



STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy and Safety of Filgotinib in the Treatment of Small Bowel Crohn's Disease (SBCD)
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CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

TABLE OF CONTENTS	2
LIST OF IN-TEXT TABLES	4
LIST OF IN-TEXT FIGURES	4
LIST OF ABBREVIATIONS.....	5
DEFINITION OF TERMS	8
1. INTRODUCTION	9
1.1. Study Objectives	9
1.2. Study Design	10
1.3. Sample Size and Power	12
2. TYPE OF PLANNED ANALYSIS	13
2.1. Data Monitoring Committee (DMC) Analyses	13
2.2. Final Analysis	13
3. GENERAL CONSIDERATIONS FOR DATA ANALYSES	14
3.1. Analysis Sets	14
3.1.1. All Randomized Analysis Set.....	14
3.1.2. Full Analysis Set	14
3.1.3. Safety Analysis Set.....	14
CCl [REDACTED]	
3.2. Subject Grouping	15
3.3. Strata and Covariates.....	15
3.4. Examination of Subject Subgroups	15
3.5. Missing Data and Outliers.....	16
3.5.1. Missing Data	16
3.5.2. Outliers	16
3.6. Data Handling Conventions and Transformations	16
3.7. Analysis Visit Windows.....	18
3.7.1. Definitions.....	18
3.7.2. Analysis Visit Windows	18
3.7.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window	20
3.8. Assess of Coronavirus Disease 2019 Impact.....	21
4. SUBJECT DISPOSITION	22
4.1. Subject Enrollment and Disposition.....	22
4.2. Extent of Study Drug Exposure and Adherence.....	23
4.2.1. Duration of Exposure to Study Drug	23
4.2.2. Adherence to Study Drug	23
4.3. Protocol Deviations	24
4.4. Missed and Virtual Visits due to COVID-19	25
5. BASELINE CHARACTERISTICS	26
5.1. Demographics and Other Baseline Characteristics	26
5.2. Baseline Disease Characteristics	26
5.3. Medical History	29
6. EFFICACY ANALYSES	30

6.1.	General Considerations	30
6.1.1.	Calculation of CDAI and PRO2 Scores	32
6.1.2.	Calculation of MaRIA Scores and Corresponding Endpoints	33
6.2.	Primary Efficacy Endpoint	33
6.2.1.	Definition of the Primary Efficacy Endpoint	33
6.2.2.	Analysis of the Primary Efficacy Endpoint	33
6.3.	Secondary Efficacy Endpoints	33
6.3.1.	Definition of the Secondary Efficacy Endpoints	33
6.3.2.	Analysis of the Secondary Efficacy Endpoints	34
CCI		
6.5.	Change from Protocol-Specified Efficacy Analyses	38
7.	SAFETY ANALYSES	39
7.1.	Adverse Events and Deaths	39
7.1.1.	Adverse Event Dictionary	39
7.1.2.	Adverse Event Severity	39
7.1.3.	Relationship of Adverse Events to Study Drug	39
7.1.4.	Serious Adverse Events	39
7.1.5.	Treatment-Emergent Adverse Events	39
7.1.6.	Summaries of Adverse Events and Deaths	40
7.1.7.	Adverse Events of Interest	42
7.2.	Laboratory Evaluations	43
7.2.1.	Summaries of Numeric Laboratory Results	44
7.2.2.	Graded Laboratory Values	45
7.2.3.	Liver-related Laboratory Evaluations	46
7.3.	Body Weight, Height and Vital Signs	46
7.4.	Prior and Concomitant Medications	47
7.4.1.	Prior Medications	47
7.4.2.	Concomitant Medications	47
7.5.	Electrocardiogram Results	48
7.6.	Other Safety Measures	48
7.7.	Changes from Protocol-Specified Safety Analyses	48
10.	REFERENCES	51
11.	SOFTWARE	52
12.	SAP REVISION	53
13.	APPENDICES	54

LIST OF IN-TEXT TABLES

Table 3-1	Analysis Visit Windows for CDAI, PRO2 CCI Endpoints	19
Table 3-2	Analysis Visit Windows for MaRIA Score-related Efficacy Endpoints.....	19
Table 3-3	Analysis Visit Windows for Body Weight, Vital Signs, ECG, Hematology, Chemistry, Fasting Lipid Profile, Serum Immunoglobulin, CCI	19
Table 6-1.	Definitions of Dichotomous Efficacy Endpoints.....	30
Table 13-1.	Calculation of CDAI Score	59
Table 13-2.	Calculation of PRO2 Components	59
Table 13-3.	Calculation of CDAI Patient-Reported Outcome Components and PRO2 Scores at Screening	61
Table 13-4.	Calculation of CDAI Patient-Reported Outcome Components and PRO2 Scores at Post-Screening Visits.....	62
Table 13-5.	Sources of Information for Calculating CDAI and PRO2 Scores	63
Table 13-6.	Examples of Search Terms for “COVID-19” and “Virtual” used to Identify Missed and Virtual Visits.....	70
Table 13-7.	Examples of Extraneous Text Terms to Eliminate from the Comment Fields	70

LIST OF IN-TEXT FIGURES

Figure 1-1.	Study Design Schematic.....	11
Figure 13-1.	Selection of Diary Data for the Calculation at Screening.....	60
Figure 13-2.	Selection of Diary Data for Calculation at Post-Screening Visits	62

LIST OF ABBREVIATIONS

6-MP	6-mercaptopurine
AE	adverse event
AEI	adverse events of interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ASTE	arterial systemic thromboembolism
BLQ	below the limit of quantitation
BMI	body mass index
CCG	eCRF Completion Guidelines
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form(s)
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CVEAC	cardiovascular safety endpoint adjudication committee
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form(s)
EQ-5D	EuroQol five dimensions
ET	early termination
FAS	Full Analysis Set
Gilead	Gilead Sciences, Inc.
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	high-density lipoprotein
HIV	Human Immunodeficiency Virus
HLGT	high-level group term
HLT	high-level term
HRQoL	health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
ID	identification
IM	intramuscularly
IV	intravenously

IWRS	interactive web response system
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
LLT	lower-level term
LOCF	last observation carried forward
LOQ	limit of quantification
LTE	long-term extension
MACE	major adverse cardiovascular events
MaRIA	Magnetic Resonance Index of Activity
MDD	minimal detectable difference
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMP-9	matrix metalloproteinase-9
MRE	Magnetic Resonance Enterography
MST	MedDRA search term
MTX	methotrexate
NLP	Natural Language Processing
NRI	non-responder imputation
O&P	ova and parasites test
OIs	opportunistic infections
PBMC	peripheral blood mononuclear cell
PBO	placebo
PK	pharmacokinetic
PO	orally
PR	rectally
PRO2	patient reported outcomes consisting of 2 items: abdominal pain severity and liquid stool frequency
PT	preferred term
PTM	placebo to match
PTx	Post-Treatment
Q1, Q3	first quartile, third quartile
RCE	relative contrast enhancement
SAE	serious adverse event
SAP	statistical analysis plan
SBCD	small bowel Crohn's disease
SD	standard deviation
SE	standard error
SF-36	short-form 36 health survey
SMQ	Standardised MedDRA Queries
SOC	system organ class
TEAE	treatment-emergent adverse event

TFLs	tables, figures, and listings
TNF α	tumor necrosis factor-alpha
ULN	upper limit of the normal range
US	United States
vPBMC	viably frozen peripheral blood mononuclear cell
V-Day	visit day
VTE	venous thromboembolism
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

DEFINITION OF TERMS

Clinical Remission by CDAI	CDAI score < 150 points
Corticosteroid-free CDAI Remission	CDAI < 150 with no steroid use for at least 4 weeks prior to Week 24 for subjects on steroids at baseline
Disease Worsening	A ≥ 100 point increase in CDAI score from the Week 10 value and CDAI score ≥ 220 points at 2 consecutive visits
Non-responder	Subjects who never achieves a ≥ 70 point CDAI reduction from baseline or CDAI < 150 at any point up to and including Week 10
Minimal Detectable Difference (MDD) by MRE	For segments with baseline MaRIA score ≥ 15 , the MDD is 6.5 units. For segments with baseline MaRIA score < 15, the MDD is 4.0 units.
Segment with Active Disease	Segmental MaRIA score ≥ 7
Segment with Presence of Ulcerative Lesions (Moderate to Severe Radiographic Disease Activity)	Segmental MaRIA score ≥ 11
Segment with Mild Radiographic Disease Activity	Segmental MaRIA score ≥ 7 but < 11
Segment Level MaRIA Remission	For segments with baseline MaRIA score ≥ 7 , a segmental MaRIA score < 7 at Week 24
Segment Level MaRIA Response	For segments with baseline MaRIA score ≥ 11 , a segmental MaRIA score < 11, or a decrease from baseline in segmental MaRIA score \geq MDD For segments with baseline MaRIA score < 11 (but ≥ 7), a segmental MaRIA score < 7 or a decrease from baseline in segmental MaRIA score \geq MDD
Segment Level Disease Stable	For segments with baseline MaRIA score ≥ 7 , absence of segment level MaRIA response and: if baseline MaRIA score ≥ 11 , no increase in segmental MaRIA score \geq MDD if baseline MaRIA score < 11, a segmental MaRIA score < 11 For segments with baseline MaRIA score < 7, no segment level disease worsening
Segment Level Disease Worsening	An increase in segmental MaRIA \geq MDD with a segmental MaRIA score ≥ 7 at Week 24, or a segmental MaRIA score ≥ 11 at Week 24 while baseline MaRIA score < 11
Subject Level Small Bowel MaRIA Remission	MaRIA score of < 7 in each of 3 segments: terminal ileum = distal 15 cm of ileum, measured from ileocecal valve distal ileum = the portion of the ileum proximal to terminal ileum jejunum = small bowel located at the left upper quadrant
Subject Level Small Bowel MaRIA Response	All small bowel segments with baseline MaRIA score ≥ 7 achieve segment level MaRIA response, with no segment level disease worsening in any other segment(s)
Subject with Stable Small Bowel Disease	At least 1 small bowel segment with baseline MaRIA score ≥ 7 doesn't achieve segment level response, while no segment level disease worsening in any other evaluable small bowel segment(s)
Subject with Small Bowel Disease Progression	At least 1 small bowel segment demonstrates segment level disease worsening

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-419-4015. This SAP is based on the study protocol Amendment 3 dated 04 February 2020 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is:

- To evaluate the efficacy of filgotinib, when compared to placebo, in establishing clinical remission, defined as CDAI < 150, at Week 24

The secondary objectives of this study are:

- To evaluate the impact of filgotinib, when compared to placebo, on change in segmental MaRIA score for all assessed small bowel segments at Week 24
- To evaluate the efficacy of filgotinib, when compared to placebo, in establishing segment level MaRIA remission at Week 24
- To evaluate the efficacy of filgotinib, when compared to placebo, in establishing segment level MaRIA response at Week 24
- To evaluate the efficacy of filgotinib, when compared to placebo, in establishing subject level small bowel MaRIA remission at Week 24
- To evaluate the efficacy of filgotinib, when compared to placebo, in establishing subject level small bowel MaRIA response at Week 24
- To evaluate the efficacy of filgotinib, when compared to placebo, in establishing clinical remission, defined as CDAI < 150, at Week 10
- To evaluate the impact of filgotinib, when compared to placebo, on change in CDAI scores
- To evaluate the safety and tolerability of filgotinib

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[REDACTED]

[REDACTED]

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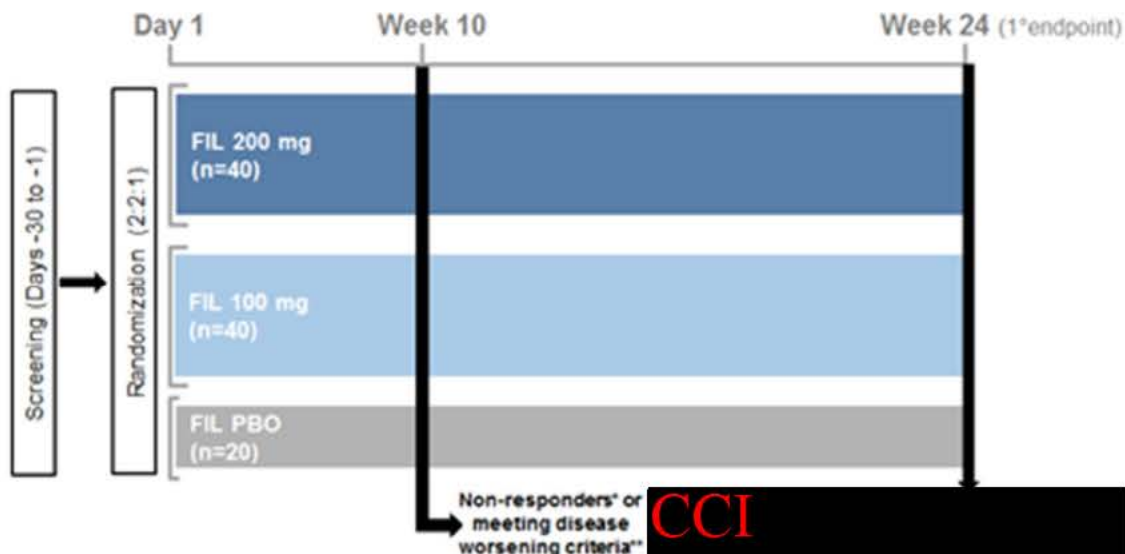
1.2. Study Design

This is a Phase 2 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of filgotinib in treating subjects with SBCD. A schematic of this study is provided in [Figure 1-1](#). Subjects who meet protocol eligibility criteria will be randomized in a blinded fashion to 1 of 3 treatment groups in a 2:2:1 ratio:

- **Treatment group 1 (n 40):** Filgotinib 200 mg and placebo-to-match (PTM) filgotinib 100 mg, once daily
- **Treatment group 2 (n 40):** Filgotinib 100 mg and PTM filgotinib 200 mg, once daily
- **Treatment group 3 (n 20):** PTM filgotinib 200 mg and PTM filgotinib 100 mg, once daily

Note: United States (US) males who have not failed at least 2 prior biologic therapies (ie, any tumor necrosis factor-alpha [TNF α] antagonist and vedolizumab) will be randomized in a 2:1 ratio to receive either filgotinib 100 mg or matching placebo.

Figure 1-1. Study Design Schematic



FIL filgotinib; PBO placebo; mg milligram.

*Non responders are subjects who never achieved a ≥ 70 point CDAI reduction from baseline or CDAI < 150 at any point up to and including Week 10

**Disease worsening is defined as a ≥ 100 point increase in CDAI score from the Week 10 value and CDAI score ≥ 220 points at 2 consecutive visits

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Treatment assignments will be stratified according to the following factors:

- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1, (Yes or No)
- Concomitant use of immunomodulators (eg, 6-mercaptopurine [6-MP], azathioprine, methotrexate [MTX]) at Day 1, (Yes or No)
- Prior exposure to biologics (eg, TNF α antagonists or vedolizumab), (Yes or No)

This study includes:

- Screening (Days -30 to -1)
- Randomization (Day 1)

- Blinded treatment (Day 1 to Week 24)

Efficacy assessment: At Week 24, CDAI score to assess clinical remission; MRE to assess radiographic changes

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- Post-Treatment (PTx) safety assessments

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CCl [REDACTED]

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- Steroid tapering must begin at Week 10 for subjects who are considered responders.

1.3. Sample Size and Power

A sample size of 40 subjects in each of the filgotinib treatment groups and 20 subjects in the placebo group is considered adequate to assess the safety, tolerability, and efficacy of filgotinib in a descriptive manner. Assuming a clinical remission rate of 40% for the filgotinib treatment groups (200 mg and 100 mg), the 2-sided 90% exact confidence interval is (26.9%, 54.2%). The clinical remission rate for placebo group is assumed to be 20%.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee (DMC) Analyses

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of the safety data in order to protect subject welfare and preserve study integrity. The DMC is to recommend to the sponsor whether the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

The DMC will meet twice to evaluate all available safety data from the study. The initial meeting will occur after approximately 20% of the planned total number of subjects reach the Week 10 visit. Following this, the next meeting will occur after approximately 50% of the subjects reach the Week 10 visit. Additional DMC meetings may be convened, if needed.

The DMC's role and responsibilities and the scope of analysis to be provided to the DMC are described in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

No formal interim efficacy analysis, which may lead to early termination for efficacy or futility, is planned.

2.2. Final Analysis

After all enrolled subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the study blind will be broken and the final analysis of the data will be performed.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented. By-subject listings will be presented for all subjects in the All Randomized Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within subject. The treatment group to which subjects were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion, as well as the number and percentage of subjects who were excluded and the reasons for their exclusion, will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1. All Randomized Analysis Set

All Randomized Analysis Set includes all subjects who were randomized in the study.

The All Randomized Analysis Sets are the primary analysis sets for by-subject listings.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects who took at least 1 dose of study drug. This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

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3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set and FAS, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set CCI, subjects will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

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3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive web response system (IWRS) in a 2:2:1 ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1, (Yes or No)
- Concomitant use of immunomodulators (eg, 6-MP, azathioprine, methotrexate) at Day 1, (Yes or No)
- Prior exposure to biologics (eg, TNF α antagonists or vedolizumab), (Yes or No)

If there are discrepancies in stratification factor values between the IWRS and the clinical database (eCRF data), the values recorded in the clinical database will be used for analyses. For derivation of concomitant medication use at Day 1, the start date of such medication should be before or on the same date of the first dose of study drug and with either the stop date of such medication being on or after the first dose of study drug or with “ongoing” status.

Efficacy endpoints will be evaluated using stratification factors as covariates or stratification variables for analyses, as specified in Section 6.

3.4. Examination of Subject Subgroups

There are no prespecified subject subgroupings for efficacy and safety analyses.

3.5. Missing Data and Outliers

3.5.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. Imputation and calculation rules for missing patient diary data and other CDAI components are described in Appendix 3. Imputation and calculation rules for missing MaRIA data are described in Section 6.3. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

Values for missing safety laboratory data will not be imputed. However, a missing baseline result will be replaced with a screening result, if available. If no pre-treatment laboratory value is available, the baseline value will be assumed to be normal (ie, no grade) for the summary of graded laboratory abnormalities. If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point.

Values for missing vital signs data will not be imputed. However, a missing baseline result will be replaced with a screening result, if available.

3.5.2. Outliers

Outliers will be identified during the data management and data analysis process. All data, including outliers, will be included in the data analysis, unless otherwise specified.

3.6. Data Handling Conventions and Transformations

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. If an enrolled subject was not dosed with any study drug, the randomization date will be used instead of the first dosing date of study drug. For screen failures, the date the informed consent was signed will be used for age calculation. If only the birth year is collected on the eCRF, “01 July” will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, “15” will be used for the unknown birth day.

Duration of CD (years) is the number of years between the diagnosis date of CD and date of first dose of study drug. The partial diagnosis date of CD (if any) will be imputed for calculation as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.
- If day is missing but the month and year are available, then the imputed day will be the first day of the month.
- Partial date will not be imputed if the year is missing.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of “< x” (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used for calculation of summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of “> x” (where x is considered the LOQ). Values with decimal points will follow the same logic as above.
- The LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of “≤ x” or “≥ x” (where x is considered the LOQ).

Natural logarithm transformation will be used for plasma concentrations. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as “BLQ” in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postbaseline time points.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as “BLQ.”
- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as “BLQ.”
- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as “BLQ.”
- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as “BLQ.”
- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as “BLQ.”

3.7. Analysis Visit Windows

3.7.1. Definitions

The First Dosing Date is defined as the date when subjects take the first dose of study drug, as recorded in the Study Drug Administration eCRF.

The Last Dosing Date is defined as the date when subjects take the last dose of study drug as recorded in the Study Drug Administration eCRF.

Study Day will be calculated from the first dosing date of study drug and derived as follows:

- For days on or after first dosing date: Assessment Date – First Dosing Date + 1
- For days prior to the first dosing date: Assessment Date – First Dosing Date

Therefore, Study Day 1 is the day of the first dose of study drug administration.

Baseline is defined as the last available observation on or prior to the first dosing date, unless specified otherwise.

3.7.2. Analysis Visit Windows

Subject visits may not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The analysis windows for efficacy endpoints including CDAI, PRO2, CCI endpoints are based on study day and are provided in Table 3-1.

The analysis windows for MaRIA score-related efficacy endpoints are based on study day and provided in Table 3-2.

The analysis windows for body weight, vital signs, ECG, safety laboratory parameters (hematology, chemistry, fasting lipid profile, and serum immunoglobulin), CCI

are provided in Table 3-3.

Table 3-1 Analysis Visit Windows for CDAI, PRO2 CCI -related Endpoints

Nominal Visit	Analysis Visit	Nominal Day (Study Day)	Lower Limit (Study Day)	Upper Limit (Study Day)
Screening/Day 1	Baseline	1	(none)	1
Week 2	Week 2	15	2	22
Week 4	Week 4	29	23	36
Week 6	Week 6	43	37	57
Week 10	Week 10	71	58	85
Week 14	Week 14	99	86	113
Week 18	Week 18	127	114	141
Week 24	Week 24	169	142	197

Note: For analysis purpose, PRO2 from Screening and Visit Day 1 will be calculated and both visits will be considered for the derivation of baseline, which is defined as the last available observation on or prior to the first dosing date of the study drug.

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Table 3-2 Analysis Visit Windows for MaRIA Score-related Efficacy Endpoints

Nominal Visit	Analysis Visit	Nominal Day (Study Day)	Lower Limit (Study Day)	Upper Limit (Study Day)
Screening	Baseline	1	(none)	1
Week 24	Week 24	169	142	197

Table 3-3 Analysis Visit Windows for Body Weight, Vital Signs, ECG, Hematology, Chemistry, Fasting Lipid Profile, Serum Immunoglobulin, CCI CCI

Nominal Visit	Analysis Visit	Nominal Day (Study Day)	Lower Limit (Study Day)	Upper Limit (Study Day)
Screening/Day 1	Baseline	1	(none)	1
Week 2	Week 2	15	2	22
Week 4	Week 4	29	23	36
Week 6	Week 6	43	37	57
Week 10	Week 10	71	58	85
Week 14	Week 14	99	86	113
Week 18	Week 18	127	114	141
Week 24	Week 24	169	142	≥ 169

Note: ECG is collected postbaseline at Week 10 and the corresponding analysis windows will be applied; fasting lipid profile, CCI are collected postbaseline at Weeks 10 and 24 and the corresponding analysis windows will be applied; serum immunoglobulin is collected postbaseline at Weeks 4, 10, and 24 and the corresponding analysis windows will be applied.

An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable.

3.7.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple, valid, nonmissing, continuous measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug, unless otherwise specified. If multiple measurements occur on the same day, the last nonmissing value prior to the first dosing date of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered the baseline value.

- For postbaseline visits:

The record closest to the nominal day for that visit will be selected.

If there are 2 records that are equidistant from the nominal day, the later record will be selected.

If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

If multiple, valid, nonmissing, categorical measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety ECG findings).

- For postbaseline visits:

The record closest to the nominal day for that visit will be selected.

If there are 2 records that are equidistant from the nominal day, the later record will be selected.

If there is more than 1 record on the selected day, the worst severity will be taken (eg, abnormal will be selected over normal for safety ECG findings), unless otherwise specified.

3.8. Assess of Coronavirus Disease 2019 Impact

This study was ongoing during the coronavirus disease 2019 (COVID-19) pandemic.

The assessment on the impact of COVID-19 will be provided in the corresponding sections (eg, Section 4) throughout this SAP. Study drug and study discontinuation due to COVID-19 are described in Section 4.1, study drug interruptions due to COVID-19 are described in Section 4.2, important and non-important protocol deviations due to COVID-19 are described in Section 4.3, and missed and virtual visits due to COVID-19 are described in Section 4.4.

Hematocrit collected from local laboratory and weight measured at home due to COVID-19 impact will be used in CDAI calculations only, and will not be included in the safety laboratory summary (Sections 7.2 and 7.3, respectively). These data will be included in listings, with a flag to indicate which records were collected at a local laboratory or at home, respectively.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group for each country, investigator within a country, and overall. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of subjects in the stratum will be the total number of enrolled subjects within that stratum. If there are discrepancies in the value used for stratification assignment between the IWRS and the clinical database, the value collected in the clinical database will be used for the summary. A listing of subjects with discrepancies in the value used for stratification assignment between the IWRS and the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group and overall. This summary will present the number of subjects screened, the number of subjects who met all eligibility criteria but were not randomized with reasons subjects not randomized, the number of subjects randomized, and the number of subjects in each of the categories listed below:

- All Randomized Analysis Set
- Full Analysis Set
- Safety Analysis Set

■ [REDACTED]

■ [REDACTED]

- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set corresponding to that column.

The following by-subject listings will be provided by subject identification (ID) number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation (A separate listing of reasons for premature study drug or study discontinuation due to COVID-19 will be created.)
- Reasons for screen failure (will be provided by screening ID number in ascending order)
- Lot number and kit ID of assigned study medication

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol. Summaries of extent of study drug exposure and adherence will be provided by treatment group for Safety Analysis Set.

A by-subject listing will be provided for subjects with study drug interruption due to COVID-19.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dosing date minus first dosing date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). If the last study drug dosing date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used.

The total duration of exposure to study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: Day 1, Weeks 2, 4, 6, 10, 14, 18, 20, and 24. Summaries will be provided by treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

The total number of tablets administered will be summarized using descriptive statistics.

The presumed total number of tablets administered to a subject will be determined by the data collected on the drug accountability eCRF using the following formula. If the bottle was not returned, it is assumed that the subject took all the study drug tablets from the dispensed bottle. The number of tablets returned will be imputed as zero for the given bottle for study drug adherence calculation purpose.

$$\begin{aligned} &\text{Total Number of Tablets Administered} \\ &= \left(\sum \text{No. of Tablets Dispensed} \right) - \left(\sum \text{No. of Tablets Returned} \right) \end{aligned}$$

4.2.2.1. On-Treatment Adherence

The level of on-treatment adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject's actual on-treatment period based on the study drug regimen.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{On-Treatment Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Study Drug Expected to be Administered on Treatment}} \right) \times 100$$

If the calculated on-treatment adherence is > 100%, it will be set to 100%. Descriptive statistics for the level of on-treatment adherence with the number and percentage of subjects belonging to adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90%) will be provided by treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

A by-subject listing of study drug administration and drug accountability will be provided by subject ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but enrolled in the study will be summarized. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by treatment group based on the All Randomized Analysis Set. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation category (eg, eligibility criteria, informed consent) will be summarized by treatment group for the All Randomized Analysis Set. A by-subject listing will be provided for subjects with any important protocol deviations.

A by-subject listing will be provided for subjects with important protocol deviations related to COVID-19. A separate listing will be provided for subjects with non-important protocol deviations related to COVID-19.

4.4. Missed and Virtual Visits due to COVID-19

A by-subject listing of subjects with missed or virtual visits due to COVID-19 will be provided by subject ID number in ascending order.

The determination of missing or virtual visits due to COVID-19 was done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is provided in [Appendix 7](#).

5. BASELINE CHARACTERISTICS

5.1. Demographics and Other Baseline Characteristics

Subject demographic variables and other baseline characteristics will be summarized by treatment group and overall using descriptive statistics for continuous variables and using the number and percentage of subjects for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set.

- Age (years, on the date of first dose of the study drug)
- Age group (< 65 years, ≥ 65 years)
- Sex at birth (female, male)
- Race
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Geographic region (United States [US], non-US)
- Weight
- Height
- Body mass index (BMI; in kg/m²)
- Smoking status (former, current, never)

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order.

5.2. Baseline Disease Characteristics

Stratification factors (listed in Section 3.3) and other baseline disease characteristics listed below will be summarized for the Safety Analysis Set by the same method as demographic tables, using descriptive statistics for continuous variables, and using number and percentage of subjects for categorical variables.

- Duration of CD (years) from date of diagnosis to first dosing date of study drug
- Duration of CD (< 1 year, ≥ 1 to < 3 years, ≥ 3 to < 7 years, ≥ 7 years)
- CDAI score
- PRO2 subscores: liquid or very soft stool subscore and abdominal pain subscore

- Active disease in (yes if segmental MaRIA ≥ 7 ; otherwise no)

Terminal ileum

Distal ileum

Jejunum

At least 2 of the following segments: terminal ileum, distal ileum, or jejunum

- Presence of ulcerative lesions in (yes if segmental MaRIA ≥ 11 ; otherwise no)

Terminal ileum

Distal ileum

Jejunum

At least 2 of the following segments: terminal ileum, distal ileum, or jejunum

■

[REDACTED]

■

[REDACTED]

■

[REDACTED]

- Complications of CD: Fistula (yes, no), Stricture (yes, no), Abscess (yes, no)
- History of surgeries due to CD (yes, no)
- CD treatment history

Number of prior exposure to biologic agent as listed in [Appendix 2](#) (0, 1, 2, ≥ 3)

Prior use of systemic corticosteroids (yes, no)

Prior use of immunomodulators (yes, no)

Prior use of TNF α antagonist as listed in [Appendix 2](#) (yes, no) and for subjects with prior use:

■ Number of TNF α antagonist used

- 1
- 2
- ≥ 3

- Worst outcome of prior use of TNF α antagonist
 - Treatment failure
 - Intolerance, including both allergic and non-allergic intolerance
 - Other

Prior use of vedolizumab (yes, no) and for subjects with prior use:

- Worst outcome of prior use of vedolizumab
 - Treatment failure
 - Intolerance, including both allergic and non-allergic intolerance
 - Other

Prior use of both TNF α antagonist and vedolizumab (yes, no)

Prior failure of both TNF-alpha antagonist and vedolizumab

- Yes (dual refractory, defined as those who have failed at least 2 classes of biologic therapies [any TNF α antagonist and vedolizumab])
 - United States (US) Males
 - Subjects other than US Males
- No
 - US Males
 - Subjects other than US Males

Prior use of ustekinumab (yes, no) and for subjects with prior use:

- Worst outcome of prior use of ustekinumab
 - Treatment failure
 - Intolerance, including both allergic and non-allergic intolerance
 - Other

Note: The worst outcome of a prior treatment is treatment failure, followed by intolerance, and then other outcomes.

- Concomitant treatment at baseline:

Concomitant use of systemically absorbed corticosteroids and/or immunomodulator at baseline including: a) systemically absorbed corticosteroids only, b) immunomodulator only, c) both, and d) neither

Prednisone equivalent dose for subjects who are on systemically absorbed corticosteroids at baseline (mg/day)

Prednisone equivalent dose for subjects who are on systemically absorbed corticosteroids at baseline (> 0 to 10 mg/day, > 10 to 20 mg/day, > 20 mg/day)

5-aminosalicylates (yes, no)

A by-subject listing of baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

Medical history (disease-specific and general conditions) and IBD family history data will be collected at screening and presented in data listings.

General medical history data will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

6. EFFICACY ANALYSES

6.1. General Considerations

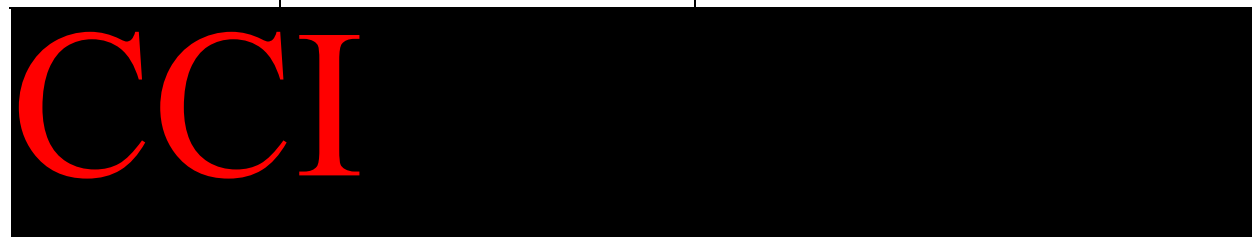
The efficacy analysis will be conducted on the FAS, defined in Section 3.1.2, unless otherwise specified.

The definitions of dichotomous efficacy endpoints are provided in Table 6-1. Appendix 6 includes a detailed definition of study treatment failure and the corresponding data handling rules for efficacy analysis.

Table 6-1. Definitions of Dichotomous Efficacy Endpoints

Type	Endpoint	Definition
Primary	Clinical remission by CDAI at Week 24	CDAI score < 150 points at Week 24
Secondary	MaRIA remission in terminal ileum segment at Week 24	MaRIA score < 7 in terminal ileum segment at Week 24 among subjects with MaRIA score ≥ 7 in the same segment at Baseline
Secondary	MaRIA remission in distal ileum segment at Week 24	MaRIA score < 7 in distal ileum segment at Week 24 among subjects with MaRIA score ≥ 7 in the same segment at Baseline
Secondary	MaRIA remission in jejunum segment at Week 24	MaRIA score < 7 in jejunum segment at Week 24 among subjects with MaRIA score ≥ 7 in the same segment at Baseline
Secondary	MaRIA response in terminal ileum segment at Week 24	<p>Among subjects with Baseline MaRIA score ≥ 7 in terminal ileum:</p> <ul style="list-style-type: none"> if baseline MaRIA score ≥ 11, a segmental MaRIA score < 11, or a decrease from baseline in segmental MaRIA score \geq MDD in terminal ileum if baseline MaRIA score < 11, a segmental MaRIA score < 7, or a decrease from baseline in segmental MaRIA score \geq MDD in terminal ileum
Secondary	MaRIA response in distal ileum segment at Week 24	<p>Among subjects with Baseline MaRIA score ≥ 7 in distal ileum:</p> <ul style="list-style-type: none"> if baseline MaRIA score ≥ 11, a segmental MaRIA score < 11, or a decrease from baseline in segmental MaRIA score \geq MDD in distal ileum if baseline MaRIA score < 11, a segmental MaRIA score < 7, or a decrease from baseline in segmental MaRIA score \geq MDD in distal ileum

Type	Endpoint	Definition
Secondary	MaRIA response in jejunum segment at Week 24	<p>Among subjects with Baseline MaRIA score ≥ 7 in jejunum:</p> <ul style="list-style-type: none"> if baseline MaRIA score ≥ 11, a segmental MaRIA score < 11, or a decrease from baseline in segmental MaRIA score \geq MDD in jejunum if baseline MaRIA score < 11, a segmental MaRIA score < 7, or a decrease from baseline in segmental MaRIA score \geq MDD in jejunum
Secondary	Subject level small bowel MaRIA remission at Week 24	MaRIA score < 7 at Week 24 in each of the 3 small bowel segments: terminal ileum, distal ileum, and jejunum, among subjects with MaRIA score ≥ 7 in at least 1 small bowel segment at Baseline
Secondary	Subject level small bowel MaRIA response at Week 24	All small bowel segments with Baseline MaRIA score ≥ 7 achieve segment level MaRIA response, with no segment level disease worsening in any other segment(s) at Week 24, among subjects with MaRIA score ≥ 7 in at least 1 small bowel segment at Baseline
Secondary	Early Clinical remission by CDAI at Week 10	CDAI score < 150 points at Week 10



Summary of Dichotomous Efficacy Endpoints

Numbers and percentages of subjects achieving each of the dichotomous efficacy endpoints defined above, and numbers and percentages of subjects not achieving those endpoints for the following reasons will be summarized by treatment, in a hierarchy order with the first reason being the highest.

- 1) Subjects who do not meet the endpoint based on observed data
- 2) Subjects who do not meet the endpoint due to study treatment failure
- 3) Subjects who are protocol-specified CDAI non-responders at Week 10 and discontinued study drug

- 4) Subjects who do not meet the endpoint due to study drug discontinuation led by protocol-specified disease worsening
- 5) Subjects who do not have sufficient measurements to determine the endpoint due to study drug discontinuation for other reasons
- 6) Subjects who do not have sufficient measurements to determine the endpoint while on study drug

Non-Responder Imputation

For analysis of binary efficacy endpoints defined in [Table 6-1](#), subjects who do not have sufficient measurements due to any reason (including treatment failures and CDAI non-responders at Week 10) to determine the endpoint will be considered non-responders (ie, non-responder imputation [NRI]).

6.1.1. Calculation of CDAI and PRO2 Scores

The CDAI system is a composite index of 8 disease activity variables (components) with scores ranging from 0 to over 600 based upon a composite of symptoms (eg, abdominal pain), signs (the presence of abdominal mass and body weight), laboratory values (eg, hematocrit), and physician assessment amongst others. The CDAI has 3 patient reported outcome components: liquid or very soft stool frequency, abdominal pain, and general wellbeing. The clinical remission by CDAI endpoint is defined by the CDAI score, calculated as a weighted sum of all 8 component subscores.

If subjects have 3 or more of the 8 component subscores missing, then the subjects will be considered as having insufficient data to determine response status and their CDAI score will be considered missing. If subjects have 1 or 2 CDAI components missing, then the missing component will be imputed by the Last Observation Carrying Forward (LOCF) method using the previous valid component score calculated at the most recent analysis visit (eg, use the component score from Week 6 to impute missing component at Week 10, or use the component score from Week 18 to impute missing component at Week 24). If the component score from the most recent analysis visit is also missing, the missing value will be imputed with corresponding component score at baseline.

The PRO2 has 2 patient reported outcome components: liquid or very soft stool frequency subscore and abdominal pain subscore. If either subscore is missing, no imputation will be done.

For further information on CDAI, PRO2, and calculation rules at screening and post-screening, refer to [Appendix 3](#).

6.1.2. Calculation of MaRIA Scores and Corresponding Endpoints

The MaRIA scoring system is a composite index of 4 components. These components are edema, ulcers, gut wall thickness, and relative contrast enhancement (RCE). A segmental MaRIA score can be calculated at Screening (used as the baseline) and Week 24 as a weighted sum of these 4 components for each of the 3 small bowel segments (terminal ileum, jejunum, and duodenum).

For segment level remission or response based on MaRIA score, if a bowel segment that was identified at baseline has a segmental MaRIA score missing at Week 24, no imputation will be done and the subject will be considered as having insufficient data to determine segment level remission or response status and treated as a non-responder in that specific segment.

For subject level remission or response based on MaRIA score, if more than one small bowel segment that was identified at baseline is missing at Week 24, the subject will be considered as having insufficient data to determine remission or response status and will be considered as a non-responder. If only one small bowel segment that was identified at baseline is missing at Week 24, then LOCF will be used to impute the missing segment. Small bowel segments with missing segmental MaRIA scores at baseline will not be considered when assessing subject level response status.

Detailed information on MaRIA score calculation rules are provided in [Appendix 5](#).

6.2. Primary Efficacy Endpoint

6.2.1. Definition of the Primary Efficacy Endpoint

The primary endpoint is the proportion of subjects achieving clinical remission, defined as CDAI score < 150 points at Week 24.

6.2.2. Analysis of the Primary Efficacy Endpoint

For the primary efficacy endpoint, the number and proportion of subjects achieving clinical remission by CDAI at Week 24 for each treatment group will be summarized with corresponding 90% exact confidence interval (CI) based on the binomial distribution (Clopper-Pearson method). The difference in proportions between each filgotinib dose group and the placebo group will be presented along with the associated 90% CI. No formal hypothesis testing will be performed. Bar-chart of proportions of subjects achieving clinical remission at Week 24, defined as CDAI score < 150 points, will be provided by treatment group.

6.3. Secondary Efficacy Endpoints

6.3.1. Definition of the Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Change from baseline in terminal ileum segmental MaRIA score at Week 24
- Change from baseline in distal ileum segmental MaRIA score at Week 24

- Change from baseline in jejunum segmental MaRIA score at Week 24
- Proportion of subjects achieving MaRIA remission in terminal ileum segment at Week 24
- Proportion of subjects achieving MaRIA remission in distal ileum segment at Week 24
- Proportion of subjects achieving MaRIA remission in jejunum segment at Week 24
- Proportion of subjects achieving MaRIA response in terminal ileum segment at Week 24
- Proportion of subjects achieving MaRIA response in distal ileum segment at Week 24
- Proportion of subjects achieving MaRIA response in jejunum segment at Week 24
- Proportion of subjects achieving subject level small bowel MaRIA remission at Week 24
- Proportion of subjects achieving subject level small bowel MaRIA response at Week 24
- Proportion of subjects achieving early clinical remission by CDAI at Week 10
- Change from baseline in CDAI scores at Week 10
- Change from baseline in CDAI scores at Week 24

Refer to [Table 6-1](#) for dichotomous secondary endpoints definitions.

6.3.2. Analysis of the Secondary Efficacy Endpoints

For binary endpoints, the same statistical analysis methods described in Section [6.2.2](#) for analyzing the primary efficacy endpoint will be utilized.

Continuous endpoints will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, maximum) by treatment group and analysis visit.

An analysis of covariance (ANCOVA) model that includes treatment (filgotinib 200 mg, filgotinib 100 mg, or placebo), stratification factors as fixed-effect factors, and baseline value as covariates will also be implemented. The estimated means of treatment effects and estimated differences in treatment effects between each filgotinib dose group and placebo will be presented with 90% CIs. Before the ANCOVA model is conducted, the following imputation will be performed:

- For change from baseline in segmental MaRIA score, if segmental MaRIA score is missing at Week 24, then corresponding segmental MaRIA score at baseline will be used to impute the missing value.
- For change from baseline in CDAI score, any missing CDAI component score will be imputed by LOCF method using the previous valid component score calculated at most recent analysis visit (eg, use the component score from Week 6 to impute missing component at Week 10, or use the component score from Week 18 to impute missing component at Week 24). If the component score from the most recent analysis visit is also missing, the missing value will be imputed with corresponding component score at baseline.

In addition, subjects' small bowel disease status (remission, response, stable, and progression) based on MaRIA score will be summarized by treatment group for Week 24. A detailed definition of disease status in MaRIA score is provided in definition of terms.

CCI

11

1

1

1

103

11

CCI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[illegible]

6.5. Change from Protocol-Specified Efficacy Analyses

The definitions of the following terms are modified in this SAP:

- In the protocol, the definition of segment level MaRIA response states “For segments with baseline MaRIA score ≥ 15 , a segmental MaRIA score < 11 , or a decrease from baseline in a segmental MaRIA score \geq MDD. For segments with baseline MaRIA score < 15 (but ≥ 7), a segmental MaRIA score < 11 ”.
In the SAP, the definition is modified to “For segments with baseline MaRIA score ≥ 11 , a segmental MaRIA score < 11 , or a decrease from baseline in segmental MaRIA score \geq MDD. For segments with baseline MaRIA score < 11 (but ≥ 7), a segmental MaRIA score < 7 or a decrease from baseline in segmental MaRIA score \geq MDD”.
- In the protocol, segment level disease stable is not defined.
In the SAP, the definition is “For segments with baseline MaRIA score ≥ 7 , absence of segment level MaRIA response and: if baseline MaRIA score ≥ 11 , no increase in segmental MaRIA score \geq MDD; if baseline MaRIA score < 11 , a segmental MaRIA score < 11 . For segments with baseline MaRIA score < 7 , no segment level disease worsening”.
- In the protocol, segment level disease worsening is not defined.
In the SAP, the definition is “An increase in segmental MaRIA \geq MDD with a segmental MaRIA score ≥ 7 at Week 24, or a segmental MaRIA score ≥ 11 at Week 24 while baseline MaRIA score < 11 ”.
- In the protocol, the definition of subject level small bowel MaRIA response states “All small bowel segments with baseline MaRIA score ≥ 7 achieve segment level MaRIA response, with no increase in MaRIA score \geq MDD in any other evaluable small bowel segment(s)”.
In the SAP, the definition is modified to “All small bowel segments with baseline MaRIA score ≥ 7 achieve segment level MaRIA response, with no segment level disease worsening in any other segment(s)”.
- In the protocol, the definition of subject with stable small bowel disease states “At least 1 small bowel segment doesn’t achieve segment level response, while no \geq MDD increase detected in any evaluable small bowel segment”.
In the SAP, the definition is modified to “At least 1 small bowel segment with baseline MaRIA score ≥ 7 doesn’t achieve segment level response, while no segment level disease worsening in any other evaluable small bowel segment(s)”.
- In the protocol, the definition of subject with small bowel disease progression states “At least 1 small bowel segment has MaRIA score > 11 , while \geq MDD increase in MaRIA score in at least 1 small bowel segment”.
In the SAP, the definition is modified to “At least 1 small bowel segment demonstrates segment level disease worsening”.

7. SAFETY ANALYSES

Unless otherwise specified, summaries of safety data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in the summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected “Related” on the AE eCRF to the question of “Related to Study Treatment.” Relatedness will always reflect the investigator assessment of causality rather than the Sponsor’s. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAEs captured in the Gilead safety database before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date (Day 1) and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment-emergent. The event is considered treatment-emergent if both of the following 2 criteria are met:

- The AE onset date is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the last dosing date of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and an incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

No formal statistical testing is planned.

7.1.6.1. Summaries of AE Incidence

The number and percentage of subjects who reported at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs of Grade 3 or higher (by maximum severity)
- TEAEs of Grade 2 or higher (by maximum severity)
- All TE treatment-related AEs
- TE treatment-related AEs of Grade 3 or higher (by maximum severity)
- TE treatment-related AEs of Grade 2 or higher (by maximum severity)
- All TE SAEs
- All TE treatment-related SAEs
- All TEAEs leading to premature discontinuation of study drug

- All TEAEs leading to premature discontinuation of study
- All TE SAEs leading to death (ie, outcome of death)
- All TEAEs leading to temporary dose interruption of study drug

A brief, high-level summary of AEs described above will be provided by treatment group presenting the number and percentage of subjects who reported the above AEs. All deaths observed in the study will be also included in this summary.

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition, the following tables will be generated and summarized by PT only, in descending order of total frequency:

- TEAEs
- TEAEs of Grade 3 or higher
- TEAEs of Grade 2 or higher
- TE SAEs
- TE treatment-related AEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study drug

Data listings will be provided for the following:

- All AEs, indicating whether the event is treatment-emergent
- All AEs of Grade 3 or higher
- All AEs of Grade 2 or higher
- SAEs
- Deaths
- All AEs leading to death (ie, outcome of death)

- AEs leading to premature discontinuation of study drug
- AEs leading to premature discontinuation of study
- AEs leading to dose temporary interruption of study drug

7.1.7. Adverse Events of Interest

Adverse events of interest (AEI) include infections, gastrointestinal perforations, herpes zoster, malignancies (excluding non-melanoma skin cancers), non-melanoma skin cancers, major adverse cardiovascular events (MACE), and thromboembolic events. Summaries of the following treatment-emergent AEIs will be produced to enhance the analysis of safety data.

- Events of infections, presented in the following subcategories:

AEs of infections, utilizing all AEs in the MedDRA Infections and Infestations SOC

AEs of serious infections, using all AEs in the MedDRA Infections and Infestations SOC that are classified as SAEs

AEs of herpes zoster, utilizing a MedDRA search term (MST) list developed by Gilead

AEs of opportunistic infections (OIs), utilizing a narrow scope Standardised MedDRA Query (SMQ)

- AEs of malignancies, excluding non-melanoma skin cancers, utilizing a MST list developed by Gilead
- AEs of non-melanoma skin cancers, utilizing an MST list developed by Gilead
- AEs of gastrointestinal perforation, utilizing an MST list developed by Gilead
- AEs of MACE, utilizing a positively adjudicated event list, presented in the following subcategories (Section 7.1.7.1):

Cardiovascular (CV) death

Non-fatal myocardial infarction (MI)

Non-fatal stroke

- AEs of arterial systemic thromboembolism (ASTE), utilizing a positively adjudicated event list (Section 7.1.7.1)
- AEs of venous thromboembolism (VTE), utilizing a positively adjudicated event list (Section 7.1.7.1)

The number and percentage of subjects with a reported event will be summarized for each treatment group by PT for each AEI category. Data listings for AEs will also be provided.

The number and percentage of subjects with positively adjudicated TE MACE, TE ASTE, and TE VTE will be summarized by treatment group using the adjudicated category if applicable.

A by-subject listing for subjects with potential events for adjudication (MACE, ASTE, and VTE) and their respective adjudication results will be provided.

A by-subject listing of thromboembolic history and risk factors will be provided for subjects with potential events for adjudication (MACE, ASTE, and VTE).

7.1.7.1. Cardiovascular Safety Endpoint Adjudication Committee

An independent cardiovascular safety endpoint adjudication committee (CVEAC) will be formed to periodically review and adjudicate all potential MACE and thromboembolic events in a blinded manner. To identify potential MACE and thromboembolic events, the following AEs will be sent for adjudication. Refer to the Cardiovascular Event Adjudication Committee Charter for more details.

- All AEs leading to death
- CV events (meeting seriousness criteria), utilizing a MST list developed by Gilead
- MI, utilizing a narrow scope SMQ
- Unstable angina (meeting hospitalization criteria), utilizing a MST list developed by Gilead
- Transient ischemic attack, utilizing a MST list developed by Gilead
- Stroke, utilizing an MST list developed by Gilead
- Cardiac failure (meeting hospitalization criteria), utilizing a MST list developed by Gilead
- Percutaneous coronary intervention, utilizing a MST list developed by Gilead
- Embolic and thrombotic events, utilizing a narrow scope SMQ

The CVEAC will review the above AEs, and related clinical data to adjudicate whether the criteria for MACE (CV death, MI, and/or stroke), ASTE, and VTE have been met for each AE.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set for data collected up to the last dose of study drug plus 30 days for subjects who have permanently discontinued study drug.

The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.6. Test results from hemolyzed samples will not be included in the analysis, but they will be listed in by-subject laboratory listings.

A by-subject listing for laboratory test results will be provided by subject ID number and time point in chronological order for hematology, serum chemistry, urinalysis, lipid profile, and serum immunoglobulin separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

Hematocrit collected from local laboratory due to COVID-19 impact will not be included in the safety laboratory summary, but they will be included in the listing with a flag to indicate which records were collected at local laboratory.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test specified in the study protocol within hematology and chemistry panels, and also laboratory tests from lipids panel including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, non-HDL cholesterol (total cholesterol minus HDL cholesterol), LDL/HDL ratio, and IgA, IgM, IgG, and total Ig, as follows:

- Baseline values
- Values at each postbaseline time point
- Change and percentage change from baseline at each postbaseline time point

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed change from baseline values for aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, serum creatinine, creatinine clearance, creatine phosphokinase, white blood cell count, absolute neutrophils, absolute lymphocytes, hemoglobin, platelets, total cholesterol, LDL, HDL, total Ig, IgG, IgA, and IgM, will be plotted using a line plot by treatment group and analysis visit.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3.

7.2.2. Graded Laboratory Values

The CTCAE Version 4.03 will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment-emergent.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities are defined as values that increase at least 3 toxicity grades from baseline at any postbaseline time point, up to and including the date of the last dose of study drug plus 30 days for subjects who permanently discontinued study drug.

If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above will be considered treatment-emergent marked abnormalities.

7.2.2.3. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of subjects in the study with the given response at baseline and each scheduled postbaseline time point.

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Grade 3 or higher laboratory abnormalities
- Marked laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 30 days after last dosing date.

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and time point in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

- AST: (a) > 3 times of upper limit of the normal range (ULN); (b) $> 5 \times \text{ULN}$; (c) $> 10 \times \text{ULN}$; (d) $> 20 \times \text{ULN}$
- ALT: (a) $> 3 \times \text{ULN}$; (b) $> 5 \times \text{ULN}$; (c) $> 10 \times \text{ULN}$; (d) $> 20 \times \text{ULN}$
- AST or ALT $> 3 \times \text{ULN}$ and total bilirubin $> 2 \times \text{ULN}$

For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date. A listing of subjects who met at least 1 of the above criteria will be provided.

7.3. Body Weight, Height and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, BMI and vital signs (resting blood pressure [systolic blood pressure and diastolic blood pressure], respiratory rate, pulse, and temperature) as follows:

- Baseline value
- Values at each postbaseline time point
- Change from baseline at each postbaseline time point

A baseline value will be defined as the last available value collected on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Body weight and vital signs measured at unscheduled visits will be included for the baseline value selection.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and time point in chronological order. Body weight, height, and BMI will be included in the vital signs listing, if space permits. If not, they will be provided separately.

Weight measured by the subjects at home from virtual visits due to COVID-19 impact will not be included in the vital signs summary, but they will be included in the listing with a flag to indicate which records were collected at home.

7.4. Prior and Concomitant Medications

Medications reported at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medication taken before a subject took the first dose of study drug at baseline.

General prior and CD-specific prior medications will be summarized separately by preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. General and CD-specific concomitant medications will be summarized, separately, by preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to or on the first dosing date of study drug and continued to take after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be

excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.5. Electrocardiogram Results

A shift table of the investigators' assessment of ECG results at each visit compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation.

No formal statistical testing is planned.

A by-subject listing for ECG assessment results will be provided by subject ID number and time point in chronological order.

7.6. Other Safety Measures

A data listing will be provided for subjects who become pregnant during the study.

7.7. Changes from Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

CC

CCI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI [REDACTED]

10. REFERENCES

Khanna R, Zou G, D'Haens G, Feagan BG, Sandborn WJ, Vandervoort MK, et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. *Aliment Pharmacol Ther* 2015;41 (1):77-86.

Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Lofberg R, Modigliani R, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology* 2002;122 (2):512-30.

11. SOFTWARE

SAS[®] Software Version 9.4 (SAS Institute Inc., Cary, NC, USA.) is to be used for all programming of tables, listings, and figures.

12. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision
Original Version			

13. APPENDICES

- Appendix 1. Schedule of Assessments
- Appendix 2. List of Biologics for CD Treatment
- Appendix 3. Crohn's Disease Activity Index (CDAI) and Patient Reported Outcomes – 2 items (PRO2)
- Appendix 4. Calculation of Standard Body Weight
- Appendix 5. MaRIA (Magnetic Resonance Index of Activity) Scoring System
- Appendix 6. Study Treatment Failure Rules
- Appendix 7. Determining Missing and Virtual Visits due to COVID-19

Appendix 1. Schedule of Assessments

Period	Screening	Treatment									Follow-Up	
Visit	1	2	3	4	5	6	7	8	9	10	PTx ^a	ET
Week		0	2	4	6	10	14	18	20	24		
Study Day	-30 to -1	1	15	29	43	71	99	127	141	169		
Visit Window (±)			±3	±3	±3	±2	±3	±3	±5	±5	±3	
Written Informed Consent	X											
Medical History & Demographics	X											
Crohn's Disease & Treatment History	X											
12 lead ECG	X					X						X ^b
Review of Inclusion/Exclusion Criteria	X	X										
Complete Physical Examination ^c	X											
Symptom Directed Physical Examination ^c		X	X	X	X	X	X	X		X	X	X
Vital Signs	X	X	X	X	X	X	X	X		X	X	X
Weight	X	X	X	X	X	X	X	X		X	X	X
Height	X											
Adverse Events	X	X	X	X	X	X	X	X		X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X		X	X	X
Randomization		X										
Study Drug Dispensing		X		X		X	X	X				
CDAI ^d	X		X	X	X	X	X	X		X		X
PRO2 ^d	X		X	X	X	X	X	X		X		X
eDiary instruction & review ^e	X	X	X	X	X	X	X	X		X		
MRE with segmental & global MaRIA scores ^o	X									X		
Stool for <i>C. diff</i> toxin, pathogenic <i>E. coli</i> , <i>Salmonella</i> , <i>Shigella</i> ,	X											

Period	Screening	Treatment									Follow-Up	
Visit	1	2	3	4	5	6	7	8	9	10	PTx ^a	ET
Week		0	2	4	6	10	14	18	20	24		
Study Day	-30 to -1	1	15	29	43	71	99	127	141	169		
Visit Window (±)			±3	±3	±3	±2	±3	±3	±5	±5	±3	
<i>Campylobacter</i> and <i>Yersinia</i> testing												
Stool O&P	X											
CCI												
Fecal MMP 9	X									X		
CCI												
Urine drug screen ^f	X											
Urinalysis ^p	X									X		
Pregnancy test ^g	X	X		X	X	X	X	X	X	X	X	X
TB screening ^h	X											
Chest x ray ^q	X											
HBV, HCV, HIV screening ⁱ	X											
Hematology	X	X	X	X	X	X	X	X		X	X	X
Chemistry	X	X	X	X	X	X	X	X		X	X	X
Fasting Lipids ^p		X				X				X		
CCI												
Blood transcriptome sample		X		X		X				X		
viPBMC ^k		X		X		X				X		
Serum immunoglobulin		X		X		X				X	X	X
CCI												
CCI												

- a The Post Treatment (PTx) visit should occur 30 days after the last dose of study drug. CCI [REDACTED]
- b For subjects who terminate prior to Week 10
- c A complete physical examination (PE) including, vital signs, body weight, and height will be performed at screening. A symptom directed PE may be done at other time points.
- d The screening CDAI will be used as the Day 1 measurement. The CDAI patient reported outcomes of stool frequency and abdominal pain will be used to derive the PRO2 score.
- e Subjects should begin filling out the eDiary the day of their initial screening visit and continue to fill it out throughout the remainder of the study.
- f Positive cocaine test disqualifies subject; positive amphetamines, barbiturates, benzodiazepines, and opioids require medical monitor review
- g All females meeting the childbearing potential criteria must have a serum pregnancy testing at screening and a urine pregnancy test must be completed every 4 weeks at a minimum. If any pregnancy test is positive, study drug must be immediately interrupted and the subject should have a serum pregnancy test in clinic.
- h Proof of no active or untreated latent TB at screening. Subjects who are diagnosed with latent TB at screening must initiate an adequate course of prophylaxis as per local standard of care for a minimum of 4 weeks prior to randomization. Subject may initiate study drug dosing only after consultation with the Gilead Medical Monitor.
- i An HIV 1/HIV 2 antibody test, a HCV antibody test, a HBV surface antigen test, a HBV surface antibody test, and a HBV core antibody test will be performed on all subjects. Subjects with positive HBcAb require reflex testing for HBV DNA (conducted locally). Refer to Protocol section 6.7.1.3 for more details.
- j [REDACTED]
- k viPBMC collection in US and Canadian sites only
- l [REDACTED]
- m [REDACTED]
- n [REDACTED]
- o Refer to Protocol Section 6.5 for details on the MRE procedure
- p Subjects should fast (no food or drinks, except water) for at least 8 hours prior to blood sample collection at Day 1, Week 10, and Week 24
- q Chest x ray (views as per local guidelines) taken at screening or within the 3 months prior to screening (with the report or films available for investigator review) without evidence of active or latent TB infection

Appendix 2. List of Biologics for CD Treatment

The drug names of biologics considered as CD treatment are listed below.

No.	Drug Class	Drug Name
1	TNF α antagonist	Adalimumab
2	TNF α antagonist	Certolizumab/Certolizumab Pegol
3	TNF α antagonist	Infliximab
4	TNF α antagonist	TNF α antagonist biosimilar (to adalimumab, Certolizumab/Certolizumab Pegol, or infliximab)
5	Integrin antagonist	Natalizumab
6	Integrin antagonist	Vedolizumab
7	Interleukin antagonist	Ustekinumab

Appendix 3. Crohn's Disease Activity Index (CDAI) and Patient Reported Outcomes – 2 items (PRO2)

The CDAI score is a weighted sum of all 8 variables as specified in Table 13-1. The PRO2 scores will be assessed according to Table 13-2. Details for the calculations of CDAI and PRO2 scores at screening and post-screening visits are provided in this appendix.

Table 13-1. Calculation of CDAI Score

Variable no.	Variable	Variable description	Multiplier
1	Liquid or very soft stool	Daily stool count is summed for 7 days	2
2	Abdominal pain	Sum of 7 days of daily ratings as 0 = none, 1 = mild, 2 = moderate, 3 = severe	5
3	General wellbeing	Sum of 7 days of daily ratings as 0 = generally well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible	7
4	Complications	Number of listed complications: Arthritis or arthralgia Erythema nodosum, pyoderma gangrenosum or aphthous stomatitis Iritis or uveitis Anal fissures or fistulae or abscess Other fistula Fever over 37.8 C [100 F] during past week	20 each
5	Use of anti-diarrheal medications	Use of diphenoxylate or loperamide or other opiate for diarrhea 0 = No, 1 = Yes	30
6	Abdominal mass	0 = none, 2 = questionable, 5 = definite	10
7	Hematocrit*	Males: 47 – Hct [%] Females: 42 – Hct [%] *Result must be greater than or equal to 0. If negative result enter 0	6 × difference
8	Weight*	Percentage deviation from standard weight (1 – weight / standard weight) × 100 *Limit of -10 (Result must be greater than or equal to -10)	1
CDAI score			TOTAL

CDAI = Crohn's Disease Activity Index; Hct = hematocrit
{Sandborn 2002}

Table 13-2. Calculation of PRO2 Components

Variable no.	Variable	Variable Description
1	Liquid or very soft stool	Mean of the daily (liquid or very soft) stool count for 7 days
2	Abdominal pain	Mean of 7 days of daily ratings as 0 = none, 1 = mild, 2 = moderate, 3 = severe

{Khanna 2015}

Each PRO2 subscore will be rounded to the nearest integer (eg, 2) for calculation of endpoints.

The 3 patient-reported outcome components for CDAI (and each subscore for PRO2) are determined using an electronic daily diary, which collects subject reported components directly. Given that the MRE procedure and lower endoscopy procedure (including protocol-directed and non-protocol-directed procedures) may impact the validity of the diary data, diary data collected 1 day prior to and on the day of the procedure (either MRE or lower endoscopy) will not be used in the calculation of CDAI and PRO2 subscores for all visits. Those days are called non-evaluable days.

Calculation of CDAI and PRO2 Scores at Screening

MRE is required to be performed during screening. The calculations of CDAI and PRO2 at screening are specified below:

- 1) Define T-Day 1 subject activation date on the electronic diary device during screening.
- 2) Define a 10-day window using T-Day 1 as the anchor date, and the window starts the day after T-Day 1 and ends 10 days after T-Day 1.
- 3) For each CDAI patient-reported outcome component, if there are 7 or more evaluable records within the 10-day window, take the **sum** of the 7 evaluable records closest to T-Day 1. For each PRO2 component, take the **average** of the 7 evaluable records within the 10-day window closest to T-Day 1.
 - a) If there are 4 or more (but less than 7) evaluable records within this 10-day window, the average of the available records will be taken, and then multiplied by 7 for the corresponding CDAI patient-reported component. For the corresponding PRO2 component, the average of the available records will be taken.
 - b) If subjects do not have at least 4 evaluable records within this 10-day window, the corresponding CDAI patient-reported component and PRO2 component will not be calculated and will be considered as missing.

A schema of this approach and some examples are included below for further illustration:

Figure 13-1. Selection of Diary Data for the Calculation at Screening

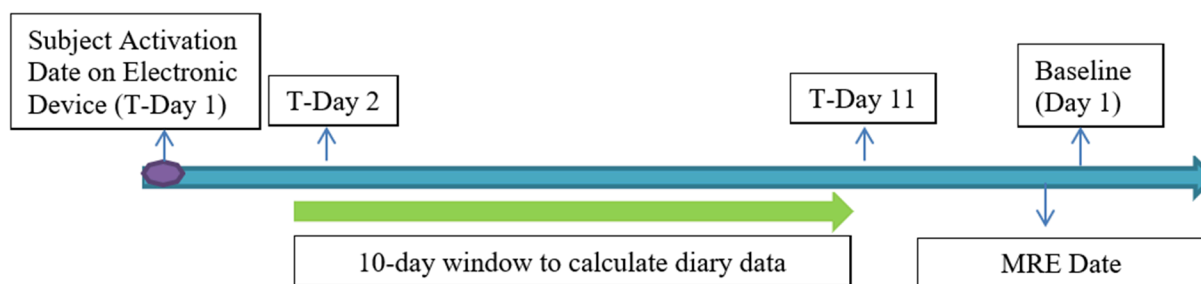


Table 13-3. Calculation of CDAI Patient-Reported Outcome Components and PRO2 Scores at Screening

Example	Diary Day Looking Forward from subject activation date (T-Day)										Days for Calculation	Sum of 7 Days (CDAI Patient-Reported Component)	Average of 7 Days (PRO2)
	2	3	4	5	6	7	8	9	10	11			
Diary Subscore 1	1	2	M	1	2	2	M	0	1	2	2,3,5,6,7,9,10	9.0	1.3
Diary Subscore 2	M	M	1	M	2	1	M	2	M	M	4,6,7,9	10.5	1.5
Diary Subscore 3	2	M	M	0	M	2	M	M	M	M	2,5,7	Missing	Missing
Diary Subscore 4	1	2	1	1	X	R	3	3	1	2	2,3,4,5,8,9,10	12.0	1.7

M Missing. R MRE day or lower endoscopy day; X non evaluable (due to preparation for MRE or lower endoscopy). Days are named relative to subject activation date on electronic diary device during screening (T Day 1). Rounding of subscores into one decimal place is for displaying purpose only. When calculating the CDAI scores, the subscores will not be rounded.

- 4) For the non-diary components (ie, complications, use of anti-diarrheal medications, abdominal mass, hematocrit, and weight) of the CDAI, in the case of multiple records collected during screening, the value collected on the same date as T-Day 1 will be used; otherwise, the earliest valid value during screening will be used. If no valid value is available during screening, then the value on Day 1 will be used.
- 5) The CDAI score at screening is based on a weighted sum (rounded to the nearest integer) of all 8 components (no rounding applied to the subscore for each component when calculating the CDAI score, but the subscore will be displayed with one decimal place for displaying purpose). The weight (multiplier) of each component is specified in [Table 13-1](#). For example, if the sum of the 7-day scores for abdominal pain is 10, then the abdominal pain CDAI subscore is $10 \times 5 = 50$, where 5 is the multiplier for abdominal pain. The CDAI score will be set to 0 in the case the calculation leads to a CDAI score of < 0 .
- 6) The PRO2 subscores at screening are based on the calculation of liquid or very soft stool frequency and abdominal pain subscores individually (rounded to the nearest integer).

Calculation of CDAI and PRO2 Scores at Post-Screening Visits

The calculations of CDAI and PRO2 scores at post-screening visits are specified below:

- 1) CDAI and PRO2 are not assessed on Day 1 by the study sites, but for analysis purpose, the PRO2 results will be calculated for Day 1. Both screening and Day 1 values will be considered for the derivation of baseline results for PRO2. CDAI at Day 1 will not be calculated and CDAI at screening will be the baseline.
- 2) The visit date will be used as the anchor day for post-screening visits. The visit date for each analysis visit will be selected among all scheduled visits and unscheduled visits where CDAI were assessed within the analysis window as defined in [Section 3.7.2](#). For Day 1, the date of visit from the nominal visit Day 1 will be used. Only diary data collected on evaluable days within a 10-day window, which starts 10 days prior to the visit date (V-Day 1) and ends on the day prior to V-Day 1 will be used for calculation.

- 3) If there are 7 or more evaluable records within the 10-day window, take the **sum** of the 7 evaluable records closest to V-Day 1 for the corresponding CDAI subject-reported component. For the corresponding PRO2 component, take the **average** of the 7 evaluable records within the 10-day window closest to V-Day 1.
 - a) If there are 4 or more (but less than 7) evaluable records within this 10-day window, the average of the available records will be taken, and then multiplied by 7 for the corresponding CDAI patient-reported component. For the corresponding PRO2 component, the average of the available records will be taken.
 - b) If subjects do not have at least 4 evaluable records within this 10-day window, the corresponding CDAI patient-reported component, and the corresponding PRO2 component will not be calculated and will be considered as missing for that visit.

A schema of this approach and some examples are included below for further explanation:

Figure 13-2. Selection of Diary Data for Calculation at Post-Screening Visits

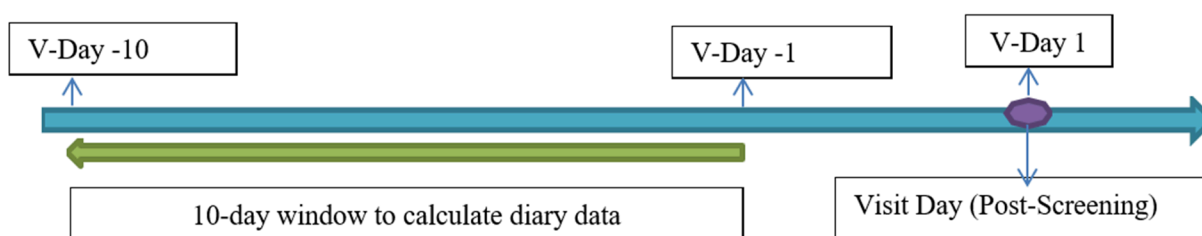


Table 13-4. Calculation of CDAI Patient-Reported Outcome Components and PRO2 Scores at Post-Screening Visits

Example	Diary Day Looking Backwards from Visit Date (V-Day)										Days for Calculation	Sum of 7 Days (CAI Patient-Reported Component)	Average of 7 Days (PRO2)
	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1			
Diary Subscore 1	1	2	2	M	0	1	2	2	1	X	-2,-3,-4,-5,-6,-8,-9	10.0	1.4
Diary Subscore 2	M	M	1	M	X	R	2	2	1	M	-2,-3,-4,-8	10.5	1.5
Diary Subscore 3	M	M	1	X	R	M	M	2	1	M	-2,-3,-8	Missing	Missing
Diary Subscore 4	0	M	2	2	1	0	M	2	X	R	-3,-5,-6,-7,-8,-10	8.2	1.2

M Missing; R MRE day or lower endoscopy day; X non evaluable (due to preparation for MRE or lower endoscopy).

Days are named relative to visit date (V Day 1), where V Day 1 is the day prior to V Day 1.

Rounding of subscores into one decimal place is for displaying purpose only. When calculating the CDAI scores, the subscores will not be rounded.

- 4) The CDAI score for a specific visit is based on a weighted sum (rounded to the nearest integer) of all 8 components. The CDAI score will be set to 0 in the case the calculation leads to a CDAI score of < 0 . Each component will be selected within the analysis window as defined in Section 3.7.2.
 - a) If subjects have 3 or more of the 8 CDAI components missing, then the subjects will be considered as having insufficient data to determine response status and their CDAI score will be considered missing. If at least 1 out of the 6 complications under the complication component is missing, then the complication component will be considered missing.
 - b) If subjects have 1 or 2 components missing, then the missing component will be imputed by the LOCF method using the previous valid component score calculated at most recent analysis visit (eg, use the component score from Week 6 to impute missing component at Week 10, or use the component score from Week 18 to impute missing component at Week 24). If the component score from the most recent analysis visit is also missing, the missing value will be imputed with corresponding component score at baseline.
- 5) The PRO2 subscores for a specific visit are based on the evaluation of liquid or very soft stool frequency and abdominal pain subscores individually (rounded to the nearest integer) within the analysis window as defined in Section 3.7.2. If either subscore is missing, no imputation will be done.

Source of Information Used for Calculation

The sources of information used for the calculations of CDAI and PRO2 scores as described above are given in Table 13-5 (the calculated scores from ERT data will not be used for data analysis). Hematocrit collected from local laboratory and weight measured at home due to COVID-19 impact will be used in CDAI calculation.

Table 13-5. Sources of Information for Calculating CDAI and PRO2 Scores

Variable in Calculation	Data Source
MRE Procedure Date	MREDAT in MRE dataset from eCRF data for Screening and Week 24
Lower Endoscopy Procedure Date	QSORRES in CDAI dataset with QSTEST “Date of Procedure” from vendor ERT data
Visit Date	VISITDAT in VISDT dataset from eCRF data
Subject Activation Date on Electronic Device	QSORRES in CDAI dataset with QSTEST “Date of Visit” and Visit “Screening” from vendor ERT data
Stool Frequency Diary Data	QSSTRESN in DIARY dataset with QSTESTCD “SOFSTOOL” from vendor ERT data
Abdominal Pain Diary Data	QSSTRESN in DIARY dataset with QSTESTCD “ABDPAIN” from vendor ERT data
Subject Standard Weight	Sex in DM dataset and HEIGHT STD in VSPERF dataset from eCRF data will be used to determine the standard weight based on Appendix 4.
Subject Actual Weight	WEIGHT STD in VSPERF dataset from eCRF data
Hematocrit Value	CNVRESN in COVLAB dataset with LBTEST “Hematocrit” from vendor Covance data or LBORRES in LB HEM dataset with LBTEST “Hematocrit” from eCRF data if collected in local laboratory due to COVID 19 impact

Note: eCRF = electronic case report form(s). ERT is the vendor that electronically collects patient and investigator reported outcomes.

Appendix 4. Calculation of Standard Body Weight

The following table will be used to determine the standard body weight for each subject. Height from the eCRF will be used and is assumed to be measured without shoes.

Women			
Height in <i>cm</i> (in shoes)*	Standard Weight in <i>kg</i>	Height in <i>cm</i> (in shoes)*	Standard Weight in <i>kg</i>
127	41.2	163	60.2
128	41.7	164	60.7
129	42.3	165	61.3
130	42.8	166	61.9
131	43.3	167	62.4
132	43.8	168	62.9
133	44.4	169	63.4
134	44.9	170	63.9
135	45.4	171	64.5
136	45.9	172	65.0
137	46.4	173	65.5
138	47.0	174	66.0
139	47.5	175	66.6
140	48.0	176	67.2
141	48.6	177	67.7
142	49.1	178	68.3
143	49.6	179	68.8
144	50.2	180	69.3
145	50.7	181	69.8
146	51.2	182	70.3
147	51.8	183	70.8
148	52.3	184	71.3
149	52.8	185	71.8
150	53.1	186	72.3
151	54.1	187	72.8
152	54.5	188	73.3
153	55.0	189	73.8
154	55.4	190	74.3
155	55.9	191	74.9
156	56.4	192	75.4
157	57.0	193	76.0
158	57.5	194	76.5
159	58.1	195	77.0
160	58.6	196	77.6
161	59.1	197	78.1
162	59.6	198	78.6

* add 2.0 cm if shoeless. Please round height to a whole number and select the appropriate standard weight (e.g., height 157.4 cm will be rounded to 157 cm; 157.5 cm will be rounded to 158 cm.)

Men			
Height in <i>cm</i> (in shoes)*	Standard Weight in <i>kg</i>	Height in <i>cm</i> (in shoes)*	Standard Weight in <i>kg</i>
142	54.4	179	71.9
143	54.9	180	72.4
144	55.4	181	73.0
145	55.8	182	73.6
146	56.3	183	74.3
147	56.8	184	74.8
148	57.2	185	75.5
149	57.7	186	76.2
150	58.2	187	76.9
151	58.6	188	77.6
152	59.1	189	78.2
153	59.6	190	78.8
154	60.0	191	79.6
155	60.5	192	80.4
156	61.0	193	81.2
157	61.4	194	82.1
158	61.9	195	82.9
159	62.2	196	83.8
160	62.6	197	84.7
161	62.9	198	85.4
162	63.3	199	86.1
163	63.7	200	86.7
164	64.1	201	87.4
165	64.6	202	88.0
166	65.0	203	88.8
167	65.5	204	89.4
168	66.0	205	90.1
169	66.6	206	90.7
170	67.1	207	91.4
171	67.6	208	92.1
172	68.1	209	92.7
173	68.7	210	93.4
174	69.2	211	94.1
175	69.7	212	94.8
176	70.3	213	95.5
177	70.8	214	96.1
178	71.3		

* add 2.0 cm if shoeless. Please round height to a whole number and select the appropriate standard weight (e.g., height 157.4 cm will be rounded to 157 cm; 157.5 cm will be rounded to 158 cm.)

Appendix 5. MaRIA (Magnetic Resonance Index of Activity) Scoring System

1) Component Details

Item	Definition	Sequence
Wall thickness (WT)	Maximum wall thickness (mm) of any portion of the segment will be the value for the segment.	T1 sequence after gadolinium injection. Perpendicular to bowel axis.
Relative Contrast Enhancement (RCE)	RCE accounts for enhancement in the intestinal wall using wall signal intensity (WSI) before and after contrast. Formula is noted below ^a ; SD is standard deviation.	T1 pre contrast, and T1 post contrast at 70 seconds.
Edema (E)	Hyperintensity on T2 wedged sequences of the colon wall relative to the signal of the psoas muscle. Edema may be a score of 0 (absent) or 1 (present).	Either single shot (SS) T2 or Balance gradient echo with fat saturation.
Ulcerations (U)	Areas of depression/irregularity in the inner surface of a thickened intestinal wall. Linear enhancing tracts within the bowel wall should be considered fissures (linear ulcers). Ulcerations may be a score of 0 (absent) or 1 (present).	All

a) $RCE: [(WSI_{postgadolinium} - WSI_{pregadolinium}) / WSI_{pregadolinium}] \times (SD_{pregadolinium} / SD_{postgadolinium}) \times 100$

2) Segmental MaRIA Score Calculation

Segmental MaRIA $[1.5 * WT(mm)] + [0.02 * RCE] + [5 * E] + [10 * U]$

Appendix 6. Study Treatment Failure Rules

Study treatment failure rules apply to treatment failure that occurs during the course of the study. Study treatment failure rules will be applied to all efficacy endpoints, unless otherwise specified. All efficacy data will be censored (set to missing) after treatment failure criteria are met, regardless of the observed data. Subjects who do not have sufficient measurements after censoring to determine the dichotomized endpoint(s) will be considered non-responder for corresponding endpoint(s). Study treatment failure rules override other data handling rules.

Subjects who have any of the following events will be considered a study treatment failure after the earliest event through the end of the Study, regardless of the actual efficacy data collected.

1) Potentially effective corticosteroid use

Potentially effective corticosteroids, for the purpose of this SAP, are corticosteroids that may impact disease under study. Potentially effective corticosteroids include the following corticosteroids when administered for an indication of CD:

a) Commencement of:

Any steroid administered intramuscularly (IM), intravenously (IV), orally (PO), or rectally (PR) at any dose for 7 or more continuous days

- This rule applies regardless if a change in drug, dose, or route (from IM to IV to PO or PR or vice versa) occurs within the seven continuous days; and it includes oral steroids with intended local actions (eg, budesonide)

b) Escalation of concomitant steroid dose above the baseline dose for 7 or more continuous days. The baseline steroid dose is defined as the dose at Day 1 of the Study. The prednisone equivalent dose will be used to determine escalation of concomitant systemic steroid dose even if there is a change in drug or route. For steroids with local actions (eg, budesonide or any rectally administered steroid), this rule will apply to scenarios where the post-baseline dose is above the baseline dose via the same drug and the same route for 7 or more continuous days.

Potentially effective steroid use only includes use of steroids administered via routes that are IM, PO, IV, or PR. The below steroids will **not** be considered potentially effective steroids regardless of indication for use:

A) ocular steroids (ie, eye drops)

B) topical steroids (eg, cutaneously applied solely to the skin, or topically applied to the nasal mucosa)

C) inhaled steroids (eg, inhalational fluticasone for asthma)

D) intra-articular steroids (steroids administered directly into a joint)

E) neuraxial steroids (steroids administered into the epidural or spinal space)

2) Potentially effective immunomodulator use

Commencement of a different class of oral, IM, SC, or IV immunomodulator drugs

(where the subject was not previously taking concomitant immunomodulators of the same class on Day 1), including but not limited to 6-MP, azathioprine, MTX, 6-thioguanine, and prohibited immunomodulators including but not limited to cyclosporine, leflunomide, tacrolimus, thalidomide regardless of dose, for 7 continuous days. The use of an immunomodulator will be considered potentially effective when it is administered for an indication of CD.

3) Potentially effective biologic agent use

Commencement of a biologic agent including but not limited to TNF α antagonists, IL-12/23 antagonists, and vedolizumab (or similar agents), regardless of indication for use and duration.

Appendix 7. Determining Missing and Virtual Visits due to COVID-19

This appendix describes the site collection of COVID-19 data as pertains to missed/virtual visits and the data processing algorithm used to determine which visits were missing and which visits were virtual.

Data collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by data management to instruct clinical trial sites with respect to data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites should enter “Visit missed due to COVID-19.” If a visit which was to be conducted in-person was conducted virtually, sites should enter “Virtual visit due to COVID-19.”

Determination of Missed and Virtual visits

Natural Language Processing (NLP) was used to search the CRF comment fields to identify instances of “COVID-19” (or synonyms, see [Table 13-6](#)) and “Virtual” (or synonyms, see [Table 13-6](#)). The search terms are maintained in a global lookup and can be modified and/or corrected to tune the NLP model. For each comment field the following algorithm was applied:

STEP 1: Eliminate extraneous text from each comment field, e.g. “and”, “or”, “for”, etc. This is done using the list of extraneous terms given in [Table 13-7](#).

STEP 2: Check each of the remaining comment text strings against the “COVID-19” terms and “Virtual” terms with the Levenshtein distance, using SAS function COMPGED (computes a generalized edit distance using the Levenshtein operations to compute/summarize the degree of difference between 2 text strings):

- i) If Levenshtein distance < 149 for any of the “COVID-19” terms then COVIDFL = 1, else COVIDFL = 0
- ii) If Levenshtein distance < 149 for any of the “Virtual” terms then VIRTFL = 1, else VIRTFL = 0

STEP 3: For any comments with COVIDFL = 1, assign “Missed Visit” or “Virtual Visit” as follows:

- i) IF COVIDFL = 1 and the visit date is missing then result is “Missed Visit”
- ii) IF COVIDFL = 1 and VIRTFL = 1 then result is “Virtual Visit”
- iii) Otherwise result is missing

Table 13-6. Examples of Search Terms for “COVID-19” and “Virtual” used to Identify Missed and Virtual Visits

Search terms for “COVID-19”	Search terms for “Virtual”
covid19	virtual
corona	telemed
coronavirus	telehealth
pandemic	telephone
outbreak	remote
crisis	telemedicine
lockdown	teleconsultation
quarantine	telephonically
shelter	phone
	home visit
	zoom
	skype

Table 13-7. Examples of Extraneous Text Terms to Eliminate from the Comment Fields

a	down	in	she'd	until
about	during	into	she'll	up
above	each	is	she's	very
after	few	it	should	was
again	for	its	so	we
against	from	it's	some	we'd
all	further	itself	such	we'll
am	had	i've	than	were
an	has	let's	that	we're
and	have	me	that's	we've
any	having	more	the	what
are	he	most	their	what's
as	he'd	my	theirs	when
at	he'll	myself	them	when's
be	her	nor	themselves	where
because	here	of	then	where's
been	here's	on	there	which
before	hers	once	there's	while
being	herself	only	these	who
below	he's	or	they	whom
between	him	other	they'd	who's
both	himself	ought	they'll	why
but	his	our	they're	why's
by	how	ours	they've	with
could	how's	ourselves	this	would

did	i	out	those	you
do	i'd	over	through	you'd
does	if	own	to	you'll
doing	i'll	same	too	your
down	i'm	she	under	you're
you've	yourself	yourselves	yours	

GS-US-419-4015 SAP v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM- yyyy hh:mm:ss)
PPD	Biostatistics eSigned	01-Oct-2020 17:23:29
PPD	Clinical Research eSigned	01-Oct-2020 18:19:18