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Clinical Protocol PR200-103

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 APOLLO-CD Study

EudraCT: 2021-000092-37

Version 5.0 (27 April 2023)

Study Sponsor:

Prometheus Biosciences, Inc.
3050 Science Park Road
San Diego, CA 92121
USA

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PROTOCOL APPROVAL PAGE

Prometheus Biosciences, Inc.

Protocol: PR200-103

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

Version 5.0 (27 April 2023)

PPD

PPD MD

27Apr2023

Date

Executive Director, Clinical Development
Prometheus Biosciences, Inc.

PROTOCOL SIGNATURE PAGE

Prometheus Biosciences, Inc.

Protocol: PR200-103

Version 5.0 (27 April 2023)

By my signature I confirm that I have read, and I understand this protocol "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", dated 27 April 2023, in its entirety, and I agree that it contains all necessary details for carrying out the study as described. I will diligently conduct this protocol as outlined herein in full accordance with the Principles of Good Clinical Practice and all applicable laws and regulations.

I will provide copies of the protocol and access to all information furnished by Prometheus Biosciences, Inc. pertinent to the study to concerned personnel under my supervision. I will discuss the material with them to ensure that they are fully informed about the study.

I agree to implement the protocol procedures only after confirming that specimens were collected with informed consent/subject information approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) permitting such use.

I understand that all information supplied by Prometheus Biosciences, Inc. is confidential, and I hereby agree to ensure that when this information is submitted to an IRB/IEC, it will be submitted with a designation that the material is confidential.

_____

Investigator Name

_____ _____

Investigator's Signature Date

_____

Institution Name

_____

Institution Address

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PROTOCOL VERSION AND AMENDMENT TRACKING

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LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
5-ASA	5-Acetylsalicylic acid
6-MP	6-Mercaptopurine
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cell-mediated phagocytosis
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{0-t}	Area under the concentration time curve from hour zero to the last measurable concentration, estimated by the linear trapezoidal rule
AZA	Azathioprine
BUN	Blood urea nitrogen
CBC	Complete blood count
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDC	Complement-dependent cytotoxicity
CDx	Companion diagnostic
CFR	Code of Federal Regulations
CK	Creatine kinase
C_{max}	Maximum concentration
CMV	Cytomegalovirus
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organization
CS	Clinically significant
CTA	Clinical trial application
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
DILI	Drug induced liver injury
DMC	Data Monitoring Committee
DMP	Data management plan
DNA	Deoxyribonucleic acid
DR3	Death receptor 3
DSS	Dextran sodium sulfate
EC	Ethics Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
eDiary	Electronic diary
EFD	Embryo-fetal development
EHI	Endoscopic healing index
ET	Early termination
FAS	Full Analysis Set
FcR	Fc receptor
FDA	Food and Drug Administration

Abbreviation or specialist term	Explanation
FSH	Follicle stimulating hormone
FU	Follow-Up
GCP	Good Clinical Practice
GD	Gestational day
GDH	Glutamate dehydrogenase
GGT	Gamma-glutamyl transferase
GHAS	Global histological activity score
GI	Gastrointestinal
GLP	Good Laboratory Practice
GM	Geometric mean
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HCV	Hepatitis C virus
HDL	High density lipoprotein
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
hsCRP	High sensitivity C-reactive protein
IBD	Inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
$IgG_1\kappa$	Immunoglobulin G subtype G_1 kappa
IgM	Immunoglobulin M
IL-12/23	Interleukin-12/23
ILC	Innate lymphoid cell
INR	International normalized ratio
IP	Induction Period
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IV	Intravenous
KLH	Keyhole limpet haemocyanin
LDH	Lactic dehydrogenase
LDL	Low density lipoprotein
LSLV	Last subject last visit
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
mRNA	Messenger ribonucleic acid
MTX	Methotrexate
Nab	Neutralizing antibody
NCI	National Cancer Institute
NCS	Not clinically significant
NK	Natural killer
NOAEL	No observed adverse effect level
NS	Normal saline

Abbreviation or specialist term	Explanation
NSAID	Non-steroidal anti-inflammatory agent
OLE	Open-Label Extension
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDAI	Perianal Disease Activity Index
PG	Pharmacogenomic
PK	Pharmacokinetic
PRO-2	Two component patient-reported outcome
PSC	Primary sclerosing cholangitis
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
sTL1A	Soluble tumor necrosis factor-like cytokine 1A
SOP	Standard operating procedure
SUSAR	Suspected, unexpected serious adverse reaction
$t_{1/2}$	Half-life
TB	Tuberculosis
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
Th1	T helper 1 cells
Th 2	T helper 2 cells
Th 9	T helper 9 cells
Th17	T helper 17 cells
TL1A	Tumor necrosis factor-like cytokine 1A
TLR	Toll like receptor
T_{max}	Time to maximum concentration
TMDD	Target-mediated drug disposition
TNF	Tumor necrosis factor
UC	Ulcerative colitis
ULN	Upper limit of normal
VLDL	Very low density lipoprotein
WBC	White blood cell
WHO-DD	World Health Organization – Drug Dictionary
WK	Week
WOCBP	Women of childbearing potential

PROTOCOL SYNOPSIS

TITLE:	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
PROTOCOL NUMBER:	PR200-103
PROJECT PHASE:	Phase 2a
OBJECTIVE:	**Primary:** • To evaluate the safety and tolerability of PRA023 following 12-weeks of induction therapy • 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 **Secondary:** • To assess the proportion of subjects with clinical remission (Crohn's disease activity index [CDAI] < 150) at Week 12 • To assess the proportion of subjects with endoscopy and clinical improvement (decrease in SES-CD ≥ 50% AND reduction in CDAI ≥ 100 points from Baseline) at Week 12 • To assess the proportion of subjects with biomarker and clinical improvement (decrease in high sensitivity C-reactive protein [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) 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 • To assess the proportion of subjects with normalization of fecal calprotectin (fecal calprotectin < ULN), among subjects with elevated concentrations at Baseline, at Week 12 • To assess the proportion of subjects with clinical improvement (reduction in CDAI ≥ 100 points from Baseline) at Week 12 • To assess the proportion of subjects with two component patient-reported outcome (PRO-2) remission (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 • To assess the pharmacokinetics (PK) of PRA023 • To assess the immunogenicity of PRA023

	Exploratory: • To assess the change in CDAI and component scores over time • To assess the effects of PRA023 on tissue and serum pharmacodynamic (PD) markers, including tumor necrosis factor-like cytokine 1A (TL1A) concentrations, endoscopic healing index (EHI), fecal calprotectin, and hsCRP in all subjects over time • To assess the change in SES-CD at Week 50 from Baseline • To characterize the change in Perianal Disease Activity Index (PDAI) score from Baseline to Week 12, Week 28, and Week 50 • To characterize the effect of PRA023 for improvement and remission of enterocutaneous and/or perianal fistula during the Induction Period (IP) and Open-Label Extension (OLE) • To assess all secondary endpoints at Week 50 • To assess the change in global histological activity score (GHAS) and Robarts histopathology index (RHI) from Baseline to Week 12 and Week 50 • To assess the proportion of subjects with histologic response and histologic remission at Week 12 and Week 50 • To assess change in PRO-2 over time • To assess change in extraintestinal manifestations over time • To assess long-term safety, tolerability, and efficacy of PRA023
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 drug will have a follow-up period of 12 weeks after the last dose. Response at Week 12 will be defined as reduction from Baseline in CDAI of ≥ 100 points. 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 170 Subjects will continue in OLE until they progress, withdraw from the study, study termination, or Week 170. For subjects assigned to the 100 mg Q4W OLE arm, the dose may be escalated to 250 mg Q4W if disease activity is not adequately controlled in the Investigator's opinion. The study is being amended by the Sponsor to extend the OLE period beyond Week 134 to Week 170 based on emerging safety data in both this study as well as a concurrent double-blind Phase 2 study in ulcerative colitis. The OLE period may be further extended beyond 170 weeks based on emerging safety data in a future amendment.
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%.
SUBJECT TYPE:	Male or female subjects ≥ 18 years of age with moderately to severely active CD.
FORMULATIONS:	PRA023 will be supplied in 10 mL vials each containing 500 mg PRA023 (60 mg/mL concentrate for solution for infusion) for IV administration after reconstitution.
DOSAGE:	Induction Period: all subjects will receive PRA023 1000 mg on Week 0/Day 1, followed by 500 mg IV on Weeks 2, 6, and 10. Non-responders at Week 12 should be discontinued from study drug treatment. Responders at the end of Week 12 have the option to enter the OLE, where all subjects will be randomized to receive one of the following regimens until disease progression, withdraw from the study, study termination, or Week 170. • PRA023 250 mg IV on Week 14 then Q4W • PRA023 100 mg IV on Week 14 then Q4W A subject may have the dose escalated from 100 mg IV Q4W to 250 mg IV Q4W during OLE if the subject's disease is not adequately controlled in the Investigator's opinion.
ROUTE OF ADMINISTRATION:	The study drug will be reconstituted in 250 mL of 0.9% normal saline (NS) and will be administered IV over 30 minutes.
STUDY ENDPOINTS:	**Primary endpoints:** • Safety and tolerability: the proportion of subjects reporting adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, and markedly abnormal laboratory values

	• The proportion of subjects with endoscopic improvement, as defined by decrease in SES-CD ≥ 50% from Baseline at Week 12 **Secondary endpoints:** • The proportion of subjects in clinical remission (CDAI < 150) at Week 12 • The proportion of subjects with endoscopic and clinical improvement, as defined by decrease in SES-CD ≥ 50% AND reduction in CDAI ≥ 100 points from Baseline at Week 12 • The 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) at Week 12 • The proportion of subjects with normalization of hsCRP (as defined by hsCRP < ULN), among subjects with elevated concentrations at Baseline, at Week 12 • The proportion of subjects with normalization of fecal calprotectin (as defined by fecal calprotectin < ULN), among subjects with elevated concentrations at Baseline, at Week 12 • The proportion of subjects in clinical response, as defined by reduction in CDAI ≥ 100 points from Baseline at Week 12 • The 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 • Change in SES-CD score at Week 12 from Baseline • Descriptive summaries of PK and immunogenicity of PRA023 • Proportion of subjects developing anti-drug antibody (ADA) and neutralizing antibody (Nab) **Exploratory endpoints:** • Change in CDAI and components from Baseline over time • Change in PD markers including TL1A concentrations, EHI, fecal calprotectin, and hsCRP over time • Change in SES-CD from Baseline at Week 50 • Change in PDAI from Baseline over time • Proportion of subjects with improvement or remission of enterocutaneous and/or perianal fistula at Week 12 and Week 50 • Change in GHAS and RHI from Baseline to Week 12 and Week 50

	• The proportion of subjects with GHAS histologic score ≤ 4 at Week 12 and Week 50 • The proportion of subjects with Robarts histologic score < 5 at Week 12 and Week 50 • The proportion of subjects with GHAS histologic remission, defined as no neutrophils in the epithelium or subscore of 0, at Week 12 and Week 50 • The proportion of subjects with Robarts histologic remission (< 3) at Week 12 and Week 50 • Change in PRO-2 over time • The proportion of subjects with extraintestinal manifestation through Week 50 • The long-term safety, tolerability, and efficacy of PRA023 through Week 170
INCLUSION CRITERIA:	Subjects are required to meet the following criteria in order to be included in the study: 1. Male or female ≥ 18 years of age. 2. Subjects must have had a diagnosis of CD (confirmed by endoscopy + histology) at least 3 months prior to screening to be eligible for study participation. For subjects with no documented confirmation of CD diagnosis or if previous diagnosis is not deemed conclusive, CD diagnosis must be confirmed at time of screening colonoscopy. Note that mention of "chronic inflammation" or "Crohn's disease" or equivalent on histology report is acceptable. 3. Moderately to severely active CD as defined by CDAI of ≥ 220 and ≤ 450. 4. SES-CD score (per central reading) ≥ 6 if ileocolonic or colonic disease; or ≥ 4 if isolated ileal disease only. 5. Subjects must satisfy **at least one** of the following criteria: a) **In the past,** had an inadequate response to **one or more** of the following treatments: • Oral prednisone ≥ 40 mg/day (or equivalent) or budesonide ≥ 9 mg/day or equivalent or beclomethasone ≥ 5 mg/day for at least 2 weeks • Corticosteroid dependence as defined by failed to successfully taper to < 10 mg/day of prednisone or equivalent (i.e., had a flare of disease) within 3 months of starting therapy, or if relapse occurs within 3 months of stopping corticosteroids • Immunosuppressants (azathioprine ≥ 2 mg/kg/day or 6-mercaptopurine ≥ 1.0 mg/kg/day, [or documentation of a

	therapeutic concentration of 6-thioguanine nucleotide] or methotrexate ≥ 15 mg/week) for at least 8 weeks. Note: a lower dosage of 6-MP or AZA is acceptable if local guidelines specify a different treatment regimen (which would need be documented in the source document) • An approved anti-TNF agent at an approved labeled dose for at least 8 weeks • An approved anti-integrin (e.g., vedolizumab) at an approved labeled dose for at least 8 weeks • An approved anti-IL-12/23 (e.g., ustekinumab) at an approved labeled dose for at least 8 weeks **OR** b) Had been intolerant to **one or more** of the above mentioned treatments (e.g., unable to achieve doses or treatment durations because of dose-limiting side effects [e.g., leukopenia, psychosis, uncontrolled diabetes, elevated liver enzymes]) **OR** c) **Currently** receiving **one or more** of the following treatments: • Oral Prednisone ≥ 10 mg/day (or equivalent) or budesonide ≥ 3 mg/day or beclomethasone ≥ 5 mg/day for at least 3 months • Immunosuppressants [azathioprine ≥ 2 mg/kg/day or 6-mercaptopurine ≥ 1.0 mg/kg/day, (or documentation of a therapeutic concentration of 6-thioguanine nucleotide)] for at least 8 weeks. Note: a lower dosage of 6-MP or AZA is acceptable if local guidelines specify a different treatment regimen (which would need be documented in the source document) Notes on subjects who have had prior approved biologic therapy(ies) (e.g., anti-TNF, anti-integrin, and/or anti-IL-12/23): • The study will include a maximum of 70% and a minimum of approximately 50% subjects who have had prior approved biologic therapy(ies) experience. Upon reaching the maximum number of allowed biologic experienced subjects (70%), subjects who have had prior biologic experience will no longer be allowed to enter the study. Upon reaching the maximum number of allowed biologic-naïve subjects (approximately 50%), subjects who have never been exposed to a prior biologic will no longer be allowed to enter the study. • Subjects cannot have had failed (no response, insufficient response, loss of response, and/or intolerance) > 4 approved biologic therapies, whether of same or different mechanism of action • Subjects previously on clinical trials only (i.e., did not receive commercial available therapy post-approval) are not considered to

	have received the approved therapy for purpose of this inclusion criteria 6. For subjects who are women of childbearing potential (WOCBP) involved in any sexual intercourse that could lead to pregnancy, the subject has used two highly effective methods of contraception for at least 4 weeks prior to Day 1 and agrees to continue to use two highly effective methods of contraception until at least 12 weeks after the last dose of study drug. 7. Male subjects must use, with their female partner of childbearing potential, two highly effective methods of contraception and refrain from sperm donation from screening to 12 weeks after the last dose of study drug. 8. Subjects must meet drug stabilization requirements, as applicable: a) Oral corticosteroid treatment must be equivalent of ≤ 20 mg prednisone or ≤ 9 mg budesonide or beclomethasone ≤ 5 mg daily at a stable dose for at least 2 weeks prior to Day 1 b) Oral aminosalicylates should be at a stable dose for at least 2 weeks prior to Day 1 c) Azathioprine, 6-mercaptopurine, and methotrexate should be at a stable dose for at least 4 weeks prior to Day 1 9. Able to provide written informed consent and understand and comply with the requirements of the study.
EXCLUSION CRITERIA:	Subjects with the following characteristics will be excluded from the study: **Sex and Reproductive Status** 1. WOCBP and men with female partners of childbearing potential who are unwilling or unable to use two highly effective methods of contraception to avoid pregnancy for the entire study period and for up to 12 weeks after the last dose of study drug. 2. Women who are pregnant or breastfeeding. 3. Women with a positive pregnancy test on enrollment or prior to Day 1. **Target Disease Exceptions** 4. Diagnosis of ulcerative colitis or indeterminate colitis. 5. CD isolated to the stomach, duodenum, jejunum, or perianal region, without colonic and/or ileal involvement. 6. Suspected or diagnosed intra-abdominal or perianal abscess at Screening. 7. Known symptomatic stricture or stenosis not passable in endoscopy (including pediatric colonoscope). 8. Current stoma or need for colostomy or ileostomy.

	9. Previous small bowel resection with combined resected length of > 100 cm or previous colonic resection of > 2 segments. 10. Currently receiving total parenteral nutrition. 11. Surgical bowel resection within 3 months before screening. 12. Concomitant primary sclerosing cholangitis (PSC). **Medical History and Concurrent Diseases** 13. Past or current evidence of definite low-grade or high-grade colonic dysplasia that has not been completely removed. 14. Subjects who are scheduled or anticipate the need for surgery, aside from dermatologic procedures. 15. Subjects who have a history of clinically significant drug or alcohol abuse. 16. Concomitant illness that in the opinion of the Investigator, is likely to require systemic glucocorticosteroid therapy during the study (e.g., moderate to severe asthma). 17. Current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, pulmonary, cardiac, neurological, ophthalmologic, or cerebral disease. Concomitant medical conditions that in the opinion of the Investigator might place the subject at unacceptable risk for participation in this study. 18. Subjects with a history of cancer within the last 5 years (other than non-melanoma skin cell cancers cured by local resection). Existing non-melanoma skin cell cancers must be removed prior to enrollment. Subjects with carcinoma in situ or localized cervical cancer, treated with definitive surgical intervention, are allowed. 19. Subjects at risk for tuberculosis (TB). Specifically, subjects with: a) A history of active TB b) Current clinical, radiographic, or laboratory evidence of active TB c) Latent TB which was not successfully treated. Subjects with a positive TB screening test indicative of latent TB will not be eligible for the study unless active TB infection has been ruled out, and an appropriate course of intervention for latent TB has been initiated at least 2 weeks prior to Day 1, and no evidence of active TB on chest x-ray during screening. 20. Subjects with any serious bacterial infection within the last 3 months, unless treated and resolved with antibiotics, or any chronic bacterial infection (such as chronic pyelonephritis, osteomyelitis, and bronchiectasis). 21. Female subjects who have had a breast cancer screening that is suspicious for malignancy, and in whom the possibility of malignancy

	cannot be reasonably excluded following additional clinical, laboratory, or other diagnostic evaluations. 22. Subjects with any active infections (excluding fungal infections of nail beds) including, but not limited to, those that require IV antimicrobial treatment 4 weeks or oral antimicrobial treatment 2 weeks prior to randomization. Subjects with evidence of Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C infection detected during screening are also excluded, but subjects with successfully treated Hepatitis C with no recurrence for ≥ 1 year are allowed. Subjects with active documented or suspected COVID-19 infection within 4 weeks of randomization or asymptomatic SARS-CoV-2 test positivity within 2 weeks of randomization are excluded. 23. Subjects with herpes zoster reactivation or cytomegalovirus (CMV) that resolved less than 2 months prior to signing informed consent. 24. Subjects who have received any live vaccines within 3 months of the anticipated first dose of study medication or who will have need of a live vaccine at any time during the study. **Physical and Laboratory Test Findings** 25. Positive stool Polymerase Chain Reaction (PCR) if Investigator deems this positivity reflects infection rather than colonization **or** positive culture for enteric pathogens. Subjects who have an infection can be retested after the completion of a full course of treatment. 26. Stool positive for *Clostridium difficile* (*C. difficile*) toxin. Subjects who are positive can be retested after the completion of a full course of treatment for *C. difficile* infection. 27. Any of the following lab values: a) Hemoglobin (Hgb) < 8.0 g/dL (80 g/L) b) White blood cell (WBC) < 2,500/mm^3 (2.5 x 10^9/L) c) Neutrophils < 1,000/mm^3 (1 x 10^9/L) d) Platelets < 100,000/mm^3 (100 x 10^9/L) d) Serum creatinine > 2 times ULN e) Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 times ULN f) Any other laboratory test results that, in the opinion of the Investigator, might place the subject at unacceptable risk for participation in this study. **Prohibited Therapies and/or Medications** 28. Failed (no response, insufficient response, loss of response, and/or intolerance) > 4 approved biologic therapies (anti-TNF, anti-integrin, anti-IL12/23), whether of same or different mechanism of action.

	29. Any marketed biologic within 8 weeks for anti-TNF agents and 12 weeks for anti-integrin agents (e.g., vedolizumab) and ustekinumab prior to Day 1 **or** if drug level per therapeutic dose monitoring is greater than lower limit of detection. 30. Any biologic immunomodulators used for CD or other conditions within 8 weeks or 5 half-lives, whichever is longer, prior to Day 1 **or** if drug level per therapeutic dose monitoring is greater than lower limit of detection. 31. Rituximab within 1 year prior to Day 1. 32. Parenteral corticosteroids within 4 weeks or rectal administration of corticosteroids within 2 weeks prior to Day 1. 33. Rectal administration of 5-ASA within 2 weeks prior to Day 1. 34. Tacrolimus, cyclosporine, mycophenolate mofetil (CellCept®), immunoadsorption columns (such as Prosorba columns), D Penicillamine, Leflunomide, Thalidomide, chronic use of non-steroidal anti-inflammatory agents (NSAIDs), and aspirin > 81 mg/day within 2 weeks prior to Day 1. 35. Other investigational chemical agent within 30 days or other investigational biologic agent within 8 weeks or 5 half-lives (whichever is longer) of entry into the IP. 36. Prior exposure to PRA023. **Other Exclusion Criteria** 37. Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness. 38. Legal or mental incapacitation, or inability to understand and comply with the requirements of the study. 39. Known allergies, hypersensitivity, or intolerance to PRA023 or its excipients.
Statistical Methods:	Statistical methods will be detailed in the Statistical Analysis Plan (SAP). The SAP will provide details about methods of analysis and the specific planned analyses, and will be prepared and approved by Prometheus Biosciences and its designees before study database lock. The analysis populations are defined as follows: • Full analysis set (FAS): all subjects treated with Baseline SES-CD score • Safety analysis set: all subjects treated The following analyses will be performed: **Efficacy:** The primary efficacy endpoint, endoscopic improvement at Week 12, will be used to assess the efficacy of PRA023. The proportion of subjects in the

	per-protocol population with endoscopic improvement will be tested against the null hypothesis of endoscopic improvement rate of 12%, at a 1-sided significance level of 0.025. If significant, the 1st secondary endpoint of proportion of subjects in FAS achieving clinical remission will be tested against the null hypothesis of clinical remission rate of 16%, at a 1-sided significance level of 0.025. The point estimates for the primary and secondary endpoints will be calculated along with 95% confidence interval and by companion diagnostic (CDx) status (CDx+ or CDx-). **Adverse Events:** AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®). A by-subject AE data listing, including verbatim term, preferred term (PT), system organ class (SOC), treatment, severity, seriousness criteria, relationship to drug, and action taken, will be provided. The number of subjects experiencing treatment-emergent adverse events (TEAEs) and number of TEAEs will be summarized by treatment using frequency counts in safety analysis set. Medical History, chest x-ray, electrocardiogram (ECG), and physical examination will be listed by subject. Changes in ECGs and physical examinations will be described in the text of the final report. **Concomitant Medications:** Concomitant medications will be coded using the most current World Health Organization (WHO) drug dictionary and listed by treatment. **Pharmacokinetics:** Summary statistics of PRA023 concentrations and ADA by visit.

1 BACKGROUND AND RATIONALE

1.1 Background

PRA023 is a humanized monoclonal antibody that binds human tumor necrosis factor-like cytokine 1A (TL1A) with high affinity and specificity. TL1A is a cytokine which is part of the tumor necrosis factor (TNF) superfamily protein and is secreted by both innate and adaptive immune cells as well as by endothelial cells.

TL1A binds to death receptor 3 (DR3) that is found primarily on T cells, natural killer (NK) and NK-T cells, innate lymphoid cells (ILC), and epithelial cells (Valatas 2019) and potently drives Th1, Th2, Th9, and Th17 responses. In addition, TL1A is induced in antigen-presenting cells by toll like receptor (TLR) ligands and FcR (Fc receptor) cross-linking and in T cells by T-cell receptor (TCR) stimulation (Prehn 2007). TL1A occurs as both membrane-bound and soluble forms (Ferdinand 2018).

TL1A has been shown to be upregulated in mucosa and serum of patients with inflammatory bowel disease (IBD) (Bamias 2003, Bamias 2010). TL1A and DR3 are abundantly localized at inflamed intestinal areas of patients with IBD and mice with experimental ileitis or colitis and actively participate in the immunological pathways that underlie mucosal homeostasis and intestinal inflammation (Valatas 2019). Furthermore, TL1A polymorphisms have been shown to be associated with susceptibility to IBD (Yamazaki 2005, Yang 2008) and with disease severity (Cleynen 2013, Richard 2015).

In dextran sodium sulfate (DSS) and adoptive transfer mouse models, antibodies against TL1A led to reduced inflammation and reversal of fibrosis, even when treatment was administered late in the course of disease, after inflammation and fibrosis has been established (Shih 2014).

Prometheus Biosciences has developed PRA023, a humanized IgG1 kappa (IgG1κ) monoclonal antibody that binds to both membrane-bound and soluble forms of TL1A with high affinity and specificity and blocks the binding of TL1A to its functional receptor DR3. Prometheus Biosciences is also developing a genetic-based companion diagnostic (CDx) to identify patients who are predisposed for increased expression of TL1A and therefore potentially more likely to respond to PRA023. By targeting both intestinal inflammation and fibrosis, PRA023 has the potential to substantially improve outcomes for moderate to severe IBD patients with increased TL1A expression.

PF-06480605 is an anti-TL1A monoclonal antibody developed by Pfizer and studied in healthy volunteers and patients with ulcerative colitis (UC) (Banfield 2020, Danese 2020). Target engagement was demonstrated in healthy volunteers as confirmed by dose-dependent increases in mean total soluble tumor necrosis factor-like cytokine 1A (sTL1A). In a Phase 2a open-label study with centrally read endoscopy in subjects with moderately to severely active UC, treatment with the anti-TL1A antibody led to significant endoscopic improvement (38%), clinical remission (24%), histologic improvement, and decrease in biomarkers (fecal calprotectin and high sensitivity c-reactive protein [hsCRP]) at Week 14. PF-06480605 appeared to have an acceptable safety and tolerability profile.

Prometheus Biosciences is undertaking a Precision Medicine approach to the development of an anti-TL1A therapeutic for treatment of moderate to severe Crohn's Disease (CD) and UC, using a CDx to identify patients most likely to respond to study drug. The advantage of this unique, precision-based approach in IBD is the ability to identify patients more likely to respond to our therapeutics in targeted clinical trials, with the ultimate goal of bringing therapeutic drugs to patients with significantly better clinical efficacy.

This study is a Phase 2a, open-label study designed to evaluate the safety, efficacy, and pharmacokinetics (PK) of PRA023 in subjects with moderately to severely active CD.

1.2 Study Rationale

IBD is a complex disease with many contributing factors including environmental influences, genetics, and immunologic factors. UC and CD are two of the most common forms of IBD. Both UC and CD are chronic, relapsing, remitting, inflammatory conditions of the gastrointestinal (GI) tract that begin most commonly during adolescence and young adulthood. UC involves the mucosal layer of the large intestine, and symptoms include abdominal pain and diarrhea, frequently with blood and mucus. CD can affect the entire thickness of the bowel wall and all parts of the GI tract from mouth to anus. CD symptoms include abdominal pain, diarrhea, and other more insidious symptoms such as weight loss, nutritional deficiencies, and fever. The prevalence of IBD globally is approximately 5 million and affects over 2 million people in the US (Ananthakrishnan 2020). A hallmark of IBD is the cytokine responses that govern the initiation, evolution, and ultimately, the resolution of these forms of inflammation. Many immune cells, cytokines, and chemokines of the adaptive and innate immune systems play a role in IBD, including but not limited to IL-12, IL-23, IFNγ, IL-17, IL-22, and TL1A (Roberts-Thomson 2011, Strober 2011).

The current standard of care for the treatment of patients with moderate to severe IBD are generally immunomodulatory agents that are anti-inflammatory. None of the therapies address fibrosis in IBD. Since the approval of the first anti-TNF agent for the treatment of CD in 1998, the availability of newer biological agents, including anti-integrin (vedolizumab and natalizumab) and anti-IL-12/23 (ustekinumab) has improved the care of moderate to severe CD. However, none of these subsequently approved therapies have demonstrated significant improvement in effect size relative to anti-TNF. Moreover, among those patients who do respond, up to 45% will lose response over time (Roda 2016). Current therapies used in the treatment of CD apply a one-size-fits-all approach without regard to genetic or biologic variations in the patient. Existing approaches continue to leave unmet patient need.

Given established clinical validation of the target with PF-06480605, the current open-label Phase 2a study is designed to demonstrate the efficacy of PRA023 in subjects with moderately to severely active CD. In addition, this study is designed to assess the effectiveness of the genetic CDx for the purpose of selection of subjects whose disease is driven by the TL1A pathway and therefore, have a higher response rate to treatment with an anti-TL1A antibody. The study is also designed with an open-label extension study to ensure that subjects who benefit from the therapy have the option to continue therapy.

In parallel, a randomized, placebo-controlled study (PR200-102) will be conducted to demonstrate the proof of concept of PRA023 for induction therapy in subjects with moderately to severely active UC.

1.3 PRA023 Mechanism of Action and Nonclinical Data

The Investigator's Brochure should be referenced for a complete summary of data and information collected about PRA023 (including the principal data and findings from the nonclinical pharmacology, pharmacokinetic, and toxicology studies conducted to date).

1.3.1 Pharmacology

PRA023 is a humanized IgG1κ antibody that binds human TL1A with high affinity and specificity and neutralizes TL1A functional activity in vitro and ex vivo cell-based assays. PRA023 binds to both human and cynomolgus TL1A with a similar sub-nanomolar EC_{50} (half maximal effective concentration) and with similarly high affinity (K_D [dissociation constant] values of CCI nM and CCI nM, respectively). In addition, PRA023 is specific for TL1A and does not bind to other TNF super family members. Together, these data show that PRA023 is a high affinity humanized monoclonal antibody with selectivity for human and cynomolgus TL1A.

PRA023 has the capacity to block human TL1A-induced caspase activation and apoptosis in the TF-1 functional assay with an IC_{50} (half maximal inhibitory concentration) of CCI nM. Similarly, PRA023 blocked monkey TL1A-induced caspase activation with an IC_{50} of CCI nM. In a monkey whole blood assay, PRA023 inhibited the immune complex/TL1A enhancement of interferon gamma (IFN-γ) release with an IC_{50} of CCI nM and IC_{90} (90% maximal inhibitory concentration) of CCI nM.

A single dose PK/PD study in cynomolgus monkeys demonstrated a dose-dependent pharmacologic effect of PRA023 on the inhibition of TL1A-mediated IFN-γ release from peripheral blood mononuclear cells (PBMCs) in whole blood at doses of ≥ CCI mg/kg. The observation that greater concentrations (approximately CCI fold) of serum PRA023 were required to elicit this effect in animals treated with PRA023 versus when PRA023 was added in vitro to monkey whole blood indicates that a higher concentration of drug is required for biologic effect in vivo. In addition, a dose-dependent increase in circulating sTL1A concentrations was observed at all dose levels. This suggests that systemic sTL1A concentrations may be a useful PD marker for target engagement by PRA023.

1.3.2 Toxicology

Six-week and 6-month Good Laboratory Practice (GLP) repeat-dose toxicity studies were conducted in cynomolgus monkeys with a 6-week recovery period and a definitive GLP embryo-fetal development (EFD) study was conducted in New Zealand White rabbits. The intravenous (IV) route of administration was selected for these studies since it is the route of clinical administration. In addition, a series of in vitro studies were conducted with PRA023 including Fc effector function (i.e., antibody-dependent cellular cytotoxicity [ADCC], complement-dependent cytotoxicity [CDC], and antibody-dependent phagocytosis cytotoxicity [ADCP]) assays, human

cytokine release assays, and a GLP tissue cross-reactivity study using human and monkey tissues.

Stand-alone safety pharmacology studies were not conducted with PRA023. Cardiovascular, central nervous system (CNS), and respiratory safety pharmacology endpoints were incorporated into the repeat-dose IV toxicity studies in monkeys. There were no functional cardiovascular, CNS, or respiratory system findings observed in monkeys after once weekly IV administration of PRA023 at ≤ 300 mg/kg/week for up to 6 months.

PRA023 was administered to monkeys once weekly via IV injection for up to 6 months. The no observed adverse effect level (NOAEL) in the 6-month study was considered to be 300 mg/kg/week (the highest dose tested). No PRA023-related mortality; adverse clinical observations; body weight or body weight alterations; hematology, coagulation, or urinalysis effects; organ weight effects; macroscopic observations; microscopic findings; ECG findings; ophthalmic or neurobehavioral observations or findings in body temperature or respiration rates were observed at the end of the dosing phase after 6 months of repeat dosing in monkeys. No PRA023-related effects were noted in mean absolute counts or relative proportions of lymphocyte subsets (total T cells, helper and cytotoxic T cells, B cells, NK cells, monocytes, and regulatory helper and cytotoxic T cells) at ≤300 mg/kg/week as measured by immunophenotyping, compared with the controls. All animals mounted a robust anti-KLH IgG and IgM response, suggesting an intact humoral immunity. There were no organ weight changes, or macroscopic or microscopic observations in male or female reproductive organs after 6 months repeat dosing of PRA023 administration in sexually mature monkeys. A normal progression of the spermatogenic cycle and the expected cell associations and proportions in the various stages of spermatogenesis were noted in the testes.

After IV administration of PRA023 to monkeys in the 6-week repeat-dose toxicity study, findings that were secondary to generation of ADA and immune complex deposition in response to administration of a foreign protein (humanized monoclonal antibody) to immunocompetent animals (including the death of one low dose animal) were observed. Similar findings were not observed in the 6-month monkey toxicity study using the same dosing regimen and dose levels confirming that the findings in the 6-week repeat-dose toxicity study were secondary to ADA formation and not directly related to the mechanism of action of PRA023.

Based on the NOAEL of 300 mg/kg/week, the exposure margin (based on area under the curve from 0 to 168 hr [$AUC_{0\text{-}168hr}$] after repeat dosing; CCI µg•hr/mL) at the NOAEL is CCI-fold, relative to the projected $AUC_{0\text{-}672hr}$ (CCI µg•hr/mL) after the last 500 mg induction dose (i.e., highest predicted exposure due to accumulation of repeat dosing) in the dosing regimen. Similarly, for maximum concentration (C_{max}), the exposure margin (based on C_{max} after repeat dosing; CCI µg/mL) at the NOAEL is CCI fold, relative to the projected exposure (CCI µg/mL) after the last 500 mg induction dose.

In the pivotal EFD study, once-weekly administration of 50, 150, or 270 mg/kg/dose PRA023 via IV injection to pregnant rabbits on gestation days (GDs) 7 and 14 was well tolerated. No PRA023-related mortality, clinical observations, or effects on mean body weight gain, mean body weight, food consumption, or cesarean section parameters were observed during the period of organogenesis (GD7 through 19). No PRA023-related fetal external, visceral, or skeletal

variations or malformations were observed. The maternal and the fetal NOAELs are CCI mg/kg/dose (C_{max} of CCI µg/mL and $AUC_{0\text{-}inf}$ of CCI µg*hr/mL). The exposure margins, based on C_{max} and $AUC_{0\text{-}inf}$, at the NOAEL are CCI- and CCI fold, respectively, relative to the projected clinical exposures after the last 500 mg induction dose.

There was no off-target binding of PRA023 noted in the tissue cross-reactivity study in a broad range of human or monkey tissues. There was no PRA023-related cytokine release in in vitro human PBMC or whole blood cytokine release assays (soluble and plate-bound formats), nor in monkeys during the 6-week repeat-dose toxicity study. PRA023 did not cause CDC, ADCC, or ADCP of target expressing cells in in vitro Fc effector function assays.

1.4 Previous Human Experience

A single and multiple ascending dose Phase 1 study of PRA023 in healthy volunteers has been completed. In this study, doses ranging from 5 mg to 1000 mg given as a single dose or three multiple doses given once every two weeks were evaluated (Study PR200-101).

A total of 69 healthy subjects completed the dosing phase, 46 subjects in single ascending dose (SAD) phase (35 subjects received active PRA023 and 11 subjects received placebo) and 23 in the multiple ascending dose (MAD) phase (17 subjects received PRA023 and 6 subjects received placebo) in Study PR200-101. In the SAD phase, doses of PRA023 tested were 5 mg, 25 mg, 100 mg, 300 mg, 600 mg, and 1000 mg given as a single IV infusion. In the MAD phase, doses of PRA023 tested were 50 mg, 200 mg, and 500 mg given as IV infusion every 2 weeks for a total of 3 doses. No clinically significant treatment-related adverse events were reported, and no clinically significant laboratory abnormalities, vital signs, or ECGs were noted with PRA023, at doses up to 1000 mg as a single dose and 500 mg as multiple doses. The study drug was well-tolerated, and no subjects met the study stopping criteria.

1.4.1 Pharmacokinetic Results (PR200-101 Healthy Volunteer Study)

PK data from the PR200-101 study indicate that the exposure to serum PRA023 increased in a greater than dose-proportional manner following the administration of single and multiple PRA023 doses as IV infusions at doses of < 100 mg; the exposure increases at doses of ≥ 100 mg were dose-proportionate. This observation is consistent with target mediated drug disposition (TMDD) at lower doses (< 100 mg). The half-life of PRA023 after 500 mg every other week dosing was approximately 19 days.

Based on the preliminary PK data available, a population PK model was built to accurately simulate and predict PRA023 PK. The PK data were best described by a 2-compartment model with linear elimination. Demographic variables (including sex, age, race, and body size related variables) and laboratory clinical variables (including hematological, urine, and chemical variables) were tested for inclusion in the model for effect on the clearance and the volume of distribution in the central compartment. None of these variables were identified as significant covariates on the two PK parameters evaluated. The results of these analyses are presented in the Investigator's Brochure for PRA023. Briefly, evaluation of the model relative to observed

data from the healthy volunteer study indicated that the population PK model could adequately predict the observed PRA023 concentrations and was suitable to be used to simulate PRA023 concentrations.

1.4.2 Safety Results

Study PR200-101 has been completed. There were no deaths, SAEs, severe AEs, or subjects who had a reduction in dose or discontinued from the study due to AEs during Study PR200-101. Additionally, there were no clinically significant laboratory abnormalities, vital signs, or ECGs.

In the SAD, treatment-emergent AEs that occurred in ≥ 2 subjects dosed with PRA023 (regardless of dose) were: headache (5 subjects [14%] in PRA023 and 1 subject [9%] on placebo), followed by fatigue (2 subjects [6%] on PRA023, 0 on placebo), back pain (2 subjects [6%] on PRA023, 0 on placebo), and cough (2 subjects [6%] on PRA023, 0 on placebo). All other AEs were reported in no more than 1 subject. There was 1 event of headache that was assessed as related to placebo that was moderate in severity. The only other AE that was assessed as related to PRA023 (600 mg) was somnolence, mild in severity.

In the MAD portion of the study, treatment-emergent AEs that occurred in ≥ 2 subjects dosed with PRA023 (regardless of dose) were: catheter site bruise (3 subjects [18%] on PRA023, 2 [33%] on placebo), followed by catheter site pain (2 subjects [12%] on PRA023, 1[17%] on placebo), and infusion site extravasation (2 subjects [12%] on PRA023, 0 on placebo). All other AEs were reported in no more than 1 subject. All AEs that were assessed as related to study drug were mild in severity. Of the AEs assessed as related to study drug by the Investigator, diarrhea was reported in 2 subjects (1 subject on PRA023 at 50 mg and 1 subject on placebo) and all other AEs (dizziness [PRA023 200 mg], headache [placebo], and somnolence [PRA023 50 mg]) were reported in 1 subject.

For the ongoing Phase 2 studies PR200-102 ARTEMIS-UC and PR200-103 APOLLO-CD (this protocol), ongoing review of unblinded efficacy and safety data by the independent external Data Monitoring Committee (DMC) has resulted in the committee's recommendation to continue the study. Subjects from the ARTEMIS-UC study have been dosed for up to 10 months (i.e., either 10 months of PRA023 or 3 months of placebo followed by 7 months of PRA023) and subjects from this study (the APOLLO-CD study, which is open-label) have been dosed for up to 9 months of PRA023 as of the date of this protocol amendment.

1.5 Dose Rationale

PRA023 is a humanized monoclonal antibody that binds human TL1A. It is expected that the ultimate goal of PRA023 treatment in humans will be to saturate the TL1A target in intestinal/colonic tissue of disease patients to obtain optimal efficacy. Based on the emerging safety, tolerability, pharmacodynamic (PD), and PK data from the PR200-101 study and modeling, the dosing regimen selected for induction in this study is PRA023 1000 mg on Week 0/Day 1 followed by 500 mg on Weeks 2, 6, and 10, administered intravenously. This regimen is expected to lead to optimal target modulation and confer pharmacologic efficacy. The NOAEL

in monkeys will provide a safety margin of ~[CCI] fold and [CCI]-fold for C_{max} and $AUC_{0-672hr}$, respectively, after the last 500 mg induction dose (i.e., highest predicted AUC due to accumulation with repeat dosing) in this dosing regimen.

A population PK model was built based on the available data from Study PR200-101. The model was adequate to predict and simulate PRA023 exposure and no significant demographic or laboratory covariates were identified. Based on the population PK model, assuming the PK is similar between healthy volunteers and moderate to severe UC patients, the dosing regimen of PRA023 1000 mg on Week 0/Day 1 followed by 500 mg on Weeks 2, 6, and 10 is expected to lead to a C_{max} (mean ± SD) of [CCI] µg/mL and an $AUC_{0-672hr}$ of [CCI] µg*hr/mL after the last 500 mg induction dose.

Of note, the predicted C_{max} after the initial 1000 mg dose in the induction phase is expected to be the highest concentration obtained during the PR200-103 clinical dosing regimen. This level of exposure has already been evaluated in the 1000 mg SAD cohort of the healthy volunteer study (Study PR200-101). As stated, the highest exposure during the PR200-103 clinical dosing regimen based on AUC is expected to be after the last 500 mg induction dose due to accumulation with repeat dosing. The predicted AUC is expected to be approximately equivalent (within 10%) to that after the Phase 1 dosing regimen of 500 mg every other week.

From an induction efficacy perspective, assuming clearance of free soluble TL1A (sTL1A) from the gut will translate into efficacy, a physiologically based pharmacokinetic model was used to predict the impact of various dosing regimen of PRA023 on the level of sTL1A in normal and disease states in the central compartment (serum) and gut. The model predicts that the proposed induction regimen will lead to sTL1A levels of lower than healthy volunteers if the production level of sTL1A in the colon is as high as 60-fold.

After the 12-week induction, subjects who are in response will continue in the open-label extension randomized to 2 maintenance regimens. The maintenance regimen of 250 mg Q4W is selected to maintain the sTL1A level to below that of healthy volunteers if the production of sTL1A in the colon is up to 20X and the 100 mg Q4W regimen is selected to maintain the sTL1A level to below that of healthy volunteers if the production of sTL1A in the colon is up to 10X.

1.6 Overall Benefit/Risk Assessment

It is the hope that PRA023 will provide comparable or better efficacy than the currently approved biologic therapy, with an alternative and novel mechanism of action. There has been no safety signal identified based on nonclinical toxicity studies, safety analyses from normal healthy volunteers treated with up to 1000 mg of PRA023, and similar therapy in class. Based on the fact that PRA023 is a monoclonal antibody and an immunomodulatory agent, theoretical risks associated with treatment includes hypersensitivity reaction, infusion site reaction, and infections.

Since there is limited experience with use of PRA023, several steps will be taken to ensure that the benefit-risk relationship of study participation continues to be favorable throughout the study. In addition to ongoing safety monitoring of data throughout this study, a formal analysis is

planned after all subjects have completed 12 weeks of treatment or early terminated from the study. Lastly, the study will be conducted under the aegis of an independent Data Monitoring Committee (DMC) which will perform safety and efficacy assessments at regularly scheduled times as well as on an ad hoc basis if needed, throughout this and a randomized, placebo-controlled study in UC (PR200-102).

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the safety and tolerability of PRA023 following 12-weeks of induction therapy
- 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

2.2 Secondary Objectives

- To assess the proportion of subjects with clinical remission (Crohn's disease activity index [CDAI] < 150) at Week 12
- To assess the proportion of subjects with endoscopy and clinical improvement (decrease in SES-CD ≥ 50% AND reduction in CDAI ≥ 100 points from Baseline) at Week 12
- To assess the proportion of subjects with 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) at Week 12
- To assess the proportion of subjects with normalization of 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
- To assess the proportion of subjects with clinical improvement (reduction in CDAI ≥ 100 points from Baseline) at Week 12
- To assess the proportion of subjects with two component patient-reported outcome (PRO-2) remission (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
- To assess the change in SES-CD score from Baseline to Week 12
- To assess the PK of PRA023
- To assess the immunogenicity of PRA023

2.3 Exploratory Objectives

- To assess the change in CDAI and component scores over time
- To assess the effects of PRA023 on tissue and serum PD markers, including TL1A concentrations, endoscopic healing index (EHI), fecal calprotectin, and hsCRP in all subjects over time
- To assess the change in SES-CD at Week 50 from Baseline

- To characterize the change in PDAI score from Baseline to Week 12, Week 28 and Week 50
- To characterize the effect of PRA023 for improvement and remission of enterocutaneous and/or perianal fistula during the Induction Period (IP) and Open-Label Extension (OLE)
- To assess all secondary endpoints at Week 50
- To assess the change in GHAS and RHI from Baseline to Week 12 and Week 50
- To assess the proportion of subjects with histologic response and histologic remission at Week 12 and Week 50
- To assess the change in PRO-2 over time
- To assess the change in extraintestinal manifestations over time
- To assess long-term safety, tolerability, and efficacy of PRA023

3 STUDY ENDPOINTS

The following will be measured for the evaluation of the study endpoints.

3.1 Primary Endpoints

- Safety and tolerability: the proportion of subjects reporting AEs, SAEs, AEs leading to discontinuation, and markedly abnormal laboratory values
- The proportion of subjects with endoscopic improvement, as defined by decrease in SES-CD ≥ 50% from Baseline at Week 12

3.2 Secondary Endpoints

- The proportion of subjects in clinical remission (CDAI < 150) at Week 12
- The proportion of subjects with endoscopic and clinical improvement, as defined by decrease in SESCD ≥ 50% AND reduction in CDAI ≥ 100 points from Baseline at Week 12
- The 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) at Week 12
- The proportion of subjects with normalization of hsCRP (as defined by hsCRP < ULN), among subjects with elevated concentrations at Baseline, at Week 12
- The proportion of subjects with normalization of fecal calprotectin (as defined by fecal calprotectin < ULN), among subjects with elevated concentrations at Baseline, at Week 12
- The proportion of subjects in clinical response, as defined by reduction in CDAI ≥ 100 points from Baseline at Week 12
- The 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
- Change in SES-CD score at Week 12 from Baseline
- Descriptive summaries of PK and immunogenicity of PRA023
- Proportion of subjects developing anti-drug antibody (ADA) and neutralizing antibody (Nab)

3.3 Exploratory Endpoints

- Change in CDAI and components from Baseline over time
- Change in PD markers including TL1A concentrations, EHI, fecal calprotectin, and hsCRP over time

- Change in SES-CD from Baseline at Week 50
- Change in PDAI from Baseline over time
- Proportion of subjects with improvement or remission of enterocutaneous and/or perianal fistula at Week 12 and Week 50
- Change in GHAS and RHI from Baseline to Week 12 and Week 50
- The proportion of subjects with GHAS histologic score ≤ 4 at Week 12 and Week 50
- The proportion of subjects with Robarts histologic score < 5 at Week 12 and Week 50
- The proportion of subjects with GHAS histologic remission, defined as no neutrophils in the epithelium or subscore of 0, at Week 12 and Week 50
- The proportion of subjects with Robarts histologic remission (< 3) at Week 12 and Week 50
- Change in PRO-2 over time
- The proportion of subjects with extraintestinal manifestation through Week 50
- The long-term safety, tolerability, and efficacy of PRA023 through Week 170

4 INVESTIGATIONAL PLAN

4.1 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 CD. This study will be conducted under the aegis of a 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 FU Period). An ileocolonoscopy must be performed during the Screening Visit between 28 to 10 days prior to the Week 0/Day 1.

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 IV administration. Subjects who discontinue from the study drug will have a follow-up period of 12 weeks after the last dose.

Response at Week 12 will be defined as reduction from Baseline in CDAI of ≥ 100 points. Non-responders at Week 12 should be discontinued 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 170. Subjects will continue in OLE until they progress, withdraw from the study, study termination, or Week 170.

For subjects assigned to the 100 mg Q4W OLE arm, the dose may be escalated to 250 mg Q4W if disease activity is not adequately controlled in the Investigator’s opinion.

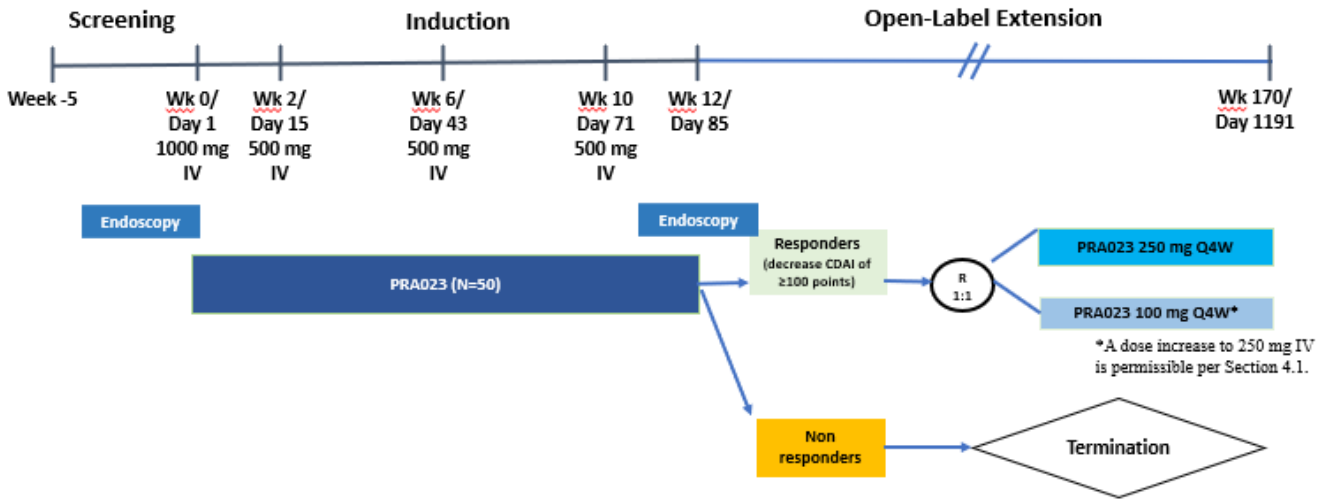
The study may be amended by the Sponsor to extend the OLE beyond 170 weeks based on emerging safety data.

4.1.1 Study Schema

The overall schema for the study is noted below.

Figure 1 Study Schema

*



Q4W = every 4 weeks; Ⓡ = Randomization

4.1.2 Number of Subjects

Approximately 50 subjects with moderately to severely active CD will be enrolled.

4.1.3 Subject Participation Duration

Time permitted from screening to dosing:	Up to 5 weeks
Duration of individual subject participation	
Induction:	12 weeks
Open-Label Extension:	Based on emerging safety data, until Week 170
Follow-Up:	12 weeks

4.1.4 Subject Numbering and Randomization

4.1.4.1 Screening Numbers

All subjects will be assigned a unique six-digit screening number. The first four digits will be the site number and the last two digits will be a number sequentially assigned by the site. This

number will be used to identify the subjects on all screening documents and during their study participation.

4.1.4.2 Randomization Numbers

Subjects who meet the required criteria for PRA023 treatment will be assigned a subject randomization number. Since this is an open-label study, there is no formal randomization per se; the randomization number will be captured in the IRT to denote that the subject has been allocated to PRA023 treatment and to ensure that appropriate number of subjects have been enrolled in the study. Responders who are re-randomized in OLE will retain their original randomization numbers.

4.2 Study Subjects/Population

All subjects must meet the study inclusion and exclusion criteria outlined below in order to participate in the study. All subjects must also meet other site-specific criteria (e.g., screening and on-study criteria established by each site for COVID-19 mitigation) in order to participate in the study. These criteria will be amended by the site(s) as situation changes during the course of the study and should be documented by each site on a site-specific COVID-19 risk mitigation plan. If absolutely necessary, for extenuating circumstances related to COVID-19, study activities may also be deviated as described by the Sponsor COVID-19 mitigation plan.

4.2.1 Inclusion/Exclusion Criteria

4.2.1.1 Inclusion Criteria

Subjects are required to meet the following criteria in order to be included in the study:

1. Male or female ≥ 18 years of age.
2. Subjects must have had a diagnosis of CD (confirmed by endoscopy + histology) at least 3 months before screening to be eligible for study participation. For subjects with no documented confirmation of CD diagnosis or if previous diagnosis is not deemed conclusive, CD diagnosis must be confirmed at time of screening colonoscopy. Note that mention of "chronic inflammation" or "Crohn's disease" or equivalent on histology report is acceptable.
3. Moderately to severely active CD as defined by CDAI of ≥ 220 and ≤ 450.
4. SES-CD score (per central reading) ≥ 6 if ileocolonic or colonic disease; or ≥ 4 if isolated ileal disease only.
5. Subjects must satisfy **at least one** of the following criteria:
   a) **In the past,** had an inadequate response to **one or more** of the following treatments:
      - Oral prednisone ≥ 40 mg/day (or equivalent) or budesonide ≥ 9 mg/day or equivalent or beclomethasone ≥ 5 mg/day for at least 2 weeks

- Corticosteroid dependence as defined by failed to successfully taper to < 10 mg/day of prednisone equivalent (i.e., had a flare of disease) within 3 months of starting therapy, or if relapse occurs within 3 months of stopping corticosteroids
- Immunosuppressants (azathioprine ≥ 2 mg/kg/day or 6-mercaptopurine ≥ 1.0 mg/kg/day, [or documentation of a therapeutic concentration of 6-thioguanine nucleotide] or methotrexate ≥ 15 mg/week) for at least 8 weeks. Note: a lower dosage of 6-MP or AZA is acceptable if local guidelines specify a different treatment regimen (which would need be documented in the source document)
- An approved anti-TNF agent at an approved labeled dose for at least 8 weeks
- An approved anti-integrin (e.g., vedolizumab) at an approved labeled dose for at least 8 weeks
- An approved anti-IL-12/23 (e.g., ustekinumab) at an approved labeled dose for at least 8 weeks

OR

b) Had been intolerant to **one or more** of the above mentioned treatments (e.g., unable to achieve doses or treatment durations because of dose- limiting side effects [e.g., leukopenia, psychosis, uncontrolled diabetes, elevated liver enzymes])

OR

c) **Currently** receiving **one or more** of the following treatments:

- Oral Prednisone ≥ 10 mg/day (or equivalent) or budesonide ≥ 3 mg/day or beclomethasone ≥ 5 mg/day for at least 3 months
- Immunosuppressants [azathioprine ≥ 2 mg/kg/day or 6-mercaptopurine ≥ 1.0 mg/kg/day, (or documentation of a therapeutic concentration of 6-thioguanine nucleotide)] for at least 8 weeks. Note: a lower dosage of 6-MP or AZA is acceptable if local guidelines specify a different treatment regimen (which would need be documented in the source document)

Notes on subjects who have had prior approved biologic therapy(ies) (e.g., anti-TNF, anti-integrin, and/or anti-IL-23):

- The study will include a maximum of 70% and a minimum of approximately 50% subjects who have had prior approved biologic therapy(ies) experience. Upon reaching the maximum number of allowed biologic experienced subjects (70%), subjects who have had prior biologic experience will no longer be allowed to enter the study. Upon reaching the maximum number of allowed biologic-naïve subjects (approximately 50%), subjects who have never been exposed to a prior biologic will no longer be allowed to enter the study.
- Subjects cannot have had failed (no response, insufficient response, loss of response, and/or intolerance) > 4 approved biologic therapies, whether of same or different mechanism of action.

- Subjects previously on clinical trials only (i.e., did not receive commercial available therapy post-approval) are not considered to have received the approved therapy for purpose of this inclusion criteria.

6. For subjects who are WOCBP involved in any sexual intercourse that could lead to pregnancy, the subject has used two highly effective methods of contraception for at least 4 weeks prior to Day 1 and agrees to continue to use two highly effective methods of contraception until at least 12 weeks after the last dose of study drug.
7. Male subjects must use, with their female partner of childbearing potential, two highly effective methods of contraception and refrain from sperm donation from screening to 12 weeks after the last dose of study drug.
8. Subjects must meet drug stabilization requirements, as applicable:
   a) Oral corticosteroid treatment must be equivalent of ≤ 20 mg prednisone or ≤ 9 mg budesonide or beclomethasone ≤ 5 mg daily at a stable dose for at least 2 weeks prior to Day 1
   b) Oral aminosalicylates should be at a stable dose for at least 2 weeks prior to Day 1
   c) Azathioprine, 6-mercaptopurine, and methotrexate should be at a stable dose for at least 4 weeks prior to Day 1
9. Able to provide written informed consent and understand and comply with the requirements of the study.

4.2.1.2 Exclusion Criteria

Subjects with the following characteristics will be excluded from the study:

Sex and Reproductive Status

1. WOCBP and men with female partners of childbearing potential who are unwilling or unable to use two highly effective methods of contraception to avoid pregnancy for the entire study period and for up to 12 weeks after the last dose of study drug.
2. Women who are pregnant or breastfeeding.
3. Women with a positive pregnancy test on enrollment or prior to Day 1.

Target Disease Exceptions

4. Diagnosis of ulcerative colitis or indeterminate colitis.
5. CD isolated to the stomach, duodenum, jejunum, or perianal region, without colonic and/or ileal involvement.
6. Suspected or diagnosed intra-abdominal or perianal abscess at Screening.
7. Known symptomatic stricture or stenosis not passable in endoscopy (including pediatric colonoscope).
8. Current stoma or need for colostomy or ileostomy.

9. Previous small bowel resection with combined resected length of > 100 cm or previous colonic resection of > 2 segments.
10. Currently receiving total parenteral nutrition.
11. Surgical bowel resection within 3 months before screening.
12. Concomitant PSC.

Medical History and Concurrent Diseases

13. Past or current evidence of definite low-grade or high-grade colonic dysplasia that has not been completely removed.
14. Subjects who are scheduled or anticipate the need for surgery, aside from dermatologic procedures.
15. Subjects who have a history of clinically significant drug or alcohol abuse.
16. Concomitant illness that in the opinion of the Investigator, is likely to require systemic glucocorticosteroid therapy during the study (e.g., moderate to severe asthma).
17. Current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, pulmonary, cardiac, neurological, ophthalmologic, or cerebral disease. Concomitant medical conditions that in the opinion of the Investigator might place the subject at unacceptable risk for participation in this study.
18. Subjects with a history of cancer within the last 5 years (other than non-melanoma skin cell cancers cured by local resection). Existing non-melanoma skin cell cancers must be removed prior to enrollment. Subjects with carcinoma in situ or localized cervical cancer, treated with definitive surgical intervention, are allowed.
19. Subjects at risk for tuberculosis (TB). Specifically, subjects with:
    a) A history of active TB
    b) Current clinical, radiographic or laboratory evidence of active TB
    c) Latent TB which was not successfully treated. Subjects with a positive TB screening test indicative of latent TB will not be eligible for the study unless active TB infection has been ruled out, and an appropriate course of intervention for latent TB has been initiated at least 2 weeks prior to Day 1, and no evidence of active TB on chest x-ray during screening.
20. Subjects with any serious bacterial infection within the last 3 months, unless treated and resolved with antibiotics, or any chronic bacterial infection (such as chronic pyelonephritis, osteomyelitis, and bronchiectasis).
21. Female subjects who have had a breast cancer screening that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory, or other diagnostic evaluations.
22. Subjects with any active infections (excluding fungal infections of nail beds) including, but not limited to, those that require IV antimicrobial treatment 4 weeks or oral antimicrobial treatment 2 weeks prior to randomization. Subjects with evidence of Human

Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C infection detected during screening are also excluded. Subjects with successfully treated Hepatitis C with no recurrence for ≥ 1 year are allowed. Subjects with active documented or suspected COVID-19 infection within 4 weeks of randomization or asymptomatic SARS-CoV-2 test positivity within 2 weeks of randomization are excluded.

23. Subjects with herpes zoster reactivation or cytomegalovirus (CMV) that resolved less than 2 months prior to signing informed consent.
24. Subjects who have received any live vaccines within 3 months of the anticipated first dose of study medication or who will have need of a live vaccine at any time during the study.

Physical and Laboratory Test Findings

25. Positive stool Polymerase Chain Reaction (PCR) if Investigator deems this positivity reflects infection rather than colonization **or** positive culture for enteric pathogens.
26. Stool positive for *Clostridium difficile (C. difficile*) toxin. Subjects who are positive can be retested after the completion of a full course of treatment for *C. difficile* infection.
27. Any of the following lab values:
    a) Hemoglobin (Hgb) < 8.0 g/dL (80 g/L)
    b) White blood cell (WBC) < 2,500/mm^3 (2.5 x 10^9/L)
    c) Neutrophils < 1,000/mm^3 (1 x 10^9/L)
    d) Platelets < 100,000/mm^3 (100 x 10^9/L)
    e) Serum creatinine > 2 times upper limit of normal (ULN)
    f) Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 times ULN
    g) Any other laboratory test results that, in the opinion of the Investigator, might place the subject at unacceptable risk for participation in this study

Prohibited Therapies and/or Medications

28. Failed (no response, insufficient response, loss of response, and/or intolerance) > 4 approved biologic therapies (anti-TNF, anti-integrin, anti-IL12/23), whether of same or different mechanism of action.
29. Any marketed biologic within 8 weeks for anti-TNF agents and 12 weeks for anti-integrin agents (e.g., vedolizumab) and ustekinumab prior to Day 1 **or** if drug level per therapeutic dose monitoring is greater than lower limit of detection.
30. Any biologic immunomodulators used for CD or other conditions within 8 weeks or 5 half-lives, whichever is longer, prior to Day 1 **or** if drug level per therapeutic dose monitoring is greater than lower limit of detection.
31. Rituximab within 1 year prior to Day 1.
32. Parenteral corticosteroids within 4 weeks or rectal administration of corticosteroids within 2 weeks prior to Day 1.
33. Rectal administration of 5-ASA within 2 weeks prior to Day 1.
34. Tacrolimus, cyclosporine, mycophenolate mofetil (CellCept®), immunoadsorption columns (such as Prosorba columns), D Penicillamine, Leflunomide, Thalidomide, chronic use of

non-steroidal anti-inflammatory agents (NSAIDs), and use of aspirin > 81 mg/day within 2 weeks prior to Day 1.

35. Other investigational chemical agent within 30 days or other investigational biologic agent within 8 weeks or 5 half-lives (whichever is longer) of entry into the IP.
36. Prior exposure to PRA023.

Other Exclusion Criteria

37. Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
38. Legal or mental incapacitation, or inability to understand and comply with the requirements of the study.
39. Known allergies, hypersensitivity, or intolerance to PRA023 or its excipients.

4.3 Contraception Guidelines

The Investigator or his/her designee will discuss with the subject the need to use two highly effective methods of contraception consistently and correctly according to Schedule of Study Assessments (Section 6.1.1) and document such conversation in the subject's chart. In addition, the Investigator or his or her designee will instruct the subject to call immediately if the selected contraception methods are discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

All women who have experienced menarche are WOCBP unless meeting criteria for women of non-childbearing potential as described below. This includes women who are using an active method of birth control, are practicing abstinence, with same sex partner, have undergone tubal ligations, or where the partner is sterile (e.g., vasectomy).

WOCBP involved in any sexual intercourse that could lead to pregnancy will be eligible for the study provided they use two highly effective methods of contraception for at least 4 weeks prior to Day 1, throughout the study and until the 12 weeks after the last dose of IP. The dose for hormonal contraceptives must have been stable for at least 4 weeks prior to Day 1.

All male subjects who are able to father children, are sexually active with female partners, and at risk for pregnancy must agree to use, with their partners, two highly effective method of contraception consistently and correctly for the duration of the active treatment period and 12 weeks after the last dose of study drug. In addition, all sexually active male subjects must also agree to prevent potential transfer of and exposure to study drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of study drug and until 12 weeks after the last dose of study drug.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (i.e., perfect use) and include the following:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of

contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness

2. Correctly placed copper-containing intrauterine device (IUD)
3. Male condom or female condom used WITH a spermicide (i.e., foam, gel, film, cream, or suppository). For countries where spermicide is not available and condoms alone are considered an effective method of contraception, at the Investigator's discretion, the use of condom alone without spermicide is acceptable and sufficient to meet this requirement.
4. Male sterilization with documented absence of sperm in the post-vasectomy ejaculate
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label)
6. Females who meet the criteria for non-childbearing potential, as described below:

   Woman of non-childbearing potential must meet at least one of the following criteria:

   - Have had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
   - Have medically confirmed ovarian failure
   - Females who are postmenopausal with amenorrhea without an alternative medical cause for at least 1 year prior to the first dose and have follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status as per investigator judgment

4.4 Concomitant Treatments and Restrictions

4.4.1 Prior and Concomitant Medications

Any prior or ongoing CD medications, including corticosteroids, immunosuppressives (AZA, 6-MP, and MTX), anti-TNFs, anti-integrins, and anti-IL-12/23 used by the subject will be recorded on the eCRF.

All concomitant medication(s) and treatment(s) administered/taken during the study must be recorded with indication, dose, and start and stop dates of administration. All subjects will be questioned about concomitant medication at each site visit.

Medication(s) administered/taken following the first dose of PRA023 will be documented as concomitant medication(s).

4.4.2 Permitted Medications with Restrictions

Subjects will be allowed to use the following medications as detailed below:

- A stable dose of 5-ASA for at least 2 weeks prior to Day 1 and throughout the IP
- A stable dose of oral corticosteroids (prednisone ≤ 20 mg/day or equivalent) for CD for at

least 2 weeks prior to Day 1 and during the IP. During the OLE period, a tapering schedule should be followed if the subject's condition allows (see Section 4.4.4).

- A stable dose of oral budesonide (≤ 9 mg/day or equivalent) or beclomethasone ≤ 5 mg/day for at least 2 weeks prior to Day 1 and during the IP. During the OLE period, a tapering schedule should be followed if the subject's condition allows (see Section 4.4.4).
- A stable dose of immunosuppressants (AZA, 6-MP, or methotrexate) for 4 weeks prior to Day 1 and during the IP.

4.4.3 Prohibited Medications

- Any marketed biologic therapy throughout the study
- IV corticosteroid for treatment of CD during the IP
- Oral corticosteroid (prednisone > 20 mg/day or equivalent) for the treatment of CD during the IP
- Oral budesonide > 9 mg/day or equivalent or beclomethasone > 5 mg/day during the IP
- Any per rectal therapy including enema (e.g., 5-ASA, budesonide, corticosteroid) during IP, other than that required for endoscopy preparation during the IP.
- Systemic tacrolimus, systemic cyclosporine, oral mycophenolate mofetil (MMF), immunoadsorption columns (such as Prosorba columns), D-penicillamine, leflunomide, Thalidomide, purified medicinal probiotics throughout the study
- Chronic use of NSAIDs or aspirin > 100 mg/day during the IP
- Any investigational drug other than the study medication throughout the study

4.4.4 Corticosteroid and Budesonide Tapering Schedule During Open-Label Period

After the completion of all Week 12 assessments, background oral corticosteroid and/or budesonide therapy should be tapered if the subject is in remission (as defined in Section 6.4) or has a satisfactory response to treatment per Investigator.

For prednisone or equivalent, dose should be reduced at a rate of 2.5 mg (daily dose) of prednisone or equivalent per week; although the Investigator may use an alternative regimen if preferred. For budesonide and beclomethasone, tapering schedule per site protocol with goal of completing the tapering regimen within 8 weeks.

4.4.5 Other Restricted Medications

Due to the risk of infection, vaccination of subjects with any live vaccine is contraindicated during the treatment period of the study (i.e., at any time after randomization into the IP), as is the administration of LIVE oral polio vaccine to household contacts. The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (CDC ACIP) recommends that subjects should not be administered a live virus vaccination for at least 3 months

after immunosuppressive therapy. Therefore, study subjects should not be administered a live vaccine for a minimum of 3 months following the last dose of study medication. Check with Medical Monitor, if uncertain, regarding use of certain COVID-19 vaccines.

4.4.6 Rescue Medication

High-dose steroids for CD, increases in oral aminosalicylates, rectal aminosalicylates, and rectal corticosteroids are permitted as rescue medications only during OLE, and other CD treatments will not be permitted during the study and will only be permitted following formal study withdrawal. Once a subject permanently discontinues PRA023 treatment and withdraws from the study, subjects will no longer need to abstain from the medications that were prohibited. However, biologic treatment(s) should not be initiated for 12 weeks after the last dose of PRA023 without discussion with the Sponsor due to the long half-life ($t_{1/2}$) of PRA023.

Subjects are free to withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor. If a subject requires initiation of a new therapy for CD, the subject should be withdrawn from the study and appropriate treatment should be administered at the discretion of the Investigator.

4.5 Removal of Subjects from Study

A genuine effort must be made to determine the reason(s) why a subject fails to return for the necessary visits or is discontinued from the study. This information and date must be recorded on the appropriate eCRF and on the Termination Sheet. Subjects MUST discontinue from the study for any of the following reasons:

- The subject decides that it is in his/her best interest. It is fully understood that all subjects volunteer for the study and that they may withdraw their consent to continue in the study at any time.
- Any AE, laboratory abnormality, or change in medical condition which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject.
    - For potential drug induced liver injury (DILI), timely confirmation of initial liver-related laboratory abnormalities should be performed. Potential drug induced liver injury is defined as:
        - ALT/AST elevation >3 x ULN, AND
        - Total bilirubin >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), AND
        - No other immediately apparent possible cause of increased ALT/AST and total bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or other drug capable of causing the observed injury
    - Subjects with suspected DILI should be discontinued from the study
- Persistent non-compliance of the subject
- Pregnancy

- Use of any investigational drug therapy for CD excluding study treatment
- Treatment with biologic therapy for CD

The Investigator must notify the Medical Monitor by telephone or by email as soon as possible if any subject prematurely withdraws from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the eCRF. If a subject is "lost to follow-up" (fails to return for study visits), a reasonable effort should be made to contact the subject in order to determine why the subject failed to return. This information must be documented in the eCRF. If a subject is withdrawn from the study early (regardless of the cause) all of the end-of-study evaluations should be performed at the time of withdrawal, and the subject followed for 12 weeks after the last dose of PRA023, if possible, due to the long $t_{1/2}$ of PRA023.

It is agreed that, for reasonable cause, either the Investigator or the Sponsor, Prometheus, may terminate this study.

4.6 Modification of Study Drug Dosing

Investigators should reference the Investigator's Brochure (IB) for PRA023 and use their best clinical judgment to determine the continuation of dosing during the study. PRA023 doses should be withheld until after the resolution of clinically significant infections. Reference Section 5.4 for dose modification recommendations related to infusion reaction.

5 INVESTIGATIONAL PRODUCT

5.1 Dosing Form and Preparation

PRA023 concentrate for solution for infusion will be provided as a single-dose glass vial containing 500 mg of PRA023 at 60 mg/mL dose strength. PRA023 will be packaged in a box containing 6 vials per box. Each vial will contain at minimum 8.4 mL of PRA023. All study drug vials will indicate the lot number and the label affixed to the vial will contain the drug identification and conditions for storage. The vials do not contain antibacterial preservatives. Therefore, any unused portion of the study drug after single use should not be stored for reuse.

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.

5.2 Storage

The study drug must be stored in a secure, lockable area in 36ºF - 46ºF (2ºC - 8ºC) controlled storage condition prior to use. All study drug must continue to be stored in a secure, lockable area until it is returned to the Sponsor or designee or destroyed upon approval by the Sponsor or designee.

5.3 Accountability

The study drug must be used in accordance with the protocol and only under the direction of the Investigator. The Investigator or designee shall keep and maintain complete and accurate records of all investigational materials. Records showing the receipt and disposition of all study drug shall include a master record listing the date of receipt of study drug shipment, the quantities received, and a dispensing record, which includes each quantity dispensed, identification of the person to whom dispensed, the date of dispensing, and the identification of the dispenser. The accountability records must be made available to the Sponsor or designee at any time.

At the termination of the study or at the request of the Sponsor or designee, the Investigator must return any unused study drug to the Sponsor or its designee according to applicable local and country regulations, and appropriately destroy any empty or used study drug vials. If return of unused study drug is not feasible, the Sponsor or designee will supply instructions as to how the supplies may be destroyed. All study drug supply destruction must be clearly documented. The Investigator must also provide a written explanation for any missing study drug.

5.4 PRA023 Administration

All doses of PRA023 will be administered intravenously as a 30-minute infusion using a calibrated infusion pump by the appropriately designated study staff at the investigational site.

Treatment of subjects with monoclonal antibodies may result in inappropriate immune responses and range from mild events with no apparent clinical manifestations to life-threatening or catastrophic reactions. Signs and symptoms of these events may develop during or shortly after infusion. As such, subjects must be closely monitored during administration of PRA023. Post-infusion observation period during the first 2 infusions (Week 0/Day 1 and Week 2) should be 1[*] hour and subsequent infusions should be 30 minutes (Table 2 and Table 3).

Some of the major safety concerns associated with immunogenicity are anaphylaxis, cytokine release syndrome, "infusion reactions", and non-acute reactions such as delayed hypersensitivity.

The information below is provided as guidance to assess anaphylaxis, but the clinical judgment of the Investigator should be considered as well.

Anaphylaxis is a serious, acute allergic reaction characterized by certain clinical features. Signs and symptoms of anaphylaxis may include:

- Generalized hives, pruritis/itching, flushing, swollen lips/tongue/uvula
- Symptoms of respiratory compromise (e.g., dyspnea, wheeze/bronchospasm,stridor, reduced peak expiratory flow, hypoxemia)
- Reduced blood pressure (systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from baseline) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
- Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

If a subject experiences anaphylaxis, PRA023 administration should be discontinued immediately and permanently. If a subject experiences symptoms that may be attributed to hypersensitivity reaction or delayed hypersensitivity (e.g., fever, rash, arthralgia, myalgia, hematuria, proteinuria, serositis, central nervous system complications, or hemolytic anemia), PRA023 infusion should be stopped.

In the event that symptoms are mild or minor in severity, at the discretion of the Investigator, the infusion may be restarted at a slower rate if symptoms are resolved within 1 hour after stopping the infusion. If symptoms return, PRA023 should be discontinued immediately and permanently.

In the event that there is an infusion interruption, the entire duration of PRA023 infusion, from the initial start of infusion, to the completion of infusion, should not exceed 24 hours of PRA023 dilution. Subjects will receive appropriate treatment at the discretion of the Investigator.

[*] 2 hours for subjects in Czech Republic

6 STUDY PROCEDURES

A schedule of study procedures is presented in Section 6.1.1. If any discrepancies should be found between the text of the protocol and the Schedule of Study Assessments tables, the tables will predominate.

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator, that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The Sponsor or designee will be informed of these incidents in a timely fashion.

6.1 Study Visit Procedures

A written, signed informed consent form (ICF) must be obtained from each subject prior to performing any study procedure. Medical/surgical history, medication record (prior and concomitant medications and therapy), and a physical examination including vitals will be obtained for all subjects at the Screening Visit. A series of laboratory and diagnostic/clinical tests and evaluations will be performed. At least two visits to the clinical facility may be necessary to complete all screening procedures, including an ileocolonoscopy. The ileocolonoscopy should be performed after all other eligibility criteria, including CDAI during Screening, have been met and within 28-10 days of Day 1 to allow SES-CD score calculation.

Subjects may be re-screened one time at the discretion of the Sponsor if they fail their initial screening.

After Week 0/Day 1, all subjects will be evaluated frequently through a series of physical examinations, and laboratory tests and assessments for safety and efficacy as described in the Schedule of Study Assessments tables (Section 6.1.1).

6.1.1 Schedule of Study Assessments

Table 1 Schedule of Study Assessments – Screening Period

Procedure	Study Visit Screening	NOTES Screening duration is up to 35 days (5 weeks)
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical and Surgical History	X	
Smoking History	X	
Prior and Current Concomitant Medications	X	
Safety Assessments		
Complete Physical Examination	X	
Targeted Physical Examination		
Vital Signs	X	Height at Screening Visit 1 only Heart rate, temperature, blood pressure
Weight	X	
ECG	X	
Chest X-Ray	X	Must be performed within 6 months of the Screening Visit 1 with documentation on file.
Adverse Events Assessment	X	
Efficacy Assessments		
Subject Training on Electronic Diary (eDiary) Completion	X	
Issue eDiary to Subject	X	Remind subjects to record in their eDiary daily
Ileocolonoscopy with Biopsy	X	Ileocolonoscopy should be performed between 28 to 10 days prior to the Week 0/Day 1 visit. Ileocolonoscopy should be performed after all other eligibility criteria have been met.
Laboratory Tests		
Pharmacogenomics (Buccal Swab and Blood)	X	In case of DNA extraction failure, additional sample should be collected for CDx testing.
Stool PCR or Culture	X	Can be performed centrally or locally. Ova and parasite examination should also be performed based on local guidelines.
C. difficile PCR/Toxin	X	Can be performed centrally or locally.
Fecal calprotectin	X	To be performed during screening, prior to Week 0/Day 1
CBC	X	
Chemistry Panel	X	
hsCRP	X	
Urinalysis	X	
QuantiFERON-TB	X	May be repeated if result indeterminate. No need to test if negative result available within 90 days of screening.
HBsAg, HBcAb, and HCV Ab	X	If HCV Ab positive, confirmation by undetectable HCV-RNA. . If HBcAb is positive and Hep B sAg negative, Hep B DNA will be done as reflexive test, and if undetectable, then not exclusionary. No need to test if negative result available within 90 days of screening.
Human Immunodeficiency Virus (HIV)	X	Per local regulations. To be assayed locally or centrally per country/regional regulations. Confirmation and documentation of

Procedure	Study Visit Screening	NOTES Screening duration is up to 35 days (5 weeks)
		a negative HIV test result within 3 months (except for subjects in Czech Republic) prior to screening will be accepted.
Serum Pregnancy Test (WOCBP only)	X	

Table 2 Schedule of Study 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	

	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								
Urinalysis	X		X	X		X	X	
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.

Table 3 Schedule of Study Assessments – Open-Label Extension Period Up to Week 50

	Study Visit								NOTES 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
Study Week	**14**	**18**	**26**	**34**	**42**	**50**	**Early Termination**	**Infusion Visits Q4W (excluding Office 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				
Vital Signs	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	
Concomitant Medication	X	X	X	X	X	X	X	X	
Efficacy Assessments									
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	X		
Ileocolonoscopy with Biopsy			X[a,b]			X	X		Ileocolonoscopy to be performed between 14 and 8 days before Week 26 and Week 50 visits or within 1 week **after** Week 50 visit or ET visit [a]If the investigator feels there is a contraindication, this Week 26 endoscopy could be considered optional. [b]Biopsies are optional.

	Study Visit								NOTES 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
Study Week	**14**	**18**	**26**	**34**	**42**	**50**	**Early Termination**	**Infusion Visits Q4W (excluding Office Visits)**	
Study Day	**99**	**127**	**183**	**239**	**295**	**351**			
Visit window (days)	+14	±7	±14	±14	±14	±14		±7/±14	
Procedure									
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		
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	X[a]	X[a]	X[a]		X[a]	X[a]	X		[a] To be taken pre-infusion.
Immunogenicity		X[a]	X[a]		X[a]	X[a]	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		
Fecal Calprotectin			X			X	X		
Infusion	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

Table 4 Schedule of Study Assessments – Open-Label Extension Period (After Week 50)

	Study Visit			NOTES Visit windows are ±14 days
Study Week	**Quarterly* Office Visits**	**Early Termination**	**Infusion Visits (excluding Office Visits)**	* Weeks 62, 74, 86, 98, 110, 122, 134, 146, 158, 170
Procedure				
Complete Physical Examination	X[a]	X		[a.] Yearly
Targeted Physical Examination	X			
Vital Signs	X[a]	X[a]	X	Heart rate, temperature, blood pressure; Take pre-dose (no more than 30 minutes pre-infusion) and end of infusion [a.] Weight needed
Adverse Events Assessment	X	X	X	
Concomitant Medication	X	X	X	
Efficacy Assessments				
Review Diary Data from Subjects	X			Paper diaries may be used
CDAI Assessment	X	X		
PDAI	X[a]	X[a]		[a.] To be performed on every subject every 6 months
Fistula Drainage Assessment	X	X		
Ileocolonoscopy with Biopsy	X[a]	X[b]		Subjects should undergo colon cancer surveillance as per local guidelines, if applicable, for clinical management [a.] Done annually (11-13 months from prior ileocolonoscopy) [b] Required if >3 months since prior ileocolonoscopy
IBDQ	X[a]	X		[a.]Every 6 months
Laboratory Testing				
CBC	X	X		
Chemistry Panel	X	X		
Fasting Lipid Panel	X[a]	X		[a.] Every 6 months
Urine Pregnancy Test (WOCBP only)	X	X	X	Pregnancy testing must be done once a month prior to dosing
Urinalysis	X[a.]	X		[a.] Every 6 months

	Study Visit			NOTES Visit windows are ±14 days
Study Week	**Quarterly* Office Visits**	**Early Termination**	**Infusion Visits (excluding Office Visits)**	* Weeks 62, 74, 86, 98, 110, 122, 134, 146, 158, 170
Procedure				
Pharmacokinetics	X[a]	X[b]		[a.] To be taken pre-infusion; every 6 months [b.] To be taken at the same time as other laboratory tests for early termination
Immunogenicity	X[a]	X		[a] To be taken pre-infusion; every 6 months
Biomarkers				
hsCRP	X[a]	X		[a.] Every 6 months
Fecal Calprotectin	X[a]	X		[a.] Every 6 months
Serum biomarkers	X[a]	X		[a.] Every 6 months; additional whole blood sample at Week 98
Infusion	X		X	Infusions should be at Q4 week interval Include date, start and stop time, volume infused, and length of the IV infusion Infusion observation period will be 30 minutes

Table 5 Post Dosing Follow-Up Period

	Study Visit		
	28 Days Post Dosing Period	**56 Days Post Dosing Period**	**84 Days Post Dosing Period**
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

6.2 Other Information for Study Visits

Unscheduled procedures may be required in addition to the procedures detailed above for subject safety and/or exacerbation assessments. The additional procedures are at the discretion of the Investigator. The details of these unscheduled procedures will be recorded in the source documents and entered into the eCRFs.

6.3 Safety Assessment Description

6.3.1 Medical History, Physical Examination, Height and Weight

Medical history, including CD history, will be collected at the Screening Visit.

The Investigator will perform a complete physical examination at the Screening Visit and at the visits specified in the schedule of study procedures (Section 6.1.1). The complete physical examination must include the following:

- General appearance
- Hair and skin
- Lymph nodes
- Head
- Eyes
- Ears, nose, and throat
- Neck
- Respiratory
- Cardiovascular
- Abdominal
- Musculoskeletal
- Mental status
- Neurological

Unless otherwise indicated, following screening visit, physical examinations should be targeted (symptom directed). Complete and targeted physical examinations are to be performed at specified visits according to the schedule of study procedures (Section 6.1.1).

Height and weight will be measured without the subject wearing shoes. Height (inches or centimeters) will be measured and recorded at the screening visit only and weight (lbs or kg) will be measured and recorded at specified visits (Section 6.1.1).

6.3.2 Vital Signs

Vital signs to be assessed are heart rate, respiratory rate, body temperature, and resting blood pressure. The body position (sitting or supine) should be recorded. Approved medical devices may be used to record these parameters.

6.3.3 Chest X-Ray

A chest x-ray (posterior-anterior and lateral views are recommended, however, local guidelines should be followed) with no evidence of current, active TB or previous inactive TB, general infections, heart failure or malignancy is to be taken at screening or within the 6 months prior to screening and read by a qualified radiologist. Documentation of the official reading must be located and available in the source documentation.

6.3.4 Electrocardiogram (ECG)

A standard 12-lead ECG for all subjects will be performed at Screening and at the subsequent visits specified in the schedule of study procedures (Section 6.1.1). **Original** ECGs with interval printouts and rhythm strip run at 25 mm/sec must be provided as source documentation.

Automatically calculated QT and QTc intervals will be reviewed and checked for gross inaccuracies by the Investigator or designated ECG reviewer. If the automatically calculated QT or QTc intervals are greater than 480 msec, or if either has increased by 50 msec or more over the baseline value, it will be manually over-read by the Investigator or designated ECG reviewer. The ECG parameters that will be assessed include heart rate, PR interval, QRS interval, and QT interval. If QT or QTc interval prolongation exceeding these limits is verified during treatment, the subject's medical background should be examined closely for risk factors that may have contributed to the event, including genotyping for hereditary long QT syndromes, if appropriate.

Any sign of arrhythmia should be noted. During treatment, any indication of QT prolongation or Torsade de Pointes, a polymorphic ventricular tachyarrhythmia that appears on the ECG as continuous twisting of the vector of the QRS complex around the isoelectric baseline, must be recorded as an adverse event and reported to the Medical Monitor.

The decision to continue the treatment of any subject with prolonged QT or QTc interval must be discussed and agreed upon by the Investigator and the Medical Monitor. All such subjects, including subjects with cardiac arrhythmias, should be monitored closely. If appropriate, ECG monitoring should be performed until the QT and QTc interval and waveform morphology have returned to normal. If the prolongation or abnormal rhythm persists, the Medical Monitor must be contacted.

6.3.5 Clinical Laboratory Evaluations

Blood and urine samples will be collected and analyzed or tested, according to the standard operating procedure (SOP) of the testing facility, for the following:

Hematology
- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count (with indices)
- Platelet count

Urinalysis
- pH
- Specific gravity
- Protein*
- Glucose
- Ketones
- Bilirubin
- Blood*
- Nitrite*
- Urobilinogen
- Leukocyte esterase*

Chemistry
- Blood Urea Nitrogen (BUN)/urea
- Bilirubin (total and direct)
- Uric acid
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Albumin
- Sodium
- Potassium
- Chloride
- Carbon dioxide/bicarbonate
- Calcium
- Phosphorus (inorganic)/phosphate
- Total protein
- Glucose
- Lactate dehydrogenase (LDH)
- Creatinine
- Creatine kinase (CK)**
- Gamma-glutamyl transferase (GGT)
- Lipid panel (total cholesterol, LDL, HDL and VLDL fractions and triglycerides)***

Serology
- HBsAg
- HBcAb
- HIV
- HCV

Other Tests
- Follicle stimulating hormone (FSH) for postmenopausal females only****
- QuantiFERON-TB
- Serum/urine pregnancy test (for female subjects only)

* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

**CK-MB reflex test (or Troponin 1) may be performed if CK is elevated.

***Fasting; refer to schedule of study procedures (Section 6.1.1) for fasting sample collection timepoints.

****If needed.

The Investigator must review the screening visit laboratory results for all the measured analytes for each subject prior to Week 0/Day 1. The subject must not be enrolled for treatment if any of the laboratory values meet the exclusion criteria or in the opinion of the Investigator, might place the subject at unacceptable risk for participation in this study.

Subjects who would not qualify to participate in the study due to a screening laboratory value abnormality can repeat the test once within the original screening time window without resulting in screen failure, if the Investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

All subjects with laboratory tests containing clinically significant abnormal values are to be followed regularly until the values return to normal ranges; until a valid reason, other than study drug-related AE, is identified; or until further follow-up is deemed medically unnecessary.

6.3.6 Stool Evaluation

6.3.6.1 Stool Culture

A stool PCR or culture (per central laboratory or local laboratory availability) is to be performed at the screening visit only and can be performed centrally or locally at the Investigator's discretion. Subjects will be provided with instructions for stool sample collection at home and will be required to submit the stool sample to the site for testing. Ova and parasite examination, if applicable, should be performed based on local guidelines.

6.3.6.2 Screening for *Clostridium Difficile*

Highly sensitive screening tests, with high negative predictive value, should be employed in evaluating subjects for eligibility for the study. The detection of *C. difficile* by toxigenic stool culture [stool culture followed by detection of toxin] is considered the gold standard for the diagnosis of the colonization or infection with pathogenic *C. difficile*. Comparable sensitivity may be achieved by direct testing of stool via point of use rapid membrane enzyme immunoassay card for both *C. difficile* toxin A and B and/or glutamate dehydrogenase (GDH) antigen on a card. Use of the card for point of care screening is encouraged where permitted by local regulation. Molecular techniques such as polymerase chain reaction (PCR) for detection of toxin RNA are also acceptable alternatives.

Subjects who are positive at Screening Visit can be retested after the completion of a full course of treatment for *C. difficile* infection.

Refer to the Central Laboratory Manual for further guidance and instruction for *C. difficile* screening if sent for central testing. If using the central lab, as the *C. difficile* PCR may be the screening test, a positive PCR test result with a negative toxin result may reflect infection or colonization, and the Investigator should decide whether PCR positivity reflects infection, in which case, treatment should be administered. Sites should follow the guidance and instructions from the local laboratory if tested locally.

6.4 Efficacy Assessment Description

The SES-CD will be used to evaluate disease activity for the primary endpoint. The SES-CD and CDAI scores will be used to evaluate disease activity for the secondary endpoints. The SES-CD is a validated endoscopic score that is used to describe ileocolonoscopic findings in CD. SES-CD assesses the size of mucosal ulcers, the ulcerative surface, the endoscopic extension, and the presence of stenosis (Daperno 2004, Moskovitz 2007).

For the current study, the following definitions will apply:

- Endoscopic Improvement – a decrease in SES-CD of ≥ 50% from Baseline
- Clinical Remission – CDAI < 150
- Clinical Response – a reduction in CDAI ≥ 100 points from Baseline
- Biomarker and Clinical Composite Improvement – a decrease in hsCRP or fecal calprotectin ≥ 50% from Baseline and reduction in CDAI ≥ 100 points from Baseline

6.4.1 Ileocolonoscopy with Biopsy

6.4.1.1 Ileocolonoscopy and SES-CD Score

An ileocolonoscopy with biopsy should be performed during Screening and Visit Week 12/ET and Week 50/ET and annually thereafter with whatever cancer surveillance technique is recommended as per local guidelines if subject has colonic involvement. The endoscopy during Screening should be performed within 28-10 days of Week 0/Day 1 Visit. The bowel preparation should be conducted as per local routine.

While the assessment by the Central Reader will be used to derive the SES-CD score for study eligibility, the Investigator should also determine the SES-CD score locally. The ileocolonoscopy report should be filed in the subject's chart. The findings of the ileocolonoscopy, including local grading of SES-CD score should be completed at the end of the procedure.

The endoscopic variables will be evaluated in 5 predefined ileocolonic segments:

- Ileum - include the full extent for which it is examined. **Do not** include the ileocecal valve or an ileocolonic anastomosis
- Right colon - include the ileocecal valve, the cecum, and the ascending colon to the hepatic flexure
- Transverse colon - between the hepatic and the splenic flexures
- Descending colon - from the splenic flexure to the rectosigmoid junction
- Rectum - distal to the rectosigmoid junction

The 4 endoscopic variables (each to be scored from 0 to 3 points) to be evaluated are (see Appendix 16.1):

- Ulcers - scored according to size (diameter 0.1 - 0.5 cm, 0.5 - 2 cm, or > 2 cm)
- Proportion of the surface covered by ulcers according to extent (< 10%, 10 - 30%, or > 30%)
- Proportion of affected surface with any other lesions according to extent (< 50%, 50 - 75%, or > 75%)
- Stenosis (single or multiple, and whether the colonoscopy could pass through the narrow lumen)

A study specific video capture kit, which includes the Endoscopy Video Instructions Manual and other Quick Reference materials, and a detailed Biopsy Procedural Manual will be provided by the Central Reader vendor.

6.4.1.2 Biopsy

During each of the ileocolonoscopies, at least 3 biopsy samples should be obtained from each of the 5 ileocolonic segments (rectum, descending colon/sigmoid, transverse colon, ascending colon, or ileum). The biopsies should be collected in the vicinity of any lesion or ulcerated area, at the edge of the ulcerated area if possible. If no lesions were present in the segment, biopsies should be collected from random sites within the segment. Two (2) of the 3 biopsy specimens from each segment should be placed into the formalin-fixed bottles pre-filled with 10% neutral buffered formalin and the 3rd of the biopsy specimens from each segment should be placed into the RNAlater bottles pre-filled with RNAlater solution.

All biopsy samples will be sent to the central laboratory for the study and processed by a designated central pathology site for histological scoring.

6.4.2 Crohn's Disease Activity Index (CDAI) Score

Subjects will use an eDiary in order to record their CD symptoms on a daily basis. eDiary data will be assessed at the clinic from screening until the end of PRA023 treatment. Subjects will record the following information:

- Number of soft/liquid stools each day
- Daily rating of abdominal pain
- Daily rating of general well-being
- Daily fever
- Daily use of anti-diarrheal medications

The information extracted will be used for calculation of CDAI score taking into account the data recorded over the last 7 days prior to each study visit. If there are less than 7 available days reported prior to the study visit, the average will be taken from the limited available data unless there is no eDiary/paper diary data reported within 7 days. Note that if there is less than 5 days of eDiary/paper diary data prior to the baseline, then the subject cannot be enrolled into the study. In case where there are not at least 5 evaluable days of symptoms available in the prior 7 days, a look back to 10 days prior to the visit is acceptable, although not preferred. Note that symptoms on days of the bowel preparation, endoscopy, and 2 days post endoscopy are not considered evaluable.

In order to encourage consistent diary recording, subjects should enter diary data continuously throughout the study. Instructions for completing the eDiary/paper diary will be provided to subjects at screening and reviewed at subsequent visits.

All other elements of the CDAI not captured in the eDiary/paper diary (Appendix 16.2) should be assessed by the site personnel at the time of the visit. The eDiaries or paper diaries and CDAI score worksheets will be source documents for this study.

6.4.3 Perianal Disease Activity Index (PDAI)

The 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 (Irvine 1995). See Appendix 16.3 for additional details.

6.4.4 Fistula Drainage Assessment

Severity of enterocutaneous and perianal disease will be assessed using the Fistula Drainage Assessment. Fistulas will be classified as either (1) open and actively draining or (2) closed, based on the Investigator's physical evaluation of the subject: a fistula is open if the Investigator can express purulent material from the fistula with the application of gentle pressure (Present 1999). Improvement is defined as a reduction ≥50% from baseline in the number of draining fistulas observed at 2 or more consecutive visits (at least 21 days apart). Remission is defined as the absence of any draining fistulas at 2 consecutive visits (at least 21 days apart).

6.4.5 Quality of Life (QoL)

Subjects will be asked to complete the Inflammatory Bowel Disease Questionnaire (IBDQ) at visits specified in Section 6.1.1 to measure disease specific quality of life (QoL). The questionnaires completed by subjects will serve as the source documents for this study.

The IBDQ is a self-administered 32-item questionnaire that evaluates QoL across 4 dimensions: (1) Bowel – symptoms related to primary bowel disturbance, (2) Systemic symptoms, (3) Emotional function, and (4) Social function. The response to each question can range from 1 to 7, with 1 indicating severe problem and 7 indicating normal health. The total IBDQ is computed as the sum of the responses to the individual IBDQ questions. The total score can range between 32 to 224 with higher scores indicating a better QoL (Guyatt 1989).

6.5 Pharmacodynamics

Serum biomarkers will be measured to determine the expression of pro-inflammatory cytokines and other soluble biomarkers that may correlate with CD disease activity. Blood samples for PD are to be drawn at the time points specified in the protocol (see Section 6.1.1). The actual date and time (24-hour clock time) of each sample will be recorded. Instructions for the handling of the PD samples will be provided in the Laboratory Manual.

Evaluations of pharmacodynamics may include, but are not limited to, the following:

Cytokines
- Soluble TL1A

Stool
- Fecal calprotectin

Biomarkers
- Endoscopic healing index (EHI)
- hsCRP
- mRNA

Any residual serum, following completion of analysis, will be stored frozen at -20°C or colder at the testing facility. Additional cytokines or other biomarkers may also be evaluated based on emerging data from the study for up to 5 years after the conclusion of the study.

6.6 Pharmacokinetics

Blood samples for the measurement of PRA023 concentration are to be drawn from each subject at the time points specified in the protocol (see Section 6.1.1). Blood samples for PK analysis of PRA023 concentrations will be analyzed using a validated assay method by or under the supervision of the Sponsor. The PK blood samples will be obtained according to the study flowchart. The actual date and time (24-hour clock time) of each sample will be recorded. Instructions for the handling of the PK samples will be provided in the Laboratory Manual.

Changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and study center study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF. PK analysis will be performed as outlined in the PK section of the Statistical Analysis Plan (SAP).

6.7 Immunogenicity (Anti-Drug Antibody)

Antibodies to PRA023 will be evaluated in blood samples collected from all subjects at the time points specified in the protocol (see Section 6.1.1). The detection and characterization of antibodies to PRA023 will be performed using a validated assay method by the Sponsor or Sponsor's designee. Instructions for the handling of ADA samples will be provided in the Laboratory Manual.

Blood samples will be screened for antibodies binding to PRA023 and the titer of confirmed positive samples will be reported. If confirmed positive, antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of PRA023. Other analyses may be performed to verify the stability of antibodies to PRA023 and/or further characterize the immunogenicity of PRA023.

6.8 Pharmacogenomics

Genetic variation may impact a subject's response to study treatment, susceptibility to, and severity and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, a 4 mL whole blood and buccal (cheek) swab samples for DNA isolation will be collected from subjects at the Screening Visit for an assessment of pharmacogenomics (i.e., CDx assessment). In the event of DNA extraction failure, a replacement genetic blood and/or buccal sample may be requested from the subject during the study.

After collection, the samples are to be shipped to the Sponsor and/or the central laboratory. Instructions for the handling of pharmacogenomic samples will be provided in the Laboratory Manual. The DNA samples will be stored in a secure storage space with adequate measures to protect confidentiality. Each stored sample will be identified only by its barcode number and will otherwise not be individually identifiable.

6.9 Potential Future Research

Blood, biopsy, and DNA samples will be stored for up to 5 years after study completion (potential for storage and duration of storage may depend on local guidelines), after which all the samples will be destroyed. Blood and biopsy samples may be tested for levels of biomarker and other pharmacodynamic markers. DNA samples may be used in the future for various evaluations, including, but not limited to, the potential association between genotype and drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease.

7 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The following definitions of terms are guided by the International Conference on Harmonisation and the U.S. Code of Federal Regulations [21 CFR 312.32] and are included herein.

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

AEs include, but are not limited to:

- Any symptom or condition not previously reported by the subject (medical history).
- An exacerbation of a pre-existing symptom or condition.
- A significant increase in frequency or intensity of a pre-existing episodic event or condition.
- A drug interaction.
- A condition first detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.

An AE does not include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or blood transfusion); the condition that leads to the procedure is an adverse event (e.g., bleeding esophageal varices, dental caries).
- Overdose of either study drug or concurrent medication without any clinical signs or symptoms.

All identified AEs after signing of informed consent until 84 days after last study drug dose must be recorded and described on the appropriate non-serious or serious AE page of the eCRF. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than individual symptoms.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An adverse reaction is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Disability/incapacity that is persistent and significant

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An AE or suspected adverse reaction is considered 'unexpected' if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents. 'Unexpected,' as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

The Sponsor will determine the expectedness of serious adverse reactions and report all suspected, unexpected serious adverse reactions (SUSARs) according to statutory requirements.

7.1 Pre-Treatment-Emergent Events

Prometheus considers AEs that occur between the time the subject signs the informed consent form for the study and the time when that subject is first administered the study drug as "pre-treatment-emergent" AEs. Any pre-treatment-emergent event will be recorded as an AE but will be clearly documented as pre-treatment emergent event in the data listings.

7.2 Laboratory Abnormalities as Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an AE of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (e.g., elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However, isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the Investigator. Criteria for a "clinically significant" laboratory abnormality are:

a) A laboratory abnormality that leads to a dose-limiting toxicity (e.g., an abnormality that results in study drug dose reduction, suspension or discontinuation), or

b) A laboratory abnormality that results in any therapeutic intervention (i.e., concomitant medication or therapy), or

c) Other laboratory abnormality judged by the Investigator to be of any particular clinical concern (e.g., significant fall in hemoglobin not requiring transfusion)

For laboratory abnormalities that do not meet the above criteria but are outside of normal range (e.g., < or > normal reference range), the Investigator should indicate whether the value is clinically significant (CS) or not clinically significant (NCS) for the subject.

7.3 Grading/Severity of Adverse Events

The Investigator must define the severity of each AE using the NCI's CTCAE Version 5.0. A severity category of mild, moderate, severe, life threatening, or death as defined in Table 6 must be entered on the AE eCRF. The Investigator will consider the range of the possible severity of the event and identify the severity that is the most appropriate according to her/his medical judgment.

Table 6 Severity of Adverse Events

Grade	Clinical Description of Severity
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 or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. Note**:** An experience may be severe but may not be serious, e.g., severe headache).
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.
Note: Activities of Daily Living (ADL):
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.4 Relationship of Adverse Events

7.4.1 Relationship of Adverse Events to Study Drug Administration

The Investigator will determine if there is a reasonable causal relationship between the study drug and an AE or not. The Investigator will use her/his best medical judgment and consider all relevant factors (e.g., temporal relationship, location of the event, the subject's relevant medical history, concomitant therapies, and concurrent conditions) to determine the relationship of the AE to the study drug. 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.

The term "reasonable causal relationship" means there are facts or arguments to suggest a causal relationship (International Conference on Harmonisation (ICH) E2A).

7.4.2 Relationship of Adverse Events to Study Procedures

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.

7.5 Recording and Reporting of Adverse Events

7.5.1 Recording Adverse Events

All AEs will be recorded in the appropriate section of the eCRF. Subjects withdrawn from the study due to AEs will be followed by the Investigator until the outcome is determined and, when appropriate, additional written reports and documentation will be provided. The Investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms.

If the AE meets the definition of an SAE, or if the Investigator becomes aware of an unexpected AE event that places the subject at risk, or if there is a pregnancy at any time after the study drug administration up to the end of the study follow-up period, the event must be documented and reported.

7.5.2 Investigator Reporting of a Serious Adverse Event

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for prompt notification of serious adverse events (SAEs) to Alimentiv Clinical Safety. The Investigator (or designee) is required to complete the SAE page in the eCRF enabling transmission to Alimentiv Safety using the electronic data capture (EDC) system. In the event EDC transmission is not possible, (e.g., there are access or system problems), then the Investigator (or designee) must report the SAE to Alimentiv Clinical Safety by emailing or faxing a completed paper SAE form to:

Fax: +1 844-652-8093
Email: CCI [redacted]

All SAEs must be reported to Alimentiv Clinical Safety within 24 hours after the Investigator recognizes/classifies the event as a SAE.

The initial SAE report should include at a minimum: subject number, a narrative description of the event, and an assessment by the Investigator of the intensity of the event and relationship of the event to study drug. The initial SAE report received from the site should be as complete as possible. A complete follow-up SAE report must be submitted when information not available at the time of the initial report becomes available. The Sponsor (or designee) may request SAE follow-up information. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

The Investigator must receive acknowledgement by Alimentiv Clinical Safety that the information about the SAE has been received. In the event that the Sponsor or designee permits an alternate delegate, the Investigator and staff will be notified and provided the alternate's contact information.

The Investigator is responsible for continuing to report to the Alimentiv Clinical Safety any new or relevant follow-up information that he/she learns about the SAE.

7.5.3 Investigator Reporting of a Pregnancy

Investigator (or designee) should notify Alimentiv Clinical Safety of all pregnancies occurring after start of study drug and 12 weeks after last dose in enrolled female subjects or the female partner of male subjects.

If a pregnancy occurs, a Pregnancy Report Form should be completed by the Investigator (or designee) and submitted to Alimentiv Clinical Safety via fax to +1-844-652-8093, or by email to CCI [redacted] within 24 hours after learning of the pregnancy.

Female subjects who become pregnant must discontinue study drug, and the Investigator should evaluate the risks and benefits of continuing with the study after discussing the risks of the pregnancy and possible effects on the fetus with the subject. A determination regarding study drug discontinuation will be made for male subjects with a partner pregnancy based on risks involved by the Investigator and/or Sponsor.

Pregnancy is not regarded as an AE unless there is a suspicion that study drug may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. Female partners of male subjects are asked to sign a separate partner pregnancy informed consent form in order to collect pertinent personal and medical information regarding the status and outcome of the pregnancy.

All reports of congenital abnormalities/birth defects are considered SAEs and should be reported per Section 7.5.2. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs unless they were therapeutic abortions. The medical reason (e.g., fetal disease) for therapeutic abortion will be reported as an SAE.

7.6 Additional Investigator Responsibilities for Serious Adverse Events

The Investigator and supporting personnel responsible for subject care should discuss with the Medical Monitor any need for supplemental investigations of SAEs. The results of these additional assessments conducted must be reported to the Sponsor. If a subject dies during participation in the study and a post-mortem examination is performed, a copy of the autopsy report must be submitted to Sponsor or designee.

7.7 Post-Study Follow-Up of Adverse Events

All AEs, including a worsening of clinically significant laboratory values or physical examination findings compared with baseline values, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up.

AEs ongoing at the final visit will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes or resolves. If resolved, a resolution date should be documented on the eCRF or reported to Sponsor or designee if the eCRFs have been collected. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals as is practical.

7.8 Notification of Post-Study Serious Adverse Events

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the Investigator becomes aware of an SAE, he/she should notify Alimentiv Clinical Safety if such events are attributable to the study drug. The notification to Alimentiv Clinical Safety of a post-study SAE by the Investigator should occur within 24 hours of becoming aware of the SAE.

7.9 IRB/IEC Notification of Serious Adverse Events

The Investigator is responsible for promptly notifying her/his IRB/IEC of all SAEs, including any follow-up information, occurring at her/his site and any SAE regulatory report, including any follow-up reports that he/she receives from the Sponsor or designee.

7.10 Health Authority Safety Reports

Prometheus or its representatives will submit a safety report to appropriate regulatory agencies, for all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities in accordance with national regulations in the countries where the study is conducted. SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. Prometheus or its representatives will also prepare and distribute an expedited report for other safety issues which might alter the current benefit-risk assessment of the study drug or impact the overall conduct of the trial. Prometheus or its representatives will send copies of each safety report submitted to the regulatory agencies to the Investigators who are actively participating in Prometheus-sponsored clinical studies. Safety reports must be submitted to the appropriate IRB/IEC according to local regulations and guidelines. Documentation of the submission to the IRB/IEC must be retained for each safety report.

7.11 Data Monitoring Committee (DMC)

Prometheus will establish an independent DMC for PRA023 to oversee the benefit-risk profile in IBD and safety across the entire program. The DMC will review safety data at periodic intervals from this and all other PRA023 studies conducted by Prometheus Biosciences. Members of the DMC will not be allowed to participate as Investigators in any of the PRA023 studies.

A charter, which will include a detailed description of the scope and the extent of its responsibilities and procedures, will be implemented prior to any data review. The charter will specify how the data will be provided to the committee member (e.g., blinded, unblinded, grouped or not, etc.) for review. These documents (charter, open and closed meeting minutes, etc.) will be considered part of the study documentation, but not of this protocol. The DMC will review data within its general remit to oversee subject safety for the PR200 program and provide recommendations and guidance to the Sponsor in accordance with the procedures stated in its charter.

A formal DMC monitoring meeting will occur **prior** to the commencement of this study, where the DMC will assess all available safety data from the normal healthy volunteer study (Study PR200-101). This study will commence following the demonstration of acceptable safety profile of PRA023 at a dose of ≥ 500 mg in multiple ascending dose study in Study PR200-101.

All Investigators, responsible IRB/IECs, and applicable regulatory agencies will be informed of any decisions made by Prometheus Biosciences based on recommendations from the DMC relating to subject safety and affect the conduct of this study. The Investigators will inform the subjects of such actions and the protocol and ICF will be revised, as appropriate.

8 ASSESSMENT OF STUDY VARIABLES

The data will be analyzed by Prometheus or an official designee (e.g., a contract research organization [CRO]).

8.1 Randomization

This is an open-label study where all subjects will receive PRA023. Eligible subjects will be assigned a subject randomization 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 re-randomized in OLE will retain their original subject numbers.

8.2 Justification of Sample Size

The planned sample size is 50 subjects, which will provide a statistical power of 80% to test against the null hypothesis of endoscopic improvement rate of 12%, at 1-sided significance level of 0.025, 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 (Table 7).

Table 7 Placebo Endoscopic Response Rates in Recent CD Clinical Trials

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

8.3 Evaluation of Safety Variables

Data will be summarized with respect to safety observations. Monitoring of AEs, physical examinations, vital signs, ECGs, safety and tolerability monitoring evaluations, clinical laboratory evaluations, and special procedures are detailed in Section 6.3.

All available safety data for all randomized subjects who receive at least one dose of PRA023 will be included in the safety analysis, which will be primarily descriptive.

The safety variables will be:

- Hematology, chemistry, and urinalysis
- Vital signs
- ECG parameters
- Physical examination
- AEs and SAEs
    - AEs of special interest: infections, acute infusion reaction (within 1 hour of completion of infusion), and peri-infusion reaction (within 24 hours of completion of infusion)
    - AEs in subjects who are ADA positive

9 STATISTICAL METHODOLOGY

This section describes the statistical analysis as it is foreseen at the time of planning the trial. Statistical methods will be further detailed in the SAP. The SAP will provide details about methods of analysis and the specific planned analyses, and will be prepared and approved by Prometheus Biosciences and its designees before study database lock.

Any deviations from the analysis plan, and the reasons for such deviations, and all alternative or additional statistical analyses that may be performed will be justified in the clinical study report.

No formal statistical evaluation will be applied to the safety and tolerability variables. However, a clinical interpretation will be made based on the side effect profile to judge the safety of PRA023. All individual data as well as results of statistical analyses will be presented in individual subject data listings and statistical summary tables. In general, continuous variables will be summarized using the following standard descriptive summary statistics: number of observations, arithmetic mean, standard deviation (SD), coefficient of variation (CV), minimum, median, and maximum. The geometric mean (GM) will be reported for PK and PD variables where appropriate. Categorical data will be summarized as number and percentage of subjects. Shift tables will be provided, where appropriate.

9.1 Analysis Populations

9.1.1 Safety Analysis Set (SAS) Population

All subjects who received at least one dose of the study drug will be included in the safety evaluations.

9.1.2 Full Analysis Set (FAS) Population

The FAS population will be a subset of the Safety population and will include all subjects who have been treated with PRA023 with Baseline SES-CD scores.

9.2 Statistical Analyses

9.2.1 Demographics and Baseline Characteristics

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.

9.2.2 Evaluation of Efficacy Parameters

The primary efficacy endpoint, endoscopic improvement at Week 12, will be used to assess the efficacy of PRA023. The proportion of subjects in the per-protocol population with endoscopic improvement at Week 12 will be tested against the null hypothesis of 12%, an observed placebo

rate from multiple CD trials. Chi-square test will be used with a 1-sided significance level of 0.025. If significant, the 1st secondary endpoint of proportion of subjects in FAS achieving clinical remission will be tested against the null hypothesis of clinical remission rate of 16% (an observed remission rate for the placebo treated patients from multiple CD trials (AbbVie 2021, Feagan 2017, Sands 2019, Selinger 2018, Vermeire 2017).

The point estimates for the primary and secondary endpoints will be calculated along with 95% confidence interval for FAS and by CDx status (CDx+ or CDx-).

9.2.3 Evaluation of Pharmacodynamic Parameters

The PD markers, circulating cytokine levels, will be summarized using descriptive statistics: N, mean, SD, min, max, median, coefficient of variation as a percent (CV %), and GM by CDx status.

Any p-values that will be calculated according to the analysis plan will be interpreted in view of the exploratory nature of the study.

9.2.4 Evaluation of Immunogenicity

The proportion of samples positive for ADA and the proportion of subjects with any sample positive for ADA will be summarized by dose, when appropriate, 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.

9.2.5 Evaluation of Exploratory Parameters

Changes from baseline in exploratory PD parameters will be computed, as appropriate. All exploratory parameters will be summarized using descriptive statistics. Graphs of change from baseline will be presented, as appropriate.

9.2.6 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, SD, min, max, median, CV %, and GM and GM CV%. Serum concentrations of PRA023 will be summarized.

9.2.7 Evaluation of Safety Parameters

9.2.7.1 Adverse Events and Adverse Events of Special Interest

All AEs will be coded using most current version of Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events will be assigned to the SOC and PT according to MedDRA. The number and percentage of subjects reporting AEs (all, serious, related) will be

tabulated by overall and treatment. AEs will be summarized by SOC and PT. AEs will also be summarized by relationship to the study drug, seriousness, and severity.

A treatment-emergent AE (TEAE) will be defined as an AE that began or worsened on or after the first treatment dose. 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.

9.2.7.2 Medical History, Chest X-ray, ECGs and Physical Examination

Medical history, chest x-ray, ECGs, and physical examination data will be listed by subject. All medical history will be coded using the most current version of MedDRA. Changes in ECGs and physical examination will be described in the text of the final study report.

9.2.7.3 Clinical Laboratory and Vital Signs

All clinical laboratory results and vital signs measurements, and their change from baseline, will be summarized by time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

9.2.7.4 Previous and Concomitant Medication

All previous and concomitant medication will be listed by subject. Prior and concomitant medications will be coded using the most current World Health Organization – Drug Dictionary (WHO-DD).

10 ETHICS AND REGULATORY REQUIREMENTS

10.1 General Requirements for Study Conduct

The Investigator or designee is responsible for ensuring that the study is conducted in accordance with the clinical protocol and is in full compliance with regulatory requirements; the basic principles outlined in 21 CFR Parts 50, 54, 56, and 312; ICH-guidelines for Good Clinical Practice as published in the Federal Register on May 9, 1997; and the Declaration of Helsinki.

The Investigator is also responsible for protecting the rights, safety, and welfare of subjects under the Investigator's care and for the control of study device under investigation.

The Investigator(s) (and sub investigators) will provide the Sponsor with her/his/their up-to-date scientific Curriculum Vitae (signed and dated) prior to start of the study and when new site personnel are added once the study commences.

10.2 Regulatory and Institutional Review Board Approval/ Independent Ethics Committee

Regulatory approval will be obtained from the appropriate regulatory authority prior to initiation of the study protocol.

The Investigator is responsible for obtaining IRB/IEC approval for the study protocol and the subject informed consent form. A copy of the dated approval letter from the IRB/IEC stating the study title, and/or study number must be provided to the Sponsor before the start of screening and release of supplies. A list of the names of the committee members will be obtained for the Sponsor's and Investigator's records.

10.3 Written Informed Consent

The Investigator will inform the subject of the nature, risks, and purpose of the study. A written informed consent form will be provided to each subject describing the study information. The consent must be reviewed and approved by IRB/IEC before use in the study. Each volunteer must sign and date this form prior to their participation in the study. A signed original consent form for each subject will be kept on file at the clinical site. A copy of the signed consent will be provided to the subject.

10.4 Confidentiality

The Investigator at each site and its designees, employees, and agents involved with the study will comply with relevant state and federal laws relating to confidentiality, privacy, and security of subject's health information. Confidential data may be disclosed to the Investigator and employees, sponsor, IRB/IEC, FDA, or other authorized representatives during the course of the

study or when requested. Information will remain confidential and will not be used for any purpose other than the type of review requested.

10.5 Protocol Modification/Amendments

Sponsor modifications made to the experimental design, study parameters, subject selection, or any other content in the protocol will be communicated with a protocol amendment(s) to the investigator, FDA and other regulatory agencies for review and approval. All amendments will require IRB/IEC review and approval prior to implementation.

10.6 Direct Access to Source Data/Documents

Investigator will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents.

11 DEFINITION OF END OF TRIAL

11.1 End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (i.e., clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

11.2 End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

12 DATA MANAGEMENT

Data will be handled and processed according to CRO's SOPs, which are written based on the principles of GCP. At all times, appropriate backup copies of the database and related software files will be maintained and the information will be appropriately protected from unauthorized access.

The eCRF development will be based on the study protocol. All eCRF data, including laboratory data, will be included in an integrated database. At the end of the study when the database is deemed clean, the integrated database will be locked (i.e., all data entry, quality control, database edits, medical coding, SAE reconciliation complete). The data will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations.

eCRFs will be kept for each subject and will document all study data. The eCRFs must be completed for each subject to allow the progress and results of the study to be closely followed by the study monitor.

The study monitor or designee will review the eCRFs for completeness and accuracy via Source Document Verification. Study written ICFs and all study specific logs will be verified for completeness, accuracy, and plausibility.

12.1 Coding of Adverse Events, Concomitant Medication, and Medical History

After data entry, the AEs and medical history will be coded according to the MedDRA®. Where required, concomitant medication will be coded according to the WHO-DD. The versions of MedDRA® and WHO-DD used in the study will be specified in the data management plan (DMP).

13 DOCUMENTATION AND ADMINISTRATIVE CONSIDERATIONS

13.1 Recordkeeping

All essential documents specific to the study (including study file, source documentation, copies of eCRF, etc.) should be retained by the Investigator until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 25 years have elapsed since completion of this clinical trial. These documents should be retained for a longer period if required by the applicable regulatory authority or if needed by the Sponsor.

Every reasonable effort should be made by the Investigator to retain records enabling the follow up of subjects who have received study medication. The Investigator should notify the Sponsor and obtain approval prior to destroying any material retained from the study.

13.2 Disclosure of Data

The Investigator agrees not to disclose data from this study without the prior written approval of the Sponsor.

13.3 Publication Policy

It is intended that the results of the study may be published as scientific literature. Results may also be used in submissions to regulatory authorities. The following conditions are to protect commercial confidential materials (patents, etc.), not to restrict publication.

All information concerning the product subsequently generated from this study (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the investigator by the Sponsor and not previously published) is considered confidential by and shall remain the sole property of the Sponsor. The Investigator agrees not to use it for other purposes without the Sponsor's written consent.

It is understood by the Investigator that the Sponsor will use the information developed in this clinical study in connection with the development of PRA023 and, therefore, may be disclosed as required to other Sponsor investigators or any appropriate international regulatory authorities. In order to allow for the use of information derived from this clinical study, the Investigator understands that he or she has an obligation to provide the Sponsor with complete test results and all data developed during this study.

Prior to submitting the results of this study for publication or presentation, the Investigator will allow the Sponsor 60 days in which to review and comment upon the publication manuscript. In accordance with generally recognized principles of scientific collaboration, co authorship with any Sponsor personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher. The publication of study data may not be performed without the written prior approval of the Sponsor, and this approval shall not be unreasonably withheld.

During the period for review of a proposed publication from the Investigator, the Sponsor shall be entitled to make a reasoned request to the Investigator that publication be delayed for a period of up to 6 months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its proprietary information, and the Investigator shall not unreasonably withhold consent to such a request. Any intended joint publication must precede any proposed individual publication.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The study monitor will maintain a close liaison with the investigational site to clarify any problems that may arise, and to ensure that the Investigator is following the protocol. This liaison may consist of personal visits before the study is initiated and at appropriate intervals during the study and will include communications via telephone, facsimile, email, and letter. During site monitoring visits, information recorded on the eCRFs will be verified against source documents.

The Investigator agrees that Prometheus, its employees or agents, and regulatory health authorities will have the right from time to time, both during and after the course of this study, to audit and review medical records relating to this study.

A statement will be obtained from each subject participating in the study permitting the release of his/her medical records as necessary for inspection by authorized personnel of Prometheus, the FDA, and/or other regulatory health authorities.

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16 APPENDIX

16.1 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.

Ulcers - scored according to size

0 = no ulcers

1 = aphthous (0.1 - 0.5 cm)

2 = large (0.5 - 2 cm)

3 = very large (> 2 cm)

Proportion of the surface covered by ulcers according to extent

0 = none

1 = < 10%

2 = 10 - 30%

3 = > 30%

Proportion of affected surface with any other lesions according to extent

0 = unaffected segment

1 = < 50%

2 = 50 - 75%

3 = > 75%

Stenosis (single or multiple, and whether the colonoscopy could pass through the narrow lumen)

0 = none

1 = single, can be passed

2 = multiple, can be passed

3 = cannot be passed

16.2 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 (modified from Best 1976). 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.

16.3 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