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A Phase 2a, Multi-Center, Open-Label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of PRA023 in Subjects with Moderately to Severely Active Crohn's Disease

STATISTICAL ANALYSIS PLAN

Protocol No.:	PR200-103
Analysis Type:	Primary Analysis of Induction Period
Version/Date:	3.0/21OCT2021
Development Phase:	2a
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APPROVAL

A Phase 2a, Multi-Center, Open-Label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of PRA023 in Subjects with Moderately to Severely Active Crohn's Disease

STATISTICAL ANALYSIS PLAN

Primary Analysis (Induction Period)

Version/Date: V02/19APR2022

Name	Position	Signature	Date
PPD			

[1] Author, signs for correctness and completeness
[2] Reviewer, signs for correctness and completeness
[3] Approver, signs for the release of the document

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DEFINITIONS / ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
ATC	Anatomical therapeutic chemical
BLQ	Limit of quantitation
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDC	Complement-dependent cytotoxicity
CDx	Companion diagnostic
CFR	Code of Federal Regulations
Cmax	Maximal concentration
CI	Confidence interval
CCI	CCI
CTCAE	Common Terminology Criteria for Adverse Events
COVID-19	Coronavirus disease 2019
CR	Central Reader
CRO	Contract Research Organization
CSR	Clinical study report
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiograms
eCRF	Electronic case report form
EHI	Endoscopic healing index
ET	Early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Follow-Up
QTcF	Fridericia's corrected QT
GCP	Good Clinical Practice
GHAS	Global histological activity score
GM	Geometric Mean
hsCRP	High sensitivity C-reactive protein
IBD	Inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed consent form
ICH	International Conference on Harmonisation
IP	Induction Period
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous
LOQ	Limit of quantitation
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
Nab	Neutralizing antibody
NCI	National Cancer Institute
NRI	Non-Responder Imputation
OLE	Open-Label Extension

PD	Pharmacodynamic
PDAI	Perianal Disease Activity Index
PG	Pharmacogenomic
PK	Pharmacokinetic
PRO-2	Two component patient-reported outcome
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QoL	Quality of life
RBC	Red blood cell
RHI	Robarts histopathology index
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SES-CD	Simple endoscopy score for Crohn's disease
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures, and listings
TL1A	tumor necrosis factor-like cytokine 1A
ULN	Upper limit of normal
WK	Week
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes in detail the analyses to be performed for the Induction Period (IP) of the study on the safety, efficacy, and pharmacokinetics of PRA023 in subjects with moderately to severely active Crohn's Disease(CD). This 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 PR-200-103. This SAP is based on the study protocol version 3.0.

There will be a primary analysis after all subjects have completed 12-week IP. The analysis will include complete data for the induction period and interim data for the OLE as of the cutoff date for the database lock. Outstanding data queries would have been resolved or adjudicated as unresolvable, and data should have been cleaned and finalized before database lock. Following the database lock after all subjects have completed Induction Period, the primary analysis of the data will be performed.

The SAP will be finalized and approved before 50% of planned subjects enrolled and initiated dosing. Any changes made after the finalization and approval of the SAP will be documented in the CSR with the rationale.

2 STUDY OBJECTIVES AND ENDPOINTS

This is a Phase 2a, Multi-Center, Open-Label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of PRA023 in Subjects with Moderately to Severely Active Crohn's Disease. The primary, secondary and exploratory study objectives and corresponding endpoints for IP analyses are listed in **Table 1** below.

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of PRA023 following 12-weeks of induction therapy	• Proportion of subjects reporting AEs, SAEs, AEs leading to discontinuation, and markedly abnormal laboratory values
To assess the proportion of subjects with endoscopic improvement (decrease in simple endoscopy score for Crohn's disease [SES-CD] ⩾ 50% from Baseline) at Week 12	• Proportion of subjects with endoscopic improvement , as defined by decrease in SES-CD ≥ 50% from Baseline at Week 12
Secondary	
To assess the proportion of subjects with clinical remission (Crohn's disease activity index [CDAI] < 150) at Week 12	• Proportion of subjects in clinical remission (CDAI < 150) at Week 12
To assess the proportion of subjects with endoscopy and clinical improvement at Week 12	• Proportion of subjects with endoscopic and clinical improvement, as defined by decrease in SES-CD ≥ 50% AND reduction in CDAI ≥ 100 points from Baseline or CDAI <150 at Week 12
To assess the proportion of subjects with biomarker and clinical improvement, among subjects with at least one elevated biomarker at Baseline, at Week 12	• Proportion of subjects with both biomarker and clinical improvement (decrease in hsCRP OR fecal calprotectin ≥ 50% from Baseline, among subjects with at least one elevated biomarker at Baseline, AND reduction in CDAI ≥ 100 points from Baseline or CDAI <150) at Week 12

To assess the proportion of subjects with normalization of C-reactive protein (hsCRP < upper limit of normal [ULN]), among subjects with elevated concentrations at Baseline, at Week 12	• Proportion of subjects with normalization of hsCRP (as defined by hsCRP < ULN), among subjects with elevated concentrations at Baseline, at Week 12
To assess the proportion of subjects with normalization of fecal calprotectin (fecal calprotectin < ULN), among subjects with elevated concentrations at Baseline, at Week 12	• Proportion of subjects with normalization of fecal calprotectin (as defined by fecal calprotectin < ULN), among subjects with elevated concentrations at Baseline, at Week 12
To assess the proportion of subjects with clinical improvement at Week 12	• Proportion of subjects in clinical response, as defined by reduction in CDAI ≥ 100 points from Baseline or CDAI<150 at Week 12
To assess the proportion of subjects with two component patient-reported outcome (PRO-2) remission at Week 12	• Proportion of subjects with PRO-2 remission (defined as average daily abdominal pain score ≤ 1 point and average daily stool frequency ≤ 3 points with abdominal pain and stool frequency no worse than Baseline) at Week 12
To assess the change in SES-CD score from Baseline to Week 12	• Change in mean SES-CD score at Week 12 from Baseline
To assess the pharmacokinetics (PK) of PRA023	• Descriptive summaries of PK and immunogenicity of PRA023
To assess the immunogenicity of PRA023	• Proportion of subjects developing anti-drug antibody (ADA) and neutralizing antibody (Nab)
	Exploratory
To assess endoscopic remission at Week 12	• Proportion of subjects with endoscopic remission, as defined as SES-CD <=4 and at least 2-point reduction from baseline and all individual score <=1 at Week 12
To assess ulcer-free at Week 12	• Proportion of subjects with SES-CD ulcerated surface score of 0 at week 12 among patients with SES-CD ulcerated surface score >=1 at baseline
To assess the change in SES-CD segment score from baseline to Week 12	• Change from baseline in SES-CD for each segment at Week 12
To assess the clinical improvement by PRO-2 score at Week 12	• Change in PRO-2 over time • Proportion of subjects with clinical improvement by PRO-2 score, defined as >=30% reduction of either score and no worsening in both scores at Week 12 • Proportion of subjects with enhanced clinical response by PRO-2 score, defined as a reduction of >=60% in averge daily stool frequency or a reduction of >=35% in average daily abdominal pain score, and no worsening in both scores at Week 12 • Proportion of subjects with >=30% reduction of PRO-2 total score
To assess the proportion of subjects with both clinical improvement and endoscopic improvement at Week 12	• Proportion of subjects who achieve both enhanced clinical response by PRO-2 score and endoscopic improvement at Week 12
To assess the IBDQ remission or IBDQ improvement at Week 12	• Proportion of subjects with IBDQ remission or IBDQ improvement at Week 12
To assess the change from baseline in IBDQ scores at Week 12	• Change from baseline in IBDQ scores
To assess the change in CDAI and component scores over time	• Change in CDAI and components from Baseline over time

To assess the effects of PRA023 on tissue and serum pharmacodynamic (PD) markers, including tumor necrosis factor-like cytokine 1A (TL1A) concentrations, fecal calprotectin, and hsCRP in all subjects over time	• Change in PD markers including TL1A concentrations, fecal calprotectin, and hsCRP over time
To characterize the change in Perianal Disease Activity Index (PDAI) score from Baseline to Week 12	• Change in PDAI from Baseline over time
To characterize the effect of PRA023 for improvement and remission of enterocutaneous and/or perianal fistula -Overtime	• Proportion of subjects with improvement or remission of enterocutaneous and/or perianal fistula Overtime , among patients with fistula at baseline
To assess the change in global histological activity score (GHAS) and Robarts histopathology index (RHI) from Baseline to Week 12	• Change in mean GHAS and RHI scores from Baseline to Week 12 • Proportion of subjects with GHAS histologic score ≤ 4 at Week 12 • Proportion of subjects with Robarts histologic score < 5 at Week 12
To assess the proportion of subjects with histologic response and histologic remission at Week 12	• Proportion of subjects with GHAS histologic remission, defined as no neutrophils in the epithelium or subscore of 0, at Week 12 • Proportion of subjects with Robarts histologic remission (< 3) at Week 12

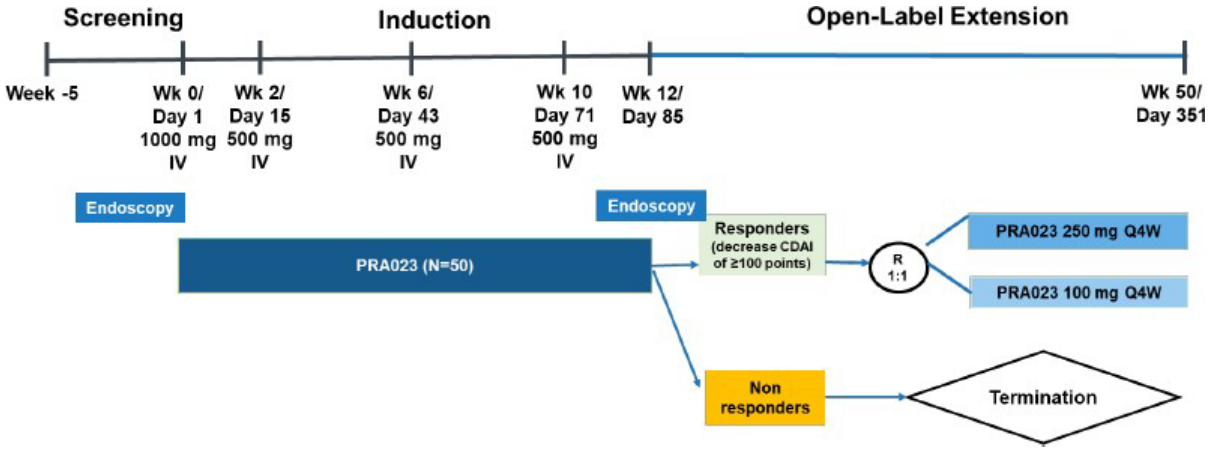
3 STUDY DESIGN

3.1 SUMMARY OF STUDY DESIGN

This is a multi-center, open-label, proof of concept study designed to assess the safety, tolerability, and preliminary efficacy of PRA023 following 12 weeks of induction therapy in subjects with Crohn's disease (CD). This study will be conducted under the aegis of a Data Monitoring Committee (DMC) and will commence following the demonstration of an acceptable safety profile of PRA023 at a dose of ≥ 500 mg in the multiple ascending dose study in normal healthy volunteers (Study PR200-101).

The study has 4 periods (Screening, IP, OLE and Follow-Up [FU] Period). Following the Screening Period, approximately 50 eligible subjects with moderately to severely active CD will enter the IP to receive PRA023 1000 mg on Week 0/Day 1, followed by 500 mg on Weeks 2, 6, and 10 via intravenous (IV) administration. Subjects who discontinue from the study will have a follow-up period of 12 weeks after the last dose. A schema for the study is in Figure 1.

Figure 1 Study Design



Q4W=every 4 weeks; R=Randomization.

Response at Week 12 is defined as reduction from Baseline in CDAI of ≥ 100 points , or CDAI < 150. Non-responders at Week 12 should discontinue from study drug treatment.
Subjects who complete the 12-week IP and have responded will have the option to enter OLE, where they will be randomized to either 250 mg IV Q4W or 100 mg IV Q4W until Week 50. Subjects will continue in OLE until they progress, withdraw from the study, study termination, or Week 50.
The study may be amended by the Sponsor to extend the OLE period beyond 50 weeks based on emerging safety data.
For additional details, please see the Schedule of Assessments are described in Appendix G.

3.2 DETERMINATION OF SAMPLE SIZE

The study is planned to enroll approximately 50 subjects. The sample size will enable a statistical power of 80%, at 1-sided significance level of 0.025, to test against the null hypothesis of endoscopic improvement rate of 12%, assuming the endoscopic improvement rate for PRA023 is 27%.
The null hypothesis of an endoscopic improvement (decrease in SES-CD ≥ 50%) rate of 12% is based on a meta-analysis estimate of the upper limit of 95% CI of the observed placebo rate (95% CI) of 9.5% (7.1, 11.9) from multiple modern-era CD clinical trials with centrally read endoscopy and similar eligibility criteria. [1]

3.3 RANDOMIZATION

3.3.1 RANDOMIZATION NUMBERS

This is an open-label study where all subjects will receive PRA023. Eligible subjects will be assigned a subject number by the IRT system at Week 0/Day 1 upon confirmation of study eligibility as a means to track the number of eligible subjects enrolled in the study. Subjects who are randomized in OLE will retain their original subject numbers.

3.3.2 BLINDED IMAGE ASSESSMENT

Endoscopy videos and histopathology images will be scored by qualified independent central readers (CR) blinded to the visit at which the videos/images were obtained.

Endoscopic assessments will be scored both locally and centrally and histologic assessments will be scored centrally. Study central readers will receive standardized training on [redacted] for assessment of endoscopy and histopathology (qualified gastroenterologists and pathologists, respectively). Central readers will enter scores in a study database. For histologic assessments, there will be a single central read. For endoscopic assessments, two central reader scores will be the primary scores for analyses and for confirming eligibility. In the case of adjudication for endoscopy, the third central reader (adjudicator) would score the endoscopy video independently.

Further details are available in the Image Review Charter.

4 GENERAL CONSIDERATIONS FOR DATA ANALYSES

4.1 REPORTING CONVENTIONS

The following reporting conventions apply generally to tables, listings, and graphs:

- Unless otherwise specified, the baseline value is defined as the last non-missing assessment before the first does of study treatment.
- If the date of interest occurs on or after the first dose date, the study day will be calculated as (date of interest – date of first dose) + 1.
- If the date of interest occurred prior to the first dose date, then study day will be calculated as (date of interest – date of first dose).
- Categorical data will be summarized by treatment group in terms of frequency counts and percentages.
- Continuous variables will be summarized by treatment group using descriptive statistics (the number of subjects (n), mean, median, standard deviation (SD), minimum (Min), and maximum (Max)) of the values at each visit and the change from baseline to each visit, unless specified otherwise.
- Confidence Intervals (CIs) will be presented as 2-sided 95% CIs.
- All mean, median and CI values will be formatted to one more decimal place than the measured values. SD values will be formatted to two more decimal places than the measured value. Min and Max will be formatted to the same number of decimal places as the measured value. The maximum number of decimal places reported shall be four for any summary statistic.
- All percentages will be rounded to one decimal place, unless specified otherwise. The number and percentage of responses will be presented in the form xx (xx.x), where the percentage is in the parentheses.
- Change from baseline is calculated as a post-baseline value minus the baseline value.
- All laboratory data will be reported using standard international units.
- All analysis and summary tables will include the analysis population sample size (ie, number of subjects) in the column headings.

- By-subject listings will be presented for all subjects in the relevant analysis sets, and sorted by treatment allocation, study site (if applicable), Subject ID, date, and visit. Numeric data will be listed to the same number of decimal places as recorded on the eCRF or other data source. Data collected on log forms, such as AEs, will be presented in chronological order within the subject, and age, and sex will be included in the listing, as space permits.
- SAS® Software Version 9.4 (SAS Institute Inc., Cary, NC, USA.) is to be used for all analyses including tables, listings, and figures.
- Non-pharmacokinetic and non-biomarker lab 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 for calculation of 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).
- PK plasma concentration values that are below the limit of quantitation (BLQ) will be treated as 0. PD/biomarker BLQ concentration values will be treated as ½ *LOQ at all time points.
- MedDRA version 24.0 will be used to code adverse events and medical history, World Health Organization (WHO) drug dictionary version March 2020 or newest will be used for medication coding.

4.2 ANALYSIS SETS

4.2.1 SCREENING SUBJECTS ANALYSIS SET

All subjects who signed informed consent and participated in screening visit will be included in the screening subjects analysis set. The number of subjects screened will be reported, and will be used for the presentation of subject disposition. Data collected on subjects who are screened but not enrolled, i.e. study medication not received, will not be included in any analyses.

4.2.2 SAFETY ANALYSIS SET

All subjects who received at least 1 dose of study drug will be included in the safety analysis set. The Safety Analysis Set is the primary analysis set for safety analyses.

4.2.3 FULL ANALYSIS SET (FAS)

All subjects who have been treated with PRA023 with Baseline CDAI and SES-CD scores will be included in the FAS. The FAS set will be used for efficacy analysis.

4.2.4 PER-PROTOCOL(PP) ANALYSIS SET

The PP analysis set is a subset of FAS. Subjects who had significant protocol deviations will be excluded from analysis based on PP analysis set.

4.2.5 OPEN LABEL EXTENSION ANALYSIS SET

The OLE analysis set includes subjects who are randomized and received at least 1 dose of OLE drug. The analysis will be presented by the randomized treatment group.

4.3 HANDLING OF MISSING DATA

In general, missing data will not be imputed for descriptive statistics unless methods for handling missing data are specified. The handling of missing or incomplete dates for prior and concomitant medications is described in Section 5.4, and for AE onset is described in Section 7.1.
The handling of missing data in analyses of the efficacy endpoints is discussed in Section 6.2 to Section 6.4.

4.4 ANALYSIS VISIT WINDOW

The following tables present the visits assigned for efficacy and safety analyses and the corresponding ranges of treatment days (window) during which an actual visit may occur. In general, data collected at nominal visits will be used for the analysis. In case of missing assessments at a nominal visit, data collected from unscheduled visits will be slotted according to the Visit Windows of Table 2 for analysis, unless specified otherwise. If multiple unscheduled visits are slotted into the same nominal visit, the one closest to the targeted visit date will be used.

Table 2 Analysis Visit Windows

Analysis Visit [a]	Assessment	Target Day of the Visit	Analysis Visit Window (Study Day)
Induction Treatment Period			
Screening	All assessments	-35 to 0	≤ 1
Randomization (Week 0)	All assessments	1	1
Week 1	Vital Signs, CBC, hsCRP, CDAI	8	2 - 11
Week 2	Vital Signs, CBC, hsCRP, CDAI	15	12 - 28
	Fistula, Chemitry panel, Urianalysis, total sTL1A, Fecal Calprotectin	15	2 - 28
Week 6	Vital Signs, CBC, Chemistry panel, Urianalysis, Fistula,	43	29 - 57

	total sTL1A, Fecal Calprotectin, CDAI		
	IBDQ	43	2 - 57
Week 10	Vital Signs, CBC, Fistula, total sTL1A, Fecal Calprotectin, CDAI	71	58 - 78
Week 12/ET	Vital Signs, CBC, Fistula, total sTL1A, Fecal Calprotectin, CDAI	85	79 - 92
	Chemistry panel, Urianalysis, IBDQ	85	58 - 92
	Ileocolonoscopy	85	71 - 98
	ECG, Lipid panel, PDAI	85	2 – 92
Post Treatment Period			
Safety Follow-up [b]	Safety Follow-up	NA	Remain as the nominal visit

a Relative to the date of the first dose of study treatment. Day 1 = the date of the first dose of study treatment.
b No visit window will be used for the post-treatment period. The nominal CRF visit description of Safety Follow-up will be used regardless of when this visit occurs. Presented in analysis tables for safety parameters, including but not limited to electrocardiograms, clinical laboratory values, and vital signs. No visit window are needed for physical examination or pregnancy test.

5 SUBJECT CHARACTERISTICS

5.1 SUBJECT DISPOSITION

Tabular summaries of subject disposition will be provided for screening and IP. These summaries will include the number of subjects screened, the number of subjects screened but not enrolled (for screening period only), and the number of subjects enrolled and treated as well as the number of subjects who discontinued the respective study period, and reasons for discontinuation.

The following subject disposition summaries will be provided based on the total number of subjects screened:

- Number of subjects screened (n)
- Number of subjects screening failures (n)
- Number of subjects enrolled (n)
- Number of subjects enrolled and treated (n)

The following subject disposition summaries will be provided based on Safety Analysis Set:

- Number of subjects completed IP (n)
- Number of subjects in FAS
- Number of subjects in PP Analysis Set
- Number of subjects discontinued prematurely during IP (n)
    - Reasons for discontinuation

The number of subjects in Safety Analysis Set will be summarized by geographic region. A listing of subject discontinuation will be provided with a reason of discontinuation indicating period (i.e., Screening or IP).

Geographic region will be defined as follows, based on the locations of sites anticipated to participate in these studies:

- North America: Canada, United States
- Western Europe: Belgium, France, ,
- Eastern Europe: Poland, Czech, Russia, Georgia, Ukraine
- Rest of World: Australia

5.2 DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

The subject's year of birth, gender, weight, height, companion diagnostic (CDx) status, prior biologic experienced, concomitant corticosteroid and immunosuppressant use, and other demographic and disease characteristics are collected at the screening visit. Age and body mass index will be calculated.

Only the year of birth is collected at screening. For the purpose of age calculation, the month and day of birth will be imputed as July 01, of the year of birth. Age is the computed as follows:

$$\text{AGE} = (\text{Informed Consent Date} - \text{Date of Birth})/365.25$$

Demographic and baseline characteristics (e.g., age (years), gender(male, female), race/ ethnicity, geographic region) will be summarized. The summary of demographic data and baseline disease characteristics will be provided for the Safety Analysis Set and OLE analysis set.

Baseline disease characteristics include duration of disease, CD complication, concomitant CD medication use (Steroids, immunomodulators, and aminosalicylates), and data for prior biologic use.

5.3 TREATMENT EXPOSURE

5.3.1 EXPOSURE

Since this is an open-label study, there is no blinding. The site pharmacist(s) or designee will be preparing study drug for infusion. Detailed study drug preparation and handling instructions will be provided to the investigational pharmacist in the Pharmacy Manual.

Total duration of exposure to study treatment during Induction period is defined as the number of days elapsed from date first dose to the date of Week 14 visit for patients who enter OLE, or otherwise, to the date of 4 weeks after last dose or the date of data cutoff for the primary analysis, whichever is earlier. The total duration of exposure to study treatment and total number of infusions received for the IP and OLE will be summarized using descriptive statistics for the Safety Analysis Set.

5.3.2 COMPLIANCE

The investigator is responsible for accountability of all study supplies, including study treatments, at the site and must maintain adequate records of all study treatment received and dispensed. These records will be used to evaluate protocol deviation with respect to treatment compliance.

The total number of infusions (PRA023) administered will be summarized using descriptive statistics during the IP for safety analysis set. Number of subjects with a missing dose during IP will be presented.
A complete infusion is defined as the infusion with at least 80% infusion volume (i.e., 200 mL) administered of the total volume (i.e., 250 mL). The total number of complete infusions administered will be summarized.

A by-subject listing of study drug administration and infusion interruption will be provided for the Induction Period and OLE period, sorted by subject ID number in ascending order.

5.4 PRIOR AND CONCOMITANT MEDICATION

Prior and concomitant medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the World Health Organization (WHO) drug dictionary version March 2020 or newer.
A tabular summary showing the number and percentage of subjects taking CD agents (including corticosteroids) prior to the enrollment, and concomitant during the Induction period will be presented for all subjects in Safety Analysis Set. A similar table will be presented for OLE period for subjects in OLE analysis set.
Summary of prior and concomitant medications, separately for CD medications and non-CD medications, will include the number and percentage of subjects by ATC Classification level 2 and preferred term. A subject will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under “Unavailable ATC classification” category. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.
Listings of prior and concomitant CD medications will be generated.

5.4.1 PRIOR MEDICATION

Prior medications are defined as the medication that started and stopped before the first dosing date. Only medications where the stop date is prior to the first dosing date will be considered prior. If the stop date is unknown or incomplete and the medications cannot definitely be considered as stopped prior to first dosing date then the medications will be considered as concomitant medications (e.g., partial stop date is May 2021, first dosing date is 15 May 2021, medication will be considered as concomitant).

5.4.2 CONCOMITANT MEDICATION

Any medication with a start date prior to or on the first dosing date and continuing to take after the first dosing date, or started after the first dosing date will be considered concomitant medications. In addition, concomitant medications with a start date after the last dosing date (concomitant medication taken during the safety follow-up period) will be presented in the follow-up medication

listing, as appropriate. If the start date of a medication is incomplete or missing, the medication will be assumed to be concomitant medication, unless the incomplete start date (month and/or year) or the stop date (complete or incomplete) clearly indicate that the medication started prior to first dosing date or later than 30 days after the last dosing date. Medication with completely missing start and stop dates will be included in the concomitant medication summary.
Additionally, the use of prohibited medications will be summarized and listed.

5.5 MEDICAL AND SURGICAL HISTORY

Medical and surgical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA version 24.0) and will include all relevant surgical and medical history including CD-related complications, other significant conditions or diseases relevant to the disease under study, previous surgeries for CD, and the extent and duration of disease at baseline.
A by-subject listing will be provided for those subjects with any medical/surgical history for the Safety Analysis Set.

5.6 PROTOCOL DEVIATIONS

Review of all protocol deviations will be performed on an ongoing basis during the conduct of the study. The number and percentage of subjects with major protocol deviations will be summarized. Subjects with important protocol deviations will be excluded from PP Analysis Set. The important protocol deviation could include, but are not limited to:

- Major protocol deviation related to certain study eligibility
  - Entry criteria that would impact on efficacy analyses: Inclusion criteria 2,3,or 4
- Major protocol deviation related to study treatment
  - Receiving incorrect investigated products, or
  - Missing ≥2 scheduled infusions during IP
- Unevaluable or missing Week 12 SES-CD score

A by-subject listing will be provided for those subjects with any protocol deviations before database lock. A separated by-subject listing will be provided for important protocol deviations that resulted in exclusion from the PP analysis set.

6 EFFICACY ANALYSES

Efficacy analyses for IP will primarily be based on the FAS, and supportive efficacy analysis will be based on PP, unless specified otherwise. Demographic data characteristics (height, weight, age, sex, race, and ethnic origin) will be listed by subject and summarized by CDx status and for the overall study population. Selected efficacy endpoints over time during the OLE will be summarized descriptively.

6.1 DERIVATION OF EFFICACY MEASURMENTS

6.1.1 SIMPLE ENDOSCOPIC SCORE – CROHN'S DISEASE (SES-CD)

The SES-CD scores 4 endoscopic items (ulcer size, proportion of ulcerated surface, proportion of the surface area affected by any disease lesion, and stenosis) from 0 to 3, with higher scores

representing more severe endoscopic disease activity. Each variable is scored for the 5 intestinal segments (ileum, right colon, transverse colon, left colon, and rectum) and summed to provide the total variable score. The sum of each variable score ranges from 0 to 15, except for stenosis, where it ranges from 0 to 11, because 3 represents a stenosis through which a colonoscope cannot be passed and therefore, can only be observed once. Total SES-CD score is then calculated by summing the item scores (0-56 points). A score of zero is imputed for the missing items within a segment; if all components are missing, the total score will also be missing. [2] See Appendix A for additional details.

In general, a total SES-CD score can be calculated if the scores are available for at least 2 segments, and the total score is the sum of available segment scores, with the exception that if any segment is missing at Baseline, in which event the post-Baseline SES-CD will not include the specific segment.

Post-Baseline endoscopy perfomed out of study window can be used for the study visit (e.g., Week 12) if the procedure date is within the time window of 2 weeks prior to and 6 weeks after the date of study visit.

6.1.1.1 Central Scoring of Endoscopy Videos

All endoscopy videos are scored for the SES-CD independently by two blinded central readers. If adjudication is required, a third central reader will also score the video. Adjudication is required if any of the follow are true:

- Screening Assessment:
  - Central readers do not agree on the subject's eligibility (SES-CD score of ≥6 for ileocolonic and colonic only disease or ≥4 for ileal only disease).
- End of Induction (Week 12) Assessment:
  - Central readers do not agree on the subject's response to treatment (≥50% decrease in SES-CD score from baseline).
- All Assessments:
  - Central readers disagree on the inability to score the video due to video quality concerns.

The medians of the two or three central reader scores are used to form the outcome scores. The medians of each component (ulcer size, proportion of ulcerated surface, proportion of the surface area affected by any disease lesion, and stenosis) within each segment are rounded up to the next whole number, the total segmental score is reported as the sum of each component's unrounded median score within the segment reported to one decimal, and the total score is calculated as the sum of all resulting segmental totals (reported to one decimal) and rounded to integer.

6.1.2 Crohn's Disease Activity Index (CDAI)

The Crohn's Disease Activity Index(CDAI) consists of 8 items including physical examination items, extraintestinal manifestations, the hematocrit, and patient-reported outcome measures (number of liquid or very soft stools/day, abdominal pain, fever and general well-being), which are recorded by the subject in the electronic diary (or paper diary as backup in case of electronic diary not be available). A lookback to the 7 days prior to the clinic visit (Appendix B) will be used for CDAI score calculation. [3] Each item is multiplied by a weighting factor and summed to give

a total CDAI score, ranging from 0 to over 600 points, with higher scores representing more severe disease activity. Evaluable days do not include days of bowel prep, day of colonoscopy, and two days after colonoscopy.

If the full seven evaluable days of daily diary information for any of the patient-reported outcome measures (number of liquid stools, abdominal pain, general well-being) are not present, the following imputation rules will be applied:

1. If five or six days are available, the available data will be summed and reweighted for seven days. E.g. for five days: $\text{Abdominal Pain Score} = \text{SUM(five days)} \times {}^{7}/_{5}$
2. If four or fewer days are available, then reach back to 10 days rather than 7 days prior to the visit. If there are at least 5 evaluable days of symptoms in the 10 day window, the available data will be summed and reweighted (if necessary) for the seven day score.
3. If there are still four or fewer evaluable days of symptoms in 10 days, then the component score will be considered missing.

The resulting days of eDiary used will apply to fever (a part of extraintestinal manifestation) and use of antidiarrheal medication.

For the component of extraintestinal manifestation, if the assessment is not done at a visit, data of evaluation from visits (including unscheduled visits) within 60 days prior to, or within 7 days after the study visit will be used. As fever is captured via eDiary, any presence of fever from the days of the eDiaries above will be counted as 1; 0 otherwise.

For the component of use of antidiarrheal medication, any recorded use of antidiarrheal medication from the days of eDiaries above will result in a 'Yes'; 'No' otherwise.

For the component of abdominal mass, if the assessment is not done at a visit, the last known status will be used.

For lab value of hemacrit, central lab value from the study visit should be used. If the study visit hemacrit is not evaluable, value from other visits within 60 days prior to, or within 7 days after the study visit will be used.

For body weight, if weight is not measured at the study visit, the last known weight prior to the study visit will be used.

CDAI score at a study visit will be considered missing if any of these components is missing according the rules above.

6.1.2.1 2-item Patient-reported Outcome Measure (PRO-2)

The PRO2 consists of two CDAI component items: daily stool frequency and abdominal pain. [4] Study participants record the number of liquid or very soft stools and rate abdominal pain (from 0-3) daily, excluding non-evaluable days. The average of the daily entries for the 7-day period is calculated and multiplied by a weighting factor to provide a total score for each component item. The total PRO2 score is then calculated by summing the component item scores. See Appendix C for additional details. The similar imputation rules (without reweighting) will be applied to the PRO-2 as in the CDAI.

6.1.3 PERIANAL DISEASE ACTIVITY INDEX (PDAI)

The Perianal Disease Activity Index Activity Index (PDAI) will be used to evaluate severity of perianal disease. The PDAI incorporates 5 items: discharge, pain, restriction of sexual activity, type of perianal disease, and degree of induration. Each category is graded on a 5-point Likert scale ranging from no symptoms (score of 0) to severe symptoms (score of 4). Scores can range from 0 - 20, with higher scores indicating more severe perianal disease. See Appendix D for additional details.

6.1.4 GLOBAL HISTOLOGIC DISEASE ACTIVITY SCORE (GHAS)

The Global Histologic Disease Activity Score (GHAS) assesses the extent and/or severity of 7 histologic variables (Appendix E). [5] The total GHAS (range: 0-16) per segment is calculated by adding up the scores for each histological variable, with higher scores representing more severe disease activity. The overall total GHAS is the sum of all affected segments. Disease activity is scored separately for colonic (CGHAS) and ileal (IGHAS) biopsies.

6.1.5 ROBERTS HISTOPATHOLOGY INDEX (RHI)

The Roberts Histopathology Index (RHI) was developed by selecting items from the Geboes score that showed at least moderate intra-rater reliability and best predicted overall microscopic disease activity on a visual analogue scale. [6] The 4 items selected for inclusion include: 1) the extent of chronic inflammatory cell infiltration, 2) neutrophils in the lamina propria, 3) neutrophils in the epithelium, and 4) erosions and ulceration (see Appendix E). Each item is scored from 0 to 3 and multiplied by a weighting factor and summed to give the overall RHI score, with total scores ranging from 0 (no disease activity) to 33 (severe disease activity).

6.2 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint, endoscopic improvement at Week 12, will be used to assess the efficacy of PRA023. The proportion of subjects in PP analysis set with endoscopic improvement at Week 12 will be tested against the null hypothesis of 12%, an upper bound of observed placebo rate from multiple CD trials (Table below and Table 6 of study protocol).

Clinical Trial	**N**	**Placebo Endoscopic Response Rate (%)**
Feagan et al. 2017	39	13
Vermeire et al. 2017	44	14
Sands et al. 2019	64	10.9
Selinger et al. 2018	59	3.4
Advance Study 2021	175	12
Motivate Study 2021	187	11
Average		10.7
Sample-size Weighted Average	568	9.5
95% CI		(7.1, 11.9)

6.2.1 PRIMARY ANALYSIS

The proportion of subjects with endoscopic improvement in PP analysis set will be estimated by the number of subjects who achieved the improvement at Week 12 divided by the total number of subjects in PP analysis set. The confidence interval for the proportion will be calculated using Wilson-score method (Wilson 1927). If the resulting lower bound of 95% CI is greater than 12%, the null hypothesis is, therefore, rejected at a 1-sided significance level of 0. 025.

6.2.2 SENSITIVITY ANALYSIS

In the sensitivity analysis, patients in FAS with missing SES-CD score at Week 12 will be considered as a non-responder for the endpoint of endoscopic improvement. The 95% confidence interval will then be calculated according to Wilson score method.

The proportion of subjects with endoscopic improvement for PP analysis set and associated 95% confidence intervals will also be estimated by the following subgroups:

- CDx status (CDx+ or CDx-)
- Number of prior biologic use (0, 1, or 2+)
- Disease extent (ileal only, colonic only, or both)
- Disease severity (baseline SES-CD<=16, or >16)
- Concomitant use of immunosuppressive including AZA, 6MP, and MTX (Yes, or No)
- Concomitant use of oral corticosteroids (Yes, or No)
- ADA status (positive, negative)

Given the small sample size of the trial, the results of subgroup analysis should be interpreted with caution. The forgoing analysis may be modified when the sample size in a subgroup is deemed too small.

6.3 SECONDARY EFFICACY ENDPOINTS

6.3.1 DICHOTOMOUS OR BINARY ENDPOINTS

The definition of the dichotomous secondary efficacy endpoints (i.e., responders) are listed in Table 3 below.

Table 3 Definition of Secondary Binary Endpoints

Outcome	Measure	Definition	Analysis Timepoints
Clinical Remission	CDAI	Crohn's disease activity index [CDAI] < 150	Week 12
Endoscopic and clinical improvement	SES-CD and CDAI	Decrease in SES-CD ≥ 50% AND reduction in CDAI ≥ 100 points from Baseline, or CDAI<150	Week 12
Biomarker and Clinical Composite Improvement	hsCRP and CDAI	Decrease in hsCRP or fecal calprotectin ≥ 50% from Baseline and reduction in	Week 12

		CDAI ≥ 100 points from Baseline, or CDAI<150	
Clinical Response	CDAI	Reduction in CDAI ≥ 100 points from Baseline or CDAI<150	Week 12
PRO-2 remission	Abdominal pain score and Stool frequency	Average daily abdominal pain score ≤ 1 point and average daily stool frequency ≤ 3 points with abdominal pain and stool frequency no worse than Baseline	Week 12
Normalization of hsCRP	hsCRP	hsCRP < ULN, among subjects whose baseline hsCRP ≥ ULN	Baseline, Week 12
Normalization of fecal calprotectin	fecal calprotectin	fecal calprotectin < ULN, among subjects whose baseline fecal calprotectin ≥ ULN	Week 12
Anti-drug antibody (ADA) and Neutralizing antibody (Nab)	ADA and Nab	Positive ADA at any time; Posotive Nab at any time	Over time

Abbreviations: SES-CD, Simple endoscopy score for Crohn's disease; CDAI, Crohn's disease activity index; hsCRP, High sensitivity C-reactive protein; PRO-2, Two component patient-reported outcome; ADA, Anti-drug antibody; Nab, Neutralizing antibody.

The proportion of clinical remission in FAS will be analyzed according to the method similar to the sensitivity analysis for the primary efficacy endpoint, in the case of missing data in CDAI at Week 12. If the resulting lower limit of 95% confidence interval is greater than 16%, the observed remission rate for the placebo treated patients from multiple prior CD trials ([1], [7], [8], [9], [10]), the null hypothesis for the first secondary endpoint of clinical remission at Week 12 will be rejected at a 1-sided significance level of 0.025.

The point estimate and 95% CI for the secondary efficacy endpoints will be calculated for FAS, while the missing values in the categorical endpoint will be imputed as non-responders.
Subgroup analysis (defined in section 6.2.2) may be performed for clinical remission, endoscopic and clinical improvement, biomarker and clinical composite improvement, clinical response, and PRO-2 remission.

6.3.2 CONTINUOUS ENDPOINTS

The mean change from baseline in SES-CD score at Week 12 for PP analysis set will be estimated using ANCOVA with baseline SES-CD score as covariates. The 95% confidence interval for the LS mean for the change from baseline at Week 12 will be calculated. The median for the change from baseline in SES-CD score at Week 12 for PP analysis set will also be estimated and p-value for testing against no change will be reported using Wilcoxon rank test.

6.4 EXPLORATORY EFFICACY ENDPOINTS

6.4.1 DICHOTOMOUS OR BINARY ENDPOINTS

The definition of the binary exploratory endpoints are listed in Table 4 below.

Table 4 Definition of Exploratory Binary Endpoints

Outcome	Measure	Definition	Analysis Timepoints
Endscopic Remission	SES-CD	SES-CD <=4 and at least 2-point reduction from baseline and all individual score <=1	Week 12
Ulcer-free	SES-CD (Ulcerated Surface)	SES-CD ulcerated surface score of 0, among patients with SES-CD ulcerated surface score >=1 at baseline	Week 12
Clinical response by PRO-2	PRO-2	>=30% reduction of either score and no worsening in both scores	Over time
Clinical response by PRO-2 total score	PRO-2	>=30% reduction of PRO-2 total score	Over time
Enhanced Clinical response by PRO-2	PRO-2	reduction of >=60% in averge daily stool frequencies or a reduction of >=35% in average daily abdominal pain score, and no worsening in both score	Over time
Enhanced Clinical response and Endoscopic improvement	PRO-2 and SES-CD	enhanced clinical response by PRO-2 score and endoscopic improvement	Week 12
IBDQ Remission	IBDQ	IBDQ total score of >170	Week 12
IBDQ Rresponse	IBDQ	>=16-point increase from baseline or an absolute score of >170	Week 12
Improvement or remission of enterocutaneous and/or perianal fistula	Fistula	Fistula Improvement from baseline among patients with fistula at baselinef	Week 12
GHAS histologic remission	GHAS	No neutrophils in the epithelium or subscore of 0	Week 12
GHAS histologic response	GHAS	GHAS histologic score ≤ 4	Week 12
Robarts histologic remission	RHI	RHI<3	Week 12
Robarts histologic response	RHI	Robarts histologic score < 5	Week 12

Abbreviations: SES-CD, Simple endoscopy score for Crohn's disease; CDAI, Crohn's disease activity index; hsCRP, High sensitivity C-reactive protein; PRO-2, Two component patient-reported outcome; GHAS, Global histological activity score; RHI, Robarts histopathology index; IBDQ, Inflammatory Bowel Disease Questionnaire.

The proportion of subjects of meeting the definition of these endpoints will be calculated in FAS, though patients with missing data will be excluded from the summary.

6.4.2 CONTINUOUS EFFICACY ENDPOINTS

The definition of the continue efficacy endpoints (Mean Change from Baseline) by visit are listed in Table 5 below.

Table 5 Definition of Exploratory Continuous Endpoints

Measure	Definition	Analysis Timepoint
SES-CD segment score	Mean change from baseline	Week 12
PD markers (TL1A concentrations, fecal calprotectin, and hsCRP)	Mean fold change from baseline	Over time
RHI	Mean change in Robarts Histopathology Index (RHI) from baseline	Week 12
GHAS	Mean change in global histological activity score (GHAS) from baseline	Week 12
PDAI	Mean change in Perianal Disease Activity Index(PDAI) subscore from baseline	Week 12
CDAI	Mean change in CDAI and components from Baseline over time	Over time
PRO-2	Mean change in PRO-2 over time	Over time
IBDQ	Mean change from baseline in IBDQ score over time	Over time

Abbreviations: CDAI, Crohn's disease activity index; hsCRP, High sensitivity C-reactive protein; PRO-2, Two component patient-reported outcome; RHI, Robarts Histopathology Index; GHAS, Global histological activity score; SES-CD, Simple endoscopy score for Crohn's disease; PDAI, Perianal Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire.

In general, continuous endpoints will be summarized using descriptive statistics of the values at each visit and the change from baseline to each post-baseline visit. Missing data will not be imputed for descriptive statistics.
The mean change in CDAI over time through Week 12, mean change in PRO-2 over time through Week 12 and mean change in IBDQ score over time through Week 12 will be estimated according to a MMRM model with baseline CDAI, visit as fixed effect and subject as random effect. The 95% confidence intervals at each time point will be calculated according to the MMRM model. This analysis will be conducted by maximum likelihood methods using the SAS PROC MIXED procedure.
Additional descriptive summary over time will be reported for patients who entered OLE based on available data as of cutoff date of the DBL for Induction period.

6.5 EVALUATION OF PHARMACODYNAMIC PARAMETERS

The PD markers (hsCRP, fecal calprotectin, and total sTL1A) will be summarized using descriptive statistics: N, mean, SD, min, max, median, coefficient of variation as a percent (CV %), and Geometric Mean (GM) by CDx status.

Stool samples for analysis of fecal calprotectin will be collected prior to any bowel preparation. Subjects will receive instructions and stool sample supplies for collection at home.
Listings and descriptive statistics (n, mean [or geometric mean], median, SD, CV%, min and max) will be provided by treatment group for each biomarkers (fecal lactoferrin, hsCRP, total sTL1A) specified in the study protocol as follows:

- Baseline values
- Values at each post-baseline visit
- Change from baseline or fold change from baseline at each post-baseline visit, depending on the data distribution of a PD marker

- % Change from baseline at each post-baseline visit, as appropriate

In the case of multiple values in an analysis visit, data will be selected for analysis as described in Section 4.4. Graphs of change from baseline will be presented, as appropriate.

6.6 EVALUATION OF PHARMACOKINETIC PARAMETERS

PK parameters will be computed, as appropriate, from the individual serum concentrations using a non-compartmental approach. All PK parameters will be summarized using descriptive statistics: N, mean[or geometric mean], SD, min, max, median, CV %, and GM and GM CV%. Serum concentrations of PRA023 will be summarized.

6.7 EVALUATION OF IMMUNOGENICITY

The proportion of subjects with any sample positive for ADA and the proportion of subjects with any sample positive for neutralizing antibody (Nab) will be summarized by the study period and dose using descriptive statistics. The PRA023 concentrations from all subjects and subjects with no sample positive for ADA will be summarized to assess whether ADA has an impact on PRA023 exposure.

6.8 MISSING DATA HANDLING

6.8.1 NON-RESPONDER IMPUTATION (NRI)

For the responder analyses as described in Table 3 of Section 6.2, unless specified otherwise, subjects who do not have sufficient measurements to determine the endpoint will be considered as non-responders (i.e., non-responder imputation (NRI). Specifically, all subjects who discontinue from the study at any time prior to the assessment timepoint (regardless of reason) or fail to have an adequate efficacy assessment at that timepoint will be considered a non-responder.

6.9 SENSITIVITY ANALYSES

To evaluate of the robustness of the primary efficacy analysis, the binary endpoint based on the NRI in PP analysis set will use the same analysis methods for FAS as described in Section 6.2.1.

6.10 MULTIPLICITY

A closed hierarchical procedure will be used to control for multiple comparisons for the primary endpoint aand the first secondary endpoint. The order of testing will be primary endpoint, followed by the secondary endpoint of clinical remission at Week 12. If the null hypothesis for the primary endpoint is not rejected, the testing procedure will be terminated. The subsequent analysis of clinical remission would be considered exploratory.

7 SAFETY ANALYSES

Safety will be evaluated via descriptive statistics and point estimates for patients in Safety Analysis Set. No inferential testing for statistical significance will be performed.

7.1 ADVERSE EVENTS

7.1.1 ADVERSE EVENT DICTIONARY

All AEs will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. System organ class (SOC) and preferred term (PT) will be provided in the AE dataset.

7.1.2 ADVERSE EVENT SEVERITY

The severity of AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (27 November 2017). The general categories for each grade are presented in Table 6.

Table 6 Adverse Event Severity Grading

Grade	Severity	Alternate Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal; local or noninvasive intervention indicated; limiting age appropriate instrumental ADL
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Very severe, life-threatening, or disabling	Life-threatening consequences; urgent intervention indicated
5	Death related to AE	Death related to AE

7.1.3 RELATIONSHIP OF ADVERSE EVENT TO STUDY TREATMENT

The relationship of the AE to study treatment (PRA023) will be assessed by the investigator. The Investigator will define the relationship of an AE to the study drug by selecting one of the following categories:

- Related: There is a reasonable possibility that there is a causal relationship between the study drug and the AE.
- Not Related: There is not a reasonable possibility that there is a causal relationship between the study drug and the AE.

Relationship (causality) to study procedures should be determined for all pre-treatment-emergent events and AEs. The relationship should be assessed as Related if the Investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

7.1.4 SERIOUS ADVERSE EVENTS

Serious adverse events will be identified and captured as SAEs if AEs met the definitions of SAEs that were specified in the study protocol (Section 10.1.4).

7.1.5 ADVERSE EVENT OF SPECIAL INTEREST

An infusion reaction is defined as adverse events reported within the terms of hypersensitivity MedDRA SMQ (20000214) that occurred within 1 hour after the end of study drug infusion. A peri-infusion reaction is defined as adverse events reported within the terms of hypersensitivity SMQ (20000214)that occurred within 24 hours after the end of study drug infusion.
An infection is defined as those events coded under MedDRA body system of Infection and Infestation.

7.1.6 TREATMENT EMERGENT ADVERSE EVENTS

7.1.6.1 Definition of Treatment Emergent Adverse Events

Treatment Emergent Adverse Events (TEAE) are defined as following:

- AE onset date ≥ 1st study treatment date; or
- AE worsened on or after the 1st study treatment date

AEs recorded prior to the first infusion of study treatment will be considered non-treatment-emergent. All reported AEs (treatment-emergent or not) will be listed. Only TEAEs will be summarized.
AEs of special interest including infections, acute infusion reaction (within 1 hour of completion of infusion), and peri-infusion reaction (within 24 hours of completion of infusion) will be summarized based on a pre-specified MedDRA list.
AEs occurring in subjects who are considered immunogenicity positive will also be summarized.

7.1.6.2 Incomplete Dates

If the onset date of AE is incomplete and the AE stop date is not prior to the first dosing date of study treatment, 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/severity worsened is the same as or after the month and year (or year) of the first dosing date of study treatment, and
- The AE onset/severity worsened is the same as or before the month and year (or year) of the last dosing date of study treatment

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 treatment, will be considered to be treatment emergent. In addition, an AE with onset date missing and 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 treatment will be considered treatment emergent.

7.1.7 SUMMARIES OF ADVERSE EVENTS

Treatment Emergent (TE) AEs will be summarized based on the Safety Analysis Set by treatment period and post-treatment period, separately.
Summary tables will be presented to provide the number and percentage of subjects experiencing any AEs, any severe AEs, any drug-related AEs, any SAEs, any drug-related SAEs, and any AEs leading to study drug interruption or discontinuation.

In addition to the above summary table, summary tables and listings of adverse events listed below will be provided.

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by SOC, PT and Max Severity
- Summary of Severe (CTCAE Grade ≥ 3) TEAEs by SOC and PT
- Summary of Related TEAEs by SOC and PT
- Summary of TESAEs by SOC and PT
- Summary of Related TESAEs by SOC and PT
- Summary of AEs in Follow-up by SOC and PT
- Listing of All AEs
- Listing of TESAEs or Death
- Listing of TEAEs Leading to Study Drug Interruption or Discontinuation

7.2 PHYSICAL EXAMINATION

Physical examination is performed at the screening visit. All abnormal findings will be presented in a by-subject listing.

7.3 VITAL SIGNS

Descriptive statistics will be provided by treatment group for vital signs (blood pressure (mm Hg), heart rate (bpm), respiratory rate, temperature, weight (kg), height (m) and BMI (kg/m^2)) as follows:

- Baseline values
- Values at each post-baseline visit
- Change from baseline at each post-baseline visit

Body mass index (BMI) will be calculated from height and weight measurements collected at screening and Week 12/EOT using the following formula:
$BMI = Weight (kg) / [Height (m)]^2$.
A by-subject listing of vital signs will be provided by treatment group, subject ID number and visit in chronological order.
Subjects with markedly abnormal vital signs (criteria depicted in Table 7) will be summarized by study period.

Table 7 Markedly Abnormal Vital Signs

Markedly Abnormal Vital Signs	
Weight	increase or decrease ≥ 20% from Baseline
Heart Rate	(Increase of > 20 bpm from Baseline **and** >120 bpm) OR (decrease of > 20 bpm and <60 bpm)
SBP	(Increase of >20 mmHg from Baseline AND >160 mmHg) OR (decrease of >20 mmHg from Baseline AND <80 mmHg)

DBP	(Increase of >20 mmHg from Baseline AND >100 mmHg) OR (decrease of >20 mmHg from Baseline AND <60 mmHg)

7.4 CLINCAL LABORATORY TESTS

Descriptive statistics will be provided by treatment group for each laboratory test (hematology, serum chemistry, and urinalysis) specified in the study protocol as follows:

- Baseline values
- Values at each post-baseline visit
- Change from baseline at each post-baseline visit

Tabulated tables will be presented by showing change in lab normal range (low, normal, and high) for clinical laboratory values by treatment group. A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

In the by subject listings, laboratory values which fall outside the reference ranges and abnormal findings will be flagged. The listing will include treatment group, subject ID, laboratory collection date/time, analyte name, and analyte finding.

Subjects with markedly abnormal lab values (criteria depicted in Table 8) will be summarized by study period.

Table 8 Markedly Abnormal Laboratory

Markedly Abnormal Laboratory	
Hematology	
Hemoglobin	<8.0 g/dL
Platelet	<50,000/mm^3
WBC	<2000/mm^3
Neutrophils (absolute)	<1000/mm^3
Lymphocytes (Absolute)	<500/mm^3 or >200,00/mm^3
Chemistry	
ALT	>5 X ULN
AST	>5X ULN
Alkalikne phosphatase	>5 X ULN
Total bilirubin	>3X ULN
GGT	>5X ULN
Potassium	>6.0 mmol/L or <3.0 mmol/L
Sodium	>155 mmol/L or <130 mmol/L
Cholesterol	>400 mg/dL
CPK	>5X ULN
Creatinine	>3X ULN or 3X of Baseline

Calcium	>12.6 mg/dL or <7 mg/dL
Glucose	>250 mg/dL or <40 mg/dL
Triglyceride	>500 mg/dL
Albumin	<2 g/dL

7.5 ELECTROCARDIOGRAMS

ECG measurements are obtained at the screening visit and Week 12. Single 12-lead ECG will be obtained using an ECG machine that may automatically report heart rate, PR, QRS, QT, and/or Fridericia's corrected QT (QTcF) intervals. If any of these parameters are not automatically reported, they may be measured or calculated.

The ECG assessment values at each visit and change from baseline to each visit will be summarized and shift table using the normal/abnormal classification to compare baseline to the post-baseline visit values will be provided. In addition, a by-subject listings, which includes treatment group, subject ID, ECG date/time, test name, test result and ECG interpretation (eg, clinical interpretation, normal abnormal, not clinically significant, abnormal, clinically significant) will be presented. If any clinically significant ECG measurement occurs, it will be recorded as an AE.

8 OTHER ANALYSES

8.1 QUALITY OF LIFE(QOL)

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a self-administered, disease-specific Health-Related Quality of Life (HRQOL) instrument for patients with IBD. [11] The IBDQ covers 4 dimensions: bowel symptoms (10 items, questions 1, 5, 9, 13, 17, 20, 22, 24, 26, and 29), systemic symptoms (5 items, questions 2, 6, 10, 14 and 18), emotional function (12 items, questions 3, 7, 11,15, 19, 21, 23, 27, 30, 31 and 32), and social function (5 items, questions 4, 8, 12, 16, and 28). Items are scored on a 7-point Likert scale, for a total global score in the range 32 to 224 (with higher scores indicating better HRQOL).

IBDQ scores will be collected at Week 0 Visit, Week 6 Visit, and Week 12 Visit. Summary statistics of the absolute and change from baseline scores for IBDQ total score and each subscale score will be displayed by treatment group and visit.

IBDQ Scores will be calculated as follows:

- The question on the same day of measurement will be used for calculation of each subscore and total score.
- For each subscore, sum of the questions will be round off to the first decimal place.
- IBDQ total score: sum of all questions and round off to the first decimal places.
- The value of each question after imputing missing data will be used for the calculation of each subscore.

The instructions on how the IBDQ score is calculated in the presence of missing or incomplete information is provided below with detailed scenarios given in Table 9. Rules for handing missing data:

1. If no response is given for a particular question and only one response per dimensional score is missing, impute the missing value to be equal to the mean score for that other item of the subscore
2. If two or more questions are unanswered for a particular domain, then the subscore will be set to missing.

If after steps 1 and 2, more than 4 questions are missing for the full IBQD, then the total IBDQ will be set to missing.

Table 9 IBDQ Missing Data Instructions

	Number of Missing Values				Comments/Actions
	Subscore 1	Subscore 2	Subscore 3	Subscore 4	
Scenario A	0	0	0	0	We can compute 4 subscores and the full IBDQ
Scenario B	1	0	0	0	We can compute both the full IBDQ and the 4 subscores, by replacing the missing value with the average mean (computed on the data available for its own subscore)
Scenario C	1	1	1	1	We can compute both the full IBDQ and the 4 subscores, by replacing the missing value with the average mean (each one computed on the data available for its own subscore)
Scenario D	2	0	0	0	We can compute the full IBDQ by replacing the 2 missing values with the average mean (computed on the data available for its own subscore). We can compute only 3 subscores.
Scenario E	2	1	0	1	We can compute the full IBDQ by replacing the missing values with the average mean (each one computed on the data available for its own subscore). We can compute only 3 subscores.
Scenario F	2	1	1	1	We cannot compute the full IBDQ (more than 4 missing values). We can compute only 3 subscores.
Scenario G	2	2	0	0	We cannot compute the full IBDQ because in more than one subscore there are 2 missing values (even though the total missing value is not exceeding 4). We can compute only 2 subscores.
Scenario H	0	0	3	0	We cannot compute the full IBDQ because there is one subscore with more than 2 missing values. We can compute only 3 subscores.

9 NUMBER AND TIMING OF ANALYSES

There will be a primary analysis after all subjects have completed 12-week IP. During the primary analysis, interim results from the OLE will be summarized descriptively. Complete analysis for the OLE will be covered in a different SAP.

10 CHANGES FROM PROTOCOL

Methods in this SAP different form the methods described in the protocol are summarized as follow:

- In Section 2, for objectives and endpoints that has accessing timepoint at Week 50, all timepoints at Week 50 were removed from this SAP. The final analysis of OLE data will be specified in a separate SAP.

- In Section 2 and Section 3.1, the definition for clinical response is refined so that responders will also include those patients who achieve clinical remission (CDAI < 150) but may not achieve >=100 point reduction in CDAI from baseline.
- In section 2, additional exploratory endpoints (endoscopic remission, ulcer-free at Week 12, change in SES-CD segment score from baseline to week 12, clinical improvement by PRO-2 score, IBDQ remission or response,(steroid-free clinical remission for CDAI and by PRO-2, steroid-free clinical improvement by CDAI and by PRO-2, Clinical response by PRO-2 total score,) were add in the overall objectives and endpoints.
- In section 2, serum PD marker EHI was removed from the SAP. It will be analyzed when it becomes available.
- For analysis populations, PP analysis set was added.
- For evaluation of primary efficacy endpoint, the analysis specified in SAP V01 based on the method of multiple imputation was removed due to the known lack of sufficient correlation between SES-CD and CDAI scores in prior CD clinical trials. Instead, PP analysis set, which requires evaluable endoscopic score at Week 12, will be used and the confidence interval for the proportion will be calculated using Wilson-score method.
- Sensitivity analysis based on FAS was added to further access the robustness of primary analysis.
- For evaluation of secondary efficacy dichotomous or binary endpoint, the confidence interval for the proportion will be calculated using Wilson-score method, while non-responder imputation may apply for missing endpoint.
- For evaluation of the continuous secondary efficacy endpoint, PP analysis set and ANCOVA will be used for the change from baseline in SES-CD at Week 12. The median for the change from baseline in SES-CD score at Week 12 for PP analysis set will also be estimated and p-value for testing against no change will be reported using Wilcoxon rank test
- For evaluation of continuous exploratory efficacy endpoints, endpoints with multiple assessments over time, MMRM will be used. The 95% confidence interval for the LS mean for the change from baseline at Week 12 will be calculated.
- For evaluation of exploratory efficacy endpoint, proportion of subjects of meeting the definition will be calculated. For evaluation of continuous exploratory efficacy endpoints, MMRM method will be used, where appropriate.

11 REVISION HISTORY

Version	Effective Date	Reason
V01	28FEB2022	New
V02	19APR2022	Amendment

12 REFERENCES

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APPENDICES

APPENDIX A. SIMPLE ENDOSCOPIC SCORE FOR CROHN'S DISEASE (SES-CD)

The Simple Endoscopic Score for Crohn's Disease (SES-CD) assesses the size of mucosal ulcers, the ulcerated surface, the endoscopic extension, and the presence of stenosis.

Variable	SES-CD Values			
	0	**1**	**2**	**3**
Size of ulcers	None	Aphthous ulcers (0.1 < 0.5cm)	Large ulcers (> 0.5 – 2cm)	Very large ulcers (> 2.0cm)
Ulcerated surface (%)	None	< 10%	10-30%	> 30%
Affected surface (%)	Unaffected segment	< 50%	50-75%	> 75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

	Ileum	Right Colon	Transverse colon	Left colon	Rectum	Total
Presence and size of ulcers (0-3)						
Extent of ulcerated surface (0-3)						
Extent of affected surface (0-3)						
Presence and type of narrowings (0-3)						
					Total SES-CD =	

Source: Daperno, et al. Gastrointest Endosc. 2004.
Note: Current Alimentiv scoring conventions are to be used.

APPENDIX B. CROHN'S DISEASE ACTIVITY INDEX (CDAI)

The Crohn's disease activity index (CDAI) scores range from 1 to approximately 600, with higher scores indicating more severe disease. Eight variables comprise the components of the CDAI score. Modification limits the contribution of the weight variable to no more than 10 points in negative contribution.

Clinical or laboratory variable	Weighting factor
Number of liquid or soft stools each day for 7 days	× 2
Abdominal pain (graded from 0 to 3 based on severity) each day for 7 days	× 5
General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days	× 7
Complications*	× 20
Use of diphenoxylate or opiates for diarrhea	× 30
An abdominal mass (0 for none; 2 for questionable; 5 for definite)	× 10
Absolute deviation of hematocrit from 47% in men and 42% in women	× 6
Percentage deviation from standard weight	× 1

*One point is added for each set of complications: arthralgia or frank arthritis; inflammation of the iris or uveitis; erythema nodosum, pyoderma gangrenosum, or aphthous ulcers; anal fissures, fistulas, or abscesses; other fistulas; and fever (>100 °F) during the previous week.

Remission: CDAI score <150 points.
Moderate-to-severe disease: CDAI score 230–400 points.

APPENDIX C. PRO2 CALCULATION

The two CDAI items included in the PRO2 are daily stool frequency (SF) and abdominal pain(AP). SF consists of the number of liquid or very soft stools that occur per day. AP is rated on a 4-point scale (from 0 to 3) of increasing severity (Table a). This information is recorded by the subject on the electronic diary (or by paper diary if electronic diary not available. The average of the daily entries for the 7-day period prior to each visit is calculated and multiplied by weighting factors (X2 for SF and X5 for AP) to provide a total score for each component item. The total PRO2 score is the sum of the component item scores (Table b)

Table **a**. PRO2 Diary Card

	Day 1	Day2	Day 3	Day 4	Day 5	Day 6	Day 7
Number of liquid or very soft stools per day							
Daily Abdominal Pain Rating (0 = none, 1 = mild, 2 = moderate, 3 = severe)							

Table **b**. Calculation of the Total PRO2 Score

	Total Component Item Score for 7 Days	**Multiplication Factor**	**Total**
Number of liquid or very soft stools per day		**X 2**	
Daily Abdominal Pain Rating		**X 5**	
		Total PRO2 Score	

Source: Khanna, et al. Aliment Pharmacol Ther. 2015.

APPENDIX D. PERIANAL DISEASE ACTIVITY INDEX (PDAI)

The perianal disease activity index (PDAI) score includes the evaluation of 5 elements:

1) discharge
2) pain
3) restriction of sexual activity
4) type of perianal disease
5) degree of induration

Each category is graded on a 5-point Likert scale ranging from no symptoms (score of 0) to severe symptoms (score of 4), with a range of 0 to 20; a higher score indicates more severe disease.

Item	Points
Discharge	
No discharge	0
Minimal mucous discharge	1
Moderate mucous or purulent discharge	2
Substantial discharge	3
Gross fecal soiling	4
Pain/restriction of activities	
No activity restriction	0
Mild discomfort, no restriction	1
Moderate discomfort, some limitation	2
Marked discomfort, marked limitation	3
Severe pain, severe limitation	4
Restriction of sexual activity	
No restriction of sexual activity	0
Slight restriction of sexual activity	1
Moderate limitation of sexual activity	2
Marked limitation of sexual activity	3
Unable to engage in sexual activity	4
Type of perianal disease	
No perianal disease	0
Anal fissure or mucosal tear	1
<3 perianal fistulas	2
>3 perianal fistulas	3
Anal sphincter ulceration or fistulas with significant undermining skin	4
Degree of induration	
No induration	0
Minimal induration	1
Moderate induration	2
Substantial induration	3
Gross fluctuance/abscess	4

APPENDIX E. GLOBAL HISTOLOGIC DISEASE ACTIVITY SCORE

Histological Variable	Description
Epithelial damage	0 normal 1 focal pathology 2 extensive pathology
Architectural changes	0 normal 1 moderately disturbed (< 50%) 2 severely disturbed (> 50%)
Infiltration of mononuclear cells in the lamina propria	0 normal 1 moderate increase 2 severe increase
Infiltration of polymorphonuclear cells in the lamina propria	0 normal 1 moderate increase 2 severe increase
Polymorphonuclear cells in epithelium	0 absent 1 in surface epithelium 2 cryptitis 3 crypt abscess
Presence of erosion and/or ulcers	0 no 1 yes
Presence of granuloma	0 no 1 yes
Number of biopsy specimens affected	0 none 1 < 33% (1 or 2 of 6) 2 33-66% (3 or 4 of 6) 3 > 66% (5 or 6 of 6)

Source: D'Haens, et al. Gastroenterology. 1998

APPENDIX F. ROBARTS HISTOPATHOLOGY INDEX

Histological Variable	Grading	Multiplication Factor
Chronic inflammatory infiltrate	0=No increase 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	X1
Lamina propria neutrophils	0=None 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	X2
Neutrophils in epithelium	0=None 1= < 5% crypts involved 2= < 50% crypts involved 3= > 50% crypts involved	X3
Erosion or ulceration	0=No erosion, ulceration, or granulation tissue 1=Recovering epithelium + adjacent inflammation 1=Probably erosion-focally stripped 2=Unequivocal erosion 3=Ulcer or granulation tissue	X5

Source: Mosli, et al. Gut. 2017.

APPENDIX G. SCHEDULE OF ASSESSMENTS – INDUCTION PERIOD

	Study Visit							NOTES
Study Week	0	1	2	6	10	12	Early Termination	
Study Day	1	8	15	43	71	85		
Visit window (days)	0	±1	±3	±3	±3	±3		
Procedure								
Eligibility Confirmation	X							
Randomization	X							Via IRT system
Complete Physical Examination						X	X	
Targeted Physical Examination	X		X	X	X			
Vital Signs	X	X	X	X	X	X	X	Heart rate, temperature, blood pressure; Take pre-dose (no more than 30 minutes pre-infusion), end of infusion, and end of observation period.
Weight	X	X	X	X	X	X	X	Needed for CDAI assessment
ECG	X					X	X	
Adverse Events Assessment	X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	
Efficacy Assessments								
Ileocolonoscopy with Biopsy						X	X	Ileocolonoscopy to be performed within 10 days after Week 12 visit, or at early termination visit
Review eDiary Data from Subjects	X	X	X	X	X	X	X	Remind subjects to record in their eDiary daily
CDAI Assessment	X	X	X	X	X	X	X	
PDAI	X					X	X	
Fistula Drainage Assessment	X		X	X	X	X	X	
IBDQ	X			X		X	X	
Laboratory Testing								
CBC	X	X	X	X	X	X	X	
Chemistry Panel	X		X	X		X	X	
Fasting Lipid Panel	X					X	X	
Urinalysis	X		X	X		X	X	

	Study Visit							NOTES
Study Week	0	1	2	6	10	12	Early Termination	
Study Day	1	8	15	43	71	85		
Visit window (days)	0	±1	±3	±3	±3	±3		
Procedure								
Urine Pregnancy Test (WOCBP only)	X			X		X	X	
Pharmacokinetics	X[a]	X	X[b]	X[b]	X[a]	X	X	a. The PK sample at Week 0/Day 1 and Week 10 must be taken pre-dose, immediately following the end of infusion (within 30 minutes), and 1 hour after the end of infusion. b. The PK sample taken at Weeks 2 and 6 must be taken pre-dose (within 30 minutes prior to dosing).
Immunogenicity	X[a]		X[a]	X[a]		X	X	[a] To be taken pre-infusion
Biomarkers								
Biomarkers	X		X	X	X	X	X	Serum at all visits; additional whole blood at Weeks 0, 6 and 12
Soluble TL1A	X		X	X	X	X	X	
hsCRP	X	X	X	X	X	X	X	
Fecal Calprotectin	X			X		X	X	
Infusion	X		X	X	X			Include date, start and stop time, volume infused, and length of the IV infusion. Infusion observation period at Week 0/Day 1 and Week 2 will be 1 hour (2 hours for subjects in Czech Republic); 30 minutes for all subsequent infusions thereafter.

APPENDIX H. SCHEDULE OF ASSESSMENTS – OPEN-LABEL EXTENSION PERIOD

	Study Visit									NOTES
Study Week	14	18	26	34	42	50	Early Termination	Potential Relapse Visit	Infusion Visits Q4W (excluding Office Visits)	Visit windows are as follows: +14 day window for Week 14 visit, ±7 day window from Week 18 to Week 24 visits, and ±14 day window if >Week 24 Subjects who achieve deep remission during IP must attend all scheduled study visits
Study Day	99	127	183	239	295	351				
Visit window (days)	+14	±7	±14	±14	±14	±14			±7/±14	
Procedure										
Enter subject into IRT for OLE	X									
Complete Physical Examination						X	X			
Targeted Physical Examination	X	X	X	X	X			X		
Vital Signs	X	X	X	X	X	X	X	X	X	Heart rate, temperature, blood pressure; Take pre-dose (no more than 30 minutes pre-infusion) and end of infusion
ECG						X	X			
Weight	X	X	X	X	X	X	X			Needed for CDAI assessment
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	
Efficacy Assessments										
Review eDiary Data from Subjects	X	X	X	X	X	X	X	X		Remind subjects to record in their eDiary daily
CDAI Assessment	X	X	X	X	X	X	X	X		
PDAI			X			X	X			
Fistula Drainage Assessment	X	X	X	X	X	X	X			
Ileocolonoscopy with Biopsy						X	X			Ileocolonoscopy to be performed between 14 and 8 days before Week 50 visit or within 1 week **after** Week 50 visit or ET visit
IBDQ			X			X	X			
Laboratory Testing										
CBC	X	X	X	X	X	X	X			
Chemistry Panel	X	X	X	X	X	X	X			
Fasting Lipid Panel			X			X	X			

	Study Visit									NOTES
Study Week	14	18	26	34	42	50	Early Termination	Potential Relapse Visit	Infusion Visits Q4W (excluding Office Visits)	Visit windows are as follows: +14 day window for Week 14 visit, ±7 day window from Week 18 to Week 24 visits, and ±14 day window if >Week 24 Subjects who achieve deep remission during IP must attend all scheduled study visits
Study Day	99	127	183	239	295	351				
Visit window (days)	+14	±7	±14	±14	±14	±14			±7/±14	
Procedure										
Urinalysis	X	X	X	X	X	X	X			
Urine Pregnancy Test (WOCBP only)	X	X	X	X	X	X	X		X	Pregnancy testing must be done once a month
Pharmacokinetics[c]	X[a]	X[a]	X[a]		X[a]	X[b]	X	X		[a] To be taken pre-infusion. [b] To be taken pre-infusion or at the same time as other laboratory tests for early termination. [c] For subjects in deep remission in therapy withdrawal, PK samples will be collected up to 112 days from last PRA023 infusion.
Immunogenicity		X[a]	X[a]		X[a]	X[a]	X	X		[a] To be taken pre-infusion
Biomarkers										
Biomarkers	X	X	X	X	X	X	X			Serum at all visits; additional whole blood at Week 50
Soluble TL1A	X	X	X	X	X	X	X			
hsCRP	X	X	X	X	X	X	X	X		
Fecal Calprotectin			X			X	X	X		
Infusion[a]	X	X	X	X	X	X			X	Include date, start and stop time, volume infused, and length of the IV infusion. Infusion observation period will be 30 minutes For subjects needing a second induction, infusion will be 1000 mg IV followed by 500 mg IV 2, 6, and 10 weeks after the first infusion [a] Not applicable for subjects who achieve deep remission and are in therapy withdrawal

APPENDIX I. SCHEDULE OF ASSESSMENTS – POST DOSING FOLLOW-UP PERIOD

	Study Visit		
	28 Days Post Dosing	56 Days Post Dosing	84 Days Post Dosing
Visit window (days)	±7	±7	±7
Procedure			
Adverse Events Assessment	X	X	X
Concomitant Medication	X	X	X
Urine Pregnancy Test (WOCBP only)	X	X	X
Pharmacokinetics	X	X	X
Immunogenicity	X	X	X