothetical strategy will be used in the efficacy analysis. Data collected after the initiation of other CD-related treatments will not be used in the analysis. Efficacy analysis will be handled by using corresponding statistical models (e.g., MMRM model).

The other CD-related medications include:

- Biologics approved for CD (Adalimumab, Certolizumab, Infliximab, Ustekinumab, Vedolizumab, Natalizumab)
- Any investigational compound
- Systemic glucocorticoids and rectal glucocorticoids
- Immunomodulators

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted in the ITT Populations in each period. All tests will be 2-sided at an alpha level of 0.1.

For all efficacy endpoints, the descriptive statistics will be provided by treatment group for each of the study period. The statistics include number of observations, mean, standard deviation, 95% CI, minimum, median, and maximum for continuous variables, and number, percent and two-sided 95% CI for discrete variables. And number of subjects with missing data due to COVID-19 pandemic will be summarized for primary and secondary efficacy endpoints.

Unless otherwise specified, any subject will be analyzed according to the actual stratum the subject belongs to.

The Primary Analysis for the Induction Period and Re-Induction Period will be performed after all subjects have completed Week 12 of the Induction Period and Re-Induction Period, respectively, or prematurely discontinued study participation. This is the final efficacy analysis for the Induction Period and Re-Induction Period, respectively.

The final analysis will be conducted after all subjects have completed Week 40 of the Maintenance Period plus the 70 day Follow-up Visit or prematurely discontinued study participation. This is the final efficacy analysis for the Maintenance Period. To ensure the

integrity of the trial, the study sites and subjects will remain blinded until the final database lock is completed.

In Section 9.0, "Baseline" refers to the last non-missing observation prior to the first administration of study drug in the Induction Period, unless specified otherwise. "Comparison of treatment groups" refers to (i) comparison of each ABBV-154 group and placebo group in the Induction Period; (ii) comparison of Re-Induction Group 2 and Re-Induction Group 1 in the Re-Induction Period; (iii) comparison of each ABBV-154 group and placebo group for the randomized portion in the Maintenance Period.

"Stratification factors for the corresponding period" refers to randomization stratification factors specified in Section 2.3 except for the Maintenance Period, the randomization stratification factors used in efficacy analyses for the Maintenance Period are

- Achievement of CR100 at entry of the Maintenance Period (Week 12 of the Induction/Re-Induction Period): Yes vs No;
- Entry to the Maintenance Period: Induction Period vs Re-Induction Period.

For the comparison between ABBV-154 80 mg SC EOW and Placebo in the Maintenance Period, all data from subjects of the corresponding ITT3/ITT3-RN population will be included.

For the comparison between ABBV-154 230 mg SC EOW and Placebo in the Maintenance Period, data from subjects of the corresponding ITT3/ITT3-RN population will be included with the exception that data from subjects who are randomized to Induction Group 1 (ABBV-154 150 mg IV + 80 mg SC EOW), considered as responder at Week 12 of the Induction Period and entered the Maintenance Period will not be included.

Analysis of Categorical Variables:

For categorical variables, frequencies and percentages will be reported for each treatment group in each of the study period. In each period, comparison of treatment groups will be performed using the Cochran Mantel-Haenszel (CMH) test adjusting for stratification

factors for the corresponding period. If there is a stratum that has no subject in it, a value of 0.1 will be added to the denominator to the corresponding stratum in order to prevent dividing by 0, as suggested in Greenland and Robins (1985).[1] Point estimates and 95% confidence intervals (CI) for the difference in proportions between treatment groups will be provided. Construction of CI for the common risk difference will be based on the Mantel-Haenszel estimate adjusting for stratification factors for the corresponding study period.

Analysis of Continuous Variables:

For continuous variables, the model based mean and standard error will be provided. The mean value of the variable at baseline and each scheduled visit will also be presented for each treatment group. Continuous variables collected longitudinally will be using a Mixed-Effect Model Repeated Measurement (MMRM) model. Continuous efficacy variables which are collected at only one post-baseline visit (such as SES-CD) will be analyzed using an Analysis of Covariance (ANCOVA) model. Point estimates and 95% CIs of mean change from baseline within each treatment group, and the difference between treatment groups for each period will be provided.

9.2 Handling of Missing Data

Missing data could occur due to various reasons, including missing visits/assessments, early withdrawal from the clinical trials, or missing due to COVID-19 infection or logistic restrictions during the pandemic. Assessments on or after any intercurrent event will be handled as specified in Section 8.0.

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. 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. 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.

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 will use **N**on-**R**esponder **I**mputation (NRI) while incorporating Multiple Imputation (MI) to handle missing data due to **C**OVID-19 (NRI-C).
  - The NRI-C 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 restriction will be handled by MI. At each visit, subjects will be characterized as responders or non-responders based on MI imputed values if missing due to COVID-19; otherwise, subjects will be considered as non-responders for missing due to other reasons in the NRI-C approach. In addition, at and after the CD-related confounding medications intercurrent event (see Section 8.1) and on/after the date of initiation of CD-related medications after premature discontinuation of study drug (see Section 8.2) in the corresponding study period, subjects will be considered as non-responders and will not be imputed by MI.
- A sensitivity analysis for binary endpoints will use **NRI** with **N**o special data handling for missing due to **C**OVID-19 (NRI-NC).
  - NRI-NC will be performed in the same way as NRI-C without the exception above. Missing due to COVID-19 infection or logistical

restriction will also be counted as non-responders. Subjects on or after the occurrence of the CD-related confounding medications intercurrent event and on/after the date of initiation of CD-related medications after premature discontinuation of study drug will still be considered as non-responders.

- Details on MI method in NRI-C are described below:
  - 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. If the binary endpoints are derived from the continuous variables, PROC MI will be applied to the continuous variables. The variables to be included in the imputation model are: treatment group, randomization stratification factors for the corresponding period, age, gender, weight, baseline measurement (if applicable) and post-baseline measurements at each visit for the respective analysis period up to the end of the analysis period. The random seed for MCMC and the random seed for PROC MI are specified in Appendix E. The imputed post-baseline measurements will be rounded to the same precision as the observed data before the determination of responder status. Subjects will be characterized as responders or non-responders based on MI imputed data. Using the CMH model adjusted by randomization stratification factors, the endpoints will be analyzed using each of the 30 imputed datasets. SAS PROC MIANALYZE will be used to generate the final inferences of the risk difference between treatment groups, using Rubin's rule.[2] Note that measurements will be set to missing 1) at or after the occurrence of the CD-related confounding medications intercurrent event, or 2) on/after the date of initiation of CD-related medications after premature discontinuation of study drug before applying MI. After the MI imputation, an NRI override will be implemented for missing values 1) missing values due to reasons other than COVID-19 infection or logistic reasons, or 2) at or after the occurrence of the CD-related confounding medications or 3) on/after the date of initiation of CD-related medications after premature discontinuation of study drug, that is, regardless of MI imputed values, subjects satisfying 1) or 2) or 3) will be considered as "non-responder" for binary efficacy endpoints.

9.2.2 Continuous Endpoints

For continuous efficacy endpoints where Mixed-Effect Model Repeat Measurement (MMRM) analysis or Analysis of Covariance (ANCOVA) is performed, missing data will be handled using the following approaches.

- MMRM: The repeat measurement analysis will be conducted using a mixed model including observed measurements at all post-baseline visits for the respective analysis period up to the end of the analysis period. The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, stratification factors at randomization, and the continuous fixed covariates of baseline measurement. An unstructured variance covariance matrix will be used. If the model cannot converge, an appropriate variance-covariance structure matrix (e.g., autoregressive or compound symmetry) will be used. Parameter estimation is based on the method of restrictive maximum likelihood (REML). MMRM will be the primary approach in the analysis of continuous variables with repeated measurements.
- ANCOVA: For continuous efficacy variables that are collected at only one post-baseline visit (such as SES-CD), ANCOVA will be used. The model includes the categorical fixed effects of treatment, stratification factors at randomization, and the continuous fixed covariates of baseline and measurement.

9.2.3 Additional Analyses

In addition, As Observed (AO) analysis will be performed as supplementary for categorical endpoints.

- AO: 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 (except data collected after initiation of ABBV-154 rescue therapy for the analyses in the Maintenance Period).

9.3 Primary Efficacy Endpoint and Analyses

9.3.1 Primary Efficacy Endpoint

The primary endpoint for the primary analysis of efficacy is:

- Achievement of endoscopic response at Week 12 of the Induction Period

9.3.2 Primary Analysis of Primary Efficacy Endpoint

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

The primary endpoint will be analyzed between each ABBV-154 group and placebo group in the Induction Period using the CMH test, stratified by the randomization factors (baseline glucocorticoid use (yes/no); endoscopic disease severity (SES-CD < 15; SES CD ≥ 15); inadequate response to adalimumab (yes/no)) based on ITT1 population.

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

Estimand Label	Attributes of the Estimand				
	Treatment	Endpoint	Population	Intercurrent Events	Statistical Summary
Primary	Each ABBV-154 group vs. placebo in the Induction Period	Achievement of endoscopic response at Week 12 of the Induction Period	Subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics	IE1: Initiation or dose escalation of CD-related confounding medications IE2: premature discontinuation of study drug All subjects will be considered as non-responders at or after IE1 All data after IE2 will be used until initiation of CD-related medications	Difference in the proportion of subjects achieving endoscopic response

The primary efficacy endpoint will be tested at two-sided significance level of 0.1. A CMH based two-sided 95% CI for the difference between treatment groups will be constructed.

The NRI-C approach for handling missing data will be used for main analysis for the primary endpoint.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

Sensitivity analyses of the primary analysis of the primary efficacy endpoint is NRI-NC.

A supplementary analysis of the primary endpoint corresponded to the AO analysis specified in Section 9.2 will be performed in which all data after IE1 and IE2 will be used. CMH analysis as detailed in Section 9.1 will be repeated using AO data handling without

any imputation as an additional analysis. The analysis will be conducted on the ITT1 population who have the efficacy measurement at Week 12 visit.

9.4 Secondary Efficacy Analyses

9.4.1 Main Analyses of Ranked Secondary Efficacy Endpoints

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

In general, secondary efficacy variables will be analyzed using the CMH test controlling for stratification factors for the corresponding period. A CMH based two-sided 95% CI for the difference between treatment groups will be constructed.

The NRI-C method will be the primary approach for missing data handling.

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

	Attributes of the Estimand				
	Treatment	**Endpoint**	**Population**	**Handling Intercurrent Events**	**Statistical Summary**
Secondary endpoints in the Induction Period	Each ABBV-154 group vs. placebo	Achievement of clinical remission per CDAI at Week 12 in the Induction Period, clinical remission per SF/AP at Week 12 in the Induction Period	Subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics	IE1: Initiation or dose escalation of CD-related confounding medications IE2: premature discontinuation of study drug All subjects will be considered as non-responders at or after IE1 All data after IE2 will be used until initiation of CD-related medications	Difference in the proportion of subjects achieving each binary secondary endpoint in the Induction Period
Secondary endpoints in the Maintenance Period	Each ABBV-154 group vs. placebo	Achievement of clinical remission per CDAI at Week 40 in the Maintenance Period, clinical remission per SF/AP at Week 40 in the Maintenance Period, endoscopic response at Week 40 in the Maintenance Period	subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics and achieved response after the 12-week induction treatment with ABBV-154	IE1: Initiation or dose escalation of CD-related confounding medications IE2: premature discontinuation of study drug All subjects will be considered as non-responders at or after IE1 All data after IE2 will be used until initiation of CD-related medications	Difference in the proportion of subjects achieving each binary secondary endpoint in the Maintenance Period

9.4.2 Sensitivity and Supplementary Analyses for Secondary Efficacy Endpoints

For secondary endpoints, sensitivity analysis of the of the main analysis is NRI-NC.

A supplementary analysis of secondary endpoints are AO analyses specified in Section 9.2 will be performed in which all data after IE1 and IE2 will be used. CMH analysis as detailed in Section 9.1 will be repeated using AO data handling without any imputation as an additional analysis. The analyses will be conducted on the ITT1 population (for the Induction Period)/ ITT3 population (for the Maintenance Period) who have the efficacy measurement at corresponding visit for the endpoint.

NRI-C analysis for the secondary endpoints in the Maintenance Period will also be performed the ITT3-RN population. Treatment difference between each ABBV-154 group and placebo with point estimate and 95% CI will be presented using NRI-C approach with the CMH method as detailed in Section 9.1 and Section 9.2.

9.5 Additional Efficacy Analyses

Other efficacy endpoints described in Section 3.3 will be analyzed at all visits assessed using the same methods listed in above and Section 9.2. For analyses for the Induction Period and the randomized portion of the Maintenance Period, NRI-C with CMH method will be performed for binary endpoints while MMRM/ANCOVA will be performed for continuous endpoints.

AO analyses will be performed for analyses in the Re-Induction Period.

9.6 Dose-Response Modeling for ABBV-154

The dose-response relationship among ABBV-154 dose groups and the placebo group will be characterized for the primary endpoint using the Multiple Comparison Procedure - Modeling (MCP-Mod) method[5,6] among the ITT1 population for the Induction Period. The summary level response rates based on the primary analysis approach above will be used, and ADDPLAN DF software will be used to perform the MCP-Mod analyses.

A set of 6 pre-specified standardized candidate dose-response models, as described in Table 3 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 two-sided $\alpha = 0.1$. The fitted dose-response curves will be presented graphically for all statistically significant models along with 95% confidence bands. The minimum effective dose (MED) will be identified for each statistically significant model based on the pre-specified clinical meaningful target of 26%. The weighted MED across all significant models will be calculated, with weight being the inverse of each candidate dose-response model AIC.

Table 3. Candidate Models

Model	$f(d,\theta)$ d = dose, θ = Model Parameters	$f^0(d,\theta)$ Standardized Model	Initial Value(s) for Parameter(s)*
Linear	$E_0 + \delta d$	D	NA
Exponential	$E_0 + E_1\left[exp\left(\frac{d}{\delta}\right) - 1\right]$	$exp\left(\frac{d}{\delta}\right) - 1$	$\delta = 1060$
Logistic	$E_0 + \frac{E_{max}}{1 + exp\left(\frac{ED_{50} - d}{\delta}\right)}$	$\frac{1}{1 + exp\left(\frac{ED_{50} - d}{\delta}\right)}$	$ED_{50} = 230$, $\delta = 101.9$
EMax	$E_0 + \frac{E_{max} d}{ED_{50} + d}$	$\frac{d}{ED_{50} + d}$	$ED_{50} = 128.9$
sigEMax	$E_0 + \frac{E_{max} d^h}{{ED_{50}}^h + d^h}$	$\frac{d^h}{{ED_{50}}^h + d^h}$	$ED_{50} = 230$, $h = 3.5$
Quadratic	$E_0 + \beta_1 d + \beta_2 d^2$	$d + \frac{\beta_2}{\lvert\beta_1\rvert} d^2$	$\delta = -0.0007$

* For Exponential model, the initial value was determined based on the assumption that ABBV-154 600 mg IV/530 mg SC EOW will achieve 95% of the maximum efficacy of ABBV-154. For Logistic, EMax, sigEMax, and Quadratic model, the initial values were determined based on the assumption that ABBV-154 600 mg IV/530 mg SC EOW and ABBV-154 300 mg IV/ 230 mg SC EOW will achieve 95% and 50% of the maximum efficacy of ABBV-154, respectively.

Steps of MCP-Mod:

1. Choose a candidate set of models as in Table 3.
2. Compute the optimum contrast for each model.
3. Use contrast test to find all significant models while preserving family-wise error rate (FWER).
4. Use all significant models to make inference about the weighted target dose of interest.

9.7 Efficacy Subgroup Analyses

To evaluate the consistency of the efficacy over demographic and other baseline characteristics, subgroup analysis will be performed for the primary endpoint for the subgroups listed in Table 4 below using ITT1.

For subgroup analysis, point estimate and 95% CI for each treatment group as well as point estimate and 95% CI for treatment differences between each ABBV-154 group and placebo group will be presented. No p-value will be provided. If any of the resulting categories for a subgroup factor listed in Table 4 (except age, sex and race), has fewer than 10% of the planned total sample size, subgroup analyses will not be presented for that category.

Table 4. Subgroups for Efficacy Analysis

Subgroup Factor	Categories
Sex	Male, Female
Age	≥ 18 years - < 40 years, ≥ 40 years - < 65 years, ≥ 65 years
Race	White, non-White
Baseline Glucocorticoid Use	Yes or No
Endoscopic Disease Severity	SES-CD < 15, SES-CD ≥ 15
Inadequate Response to adalimumab	Yes or No
Inadequate response to prior anti-TNF biologics	Yes or No

9.8 Efficacy Analyses for ABBV-154 Rescue Therapy

To evaluate the efficacy for ABBV-154 rescue therapy, the following endpoints will be analyzed on ITT3-RES population and AO analysis will be performed:

- Achievement of clinical remission per CDAI at Week 12 and Week 24 after ABBV-154 rescue therapy
- Achievement of clinical remission per SF/AP at Week 12 and Week 24 after ABBV-154 rescue therapy
- Achievement of CR100 at Week 12 and Week 24 after ABBV-154 rescue therapy
- Mean FCP at Week 12 and Week 24 after ABBV-154 rescue therapy
- Mean hs-CRP at Week 12 and Week 24 after ABBV-154 rescue therapy

10.0 Safety Analyses

10.1 General Considerations

Safety analyses will be performed on the safety population for the Induction Period (SA1), the Re-Induction Period (SA2), the Maintenance Period (SA3) and SA-RES, SA-ALL154 population as defined in Section 4.0. In addition, safety summaries will be

performed on the safety analysis set for combined data from different periods (SA-IN2, SA-INMN, SA-IN2MN).

The standard safety analyses will include reporting of adverse events (AEs), adverse events of special interest (AESIs), laboratory, and vital signs measurements. Frequency tables and exposure adjusted event rate per 100 patient-years 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 treatment group. Frequency tables of subjects meeting criteria for potentially clinically important vital sign values and for potentially clinically important laboratory values will be provided by treatment group.

For safety analyses (such as analyses of laboratory and vital signs measurements) in the Induction Period, the baseline value is defined as the last available measurement before study drug administration for all subjects (including subjects who received placebo). For all other safety analyses, the baseline value is defined as the last available measurement before first administration of ABBV-154 for all subjects.

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

Missing safety data will not be imputed.

10.2 Adverse Events

AEs will be summarized and presented using primary MedDRA SOCs and 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 AEs 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

Induction Period (SA1 population): TEAEs for the Induction Period are defined as events that begin either on or after the first dose of the study drug in the Induction Period and until (i) the first dose of study drug in the Re-Induction Period (if applicable), or (ii) until first dose of study drug in the Maintenance Period (if applicable), or (iii) within 70 days after the last dose administration of the study drug in the Induction Period, whichever is earlier.

Re-Induction Period (SA2 population): TEAEs for the Re-Induction Period are defined as events that begin either on or after the first dose of the study drug in the Re-Induction Period and until (i) first dose of study drug in the Maintenance Period (if applicable), or (ii) within 70 days after the last dose administration of the study drug in the Re-Induction Period, whichever is earlier.

Maintenance Period (SA3 population): TEAEs for the Maintenance Period are defined as events that begin either on or after the first dose of the study drug in the Maintenance Period and until (i) within 70 days after the last dose administration of the blinded study drug in the Maintenance Period, or (ii) initiation of ABBV-154 rescue therapy, whichever is earlier.

ABBV-154 Rescue Therapy (SA-RES population): TEAEs for the ABBV-154 rescue therapy are defined as events that begin either on or after the first dose of the ABBV-154 rescue therapy in the Maintenance Period and until 70 days after the last dose administration of the study drug in the Maintenance Period.

All ABBV-154 (SA-ALL154 population): TEAEs for "All ABBV-154" are defined as events that begin either on or after the first dose of ABBV-154 and within 70 days after the last dose of ABBV-154 in the study. Events that begin when subjects on Placebo will be not included.

Safety analyses from combined periods:

Induction Period + Re-Induction Period ABBV-154 (SA-IN2 population): TEAEs for "Induction Period + Re-Induction Period ABBV-154" (SA_IN2) are defined as events that begin either on or after the first dose of ABBV-154 in the Induction Period and until (i) first dose of study drug in the Maintenance Period (if applicable), or (ii) within 70 days after the last dose of study drug in the study, whichever is earlier.

Induction Period/Re-Induction Period + Maintenance Period ABBV-154 (SA-INMN population): TEAEs for "Induction Period/Re-Induction Period + Maintenance Period ABBV-154" (SA_INMN) are defined as events that begin either on or after the first dose of ABBV-154 in the Induction Period/Re-Induction Period and until (i) within 70 days after the last dose of study drug in the study, or (ii) initiation of ABBV-154 rescue therapy, whichever is earlier.

Induction Period + Re-Induction Period + Maintenance Period ABBV-154 (SA-IN2MN population): TEAEs for "Induction Period + Re-Induction Period + Maintenance Period ABBV-154" (SA-IN2MN) are defined as events that begin either on or after the first dose of ABBV-154 in the Induction Period and until (i) within 70 days after the last dose of study drug in the study, or (ii) initiation of ABBV-154 rescue therapy, whichever is earlier.

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). 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 TEAE
- Any TEAE related to COVID-19
- Any TEAE that was rated as with reasonable possibility to study drug by the investigator.
- Any TEAE with CTCAE grade ≥ 3
- Any serious TEAE.
- Any TEAE leading to discontinuation of study drug.
- Any TEAE leading to death.
- Treatment-emergent AESI (See ABBV-154 Product Safety SAP (PSSAP) for details).
- All deaths
  - Deaths occurring ≤ 70 days after last dose of study drug
  - Deaths occurring > 70 days after last dose of study drug
  - Deaths related to COVID-19

In addition, an overview of AEs per 100 patient-years of study exposure will be presented for the AE categories defined above. 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.

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

TEAEs 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 AEs will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same AE occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

For summary by maximum severity, if a subject has an AE with an unknown severity, then the subject will be counted in the severity category of unknown, even if the subject

has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same AE in the same analysis period with grade ≥ 3. In this case, the subject will be counted under the maximum AE grade.

For summary by maximum relationship to study drug, if a subject has an AE with an unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same AE in the same analysis period with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.

In addition, TEAEs will be summarized by PT and sorted by decreasing frequency for the total ABBV-154 group.

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

TEAEs will be summarized by event rate per 100 subject years, defined as

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

where total patient years is defined as the sum of the study drug exposure of all subjects, normalized by 365.25, and rounded to 1 decimal place. Note that one event per preferred term per day per subject will be counted in the calculation of the number of AEs (i.e., a preferred term will not be counted twice on the same day for the same subject).

The TEAE rates per 100 patient-years of exposure will be provided for each AE category in the AE overview summary (defined in Section 10.2.2) and for TEAE summary by SOC and PT.

The study drug exposure for each safety population is defined as last dose date plus 70 days, minus the first dose date. For SA-All154 safety population, the duration when subjects on Placebo will not be included in the calculation.

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.

10.2.6 Adverse Events of Special Interest

Treatment-emergent AESIs 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, as specified in Appendix G.

Treatment-emergent AESIs will be summarized by SOC and PT and listing format. Additionally, the event rate per 100 patient years of exposure will be provided for provided by SOC and PT for each AESI in the AE overview summary.

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 the analyses. Baseline values collected for SAE-related laboratory assessments on or before the first dose of study drug will be excluded. Data collected more than 70 days after the last dose of study drug of the analysis period (See Section 10.2.1) for the corresponding analysis populations 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

Each laboratory variable will be summarized at all time points (starting at baseline) with the number of observations, mean, standard deviation, median, minimum and maximum

for non-missing observations. The change from Baseline at each applicable post-baseline visit will be summarized for selected laboratory variables, with the number of observations, baseline mean, and visit mean. The mean, standard error, and 95% CI will be presented for the change from Baseline for each treatment group.

For each period, treatment group differences for the 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

Changes in laboratory parameters will be tabulated using shift tables categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table summarizes shifts from baseline to minimum and maximum values (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

The criteria for potentially clinically significant laboratory values will be determined by CTCAE criteria of Grade 3, Grade 4 and ≥ Grade 3, with a grade worsening compared to baseline. Toxicity grading scale is based on National Cancer Institute Common Toxicity Criteria (NCI CTC) AE version 5.0. The number and percentage of subjects meeting the criteria for potentially clinically significant laboratory values will be summarized by treatment group. Listings of subject-level laboratory data will be provided for subjects meeting the criteria.

Assessment of Liver Elevations

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 > 3 × ULN
- ALT > 5 × ULN
- ALT > 10 × ULN
- ALT > 20 × ULN
- AST > 3 × ULN
- AST > 5 × ULN
- AST > 10 × ULN
- AST > 20 × ULN
- TBL > 1.5 × ULN
- TBL > 2 × ULN
- ALP > 1.5 × ULN
- ALT and/or AST > 3 × ULN and TBL > 1.5 × ULN
- ALT and/or AST > 3 × ULN and TBL > 2 × ULN
- ALT > 3 × ULN and TBL > 1.5 × ULN
- ALT > 3 × ULN and TBL > 2 × ULN,

where ULN is the upper normal limit. The maximum ratio relative to the ULN will be used to determine if subjects meet any of the criteria listed above.

A listing of subjects, defined as those meeting the following criteria will also be provided:

- ALT and/or AST > 3 × ULN and/or ALP > 1.5 × ULN and TBL > 1.5 × ULN

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, pulse rate, body weight, respiratory rate and body temperature will be summarized. Data collected more than 70

days after the last dose of study drug of the analysis period (See Section 10.2.1) for the corresponding analysis populations will not be included.

Each vital sign variable will be summarized at all time points (starting with Baseline) with the number of observations, mean and standard deviation, median, minimum and maximum for non-missing observations. Change from Baseline at each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, Baseline mean, and visit mean. The mean, standard error, and 95% CI will be presented for the change from Baseline for each treatment group.

For each period, treatment group differences 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.

Vital sign variables will be evaluated based on potentially clinically important (PCI) criteria (See ABBV-154 PSSAP). 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.

11.0 Interim Analyses

An interim analysis will be performed when approximately 66% of the subjects (35 subjects per group) have reached Week 12 of the Induction Period or have prematurely discontinued the study to inform the development of future studies. The interim analysis will be conducted by an independent AbbVie team outside of the blinded M20-371 study team. The interim analysis result will be reviewed by Internal Executive Review Committee (IERC) from AbbVie.

IERC members are not involved in this study but have the scientific and technical expertise and experiences for making decisions based on the interim analysis results. The interim analysis result will not be reviewed by external Data Monitoring Committee (DMC).

A separate interim unblinding plan will be developed to describe the detailed interim analysis plan, including the interim unblinding team, decision rules, execution logistics, and data chain of custody to protect the integrity of the clinical study. The interim analysis plan will not be documented in the DMC charter.

An additional interim analysis in the Maintenance Period might be performed to inform the development of future studies. The results from this analysis will not impact the conduct of the current study.

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 is 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.

12.0 Overall Type-I Error Control

Overall Type I error control is not planned for this Phase 2 study.

13.0 Version History

Table 5. SAP Version History Summary

Version	Date	Summary
1.0	17 April 2022	Original version
2.0	10 February 2023	• Provided clarification that PGIC-CD+, PGIS-CD+, and data collected in the Wearable Device Substudy are not in the scope of the SAP, removed endpoints related to PGIC-CD+, PGIS-CD+ and the endpoints from the Wearable Device Substudy from SAP (Section 1.0, Section 3.4). • To be more precise in terms of definition of study populations.

Version	Date	Summary
		○ Updated the population attribute to target population (Section 2.1, Table 1, Table 2) ○ Specified the terminology of ITT1 population (Section 4.0) ○ Provided additional clarifications on the definition of ITT3 population (Section 4.0) • The following changes have occurred to reflect changes in the protocol amendment to add Rescue Therapy option with ABBV-154 during the Maintenance Period and removal of the Long-Term Extension study. ○ Provided description of ABBV-154 rescue therapy (Section 2.2, Figure 1) ○ Added ITT3-RES and SA-RES for the efficacy/safety analyses on the subjects who receive Rescue Therapy option with ABBV-154 (Section 4.0, Section 10.1) ○ Added the analyses to evaluate the efficacy of ABBV-154 rescue therapy (Section 9.8) ○ Provided clarification that TEAEs for the Maintenance Period (SA3 population) and combined period analyses (SA-INMN, SA-IN2MN population) don't include AEs with onset date after initiation of ABBV-154 rescue therapy (Section 10.2.1) ○ Added the definition of TEAE for SA-RES population (Section 10.2.1) ○ Removed language related to the Long-Term Extension study (Section 2.2, Section 9.1) • Provided additional clarity for the timing of the primary analysis for each period (Section 2.2, Section 9.1). • Provided additional clarification for the summary of subject disposition (Section 5.0). • Provided clarification for the calculation of duration of treatment that only duration of blinded study drug will be considered for SA1/SA2/SA3 populations, and also provide more clarification of study drug duration of Induction Group 4 (Section 6.0).

Version	Date	Summary
		• Provided clarification that medications started after initiation of ABBV-154 rescue therapy will not be considered as concomitant medications for the Maintenance Period, and updated concomitant medications definition following the removal of Long-Term Extension study (Section 7.0). • Updated the handling strategy for the intercurrent event of premature discontinuation of study drug (Section 8.2, Section 9.2.1, Table 1, Table 2). • Provided additional clarity that data from subjects randomized to Induction Group 1, considered as responder at Week 12 of the Induction Period and entered the Maintenance Period will not be included in the comparison between ABBV-154 230 mg SC EOW versus Placebo as they are not from the same randomization (Section 9.1). • Provided clarification that data collected after initiation of ABBV-154 rescue therapy will not be included in the AO analysis (Section 9.2.3). • Provided clarification for the planned analysis method for the additional efficacy analyses (Section 9.5). • Updated the terminology "safety topics of interest" to "adverse events of special interest" and provided list of AESIs and the corresponding identification criteria (Section 10.1. Section 10.2.2, Section 10.2.6, Appendix G). • Updated TEAE definition following the removal of Long-Term Extension study, and also provided additional clarifications on TEAE definition for the SA-ALL154 population and patient-year duration calculation method for the SA-ALL154 population (Section 10.2.1, Section 10.2.4). • Updated AE severity grade to CTCAE grade to align with AE collection strategy (Section 10.2.2, Section 10.2.3). • Provided additional clarity that laboratory/vital sign collected 70 days after last dose of study drug within each analysis period will not be included in the analysis for that period (Section 10.3, Section 10.4). • Provided additional clarity that additional interim analysis may be performed for the Maintenance Period (Section 11.0).

14.0 References

1. Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics. 1985;41(1):55-68.
2. Rubin DB. Multiple imputation for nonresponse in surveys. John Wiley & Sons, Inc. 1987.
3. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat. 1979;6:65-70.
4. Qu Y, Shurzinske L, Sethuraman S. Defining estimands using a mix of strategies to handle intercurrent events in clinical trials. Pharm Stat. 2021;20(2):314-23.
5. 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.
6. Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics. 2005;61(3):738-48.

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. Crohn's Disease Activity Index (CDAI)

The Crohn's Disease Activity Index (CDAI) is a composite instrument that includes patient symptoms evaluated over 7 days (abdominal pain, stool frequency and general well-being), as well as physical and laboratory findings. These items are scored individually, weighted, and do not contribute equally to the overall score. The CDAI is derived from summing up the weighted individual scores of eight items as detailed below:

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	×	2	
2. Abdominal pain rating: 0 = none, 1 = mild, 2 = moderate, 3 = severe	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	×	5	
3. General well-being: 0 = generally well, 1 = slightly underpar, 2 = poor, 3 = very poor, 4 = terrible	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	×	7	
4. Number of 6 listed categories the subject now has **Check all items that apply:** ☐ Arthritis/arthralgia ☐ Iritis/uveitis ☐ Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis ☐ Fissure, abscess and/or anal fistula (draining/non-draining) ☐ Other fistula (draining/non-draining) ☐ Fever over 100°F (37.8°C) during past week	Record "0" if no categories checked	×	20	
5. Taking Lomotil/Imodium/ Loperamide/opiates for diarrhea 0 = no, 1 = yes	_____	×	30	
6. Abdominal mass 0 = none, 2 = questionable, 5 = defined	_____	×	10	
7. Hematocrit: ___.__	Male: (47 – hematocrit) = Female: (42 – hematocrit) = Subtotal If hematocrit > normal, enter "0"	×	6	
8. Body weight: ___.__(kg) Standard weight: ___.__(kg)	100 × [1 – (Body wt/Standard wt)] = Percent below standard weight: _____ If body wt > std. wt, enter "0"	×	1	
			Total	

Higher CDAI scores indicate more severe disease. For the calculation of CDAI and components (daily stool frequency, abdominal pain score and general well-being) at each visit, the following rules will be applied:

1. Identify the visit date with CDAI components that are collected, and set it as the CDAI calculation date.
2. Calculate the subtotal scores from the component 1-3 (liquid or very soft stool frequency, abdominal pain score and general well-being) as follows:
    a. Select the diary data from 14 days prior to the CDAI calculation date, and set the data from the 4 days (the day prior to, on the day of and two days after the endoscopy date) to missing;
    b. Take non-missing diary data from 7 most recent days from step i. If there are multiple entries on the same day for the eDiary component, use the worst result (larger number);
    c. If there are non-missing diary data from 7 days, the subtotal score is calculated as the sum of the 7-day scores, and multiplying the factor for the corresponding component as listed in the table above;
    d. If there are non-missing diary data from less than 7 days but greater than 3 days (4, 5, 6 days), the subtotal score is calculated as average of the dairy data and times 7, and multiplying the factor for the corresponding component as listed in the table above;
    e. If there are only less than 4 days of non-missing diary data available, the subtotal score will be set to missing.

    Of note, Average daily SF/AP will be determined in the same way as described above to derive SF/AP-related endpoints (for example, clinical remission per SF/AP).
3. Subtotal scores for components 4-6 (Number of 6 listed categories, usage of Lomotil/Imodium/Loperamide/opiates for diarrhea and abdominal mass) will be determined using the data collected on the CDAI calculation date and the corresponding formula in the table above;

4. Subtotal score for component 7 (Hematocrit) is calculated as follows:
    a. Identify the Hematocrit (%) value form the same visit as the CDAI calculation date, use the Hematocrit that is closest to the CDAI calculation date;
    b. Hematocrit values obtained from previous visits can be used.
    c. The subtotal score for Hematocrit is calculated using the formula in the table above. If Hematocrit value is greater or equal to 47% for male subjects (greater or equal to 42% for female subjects), the subtotal score is set to 0.
5. Subtotal score for component 8 (percentage below standard weight) is calculated as follows:
    a. Standard weight is calculated based on height obtained at screening, sex and study operations manual Section 7.2;
    b. Body weight is based on the measurement obtained on the CDAI calculation data, or previous visits if the measurement is missing.
    c. The subtotal score for percentage below standard weight is calculated using the formula in the table above.
6. CDAI score is calculated as the sum of subtotal scores of 8 components, and the total CDAI score will be rounded to 1 decimal. If any of the subtotal scores are missing, the CDAI score will be missing.

Appendix C. Simple Endoscopic Score – CD (SES-CD)

SES-CD is calculated based the sum of individual segment values for four endoscopic variables (presence and size of ulcers, ulcerated surface, affected surface and presence of narrowing). Each variable in each segment be scored 0 to 3 resulting in SES-CD values ranging from 0 to 56 with higher scores indicating more severe disease.

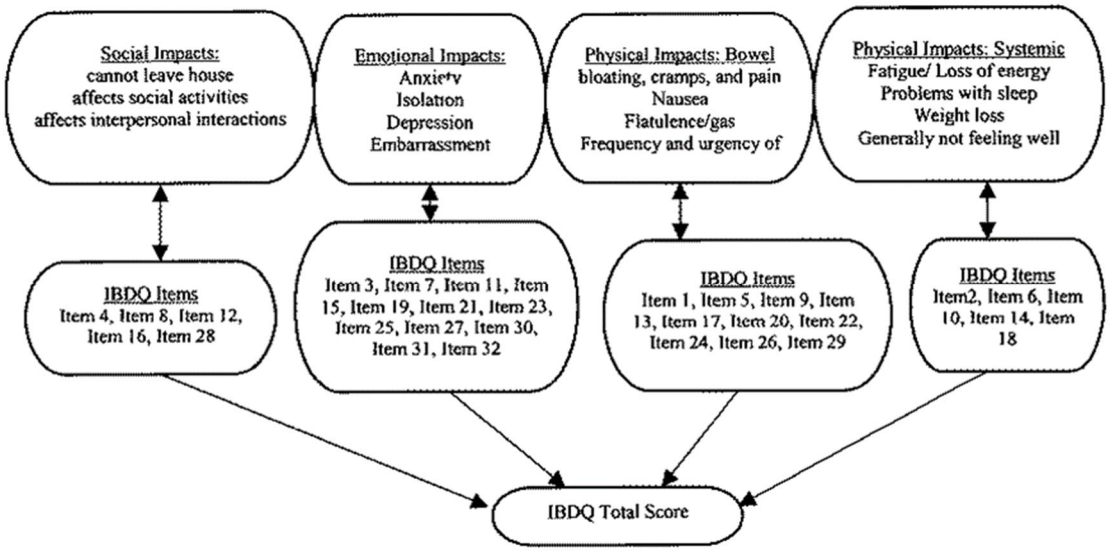
SES-CD Scoring:

	Rectum	Sigmoid and Left Colon	Transverse Colon	Right Colon	Ileum	Total
Size of Ulcers Enter: 0 if none 1 if aphthous ulcers (0.1 to ≤ 0.5 cm) 2 if large ulcers (> 0.5 to 2 cm) 3 if very large ulcers (> 2 cm)						
Ulcerated Surface Enter: 0 if none 1 if < 10% 2 if 10% – 30% 3 if > 30%						
Affected Surface Enter: 0 if unaffected segments 1 if < 50% 2 if 50% – 75% 3 if > 75%						
Presence of Narrowing Enter: 0 if none 1 if single, can be passed 2 if multiple, can be passed 3 if cannot be passed						
					TOTAL =	

Appendix D. Patient Reported Outcomes Questionnaires Descriptions

IBDQ – Inflammatory Bowel Disease Questionnaire

The IBDQ is a 32-item (ranges 1 – 7) self-report questionnaire for patients with IBD to evaluate the patient reported outcomes across 4 dimensions: bowel symptoms (loose stools, abdominal pain), systemic symptoms (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional function (anger, depression, irritability). The IBDQ total Score ranges from 32 to 224 with a higher score indicating better outcome.



The derivation of the IBDQ total score and the four IBDQ domain scores are as follows:

Domain Scores:

S1. BOWEL SYMPTOM: Q1 + Q5 + Q9 + Q13 + Q17 + Q20 + Q22 + Q24 + Q26 + Q29
[score ranges from 10 - 70],

S2. SOCIAL FUNCTION: Q4 + Q8 + Q12 + Q16 + Q28
[score ranges from 5 - 35],

S3. SYSTEMIC SYMPTOM: Q2 + Q6 + Q10 + Q14 + Q18
[score ranges from 5 - 35],

S4. EMOTIONAL FUNCTION: Q3 + Q7 + Q11 + Q15 + Q19 + Q21 + Q23 + Q25 + Q27 + Q30 + Q31 + Q32
[score ranges from 12 - 84].

Total Score:

IBDQ Total Score = SUM of (bowel symptom domain score, social function domain score, systemic symptom domain score, emotional function domain score).

The following convention applies to IBDQ:

When not more than 20% of items in a domain of IBDQ were missing, it was substituted with the mean values from the items completed in the particular domain; otherwise, they were treated as missing. The 20% threshold in each domain is: bowel symptom domain: 2 items, systemic symptom domain: 1 item, social function domain: 1 item, emotional function domain: 2 items. If any of the 4 domain scores is missing, the total IBDQ score will be set to missing.

SF-36 – Short Form 36

The SF-36 questionnaire is a self-administered multi-domain scale with 36 items. Eight subscales cover a range of functioning: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The scoring yields a physical component score, a mental component summary score, and subscale scores. Higher scores represent better outcomes. The concepts measured by the

SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the benefit of different treatments.

FACIT-F – Functional Assessment of Chronic Illness Therapy-Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system is a comprehensive compilation of questions that measure health related quality of life in patients with cancer and other chronic diseases (www.facit.org). The FACIT-F scale is a symptom-specific subscale of FACIT and is composed of 13 fatigue-related questions as follows. The response to each question is as follows: 0=Not at all, 1=A little bit, 2=Somewhat, 3=Quite a bit, 4=Very much.

1. I feel fatigued
2. I feel weak all over
3. I feel listless ("washed out")
4. I feel tired
5. I have trouble starting things because I am tired
6. I have trouble finishing things because I am tired
7. I have energy
8. I am able to do my usual activities
9. I need to sleep during the day
10. I am too tired to eat
11. I need help doing my usual activities
12. I am frustrated by being too tired to do the things I want to do
13. I have to limit my social activity because I am tired

In order to have higher values representing lower level of fatigue, all of the items, except for item 7 "I have energy" and item 8 "I am able to do my usual activities," are assigned reversed scores: reversed score = 4 – raw score. The total FACIT-F score will then be calculated as follows:

- FACIT-F score = 13×[Sum of answered-item scores / Number of items answered]

The score ranges from 0 to 52, 52 being the lowest level of fatigue.

When there are missing data, provided that more than 50% of the items (i.e., at least 7 of 13 items) were answered in FACIT-F questionnaire, the total score will not be deemed as missing but be calculated as the mean response for all the non-missing-value items. If less than 50% of the items were answered, the total score will have a missing value.

Appendix E. Random Seeds

In case of non-convergence, the random seed will be updated by adding 100000 at each attempt until convergence of model happens.

Table I-1. Random Seeds for NRI-C

Variables	Random Seed	
	MCMC Procedure	**PROC MI**
CDAI	20371	30371
SES-CD (for 20 individual variables)	N/A	31371
SF	22371	32371
AP score	23371	33371
IBDQ total score	24371	34371
Bowl Urgency	25371	35371
Rectal Bleeding	26371	36371

Appendix F. Crohn's Disease Location Per SES-CD

For isolated ileal disease in the analysis using SES-CD: Patients who have SES-CD = 0 in all segments other than ileum are considered to have isolated ileitis.

For ileocolonic disease in the analysis using SES-CD: Patients who have SES-CD different than 0 in the ileum and at least one of the colonic segments.

For colonic disease in the analysis using SES-CD: Patients who have SES-CD = 0 in the ileum and SES-CD different than 0 in at least one of the colonic segments.

Appendix G. List of Adverse Events of Special Interest (AESIs)

AESI	Criteria for Identification of Events
Serious infections	"Infections" CMQ (subset for SAEs)
Opportunistic infections	"Opportunistic Infection" CMQ for Opportunistic Infections excluding Tuberculosis and Herpes Zoster
Active TB	"Active Tuberculosis" CMQ
Hypersensitivity reactions	"Hypersensitivity" SMQ narrow
Serious allergic reactions	"Anaphylactic Reaction" SMQ (Narrow) or "Angioedema" SMQ (Narrow) (subset to SAEs)
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 Tumours SMQ (Broad) excluding PTs identified by Melanoma CMQ
Lymphoma	Malignant Lymphomas SMQ (Narrow)
Systemic glucocorticoid side effects	Based on adjudicated results (the identification of events to be adjudicated are described in the GC Adjudication Charter)
Adrenal insufficiency	"Tertiary Adrenal Insufficiency (ABBV-154 Product Specific)" CMQ
Iatrogenic Cushing's syndrome	"Iatrogenic Cushing's Syndrome (ABBV-154 Product Specific)" CMQ