STUDY PROTOCOL

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Protocol No.: RCT01519
NCT No.: NCT05230173

Treat-to-Target of Endoscopic Remission in Patients with IBD in Symptomatic Remission: The QUOTIENT Trial

Protocol Version 05
04 December 2025

Sponsor: Mayo Clinic Arizona
13400 E Shea Blvd
Scottsdale, AZ 85259

Collaborators: Baylor College of Medicine
1 Baylor Plaza
Houston, TX 77030, USA

Crohn's & Colitis Foundation
733 Third Ave, Suite 510
New York, NY 10017, USA

Clinical Research Organization: Alimentiv Inc.
800 Collip Circle, Suite 104
London, Ontario, Canada
N6G 4X8

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PROTOCOL APPROVAL PAGE

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Protocol Version 05
04 December 2025



Electronically signed by: Siddharth Singh
Reason: I have reviewed/verified this document
Date: Dec 10, 2025 13:15:53 MST

Siddharth Singh, MD
Co-Primary Investigator
Mayo Clinic Arizona

Date



Electronically signed by: Jason Hou
Reason: I have reviewed/verified this document
Date: Dec 11, 2025 14:11:49 CST

Jason K. Hou, MD
Co-Primary Investigator
Baylor College of Medicine

Date



Electronically signed by: Vipul Jairath
Reason: I have reviewed/verified this document
Date: Dec 13, 2025 07:26:35 EST

Vipul Jairath, MD PhD
Co-Investigator
Western University, London, ON

Date



Electronically signed by: GY Zou
Reason: I have reviewed/verified this document
Date: Dec 13, 2025 08:37:34 EST

GY Zou, PhD
Co-Investigator
Western University, London, ON

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Protocol Version History	
Document	**Date**
Version 01	11 February 2022
Version 02	12 May 2022
Version 03	12 September 2023
Version 04	14 December 2023
Version 05	04 December 2025

Summary of change(s)	Rationale for change	Revised section(s)
Updated Sponsor information.	The Principal Investigator has changed professional affiliation from University of California San Diego (UCSD) to Mayo Clinic Arizona.	Cover page and signature page; Section 8.3 (Data Management).

Summary of change(s)	Rationale for change	Revised section(s)
Revised sample size enrollment from 250 to 216 in tandem with a revision to the number of participants followed for 1 year, 18 months, and 2 years. Number of sites in the US is now 25.	Revised sample size calculations based on recent work from Ben-Horin et al with input from Patient-Centered Outcomes Research Institute (PCORI) and the Data Safety Monitoring Board (DSMB). While acknowledging that a reduced sample size may carry some risk of insufficient power to detect smaller but potentially important treatment effects, the DSMB endorsed the revised sample size in light of recruitment challenges and the importance of completing the trial within the funded timeline. The DSMB also recognized that most outcome events in this trial have occurred within the first 12 months post-randomization. Accordingly, they suggested that continuing to enroll beyond a sample size of 156 patients followed completely for 2 years, to a number closer to 250 (as originally proposed) with a shorter albeit variable follow-up (1-2 years, rather than strictly 2 years) would augment the power of the study as set up as a time-to-event outcome. ▪ 156 patients will be followed fully for 2 years ▪ 60 patients will be followed variably for 1-2 years (approximately 30 patients followed for 18 months, and 30 patients followed for 12 months.	Protocol Synopsis (Study Design and Study Population), Figure 2 (Overview of Trial), and Sections 3.1 (Overall Study Design), 3.2.2 (Site Selection), 3.3 (Study Population), 4.3.2.3 (End of Study), and 6.1 (Sample Size Determination).
Added language that the data that is collected on this trial will be securely stored and will be maintained by Mayo Clinic Arizona and will remain available for future research.	Harmonization with Mayo Clinic Arizona requirements.	Section 7.4 (Confidentiality of Participant Records).
Adjusted time interval for retention of study records	Harmonization with Mayo Clinic Arizona requirements.	Section 8.6 (Retention of Study Documents).
Minor editorial, formatting, or consistency changes.	Not applicable.	Throughout.

INVESTIGATOR AGREEMENT

Treat-to-Target of Endoscopic Remission in Patients with IBD in Symptomatic Remission: The QUOTIENT Trial

I have read the protocol and agree that it contains all necessary details for carrying out this trial.

I undertake to conduct this trial within the time designated.

I understand that all information supplied to me by the sponsor in connection with this trial and not previously published is considered confidential information.

The information includes the clinical protocol, the case report form, and technical methodology. I agree that documents and other data pertinent to this trial are the property of the sponsor.

Furthermore, I understand that any changes in the protocol must be approved in writing by the sponsor.

By my signature below, I hereby attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in the above protocol.

Investigator:

Name and Title	Signature	Date

Name, Address, and Telephone Number of Investigational Site:

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PROTOCOL SYNOPSIS

Title

Treat-to-Target of Endoscopic Remission in Patients with IBD in Symptomatic Remission

Objectives

The purpose of this study is to compare the effectiveness and safety of a strategy of switching to an alternative targeted immunomodulator (TIM) therapy to treat to a target of endoscopic remission, versus continuing index TIM in patients with inflammatory bowel disease (IBD) (Crohn's disease [CD] or ulcerative colitis [UC]) in symptomatic remission with moderate to severe endoscopic inflammation despite optimization of index TIM in a real-world setting.

The objectives of this study are:

1. To compare the effectiveness of switching to an alternative TIM to treat to a target of endoscopic remission versus continuing index TIM in asymptomatic patients with IBD with ongoing endoscopic inflammation.
2. To compare the burden and safety of switching to an alternative TIM to treat to a target of endoscopic remission versus continuing index therapy in asymptomatic patients with IBD with ongoing endoscopic inflammation.
3. To identify heterogeneity of treatment effects, through preplanned subgroup analyses.

Study Design

Overall Study Design

This is a pragmatic, open-label, multicenter randomized controlled trial (RCT) conducted in asymptomatic patients with IBD who have persistent moderate to severe endoscopic inflammation despite optimization of index TIM. This study plans to enroll 216 participants in the United States and Canada, who will either switch to treatment with alternative TIM to treat to a target of endoscopic remission or continue index-optimized TIM. After randomization, participants will be followed prospectively within routine clinical practice over 2 years (104 weeks); 156 patients will be followed for the full 104 weeks, whereas 60 patients will be followed for a variable time period between 52 to 104 weeks.

This trial will be conducted within select sites in the United States and Canada.

The primary outcome will be time from randomization to treatment failure, as a composite of:

1) Moderate-severe symptomatic relapse based on PRO2 (2-item patient reported outcome), with objective confirmation of inflammation within 2 months of event (fecal calprotectin [FC] >150 mcg/g, or C-reactive protein [CRP] >5mg/L, or endoscopy showing moderate-severe inflammation, or magnetic resonance enterography [MRE]/computed tomography enterography [CTE]/intestinal ultrasound [IUS] showing active inflammation) with need for escalation of therapy;
2) Need for rescue therapy with corticosteroids for a documented symptomatic IBD flare;
3) IBD-related hospitalization;
4) IBD-related surgery;
5) IBD-related structural complications (CD: symptomatic stricture, fistula, or abscess; UC: symptomatic stricture);
6) Treatment-emergent adverse event requiring drug discontinuation.

Secondary outcomes will include treatment failure as defined in the composite primary outcome (binary outcome) and time from randomization to each of the components in the primary outcome (time to event outcome), quality of life (overall quality of life, fatigue, IBD-related disability), burden of treatment (financial burden, burden of monitoring, treatment side effects), treatment satisfaction, and safety.

In compliance with the pragmatic methodology of this study embedded in routine clinical care, there is no study visit mandated per study protocol. Participant visit schedules will follow local standard of care (SOC) with any additional visits at the treating physician's discretion. Data on all effectiveness, treatment burden, and safety outcomes will be captured using a REDCap (Research Electronic Data Capture) database hosted at the Crohn's and Colitis Foundation. Data for the study will be extracted from medical record information and entered into REDCap at baseline and then approximately every 6 months (at a minimum) thereafter, up to a 2-year follow-up period. Patient-reported outcome (PRO) measures (self-assessment questionnaires) will be utilized in this study to

determine primary (efficacy) and secondary (quality of life and treatment burden and satisfaction) outcomes. Participants will complete the PRO2 at baseline and approximately every 12 weeks during a 2-year follow-up period; additional questionnaires (IBD-Control, PROMIS-7, Short Inflammatory Bowel Disease Questionnaire [SIBDQ], the IBD Disability Index for self-report [IBD-DI-SR], Treatment Burden Questionnaire [TBQ], Treatment Satisfaction Questionnaire for Medication [TSQM], and Costs for Patients Questionnaire [CoPaQ]) will be completed at baseline (following randomization) and up to 3 additional times during a 2-year follow-up period.

Data Source and Collection

eCRFs will be designed to capture the data needed for the study that are collected as part of local SOC of the study participants. Clinical information recorded in the patients' medical record will be entered into the relevant eCRFs within the REDCap electronic data capture (EDC) system. As well, participants will complete the PRO questionnaires throughout the study and the patient-reported survey. Patients consenting to participate in this study will agree and authorize the release of their electronic medical record data to be stored on a secure platform. A full data set will be extracted from REDCap and transferred for analysis every 6 months.

DSMB Review

A Data Safety Monitoring Board (DSMB) will be established for this study. The DSMB will regularly review unblinded data every 6 months (interim data) to monitor safety and effectiveness and provide recommendations to the trial management group to ensure that participants are not exposed to undue risks. Reports for DSMB review will be formulated in accordance with the DSMB charter.

Study Population

The study population will include patients with IBD (UC or CD) with persistent moderate to severe endoscopic inflammation despite optimization of index TIM. The study will aim to enroll 216 adult patients, ≥ 18 years of age, from approximately 25 or more sites in the United States and approximately 6 or more sites in Canada.

Inclusion criteria:

Participants must meet all the following criteria for enrolment into the study:

1. Male or nonpregnant, nonlactating females, ≥ 18 years of age.
2. An established diagnosis of CD or UC for at least 6 months based on standard clinical criteria, confirmed by the treating provider.
3. Current treatment with an approved TIM for treatment of IBD, including biologic agents (e.g., tumor necrosis factor-α [TNFα] antagonists, ustekinumab, vedolizumab) and small molecule inhibitors (e.g., Janus kinase inhibitors, ozanimod), including future TIMs that become commercially available during the conduct of the trial.
4. Dose of TIM should be stable for 3 or more months prior to qualifying endoscopy/radiology. No treatment escalation of TIM or addition of IMMs, corticosteroids, or mesalamines after the qualifying endoscopy/radiology procedure up to randomization is permitted. Dose de-escalation after qualifying procedure is permissible at the discretion of the treating provider.
5. In corticosteroid-free symptomatic remission based on validated PROs (PRO2 score) and deemed to be experiencing no other IBD-related symptoms in the opinion of the treating provider. Includes patients who may be in medically induced remission (on index TIM); or surgically induced remission with post-op initiation of index TIM for prophylaxis and endoscopy/imaging performed at least 3 months after initiation/optimization of TIM showing moderate-severe bowel inflammation. Validated PROs are defined as:
    a. CD: PRO2 (2-item patient reported outcome) mean daily score of abdominal pain score ≤1 and stool frequency score ≤ 3; or
    b. UC: PRO2, with absence of rectal bleeding (rectal bleeding score = 0) and with stool frequency score ≤1.
6. Evidence of moderate to severe bowel inflammation on local reading of colonoscopy, flexible sigmoidoscopy or balloon-assisted enteroscopy, capsule endoscopy, MRE, CTE, or IUS, performed within 6 months prior to screening, defined at the investigator's discretion or as follows:
    a. CD: Colonoscopy showing moderately to severely active inflammation based on **1** of the following variables/scores:

- Simple Endoscopic Score for Crohn's Disease (SES-CD) score ≥7 or score ≥4 for those with isolated ileal disease, or
- Presence of mucosal ulcers >5 mm in size if SES-CD has not been recorded, or
- Simplified Endoscopic Mucosal Assessment for Crohn's Disease (SEMA-CD) score ≥2, or
- Rutgeerts score i2b or higher for patients in surgically induced remission with post-operative endoscopic recurrence [Note, either SES-CD or Rutgeerts score can be used for participants with post-operative recurrence]; or

b. CD: MRE or CTE showing moderately to severely active inflammation based on **1** of the following variables:
   - Increased bowel wall thickness, or
   - Mural hyperenhancement, or
   - Peri-enteric fat stranding, or
   - Radiographic features of ulceration, or
   - Intramural T2 signal on fat suppressed images; or

c. CD: Capsule endoscopy showing moderate to severely active small bowel disease based on Lewis score >790 (in case the disease is not accessible via endoscopy), or per local endoscopist's impression if Lewis score is not reported; or

d. CD: IUS showing at least **1** of the following variables:
   - Increased bowel wall thickness >5 mm, or
   - Color doppler score >5/cm^2, or
   - Bowel stenosis, or
   - Bowel stratification, or
   - Fatty wrapping; or

e. UC: modified MES of 2 to 3, or documentation of any endoscopic features that would define a MES of 2 to 3 (e.g., friability, ulceration, spontaneous bleeding, complete loss of vascular pattern), if an MES has not been recorded.

7. Eligible to receive at least 1 alternative TIM (excluding their index TIM) for the treatment of their disease per approved drug label, based on clinical and reimbursement guidelines.
8. Able to participate fully in all aspects of this clinical trial.
9. Informed consent must be obtained and documented.

Exclusion criteria:

Participants who exhibit any of the following conditions are to be excluded from the study:

1. Presence of ostomy or ileoanal pouches.
2. Serious underlying disease other than UC or CD that in the opinion of the investigator may interfere with the participant's ability to participate fully in the study.
3. History of alcohol or drug abuse or any other medical or health condition that in the opinion of the investigator may interfere with the participant's ability to comply with the study procedures.
4. Prior enrolment in the current study.
5. Mild endoscopic disease activity, where treating providers would not consider switching TIM.

Treatments, Dosage, and Administration

Randomization (to a strategy of switching TIMs or continuing index TIM treatment) will be centrally generated and provided to sites. Patients randomized to a strategy of switching TIMs will be switched to 1 of the preferred agents recommended by clinical guidelines and covered by the patients' insurance formulary as part of routine care, and at the discretion of the site investigator and treating provider. No study-related medications will be provided.

Patients (and their providers) in either treatment arm will be allowed to stop or start new TIMs and other IBD-directed therapies in case of symptomatic relapse or intolerance to therapies, at the discretion of the treating provider-patient team.

Effectiveness Outcomes

Primary – Clinical status:

- Time to treatment failure, as a composite of: (1) moderate-severe symptomatic relapse based on PRO2, with objective confirmation of inflammation within 2 months of event (FC >150 mcg/g, or CRP >5mg/L, or endoscopy showing moderate-severe inflammation, or MRE/CTE/IUS showing active inflammation) with need for escalation of therapy; (2) need for rescue therapy with corticosteroids for a documented symptomatic IBD flare; (3) IBD-related hospitalization; (4) IBD-related surgery; (5) IBD-related structural complications (CD: symptomatic stricture, fistula or abscess; UC: symptomatic stricture); (6) treatment-emergent adverse event requiring drug discontinuation

Secondary – Clinical status:

- Treatment failure, as defined in the composite primary outcome, at 104 weeks
- Time to each individual component of the composite primary outcome

Secondary – Quality of life

- Scores of the SIBDQ
- Scores of the IBD-Control
- Scores of the PROMIS-7 scale
- Scores of the on IBD-DI-SR

Treatment Burden/Satisfaction and Safety Outcomes

Secondary – Treatment burden/satisfaction

- Scores of the TBQ, including medication, time and administrative, lifestyle change, social life, and financial burden
- Scores of the TSQM, measuring treatment satisfaction across domains of effectiveness, side effects, convenience, and global satisfaction
- Scores of the CoPaQ, including out-of-pocket costs, for management of IBD, including treatment, monitoring, outpatient visits, and any unplanned healthcare utilization

Secondary – Safety

- Treatment-related serious adverse events (SAEs) or unexpected SAEs
- Serious infections, defined as infections requiring hospitalization and/or intravenous antibiotics

Statistical Methods

Analysis Sets

The primary analysis will be based on all patients who are randomized to a strategy of switching to an alternative TIM to treat to a target of endoscopic remission versus continuing index therapy ("full analysis set "), in an intention-to-treat (ITT) principle. Patients randomized to switching TIMs who are unable to switch due to insurance denial will be analyzed in the treatment group they were assigned to, in ITT analysis.

Secondary analyses will be conducted based on the "modified ITT (mITT) analysis set" (patients randomized to switching who receive at least 1 dose of the alternative TIM). In both the primary and secondary datasets, participants who drop out after randomization (in 'full analysis/ITT set') and receipt of first dose of alternative TIM (in 'mITT analysis set') will be considered censored. Participants randomized to switching TIMs who are unable to switch will also be considered censored, in mITT analysis.

Participants will also be analyzed in a "per-protocol (PP)" analysis (participants who continue in the group they were allocated to after randomization, throughout the study until study end or until they meet the primary outcome, whichever comes first). The PP analysis will exclude participants who were switched to an alternative TIM from the continuation arm at their providers' discretion in the absence of patient-related symptoms).

Outcome Analysis

For the primary composite outcome between-group comparisons will use the Mantel log rank test, with magnitudes of treatment quantified by hazard ratios obtained from Cox proportional hazard regression analysis. Alternatively, the win probability by treatment will also be estimated to account for outcome hierarchy of surgery, hospitalization, structural complication, severe symptoms, and adverse events.

For secondary outcomes, Cox proportional hazard analysis (for time-to-event outcomes), the modified Poisson regression (to estimate risk ratio and 95% confidence interval for binary variables), and direct-likelihood linear mixed effects model analyses (for continuous data) will be performed. These analyses will be repeated in the PP analysis set. All analyses will be adjusted for stratification factors used in the randomization. Nonparametric methods will also be used to estimate win probabilities by treatment for binary, ordinal, counts, and continuous outcomes.

After 30 participants in each arm have reached the 24-week assessment, the statistician will perform an interim analysis of effectiveness and safety outcomes for DSMB review (to be reviewed in the corresponding 6-month meeting or at an ad hoc meeting as required and dependent on timing). Any recommendations from the DSMB will be communicated to the trial leadership committee for consideration.

Reasons for participant drop out and missing data will be recorded. For the primary composite outcome, time-to-event analysis will be performed and participants lost to follow-up will be censored. For secondary continuous outcomes, mixed effects model analyses will be conducted to allow for data missing at random.

STUDY SCHEDULE

	Baseline		Follow-up Observation Period								EOS/ ED	UNS [17]
Week	**SCR (-8 to 0)**	**RAND**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**104**	**NA**
EDC (site data collection) (±4 weeks) [1, 2]	**x**	**x**		**x**		**x**		**x**			**x**	**x**
Eligibility screen [3, 4]	x											
Informed consent	x											
Assess inclusion/exclusion criteria	x											
SOC Assessments												
Lower endoscopy/imaging [5, 6, 7]	(x)		(x)								(x)	(x)
Demographics		(x)										
Medical, disease, and surgical history (IBD-related), and comorbidities		(x)										
Prior and concomitant IBD-related medications and TIM treatment details [8]		(x)	(x)								(x)	(x)
Clinical laboratory tests (FC, CRP) [5]		(x)	(x)								(x)	(x)
Safety information [9]		(x)	(x)								(x)	(x)
Trial-related activities												
Confirm inclusion/exclusion criteria [10]		x										
Randomization (continuing index TIM or switching to alternative TIM) [11]		x										
Local outcome assessment [12, 13]		x	x								x	x
Central adjudication of outcomes [12, 13]			x								x	x
Protocol/treatment strategy compliance [8]		x	x									x
Patient-reported outcomes [14]												
PRO2 (3-day recall) [15]	x	x	x	x	x	x	x	x	x	x	x	x
SIBDQ		x		x		x					x	
IBD-Control		x		x		x					x	
PROMIS-7		x		x		x					x	
IBD-DI-SR		x		x		x					x	
TBQ		x		x		x					x	
TSQM		x		x		x					x	
CoPaQ		x		x		x					x	
Patient Survey [16]		x	x	x	x	x	x	x	x	x	x	x

Abbreviations: CoPaQ; Costs for Patients Questionnaire; CRP, C-reactive protein; ED, early discontinuation; EDC, electronic data capture; EOS, end of study; FC, fecal calprotectin; HRU, healthcare resource utilization; IBD, inflammatory bowel disease; IBD-DI, IBD Disability Index for self-report; MES, Mayo endoscopic subscore; NA, not applicable; PRO, patient-reported outcome; PRO2, 2-item patient-reported outcome measure; PROMIS-7, Patient-Reported Outcomes Measurement Information System (Fatigue – Short Form 7a); RAND, randomization; SCR, screening; SES-CD, Simple Endoscopic Score for Crohn's Disease; SEMA-CD, Simplified Endoscopic Mucosal Assessment for Crohn's Disease; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; SOC, standard of care; TBQ, Treatment Burden Questionnaire; TIM, targeted immunomodulator; TSQM, Treatment Satisfaction Questionnaire for Medicine; UNS, unscheduled.

Note, as a pragmatic trial being conducted within usual clinical practice, comparing 2 commonly accepted treatment strategies, *no trial-related endoscopies, medications, or laboratory assessments are mandated*. "X" denotes trial-mandated activities, and "(X)" denotes timing of tests and endoscopies performed within typical clinical practice which will be used for the study when and as performed. *Note, no trial mandated endoscopies will be performed*.

1 Clinical information will be recorded in the patient's records during standard of care (SOC) treatment/clinical visits; however, data entry into the electronic data capture (EDC) system (REDCap) will occur at baseline and approximately every 6 months (±4 weeks) thereafter up to a 2-year follow up period.
2 Patients that meet the primary trial outcome will continue to be monitored until the end of the data collection period (i.e., 2 years following randomization) for major IBD-related health outcomes (information on clinical remission or relapse, IBD-related hospitalization, IBD-related surgery, and/or structural complications due to IBD). This information will be completed by site investigators using a simplified eCRF every 6 months. Patients who discontinue TIM and do not switch to another will be asked to complete the PROs at the time of discontinuation but will not be required to complete any subsequent PRO questionnaires.
3 During the prescreening process (eligibility screen), investigators will identify potentially eligible participants at point of care considering endoscopic remission status, current IBD medications, and plan for treat-to-target of endoscopic remission (switching to an alternative TIM or continuing index TIM). The project team will also review data reports from study sites and will reach out to local site investigators to facilitate trial recruitment. Local site investigators will approach potentially eligible patients for consent to participate in this trial. Consent may be obtained by trained research personnel other than the treating physician. Collection of baseline data is to occur once informed consent has been obtained.
4 Prior to randomization (during the prescreening process), relevant medical history required for stratification will be collected (i.e., CD or UC diagnosis, prior TIM treatment); detailed demographics will be collected from the patient's medical records following randomization.
5 Endoscopy/imaging results and clinical laboratory results (CRP and FC) will be collected if/when they are performed in the context of routine clinical care; no trial related endoscopies or assessments will be performed. Baseline data will be collected for the most recent SOC assessments that occurred within 6 months prior to informed consent. If multiple endoscopy/imaging procedures have been performed in the preceding 6 months, then the most recent qualifying procedure will be captured.
6 The screening endoscopy/imaging assessment (colonoscopy, flexible sigmoidoscopy or balloon-assisted enteroscopy, capsule endoscopy, MRE, CTE, or IUS) with evidence of moderate to severe bowel inflammation within 6 months prior to screening.
7 Participants randomized to switching TIM to pursue a target of endoscopic remission typically undergo SOC endoscopy to assess resolution of inflammation 6 to 9 months after treatment switching, followed by optimization of switched TIM in case of failure to achieve endoscopic remission. Results will be documented in the EDC. Ultimately, participants randomized to continuation of index TIM will undergo testing for resolution of inflammation at the discretion of the treating provider-patient team.
8 Medication records of randomized participants and a physician-reported survey will be used to assess adherence to the selected treatment strategy. Investigators will be asked to document if the treatment strategy is being followed and the reasons for any deviations from treatment strategy implementation. See Section 4.2.2.
9 Safety information reported during SOC treatment/clinical visits will be collected from medical records (captured using REDCap); patient-reported safety events (reported via patient survey and/or PRO questionnaires) will be confirmed against the patient medical records.
10 Confirm inclusion criterion #5 "corticosteroid-free symptomatic remission based on validated PROs (with 3-day recall)" defined as CD: PRO2 mean daily score of abdominal pain score ≤1 and stool frequency score ≤ 3; or UC: PRO2, with absence of rectal bleeding (rectal bleeding score = 0) and with stool frequency score ≤1.
11 Eligible and consenting patients will be randomized to a treatment strategy of switching to an alternative TIM to treat to a target of endoscopic remission versus continuing index TIM. Participants randomized to a strategy of switching TIM will be switched to 1 of the preferred agents recommended by clinical guidelines and covered by the patients' insurance formulary as part of routine care by the site investigator and treating provider. No study-related medications will be provided. Participants randomized to switching TIMs, who are unable to switch due to insurance denial will be analyzed in the treatment group they were assigned to, in intent-to-treat (ITT) analysis.
12 If a participant self-reports symptomatic relapse through the PRO questionnaires and/or patient survey or during a SOC visit, and in the primary treating physician's opinion meets the primary trial outcome, the event will be reported to the study team, and will be promptly reviewed by independent blinded central adjudicators as per the Study Adjudication Charter. If the relapse is reported during an SOC visit, participants will be asked to complete the PRO2 (with 3-day recall) at the time of self-report.
13 Completion of endoscopic disease activity assessments (e.g., SES-CD or SEMA-CD, or MES) will be at the discretion of the treating physician and will be completed as per local SOC.

14 Participants will require internet access as the questionnaires are administered electronically through an online portal (via REDCap™). For participants unable to utilize the online questionnaires, paper versions of questionnaires will be provided. Questionnaires should still be completed, even if they are not completed within the 4-week EDC window.
15 The PRO2 score entries into the participant's diary (or via phone at screening) will be based on the 3 days prior to each scheduled timepoint and will be averaged and used for the PRO2 score for each scheduled timepoint. Participants will be asked to complete the PRO2 (with 3-day recall) if at any time they self-report a symptomatic relapse occurring outside of the scheduled PRO2 collection (i.e., outside of the 12-week collection schedule).
16 The patient survey will include questions regarding treatment strategy compliance (including corticosteroid and biologic use) and number of health care related visits to assess HRU; see Sections 4.2.2 and 4.4.2.9.
17 If a participant experiences a symptomatic relapse in between the 12-week collection schedule, the patient survey and PRO2 questionnaire will be administered, and SOC clinical data will be collected if available.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AGA	American Gastroenterological Association
AHRQ	Agency for Healthcare Research and Quality
AP	abdominal pain
BMI	body mass index
CCF	Crohn's & Colitis Foundation
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CF	corticosteroid free
CFR	Code of Federal Regulations
CoPaQ	Costs for Patients Questionnaire
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRP	C-reactive protein
CTE	computed tomography enterography
DSMB	Data Safety Monitoring Board
EBD	endoscopic balloon dilation
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
EOS	end of study
FAS	full analysis set
FC	fecal calprotectin
GCP	Good Clinical Practice
HRU	healthcare resource utilization
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBD-DI-SR	IBD Disability Index (self-report)
IBDRE	inflammatory bowel disease related event
ICH	International Council for Harmonisation
IEC/IRB	independent ethics committee/institutional review board
IMM	immunomodulator
ITT	intention-to-treat (analysis set)
LOCF	last observation carried forward
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MES	Mayo Endoscopic Subscore
mITT	modified intent-to-treat
MRE	magnetic resonance enterography
PCORI	Patient-Centered Outcomes Research Institute
PP	per protocol (analysis set)
PRO	patient-reported outcome
PRO2	2-item patient-reported outcome (measure)
PROMIS-7	Patient-Reported Outcomes Measurement Information System (Fatigue – Short Form 7a)
RB	rectal bleeding
RCT	randomized controlled trial

Abbreviation	Definition
REDCap	research electronic data capture
RR	risk ratio
SAE	serious adverse event
SAP	statistical analysis plan
SEMA-CD	Simplified Endoscopic Mucosal Assessment for Crohn's Disease
SES-CD	Simple Endoscopic Score for Crohn's Disease
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SOC	standard of care
TBQ	Treatment Burden Questionnaire
TDM	therapeutic drug monitoring
TIM	targeted immunomodulator
TSQM	Treatment Satisfaction Questionnaire for Medication
TTT	treat-to-target
UC	ulcerative colitis

1 INTRODUCTION

1.1 BACKGROUND

Crohn's disease (CD) and ulcerative colitis (UC), collectively referred to as inflammatory bowel disease (IBD), affect approximately 3 million individuals in the United States, cost over $25 billion annually, and cause substantial patient morbidity, diminished quality of life and work productivity.[1-3] As a chronic relapsing-remitting disease, treatment goals for patients with IBD involve resolution of active symptoms (symptomatic remission), minimizing unpredictable relapses and unplanned healthcare utilization, and reducing disease-related complications. Targeted immunomodulators (TIMs), including biologic agents and small molecule inhibitors, are highly effective in achieving symptomatic remission in patients with IBD. However, approximately 25-50% of patients with IBD who achieve symptomatic remission with an index TIM may continue to harbor significant bowel inflammation and damage detectable on endoscopy.[4-7] This persistent bowel inflammation increases the risk of unpredictable relapses, unplanned healthcare utilization and disease-related complications in a substantial subset of patients who are otherwise in symptomatic remission, and contributes to patients' worries and fears about the disease.[8] Treating patients to a target of endoscopic remission (resolution of bowel inflammation), beyond symptomatic remission, may decrease this risk, and has been recommended in clinical guidelines and expert consensus statements.[9,10] However, treating to a target of endoscopic remission frequently involves iterative treatment adjustments in patients who have already achieved symptom relief, through optimization of index TIM with dose adjustments, followed by switching to an alternative TIM in patients who fail to achieve endoscopic remission. While most patients routinely accept, and providers routinely implement, treatment optimization of the index TIM through therapeutic drug monitoring, this strategy is only modestly successful in achieving endoscopic remission; a substantial proportion of patients and providers face a dilemma as to whether switching to an alternative TIM in asymptomatic patients with ongoing bowel inflammation would be beneficial. Switching involves stopping a TIM that resulted in symptomatic, but not endoscopic, remission and starting a new, alternative TIM with the hope of achieving endoscopic remission while maintaining clinical remission. With limited evidence on comparative efficacy of TIMs and a lack of predictive biomarkers to personalize choice of TIMs, this empiric treatment switch may inadvertently be to a less effective therapy, increasing risk of relapse and complications. This equipoise represents a key evidence gap in the management of patients with IBD.

1.1.1 IMPACT OF IBD ON THE HEALTH OF INDIVIDUALS AND POPULATIONS

IBD is a chronic debilitating autoimmune disease, with rising global incidence and prevalence.[1] By 2030, IBD is anticipated to affect 1% of individuals in Canada.[11] Typical symptoms in patients with CD and UC include abdominal pain, diarrhea, rectal bleeding and fatigue, with a lifelong unpredictable relapsing-remitting course, leading to substantial morbidity, diminished quality of life and disability.[12] If these progressive diseases are not adequately treated, they lead to structural and functional bowel damage with further potential complications of strictures, fistulae and abscesses, fecal incontinence, colon cancer, and extra-intestinal complications including anemia, malnutrition and fractures. Approximately 50% of patients with CD and 15% of patients with UC require bowel surgery.[13,14]

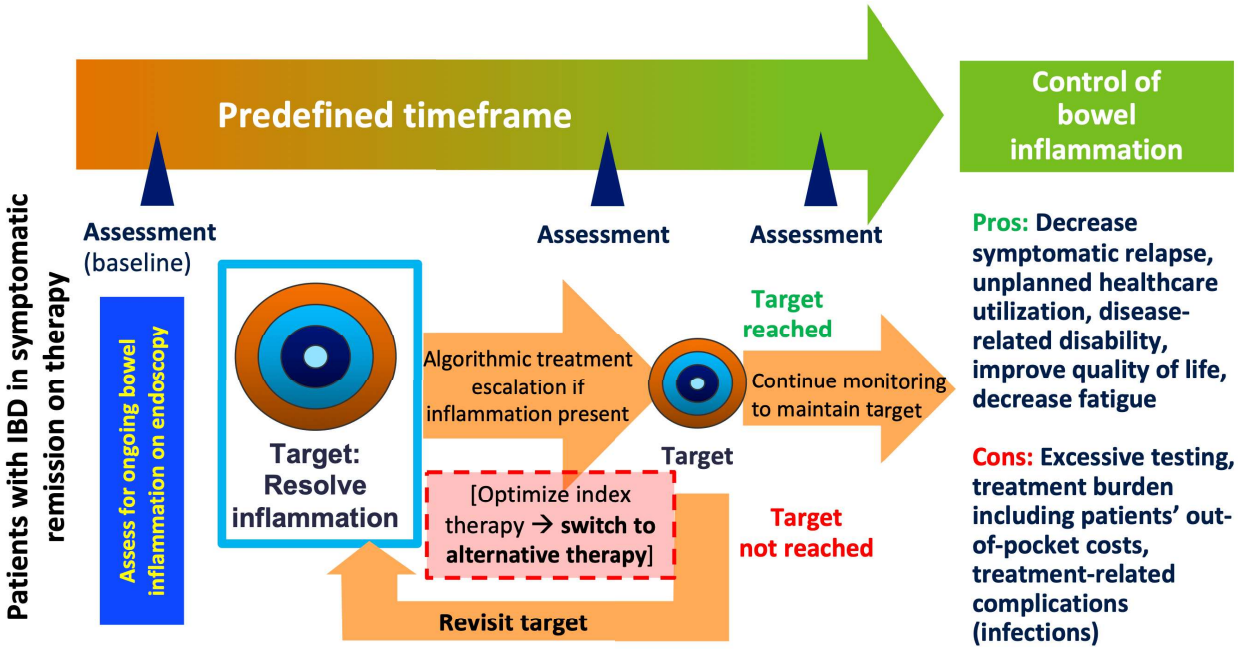
Treatment of IBD often involves long-term use of potent TIM therapies including biologic agents (e.g., tumor necrosis factor-α [TNFα] antagonists) and small molecule inhibitors (e.g., Janus kinase inhibitors). These agents have revolutionized the management of IBD – approximately 40 to 60% of patients achieve symptomatic remission with these agents and avoid disease-related complications, surgery, and hospitalization. However, these medications impose substantial treatment burden across all aspects of life, and also increase the risk of serious infections and certain cancers like lymphoma.[15-17] TIMs are also very expensive and contribute substantially to the rising cost of managing IBD.

1.1.2 Identifying Optimal Treatment Strategy in IBD

A substantial proportion of patients with IBD in remission will subsequently relapse and experience unplanned healthcare utilization. In preliminary studies conducted in IBD Qorus, 25-30% of asymptomatic patients relapse every year, and approximately 10% of patients experience unplanned hospitalization despite adherence to therapy.[18] This constant "worry and fear" about future clinical course (avoiding relapse, corticosteroids and surgery) is one of the main concerns that patients with IBD have.[19]

Persistence of bowel inflammation in asymptomatic patients is a major contributor to disease relapse and unplanned healthcare utilization. There is only modest correlation between symptoms and presence of intestinal inflammation: 47% of patients with CD and 23% of patients with UC in symptomatic remission have significant bowel inflammation detectable on endoscopy.[4-7] Cohort studies and sub-analyses of clinical trials have demonstrated that, compared to patients who achieve endoscopic remission (resolution of bowel inflammation on endoscopy), patients with ongoing inflammation have substantially higher risk of relapse and unplanned healthcare utilization, due to disease-related complications, and inferior quality of life.[13,20-24] To overcome this, a strategy of treat-to-target of endoscopic remission has been recommended, which forms the basis for this trial (Figure 1).[10,25-27] This involves systematically testing for endoscopic inflammation, optimizing index therapy (dose adjustment), and if inflammation persists, switching to an alternative therapy until inflammation is resolved.

Figure 1. Core concept of treat-to-target of endoscopic remission in patients with IBD



Abbreviations: IBD, inflammatory bowel disease.
Source: Adapted from Bouguen et al. Clin Gastroenterol Hepatol. 2015.

A strategy of treat-to-target of endoscopic remission, centered on optimization of index therapy, is effective in achieving endoscopic remission based on the results of a randomized explanatory trial of treat-to-target strategies in adalimumab-treated patients with CD (CALM trial). In this study, treatment optimization (without treatment switching) using clinical and biochemical measures of bowel inflammation was more effective than treatment adjustment based on symptoms alone in achieving deep remission at 1 year (23% versus 37%, p=0.014) in patients with baseline endoscopic inflammation and symptoms.[28] Cohort studies have also confirmed that 2-38% of patients with IBD treated with TIMs require dose optimization and approximately 30-54% of these patients achieve clinical and/or endoscopic remission.[29-31] As a result, clinical guidelines and expert consensus statements recommend optimization of index therapy based on therapeutic drug monitoring in patients who do not achieve symptomatic and endoscopic remission targets.[9,32,33]

Despite optimization of TIM, a substantial proportion of patients still do not achieve endoscopic remission and may warrant switching therapies. Despite iterative optimization of TIM, 35% of patients with CD and 15% of patients with UC who are in symptomatic remission continue to have significant bowel inflammation.[34] The CALM trial did not examine benefits (or harms) of switching to an alternative TIM in patients with persistent bowel inflammation despite optimization. With regulatory approval of 4 classes of TIMs for managing IBD (with more in advanced stages of development), switching to an alternative TIM within a treat-to-target paradigm may achieve endoscopic remission in these patients with persistent bowel inflammation;[35,36] however, it is unknown whether switching treatments in asymptomatic patients is beneficial and advisable in real-world practice.

Switching therapies in asymptomatic patients to achieve endoscopic remission is a difficult choice for both patients and providers. Though patients and providers highly prioritize treatment efficacy, there is discordance in patients' and providers' definitions of remission and approach to achieving it. In a global survey of 2398 patients with IBD and 654 gastroenterologists, gastroenterologists defined remission as resolution of inflammation on endoscopy (64% of gastroenterologists for CD and 70% for UC), while 45% of patients defined remission based on absence of symptoms.[37] Hence, a systematic approach of treat-to-target of endoscopic remission may not align with patients' treatment goals and preferences. Switching TIM poses a difficult choice for patients and providers as the alternative TIM may be less effective for symptom control, could lead to worsening of underlying disease activity or may cause new side effects related to the new therapy. Moreover, only 18-33% of patients treated with TIMs achieve endoscopic remission.[25,27,38] Since most TIMs are immunogenic monoclonal antibodies, treatment interruption of an index TIM (while trying an alternative TIM in the treat-to-target paradigm), may render it ineffective in case retreatment is warranted due to development of anti-drug antibodies in 20% of patients.[39] In preparation for this trial, an internet-based survey study of 307 gastroenterologists and 324 patients with IBD was conducted to understand their preferences for managing asymptomatic IBD with ongoing bowel inflammation. In this survey, 45% of physicians favored switching TIMs and 38% preferred to stay on the same drug. In contrast, 58% of patients preferred to stay on the drug that helped them achieve symptomatic remission while 31% of patients were open to switching therapies. These data suggest equipoise both for clinicians and patients. Hence, a treat-to-target strategy will need to factor in patients' values, preferences, or personal, social and clinical contexts.[26] While treat-to-target strategies are recommended over a non-targeted treatment approach in other chronic diseases like rheumatoid arthritis, optimal treatment targets are set at clinical remission in these diseases, rather than aiming for complete resolution of inflammation.[40]

There is considerable variability in guidelines and recommendations, and consequently, practice patterns for treat-to-target in IBD. Clinical guidelines from the American College of Gastroenterology (2019) and expert consensus statements (STRIDE-II, Selecting Therapeutic Targets in Inflammatory Bowel Disease, by the International Organization for the Study of Inflammatory Bowel Diseases [IOIBD, 2020]) recommend symptomatic and endoscopic remission as preferred treatment targets in patients with IBD, and suggest changing treatment iteratively in order to achieve a target of endoscopic remission.[9,10,33] In contrast, clinical guidelines from the American Gastroenterological Association (AGA, 2020), Future Research Needs documents from the Agency for Healthcare Research and Quality (AHRQ, 2014), and others identify risk-benefit synthesis of targeting symptomatic remission versus incrementally treating to endoscopic remission as a key knowledge gap.[32,41-43] An integral component of treat-to-target centers around optimal use of biologic agents and other TIMs, which has been prioritized by the Institute of Medicine, Patient-Centered Outcomes Research Institute (PCORI), AHRQ, the Crohn's & Colitis Foundation (CCF) and others.[42-46] Furthermore, despite guidelines, there is considerable variability in practice patterns for treat-to-target strategies in the real-world.[8]

In summary, there is a critical unmet need for a real-world, patient-centered evaluation of effectiveness and safety of treat-to-target strategies in patients with IBD. To inform this, this trial protocol describes a pragmatic, patient-centered, randomized controlled trial (RCT) comparing a strategy of switching TIMs (to treat to a target of endoscopic remission) versus continuing index TIM, in asymptomatic patients with IBD with persistent bowel inflammation despite optimization of index TIM.

1.2 RATIONALE FOR STUDY

The purpose of this study is to compare the effectiveness and safety of a strategy of switching to an alternative TIM to treat to a target of endoscopic remission, versus continuing index TIM in TIM-treated IBD patients in symptomatic remission with moderate to severe endoscopic inflammation despite optimization of index TIM, using a 104-week pragmatic, open-label, RCT.

The central hypothesis is that, in asymptomatic TIM-treated patients with IBD and ongoing endoscopic inflammation despite optimized index TIM, switching to an alternative TIM is superior to continuing index TIM in improving patient-centered outcomes without substantially increasing treatment burden or adverse events (AEs). The rationale for this proposal is that a TIM change in asymptomatic IBD patients will reduce bowel inflammation and achieve durable deep remission.

1.3 RISK-BENEFIT ASSESSMENT

1.3.1 POTENTIAL RISKS

Risks associated with switching to a new TIM therapy may include worsening of underlying disease activity, potential progression to disease-related complications, and/or side effects related to the new TIM therapy. As well, treatment interruption of an index TIM (while trying an alternative TIM in the treat-to-target paradigm), may render the index therapy ineffective in case retreatment is warranted due to potential development of anti-drug antibodies. In contrast, continuing treatment with index TIM in patients with ongoing inflammation may result in ongoing or worsening bowel inflammation that leads to a higher risk of relapse, unplanned healthcare utilization due to disease-related complications, and inferior quality of life that can lead to other complications. However, all treatment scenarios proposed in this protocol will be part of routine clinical care and therefore, the risks and benefits are not different to what would be observed in routine clinical care.

As with any study, there is a risk to participants of inadvertent disclosure of personal information or a loss of confidentiality. To protect participants from risk of stress related to breach of confidentiality, several procedures will be put into place. Specific measures for privacy preservation will include limiting the number of users with access to sensitive information; limiting the scope of sensitive information that is collected to only that which is necessary for this study; encrypting such data at all times; enforcing password strength rules; audit logging of all activity in the EDC; regular active and passive scans for suspicious activity, viruses and intrusions; appropriate physical security for all systems; and implementation of an appropriate response and disclosure policy in the event of a security breach.

In general, considering measures to minimize risk, the potential risks of study participation are believed to be justified by the potential benefits.

1.3.2 POTENTIAL BENEFITS

This research will determine whether medication change, in presence of endoscopic inflammation in patients with IBD who are already in symptomatic remission, may be beneficial in reducing risk of flare requiring corticosteroids, unplanned healthcare utilization, fatigue and pain interference. Participants may not directly benefit from this study, but the data collected will benefit future patients by improving the quality of care for patients with CD and UC.

2 STUDY OBJECTIVES AND ENDPOINTS

The objectives of this study are:

1. To compare the effectiveness of switching to an alternative TIM to treat to a target of endoscopic remission versus continuing index TIM in asymptomatic patients with IBD with ongoing endoscopic inflammation.
2. To compare the burden and safety of switching to an alternative TIM to treat to a target of endoscopic remission versus continuing index therapy in asymptomatic patients with IBD with ongoing endoscopic inflammation.
3. To identify heterogeneity of treatment effects, through preplanned subgroup analyses.

The planned trial primary and secondary outcomes and endpoint measures are listed in Table 1.

Table 1. Planned trial outcomes and measures

Primary or secondary	Outcome	Specific measure to be used	Timepoints	Powered? Yes or No
Effectiveness				
Primary	Clinical status	Time to treatment failure, as a composite of: (1) moderate-severe symptomatic relapse based on PRO2[a], with objective confirmation of inflammation within 2 months of event (FC >150 mcg/g, or CRP >5mg/L, or endoscopy showing moderate-severe inflammation, or MRE/CTE/IUS showing active inflammation) with need for escalation of therapy[b]; (2) need for rescue therapy with corticosteroids[c] for a documented symptomatic IBD flare; (3) IBD-related hospitalization[d]; (4) IBD-related surgery; (5) IBD-related structural complications (CD: symptomatic stricture, fistula or abscess; UC: symptomatic stricture)[e]; (6) TEAE requiring drug discontinuation	From randomization up to 104 weeks	Yes
Secondary	Clinical status	Treatment failure as defined in the composite primary outcome	Binary, 104 weeks	Yes
Secondary	Clinical status	Time to each individual component of the composite primary outcome	From randomization up to 104 weeks	Yes
Secondary	Quality of life	• Scores of the SIBDQ • Scores of the PROMIS-7 • Scores of the IBD-DI-SR • Scores of the IBD-Control	Continuous, EOS (104 weeks) or ED	Yes
Treatment Burden/Safety				
Secondary	Treatment burden	Scores of the Treatment Burden Questionnaire, including medication, time and administrative burden, lifestyle change, social life, and financial burden	Continuous, EOS (104 weeks) or ED	Yes
Secondary	Treatment satisfaction	Scores of the Treatment Satisfaction Questionnaire for Medication, measuring treatment satisfaction across domains of effectiveness, side effects, convenience, and global satisfaction	Continuous, EOS (104 weeks) or ED	Yes
Secondary	Patient cost	Scores of the CoPaQ, including out-of-pocket costs, for management of IBD, including treatment, monitoring, outpatient visits, and any unplanned healthcare utilization	Continuous, EOS (104 weeks) or ED	Yes

Primary or secondary	Outcome	Specific measure to be used	Timepoints	Powered? Yes or No
Secondary	Safety	• Treatment-related SAEs or unexpected SAEs • Serious infections, defined as infections requiring hospitalization and/or intravenous antibiotics	From randomization up to 104 weeks	No

Abbreviations: CoPaQ, Costs for Patients Questionnaire; CTE, computed tomography enterography; CD, Crohn's disease; ED, early discontinuation (i.e., discontinuation due to investigator/sponsor or participant decision or lost to follow-up); EOS, end of study; IBD, inflammatory bowel disease; IBD-DI-SR; IBD Disability Index for self-report; IUS, intestinal ultrasound; MRE, magnetic resonance enterography; PROMIS-7, Patient-Reported Outcomes Measurement Information System (Fatigue – Short Form 7a); SAE, serious adverse event; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TEAE, treatment-emergent adverse event; UC, ulcerative colitis.

a Moderate to severe symptomatic relapse based on PRO2 is defined as stool frequency > 4 and/or abdominal pain ≥2 (CD) or rectal bleeding (RB) score ≥2 and with SF score ≥2 (UC)

b Need for escalation of therapy includes adding corticosteroids/budesonide, adding IMM, adding another TIM, or dose-escalating existing TIM

c Corticosteroid requirement will be ≥30mg/d prednisone equivalent (or 9mg/d budesonide) being planned taper over ≥4 weeks

d IBD-related hospitalization for a flare requiring initiation of corticosteroids with intention of treating for ≥ 4 weeks and/or need for escalation of index therapy, or hospitalization for symptomatic structural complication of IBD

e Structural complications can be new or already present, but now causing moderate-severe symptoms in the opinion of investigator. This includes new or relapse of perianal/intra-abdominal abscess, symptomatic intra-abdominal phlegmon or significant increase in fistula drainage, or new obstructive symptoms in setting of stricture

3 STUDY DESIGN

3.1 OVERALL STUDY DESIGN

This is a pragmatic, open-label, multicenter RCT conducted in asymptomatic patients with IBD who have persistent moderate to severe endoscopic inflammation despite optimization of index TIM. This study plans to enroll approximately 216 participants in the United States and Canada either switching to treatment with alternative TIM to treat to a target of endoscopic remission or continuing index optimized TIM. After randomization, participants will be followed prospectively within routine clinical practice over 2 years (104 weeks); 156 patients will be followed for the full 104 weeks, whereas 60 patients will be followed for a variable time period between 52 to 104 weeks.

This trial will be conducted within selected sites in the United States and Canada.

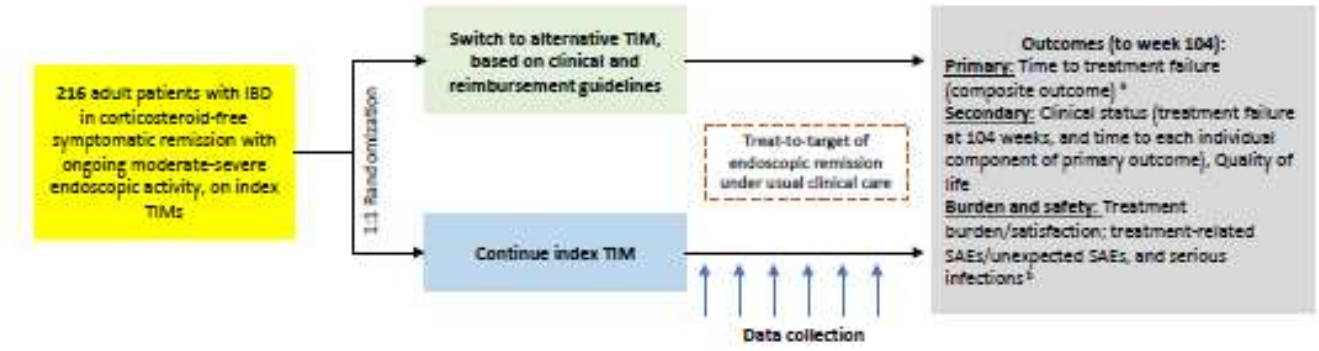
The primary outcome will be time from randomization to treatment failure, as a composite of:

1) Moderate-severe symptomatic relapse based on PRO2, with objective confirmation of inflammation within 2 months of event (FC >150 mcg/g, or CRP >5mg/L, or endoscopy showing moderate-severe inflammation, or magnetic resonance enterography (MRE)/computed tomography enterography (CTE)/intestinal ultrasound (IUS) showing active inflammation) with need for escalation of therapy;
2) Need for rescue therapy with corticosteroids for a documented symptomatic IBD flare;
3) IBD-related hospitalization;
4) IBD-related surgery;
5) IBD-related structural complications (CD: symptomatic stricture, fistula, or abscess; UC: symptomatic stricture);
6) Treatment-emergent adverse event requiring drug discontinuation.

Secondary outcomes will include treatment failure (yes/no) as defined in the composite primary outcome (binary outcome) and time from randomization to each of the components in the primary outcome (time to event outcome), quality of life (overall quality of life, fatigue, IBD-related disability), burden of treatment (financial burden, burden of monitoring, treatment side effects), treatment satisfaction, and safety.

In compliance with the pragmatic methodology of this study embedded in routine clinical care, there is no study visit mandated per study protocol. Participant visit schedules will follow local SOC with any additional visits at the treating physician's discretion. Data on all effectiveness, treatment burden and safety outcomes will be captured using a REDCap (Research Electronic Data Capture)[47] database hosted at CCF. Data for the study will be extracted from medical record information and entered into the EDC system at baseline and then approximately every 6 months (at a minimum) thereafter, up to a 2-year follow-up period. Patient-reported outcome (PRO) measures (self-assessment questionnaires) will be utilized in this study to determine primary (efficacy) and secondary (quality of life and treatment burden and satisfaction) outcomes. Participants will complete the PRO2 at baseline and approximately every 12 weeks during a 2-year follow-up period; additional questionnaires (IBD-Control, PROMIS-7, SIBDQ, IBD-DI-SR, Treatment Burden Questionnaire (TBQ), Treatment Satisfaction Questionnaire for Medication (TSQM), and the Costs for Patients Questionnaire [CoPaQ]) will be completed at baseline (following randomization) and up to 3 additional times during a 2-year follow-up period. An overview of the trial design is provided in Figure 2.

Figure 2. Overview of trial – pragmatic, multi-center, open-label, randomized trial of treat-to-target strategies in IBD



Abbreviations: IBD, inflammatory bowel disease; SAE, serious adverse event; TIM, targeted immunomodulator.
[a] Time to treatment failure (composite outcome) as defined in Table 1.
[b] Serious infections, defined as infections requiring hospitalization and/or intravenous antibiotics.

3.2 STUDY SETTING

3.2.1 IBD QORUS LEARNING HEALTH SYSTEM

The IBD Qorus initiative is a learning health system built on a collaboration between patients and providers that aims to improve the healthcare value for patients with IBD. A key feature of learning health systems is the use of data within a collaborative network of patients and providers to inform healthcare delivery, quality improvement, and research.

3.2.2 SITE SELECTION

The trial will be conducted within approximately 25 or more select active sites, both academic and private practices, in IBD Qorus, and 6 or more active sites in Canada. IBD Qorus consists of 55 geographically diverse academic and private practices in the United States.

3.3 STUDY POPULATION

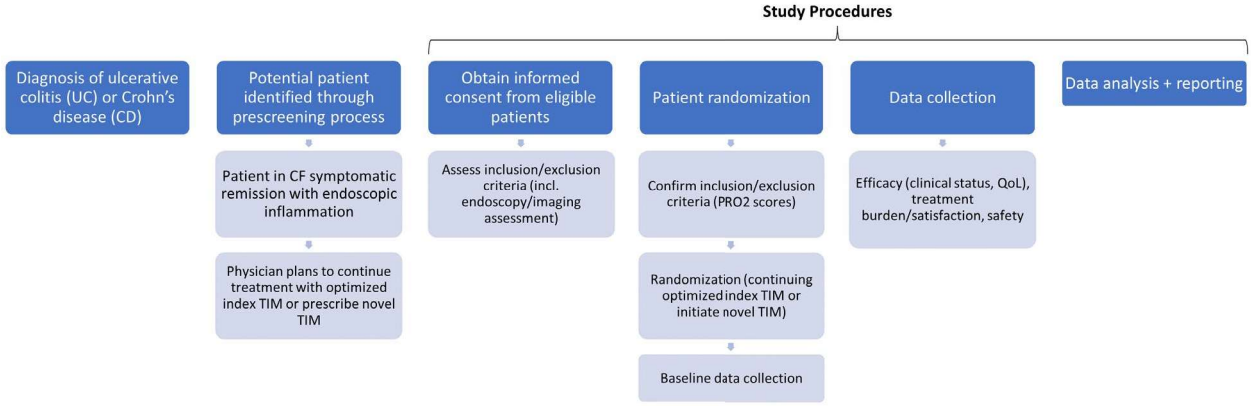
This trial plans to enroll approximately 216 patients (accounting for attrition) with IBD and persistent moderate to severe endoscopic inflammation despite optimization of index TIM.

3.3.1 PARTICIPANT RECRUITMENT

Investigators will identify eligible participants at local sites. Providers will evaluate clinical data related to treat-to-target, including endoscopic remission status, current IBD medications, and plan for treat-to-target of endoscopic remission (either optimization of index TIM or switching to an alternative TIM) during the prescreening process. In addition, the project team will also review data reports from study sites and will reach out to local site investigators to facilitate trial recruitment. Local site investigators will approach potentially eligible patients for consent to participate in this trial. Consent may be obtained by trained research personnel other than the treating physician (see Section 7.2 for more details).

A study flow diagram of the recruitment and study procedures is presented in Figure 3.

Figure 3. Study flow diagram



Abbreviations: CD, Crohn's disease; CF, corticosteroid-free; PRO2, 2-item patient reported outcome; QoL, quality of life; TIM, targeted immunomodulator; UC, ulcerative colitis.

3.3.2 INCLUSION CRITERIA

Participants must meet all of the following criteria for enrolment into the study:

1. Male or nonpregnant, nonlactating females, ≥ 18 years of age.
2. An established diagnosis of CD or UC for at least 6 months based on standard clinical criteria, confirmed by the treating provider.
3. Current treatment with an approved TIM for treatment of IBD, including biologic agents (e.g., TNFα antagonists, ustekinumab, vedolizumab) and small molecule inhibitors (e.g.,

Janus kinase inhibitors, ozanimod), including future TIMs that become commercially available during the conduct of the trial.

4. Dose of TIM should be stable for 3 or more months prior to qualifying endoscopy/radiology. No treatment escalation of TIM or addition of IMM, corticosteroid, or mesalamines after the qualifying endoscopy/radiology procedure up to randomization is permitted. Dose de-escalation after qualifying procedure is permissible at the discretion of the treating provider.
5. In corticosteroid-free symptomatic remission based on validated PROs (PRO2 score) and deemed to be experiencing no other IBD-related symptoms in the opinion of the treating provider. Includes patients who may be in medically induced remission (on index TIM); or surgically induced remission with post-op initiation of index TIM for prophylaxis and colonoscopy/imaging performed at least 3 months after initiation/optimization of TIM showing moderate-severe bowel inflammation. Validated PROs are defined as:
    a. CD: PRO2 (2-item patient reported outcome) mean daily score of abdominal pain score ≤1 and stool frequency score ≤ 3; or
    b. UC: PRO2, with absence of rectal bleeding (rectal bleeding score = 0) and with stool frequency score ≤1.
6. Evidence of moderate to severe bowel inflammation on local reading of colonoscopy, flexible sigmoidoscopy, balloon-assisted enteroscopy, capsule endoscopy or MR, CT enterography, or intestinal ultrasound, performed within 6 months prior to screening, defined at the investigator's discretion or as follows:
    a. CD: Colonoscopy showing moderately to severely active inflammation based on **1** of the following variables/scores:
        - Simple Endoscopic Score for Crohn's Disease (SES-CD) score ≥7 or score ≥4 for those with isolated ileal disease, or
        - Presence of mucosal ulcers >5 mm in size if SES-CD has not been recorded, or
        - Simplified Endoscopic Mucosal Assessment for Crohn's Disease (SEMA-CD) score ≥2, or
        - Rutgeerts score i2b or higher for patients in surgically induced remission with post-operative endoscopic recurrence [Note, either SES-CD or Rutgeerts score can be used for participants with post-operative recurrence]; or
    b. CD: MRE or CTE showing moderately to severely active inflammation based on **1** of the following variables:
        - Increased bowel wall thickness, or
        - Mural hyperenhancement, or
        - Peri-enteric fat stranding, or
        - Radiographic features of ulceration, or
        - Intramural T2 signal on fat suppressed images; or

c. CD: Capsule endoscopy showing moderately to severely active small bowel disease based on Lewis score >790 (in case the disease is not accessible via endoscopy), or per local endoscopist if Lewis score is not reported; or

d. CD: Gastrointestinal ultrasound showing at least **1** of the following variables:

- Increased bowel wall thickness >5 mm, or
- Color doppler score >5/cm^2, or
- Bowel stenosis, or
- Bowel stratification, or
- Fatty wrapping; or

e. UC: modified MES score of 2 to 3, or documentation of any endoscopic feature that would define an MES of 2 to 3 (e.g., friability, ulceration, spontaneous bleeding, complete loss of vascular pattern), if an MES has not been recorded.

7. Eligible to receive at least 1 alternative TIM (excluding their index TIM) for the treatment of their disease per approved drug label, based on clinical and reimbursement guidelines.
8. Able to participate fully in all aspects of this clinical trial.
9. Informed consent must be obtained and documented.

3.3.3 Exclusion Criteria

Participants who exhibit any of the following conditions are to be excluded from the study:

1. Presence of ostomy or ileoanal pouches.
2. Serious underlying disease other than UC or CD that in the opinion of the investigator may interfere with the participant's ability to participate fully in the study.
3. History of alcohol or drug abuse or any other medical or health condition that in the opinion of the investigator may interfere with the participant's ability to comply with the study procedures.
4. Prior enrolment in the current study.
5. Mild endoscopic disease activity, where treating providers would not consider switching TIM.

3.3.4 Early Withdrawal From The Study

Participants can withdraw consent at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons (i.e., withdrawal of consent; lost-to-follow-up; participant fails to respond to questionnaires despite repeated reminders). If a participant prematurely discontinues from the study, the participant's name, reason for early withdrawal, and date of withdrawal will be entered into the electronic data capture (EDC) system (REDCap).

4 STUDY PROCEDURES

4.1 RANDOMIZATION AND BLINDING

Eligible participants will be randomly assigned in a 1:1 allocation ratio to 1 of 2 treatment strategies, i.e., either continuing index TIM or switching to an alternative TIM. Randomization will occur through a computer-generated, centralized randomization service with permuted block randomization of alternating sizes to ensure allocation concealment. Randomization will be stratified by disease phenotype (CD versus UC).

This is an open-label study; participants and site investigators will not be blinded to treatment allocation. To minimize bias related to open-label design, healthcare utilization (corticosteroid use for IBD, IBD-related hospitalization, surgery, and complications) will be adjudicated by blinded outcome assessors.

4.2 STUDY TREATMENT

4.2.1 STUDY TREATMENT AND IMPLEMENTING TREATMENT SWITCH IN CLINICAL TRIAL

Participants in both treatment arms will continue routine clinical care with their treating provider, including testing and continuation or discontinuation of any concomitant therapies.

Participants randomized to a strategy of switching TIM will be switched to an alternative TIM covered by the participants' insurance formulary as part of routine care. Participants may be switched to another medication in the same drug class. Participants randomized to switching TIM will discontinue their existing TIM. Addition of another TIM (i.e., dual biologic or biologic combined with advanced oral molecule drug) to an existing TIM does not constitute a switch. No study-related medications will be provided. The selection of an alternative agent will be determined at the discretion of the local site physician in accordance with clinical guidelines on the management of moderate to severe UC, and management of moderate to severe CD from the AGA and ACG.[9,32,33] These guidelines include recommendations on positioning of TIMs for first-line use (TIM-naïve patients) and second-line use (in patients with prior exposure to TIMs).

Participants (and their providers) in either treatment arm will be allowed to stop or start new TIMs and other IBD-directed therapies in case of symptomatic relapse or intolerance to therapies, at the discretion of the treating provider-patient team.

4.2.2 COMPLIANCE

Medication records of randomized participants will be used to assess adherence to the selected treatment strategy. Investigators will be asked to document if the treatment strategy is being followed and the reasons for any deviations from treatment strategy implementation.

Fidelity measures will be analyzed by measuring adherence and nonadherence to the trial protocol using a physician-reported survey to assess whether participants were switched to an alternative TIM when they were supposed to be, and when they were not supposed to be. Given potential heterogeneity in the TIM switching arm, survey questions will include the type of medication switch and reasons for choosing specific medications: a) participant preference, b) provider preference, c) access/cost, d) other (with brief explanation). We will ascertain whether the medication switch is concordant with clinical guidelines or not and conduct sensitivity analyses

including only participants with guideline congruent treatment switch. Descriptive analyses of reasons for medication switching that is not concordant with clinical guidelines will be performed.

Participants (and their providers) in either treatment arm will be allowed to stop or start new TIMs and other IBD-directed therapies in case of symptomatic relapse or intolerance to therapies, at the discretion of the treating provider-patient team.

4.2.3 Concomitant Therapies

Participants will be permitted to continue taking, starting, or stopping mesalamine, thiopurines or methotrexate, or adding other TIMs (to existing index TIM) after randomization, at the discretion of the treating provider-patient team. If IBD-related medications are added/modified in response to a symptomatic flare (e.g., adding corticosteroids/budesonide, adding IMM, adding another TIM, or dose-escalating existing TIM), the participant will have met the primary outcome. If administered to an asymptomatic participant, the participant will be encouraged to continue in the trial. At enrollment, participants cannot be on prednisone (or equivalent); initiation of corticosteroids as rescue therapy (for a documented symptomatic IBD flare) during the course of the trial will be considered treatment failure (i.e., deemed to have met the primary outcome, as defined in Table 1).

All oral and/or rectal IBD-related medications (e.g., mesalamine, corticosteroids, thiopurines, methotrexate, TIMs, etc.) received by the participant following randomization will be reported in the eCRF.

4.3 DATA COLLECTION

4.3.1 Data Sources

The study data collection schedule is summarized in the Study Schedule. eCRFs will be designed to capture the study data from procedures performed as part of local SOC of the study participants. Clinical information recorded in the participants' medical record information will be entered into the relevant eCRFs within the REDCap electronic data capture (EDC) system. As well, participants will complete the electronic PRO questionnaires and the patient-reported survey throughout the study.

4.3.2 Data Collection Schedule

4.3.2.1 Baseline

Patients at participating sites will be screened for inclusion and exclusion criteria (see Sections 3.3.2 and 3.3.3) and consented at the time of routine clinical care.

Screening procedures may not be performed until informed consent is obtained. Screening procedures may be performed at any time during the screening period within 8 weeks prior to randomization. Central randomization may occur when all eligibility criteria are confirmed.

Baseline data will be collected for the most recent SOC assessments that occurred within 6 months prior to informed consent [see Section 4.4.1]). Demographic, medical, disease, and surgical history variables collected at baseline may include, but are not limited to, those listed in Table 2.

Table 2. Baseline data assessments and variables

Assessment	Variable(s)
Patient demographics	• Patient age at baseline • Sex • Race and ethnicity • Height and weight/BMI • Smoking status at baseline (current; prior; never) • Marijuana use at baseline (current; prior; never)
Disease history	• Diagnosis (CD or UC) • Disease onset (date of disease diagnosis) • Disease location • Montreal classification of disease at baseline • History of perianal disease (yes; no) at baseline
Medical history	• Prior malignancy in last 5 years (and type of cancer) • Major comorbidities (diabetes, hypertension, COPD, coronary artery disease, chronic kidney disease) • Other pertinent chronic diseases • Prior serious infection (requiring IV antibiotics or hospitalization) within past year
Prior and concomitant IBD-related medications	• Prior TIM medication history (with duration of previous TIM use, name of therapy, reason for discontinuation) • Prior (within 3 months of randomization) and concomitant medications for IBD (aminosalicylates, corticosteroids, immunomodulators, immunosuppressants, biologics, antibiotics) with duration of current/previous use, name of therapy, and (if applicable) reason for discontinuation.
Surgical history	• Prior IBD-related major surgery (resection, stoma, stricturoplasty) • Prior IBD-related minor surgery (EBD, exam under anesthesia and seton placement)
Disease monitoring assessments	• Clinical laboratory assessments (FC and CRP) • Imaging assessment for disease activity, locally read
PRO assessments	• PRO2 • IBD-Control • PROMIS-7 • SIBDQ • IBD-DI-SR • TBQ • TSQM • CoPaQ • Patient survey

Abbreviations: AE, adverse event; CoPaQ, Costs for Patients Questionnaire; CRP, C-reactive protein; EBD, endoscopic balloon dilation; FC, fecal calprotectin; IBD, inflammatory bowel disease; IBD-DI, IBD Disability Index for self-report; IV, intravenous; PRO, patient reported outcome; PRO2, 2-item patient reported outcome; PROMIS-7, Patient-Reported Outcomes Measurement Information System (Fatigue – Short Form 7a); SAE, serious adverse event; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TIM, targeted immunomodulator.

4.3.2.2 Follow-Up Data Collection

The follow-up period will commence once the patient is randomized and will continue up to a maximum of 2 years. Following randomization, participants in both treatment arms will continue routine clinical care with their treating physician and will be scheduled for routine clinical follow-up, either in-person or using telemedicine, as per local site practice, at the discretion of their

treating physician. There is no study-mandated visit schedule; however, participants will be required to complete the PRO questionnaires at predefined timepoints.

Data for the study will be collected from sites by trained site personnel and entered into the EDC system. Sites will be asked to collect routine clinical data at the following time points: at baseline and then approximately every 6 months thereafter up to a 2-year follow-up period. In addition, data on primary effectiveness outcomes will be captured in-between visits (self-reported every 12 weeks in the patient-facing REDCap survey, through a short 5-question questionnaire eliciting clinical, functional status and health care utilization); additionally, at predetermined intervals as outlined in Section 4.4.2, more detailed PRO questionnaires will be administered electronically.

Follow-up data variables collected may include, but are not limited to, those listed in Table 3.

Table 3. Follow-up data assessments and variables

Assessment	Variable(s)/description
TIM treatment details	• Name of therapy, dose, treatment adjustment (dose change/interruption) and reason, treatment discontinuation and reason
IBD-related concomitant medications	• Mesalamine (oral and/or rectal), corticosteroids (oral and/or rectal), thiopurines, methotrexate, TIMs, etc. • Major treatment decisions including switching TIMs or proceeding with surgery
Disease monitoring assessments	• Clinical laboratory assessments (FC and CRP) • Imaging assessment for disease activity, locally read
PRO assessments	• PRO2 • IBD-Control • PROMIS-7 • SIBDQ • IBD-DI-SR • TBQ • TSQM • CoPaQ • Patient survey
Safety assessments	• Treatment-related SAEs • Unexpected SAEs • Treatment-emergent AEs requiring discontinuation • IBDREs of greater intensity, frequency, or duration than expected for the individual participant • Serious infections (defined as infections requiring hospitalization and/or IV antibiotics) • Malignancy • Major adverse cardiovascular event (MACE)
Health resource utilization	• Total number of IBD-related health care related visits at each time point, including hospitalizations, ED visits, office visits

Abbreviations: AE, adverse event; CoPaQ, Costs for Patients Questionnaire; CRP, C-reactive protein; ED, emergency department; FC, fecal calprotectin; IBD, inflammatory bowel disease; IBD-DI, IBD Disability Index for self-report; IV, intravenous; PRO, patient reported outcome; PRO2, 2-item patient reported outcome; PROMIS-7, Patient-Reported Outcomes Measurement Information System (Fatigue – Short Form 7a); SAE, serious adverse event; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TIM, targeted immunomodulator.

4.3.2.3 End of Study

Following randomization, all participants will be followed prospectively within routine clinical practice up to 2 years (104 weeks); 156 patients will be followed for the full 104 weeks, whereas 60 patients will be followed for a variable time period between 52 to 104 weeks. Participants will

be followed for up to 2 years or until loss to follow-up or withdrawal of consent (investigator/sponsor or participant decision), whichever occurs first. End of study is defined as 2 years following randomization. (see Section 4.3.3).

4.3.3 Discontinuation of Treatment

Participants who discontinue treatment with TIM will continue to be monitored until the end of the data collection period (i.e., 2 years following randomization). Where feasible, a minimal dataset will continue to be collected for those who discontinue the study early including major IBD-related health outcomes (information on clinical remission or relapse, IBD-related hospitalization, IBD-related surgery, and/or structural complications due to IBD). These participants will be asked to complete PRO2 (with 3-day recall) at the time of treatment failure but will not be required to complete any subsequent PRO questionnaires.

4.4 OUTCOME VARIABLES

4.4.1 Endoscopic Disease Activity

Endoscopy results will be collected if/when they are performed in the context of routine clinical care; no trial-mandated endoscopies will be performed. The baseline qualifying endoscopy should be within 6 months of screening. All endoscopy results will be assessed by local readers, including for confirmation of eligibility; all site investigators will be trained to standardize endoscopy reading.

Participants randomized to switching TIM to pursue a target of endoscopic remission typically undergo SOC endoscopy to assess resolution of inflammation approximately 6 to 9 months after the treatment switch, followed by optimization of switched TIM in case of failure to achieve endoscopic remission. Participants randomized to continuation of index TIM will undergo testing for resolution of inflammation at the discretion of the treating provider-patient team.

Completion of endoscopic disease activity assessments will be at the discretion of the treating physician and will be completed as per local SOC. The endoscopic remission target is typically assessed in both treatment arms at approximately 52 weeks following study enrollment with endoscopic remission defined as:

- CD: SES-CD score <3, or SEMA-CD score <2, or resolution of ulcers
- UC: MES = 0
- Endoscopic response will also be measured, defined as >50% reduction from baseline.

The SES-CD scores 4 endoscopic items (ulcer size, proportion of ulcerated surface, proportion of the surface area affected by any disease lesion, and stenosis) from 0 to 3, with higher scores representing more severe endoscopic disease activity. See Appendix 1.

The SEMA-CD scores endoscopic disease activity on a 5-point scale (0-4 points) for each bowel region (ileum and colon), from endoscopic remission to severe disease activity.[48] See Appendix 1.

The MES assesses endoscopic disease activity on a 4-point scale (0-3 points), from normal or inactive disease to severe disease activity. See Appendix 2.

4.4.2 PATIENT-REPORTED OUTCOME QUESTIONNAIRES

Self-assessment questionnaires will be utilized in this study to determine how participants perceive their condition and its impact on their life. Patients will complete the following PROs and patient survey at the timepoints listed in the Study Schedule.

Patients will require internet access as the questionnaires are administered electronically through an online portal (via REDCap™), with the exception of the PRO2 at screening, which may instead be administered via phone. For patients unable to utilize the online questionnaires paper versions of questionnaires will be provided. Patients will receive reminders (e.g., email from local site coordinator) to ensure compliance to questionnaire completion.

4.4.2.1 PRO2 UC and PRO2 CD

The PRO2 UC consists of the stool frequency and rectal bleeding subscores of the Mayo Clinic Score.[49,50] The PRO2 CD consists of the 2 CDAI component items: daily stool frequency and abdominal pain. Study participants will complete the PRO2 daily utilizing a 3-day recall period (excluding days of bowel preparation and ileocolonoscopy, if applicable). Average scores over the 3-day period will be calculated. See Appendix 3 and Appendix 4.

Patients will be asked to complete the PRO2 (with 3-day recall) if at any time they self-report a symptomatic relapse occurring outside of the scheduled PRO2 collection (i.e., outside of the 12-week collection schedule).

4.4.2.2 SIBDQ

The SIBDQ is a validated 10-item questionnaire which measures quality of life across physical, social, and emotional domains in patients with IBD. The score on this questionnaire ranges from 10 to 70, with a minimal clinically important difference (MCID) of 9 points. See Appendix 5.

4.4.2.3 IBD-Control

The Inflammatory Bowel Disease-Control (IBD-Control) questionnaire assesses disease control from the patient's perspective.[51] The IBD-Control consists of 14 questions divided into 5 sections. The first 4 sections consist of 13 categorical questions with 3 response options and the fifth section consists of a 100-mm visual analog scale where respondents rate the overall control of their IBD in the past 2 weeks, from 0 for "worst possible control" to 100 for "best possible control." Scoring for the IBD-Control consists of summing scores for 8 questions (1a, 1b and 3a-f) (IBD-Control-8). A score of 0 points is assigned to the least favorable response, 1 point for indeterminate or immediate responses, and 2 points for the most favorable response. Individual scores are summed to calculate the total IBD-Control-8 score (range, 0 to 16 points), with higher scores representing worse disease control. See Appendix 6.

4.4.2.4 PROMIS-7 – Fatigue

Fatigue, a common symptom in patients with IBD with or without associated bowel symptoms, will be measured using the PROMIS-7 questionnaire.[52] PROMIS scales are continuous measures, calibrated using a T-score metric to the US general population with a mean (SD) of 50. For the PROMIS-7 scale, MCID in T-score is 3.0-5.0 points, with a longitudinal effect size of 0.24-0.51. See Appendix 7.

4.4.2.5 IBD-DI-SR

IBD-related disability will be measured using the IBD-DI-SR, a validated 14-item questionnaire, with scores ranging from 0-100 that correlates with disease activity, quality of life and generic measures of disability, modified to be suitable as a self-report.[53] In this index, scores from 0-20, 21-35, 36-50 and 51-100 correspond to no, mild, moderate and severe disability, respectively. See Appendix 8.

4.4.2.6 Treatment Burden Questionnaire

Treatment burden will be measured using the validated 15-item TBQ, related to the burden associated with taking medicine, self-monitoring, laboratory tests, physician visits, need for organization, administrative tasks, following advice on diet and physical activity, and social impact of the treatment, rated on a Likert scale ranging from 0 (not a problem) to 10 (big problem).[54,55] See Appendix 9.

4.4.2.7 Treatment Satisfaction Questionnaire for Medication

Treatment satisfaction will be measured using the validated TSQM, which measures patients' experiences with their medications across domains of effectiveness, side effects, convenience and global satisfaction.[56] See Appendix 10.

4.4.2.8 Costs for Patients Questionnaire

The CoPaQ is a 32-item questionnaire developed to measure health-related out-of-pocket costs, patient health care costs not reimbursed by insurance companies. The questionnaire is divided in 3 sections and assesses costs associated with the patients underlying health condition as it relates to their daily life, or costs directly linked with the use of health care services needed to treat their condition.[57] See Appendix 11.

4.4.2.9 Healthcare Resource Utilization Use (Patient Survey)

Participants will complete a survey to assess IBD-related healthcare resource use throughout the duration of the study. The survey may include, but is not limited to, the following variables:

- Count of health care related visits at each time point, including hospitalizations, ED visits, office visits (in-person or telehealth), endoscopies, imaging studies (e.g., CT/MR enterography), and stool tests.

4.4.3 Safety Assessments

Definitions, documentation and reporting of AEs are described in detail in Section 5. Relevant safety data will be recorded from informed consent up to and including EOS.

4.5 PRIMARY OUTCOME ADJUDICATION

All outcomes will be independently adjudicated by 2 investigators, not directly participating in the current trial, and are blinded to treatment assignment. The adjudication process and methods will be documented in a Central Adjudication Charter. For participants with high scores on PROs and/or who require corticosteroids, are hospitalized, or undergo surgery for reasons unrelated to IBD, outcomes will be adjudicated by blinded outcome assessors and will not be considered treatment failure.

5 SAFETY REPORTING

5.1 DEFINITIONS

5.1.1 ADVERSE EVENT

An AE is any untoward medical occurrence in a participant or clinical investigation participant that does not necessarily have a causal relationship with the administration of a pharmaceutical or an investigational product. An AE can therefore be any unfavorable or unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. An AE may be a new illness, worsening of a sign or symptom of a condition, or an effect of the study medication, including the comparator.

5.1.2 ADVERSE DRUG REACTION

Adverse drug reactions (ADRs) are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

5.1.3 UNEXPECTED ADVERSE DRUG REACTION

An unexpected ADR is an ADR, the nature and severity of which is not consistent with the applicable product information (i.e., product label).

5.1.4 SERIOUS ADVERSE Event

An SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening, i.e., the participant was at immediate risk of death at the time of the event; it does not include any event that hypothetically might have caused death if it had occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization that is not related to exacerbation of IBD or a known complication of IBD (see Section 5.1.5, for events related to IBD). Hospitalizations and/or surgical procedures that are scheduled to occur during the study period, for an illness or disease that existed before participant enrolment in the trial, will not be considered AEs provided the pre-existing condition did not deteriorate (e.g., surgery performed earlier than the planned date).
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether an event should be considered an SAE and if expedited reporting is appropriate. In other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes listed in the definition above. These should also usually be considered serious.

5.1.5 IBD-Related Event

A nonfatal SAE that, in the opinion of the investigator, can be characterized as an exacerbation of CD or UC, or as a known gastrointestinal complication of CD or UC, will be considered an IBD-related event (IBDRE). IBDREs may include, but are not limited to, the following examples:

Table 4. Expected IBD-related events

- Abdominal mass
- Abdominal pain
- Abdominal tenderness
- Abnormal loss of weight
- Abscess (anal, perianal, intestinal)
- CD flare
- Diarrhea
- Diarrhea hemorrhagic
- Fatigue
- Fistula (anal, anastomotic, rectovaginal, colonic, duodenal, enterocolonic, entero-enteric, enterocutaneous, enterovesical, ileal, intestinal, jejunal, gastric, gastrointestinal, perianal)
- Fissure (anal)
- Ileus (gastric, mechanical, paralytic, spastic)
- Obstruction (gastrointestinal, large or small intestinal) or obstructive symptoms
- Perforation (gastrointestinal, large or small intestinal)
- Postoperative infection, abscess or phlegmon
- Nausea
- Pyrexia
- Rectal hemorrhage
- Vomiting
- Stenosis (anal, anorectal, colonic, duodenal, gastrointestinal, ileal, intestinal, jejunal, rectal, small or large intestinal)
- Stricture (small or large intestinal)

Since these events are typically associated with IBD, they will be considered expected events and documented in the participant's medical records as part of routine care and site's local practice, unless the event meets the criteria for seriousness or results in discontinuation of treatment in which case the event should be recorded in the eCRF.

If an event meets the definition of a IBDRE above, but the event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, then the event should be reported as outlined in Section 5.4.

5.2 CLASSIFICATION

5.2.1 Severity

The severity of adverse events will be classified as mild, moderate, or severe as follows:

- Mild: Discomfort noticed but no disruption of normal daily activity.
- Moderate: Discomfort sufficient to reduce or affect normal daily activity.
- Severe: Incapacitating with inability to work or perform normal daily activity.

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on participant/event outcome or action criteria usually associated with events that pose a threat to

a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

5.2.2 ATTRIBUTION

The relationship of the AE to study treatment will be assessed by the investigator to be not related (unlikely), or related (possibly, probably, definitely), as follows:

- Not related: No relationship or unlikely relationship between the AE or SAE and the administration of TIM therapy. The use of concomitant medication(s), or the participant's clinical state, or other factors are determined to be the cause or likely to be the cause of the AE or SAE.
- Related: The AE or SAE is assessed to have a possible, probable, or definite relationship to the use of TIM therapy. As the use of concomitant medication(s), the participant's clinical disease state, as well as the de-challenge or re-challenge to the use of TIM therapy may suggest a causal relationship is possible, probable, or definite.

For the purposes of safety analyses, all AEs or SAEs classified with a relationship to study drug administration of possible, probable, or definite will be considered treatment-related events.

5.3 COLLECTION AND RECORDING OF ADVERSE EVENTS

All AEs, including SAEs, experienced by the participant between informed consent and discontinuation of TIM treatment or study completion will be recorded in the participant's medical records, as per site local practice.

However, **only the following safety events will be entered into the relevant eCRFs (within the REDCap EDC system)**, from informed consent up to and including EOS:

- Treatment-related SAEs
- Unexpected SAEs
- Treatment-emergent AEs requiring study drug discontinuation
- IBDREs of greater intensity, frequency, or duration than expected for the individual participant
- Serious infections, defined as infections requiring hospitalization and/or intravenous antibiotics
- Malignancy
- Major adverse cardiovascular event

5.4 PROCEDURES FOR AE AND SAE REPORTING

In this study, only unexpected (in the opinion of the investigator based on the participant's current SOC therapy or intervention) and treatment-related SAEs will be subject to expedited reporting to the Alimentiv Clinical Safety Specialist.

All unexpected and treatment-related SAEs must be recorded in the eCRF (within the REDCap EDC system) within 1 working day of site personnel being notified of the occurrence of the event. The site will also email the SAE report form, in addition to recording the event in the eCRF:

Clinical Safety Specialist
Alimentiv
Fax: 1-800-381-4195
Email: clinicalsafety@alimentiv.com

The initial SAE report should include at a minimum: participant 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 the information, not available at the time of the initial report, becomes available. The sponsor (or designee) may request SAE follow-up information. As only approved treatments for IBD are being used in this study, all unexpected and treatment-related SAEs will be reported by the investigator to the respective manufacturers as per local postmarketing safety reporting requirements. An unexpected event is one that is not reported in the product label.

5.4.1 Expedited Reporting

It is the responsibility of the investigator to promptly notify the independent ethics committee (IEC)/institutional review board (IRB) of all unexpected serious ADRs involving risk to human participants. An unexpected event is one that is not reported in the product label.

5.4.2 Monitoring of Adverse Events and Period of Observation

All AEs should be monitored to determine the outcome or until the physician considers it medically justifiable to terminate follow-up.

All SAEs should be monitored by the site investigator until resolved or until the SAE is clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es).

6 STATISTICAL METHODS

Statistical considerations are briefly described below. More details on the analysis and presentation of study results will be provided in the statistical analysis plan (SAP).

Appropriate descriptive statistics (mean, SD, quantiles, counts, frequencies and percentages, etc.) will be computed for all relevant study variables.

6.1 SAMPLE SIZE DETERMINATION

The sample size estimation is based on a primary analysis of time to the first occurrence of a composite event, using methods described by Lachin.[58] Based on information from American Gastroenterological Association guidelines, the estimated 1 to 2 years risk of relapse and complications in asymptomatic patients with IBD with significant bowel inflammation is approximately 50-60%.[59,60]

To justify switching TIMs, the expected benefit with treatment switching should be 25-50% lower risk of relapse and unplanned healthcare utilization. Beginning with V05 of this protocol, the sample size has been recalculated at the advice of PCORI and the DSMB. Ben-Horin and colleagues randomized asymptomatic patients with Crohn's disease with evidence of "high-risk"

bowel inflammation of the small intestine on capsule endoscopy (Lewis score >350) to a strategy of proactive treat-to-target (iterative treatment modification to treat inflammation) versus continuing current care, conceptually similar to the current treatment strategy trial.[61] With 20 patients in each arm, they observed that only 5/20 patients (25%) in the proactive treat-to-target arm met primary outcome of clinical flare at 24 months versus 14/20 (70%) in the continued standard care arm. This suggests a 64% lower risk of flare with treatment modification. Cox regression, accounting for biologics at enrollment and for disease duration as covariates, confirmed this finding, with a treat-to-target group allocation associated with reduced risk of flare compared with continued standard care (hazard ratio, 0.22; 95% CI, 0.07–0.67).

Based on this data, the updated sample size in the current trial is as follows:

- 156 patients will be followed fully for 2 years
- 60 patients will be followed variably for 1-2 years (approximately 30 patients followed for 18 months, and 30 patients followed for 12 months).

With this approach, assuming a drop-out rate of 5% between 0 to 6 months, 5% between 6 to 12 months, 5% between 12 to 18 months, and 5% between 18 to 24 months of follow-up, with an event rate of 50% in the control arm, we will be able to detect a 40.4% lower risk of events in the control arm. If there are no drop-outs, then this sample size will be able to detect a 38.8% effect size.

6.2 ANALYSIS SETS

The primary analysis will be based on all participants who are randomized to a strategy of switching to an alternative TIM to treat to a target of endoscopic remission versus continuing index therapy ("full analysis set [FAS]"), in an intention-to-treat (ITT) principle. Participants randomized to switching TIMs who are unable to switch due to insurance denial will be analyzed in the treatment group they were assigned to, in ITT analysis.

Secondary analyses will be conducted based on the "modified ITT (mITT) analysis set" (participants randomized to switching who receive at least 1 dose of the alternative TIM).

In both the primary and secondary datasets, participants who drop out after randomization (in 'full analysis/ITT set') and receipt of first dose of alternative TIM (in 'mITT analysis set') will be considered censored. Participants randomized to switching TIMs who are unable to switch will also be considered censored, in mITT analysis.

Participants will also be analyzed in a "per-protocol (PP)" analysis (participants who continue in the group they were allocated to after randomization, throughout the study until study end or until they meet the primary outcome, whichever comes first). The PP analysis will exclude participants who were switched to an alternative TIM from the continuation arm at their providers' discretion in the absence of patient-related symptoms).

6.3 OUTCOME ANALYSIS

Outcome endpoints that will be evaluated for each objective are summarized in Table 1.

For the primary composite outcome, time to treatment failure, between-group comparisons will use the Mantel log rank test, with magnitudes of treatment quantified by hazard ratios obtained from Cox proportional hazard regression analysis. Alternatively, win probability by treatment will also be estimated to account for outcome hierarchy of surgery, hospitalization, structural complication, severe symptoms, and adverse events, using methods similar to that in cardiovascular research literature.[62] The modified Poisson regression to adjust for stratification factors will be performed in the FAS, with results presented using risk ratio (RR) and 95% confidence interval (CI).[63]

For the secondary outcomes, Cox proportional hazard analysis (for time-to-event outcomes), the modified Poisson regression (to estimate RR and 95% CI for binary variables), and direct-likelihood linear mixed effects model analyses (for continuous data) will be performed. [64] These analyses will be repeated in the PP analysis set. All analyses will be adjusted for stratification factors used in the randomization. Nonparametric methods will also be used to estimate win probabilities by treatment for binary, ordinal, counts, and continuous data using methods by Zou et al.[65] More details on the analysis and presentation of secondary and exploratory outcomes will be provided in the SAP.

To ascertain differences in treatment burden and satisfaction, a between-group comparisons will be conducted using modified Poisson regression, linear regression, or Cox proportional hazard analysis, depending on outcome.

6.4 SAFETY ANALYSIS

Safety analyses will be based on the FAS analysis set. Safety data for this study includes serious infections, defined as infections requiring hospitalization and/or intravenous antibiotics. AEs (as defined in Section 5.1) will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0. The primary safety outcome will be risk of serious infections (infections requiring hospitalization and/or intravenous antibiotics) any time over 104 weeks of follow-up. Hospitalization due to complications of testing/monitoring and incident cancer on TIMs will also be captured.

SAEs will be summarized by the number and percentage of participants experiencing any severe SAEs, and any AEs leading to study drug discontinuation and will also be summarized by 1) system organ class and preferred term; 2) system organ class, preferred term, and severity; and 3) system organ class, preferred term, and relationship to study drug. If a participant experienced more than 2 SAEs for a given preferred term, severity is defined as the severity of the most severe event and relationship to study drug is the relationship of the most related event.

The primary safety outcome variable will be number of serious infections (infections requiring hospitalization and/or intravenous antibiotics) over 104 weeks of follow-up, analyzed using the negative binomial regression. Hospitalization due to complications of testing/monitoring and incidental cancer on TIMs will also be captured. Comparison of treat effects will be conducted using the extended modified Poisson regression.[66] Data on SAEs will be presented by treatment group. Descriptive statistics will be presented. No formal statistical tests will be performed because of data sparsity.

6.5 EXPLORATORY ANALYSIS

6.5.1 POWER FOR SUBGROUP ANALYSES AND ASSESSMENT OF HETEROGENEITY OF TREATMENT EFFECTS

Although *a priori* subgroups of interest with an analytical plan for heterogeneity of treatment effects have been identified, the study may be underpowered to detect clinically meaningful differences. Any strong signals on exploratory subgroup analyses will be considered hypothesis-generating and will warrant further exploration. Further observational studies to explore such signals will be possible using the IBD Qorus Learning Health System platform.

6.5.2 ADDITIONAL EXPLORATORY ANALYSES

Additional exploratory analyses may be defined in the SAP.

6.6 INTERIM ANALYSIS

After 30 participants in each arm have reached the 24-week assessment, the statistician will perform an interim analysis of effectiveness and safety outcomes, for Data Safety Monitoring Board (DSMB) review (to be reviewed in the corresponding 6-month meeting or at an ad hoc meeting as required and dependent on timing). Any recommendations from the DSMB will be communicated to the trial leadership committee for consideration (see Section 8.5).

6.7 HANDLING OF MISSING, UNUSED, AND SPURIOUS DATA

Central study coordinators will monitor the frequency of data reporting and follow up with local site coordinators to minimize missing data. Reasons for participant drop out and missing data will be recorded. For the primary composite outcome, time-to-event analysis is being performed and participants lost to follow-up will be censored. For secondary continuous outcomes, last observation carried forward (LOCF) will be used for analysis.

6.8 REPORTING OF DEVIATIONS TO ORIGINAL SAP

All deviations from the original SAP will be reported in the study report.

7 ETHICAL CONSIDERATIONS

The current study will be conducted in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH-GCP), and the applicable regulatory requirements.

7.1 INSTITUTIONAL REVIEW BOARD

All relevant documents for this study will be submitted to an appropriate IRB or IEC for review. A signed and dated letter documenting IRB/IEC approval must be obtained prior to any participant enrolment at the site. The IRB/IEC must be notified of all subsequent protocol amendments.

7.2 INFORMED CONSENT

Prior to any study procedures, it is the responsibility of the investigator to fully inform the participant of all pertinent aspects of the study. Each participant must give documented informed consent prior to their participation in the study. The method of obtaining and documenting the

informed consent and the contents of the consent must comply with ICH-GCP and all applicable regulatory requirement(s).

Participants can withdraw consent at any time by contacting their site and requesting to withdraw consent. Withdrawal would be documented in the REDCap database and by the PI to include participant's name, reason, and date of withdrawal. Trial-related information collected from the participant up to the time of withdrawal may be accessed and used for future purposes.

7.3 LOST TO FOLLOW-UP

All participants will be followed for up to a 2-year follow-up period (end of study), or until loss to follow-up or withdrawal of consent (investigator/sponsor or participant decision), whichever occurs first. A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits or are persistently noncompliant with questionnaires despite repeated reminders and are unable to be contacted by the study site.

If a participant fails to return for a required study visit, every effort should be made to attempt to contact them and reschedule the visit as soon as possible. If contact is made, the participant should be reminded of the importance of maintaining the assigned visit schedule and it should be determined whether they wish to and/or should continue in the study. All contact attempts should be documented in the participant's medical record. If a participant continues to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.4 CONFIDENTIALITY OF PARTICIPANT RECORDS

All study records containing participant details will identify the participant by initials where permitted and the assigned participant identification number. Participant information collected will comply with the requirements for the protection of privacy of individually identifiable health information.

The data that is collected on this trial will be securely stored and will be maintained by Mayo Clinic Arizona and will remain available for future research.

While every effort will be taken to protect the identity of the participants in this study, there is no guarantee that the information cannot be obtained by legal process or court order. No participants will be identified in any report or publication of this study or its results. All study-related documents containing identifiers will be locked in filing cabinets located in secured offices. If such documents are no longer needed, they will be shredded or discarded in locked bins intended for the disposal of confidential information. All study information collected by the Foundation's data management system will employ similar provisions for the protection of participant privacy.

The investigator will grant monitor(s) and auditor(s) from the sponsor or its designee access to the participant's original medical records for verification of the data gathered and to audit the data collection process. The participant's confidentiality will be maintained, and the participant's information will be made available to the extent permitted by the applicable laws and regulations.

8 ADMINISTRATIVE REQUIREMENTS

8.1 PROTOCOL AMENDMENTS

The sponsor may modify the protocol at any time during the life of the protocol. Protocol amendments will require IRB/IEC approval prior to implementation except when changes to the protocol are required to eliminate immediate hazards to the study participants. The sponsor and IRB/IEC must be notified immediately after such changes have occurred.

8.2 PREMATURE TERMINATION OF THE TRIAL

If the investigator or sponsor discovers sufficient reasonable cause for the premature termination of the study, the terminating party will provide written notification documenting the reason for study termination. The appropriate regulatory agencies and IRB/IEC must be notified.

8.3 DATA MANAGEMENT

8.3.1 DATA COLLECTION, TRANSFER, AND STORAGE

The Research Electronic Data Capture (REDCap) web-based application will be used to manage online patient surveys and questionnaires and to capture clinical research data. For analysis, a full data set will be extracted from REDCap and transferred to Mayo Clinic Arizona every 6 months. Additional details of the data collection and transfer, and security and storage procedures will be detailed in the data transfer agreement (DTA).

8.3.2 ACCESS TO SOURCE DATA/DOCUMENTS

The investigator will permit study related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

8.4 QUALITY ASSURANCE

The sponsor or its designee may perform onsite monitoring visits periodically during the study. At these visits, the monitor will review study documents to ensure adherence to the study protocol and regulatory requirements, and to review CRF entries against source documents. Findings from the visit will be discussed with the investigator.

Study data will be entered in the eCRF by trained study personnel. Data validation edit checks will be defined and implemented. Inconsistent and questionable data detected during data entry or data validation process will be queried. Data clarification forms will be generated, and any discrepancies will be resolved.

8.5 DATA SAFETY MONITORING BOARD

A DSMB will be established for this study. The DSMB will review interim unblinded data every 6 months to monitor safety and effectiveness and provide recommendations to the trial management group to ensure that participants are not exposed to undue risks. The roles and responsibilities of members of the DSMB and the procedures to be followed will be described in a separate charter.

8.6 RETENTION OF STUDY DOCUMENTS

The investigator must retain all hard-copy study records for 15 years and electronic copies indefinitely after the notification of the IRB/IEC regarding the end of the study or according to applicable regulatory requirements.

If the investigator retires, relocates, or withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The sponsor must be notified in writing if a custodial change occurs.

8.7 PUBLICATION POLICY

The sponsor will support publication of trial results in accordance with standard editorial and ethical practice. CCF will utilize its existing education, support and advocacy framework to widely disseminate findings from this study to impact clinical care of patients through multiple avenues including: 1) conferences and national scientific meeting, 2) scientific journals, 3) development of patient and clinician education materials, and 4) advocacy at the state and federal levels to implement policy change.

Prior to submission for publication or presentation of any data or results obtained in this study, written permission of the sponsor is required. Draft manuscripts, abstracts, and presentations should be submitted to the sponsor for review and approval. Permission will not be unreasonably withheld by the sponsor. The sponsor will retain ownership of the data obtained in this study. Authorship of publications resulting from this study should accurately reflect the academic contribution of individuals to the design and implementation of the trial, analysis of the data, and preparation of the manuscript.

8.8 STUDY CONFIDENTIALITY

All confidential information, verbal and written, provided to the investigator by the sponsor will be kept in strict confidence, and restricted to the study personnel involved in conducting the study, except if the information is required by the IRB/IEC or similar committees.

8.9 FINANCING AND INSURANCE

Financing and insurance will be addressed in a separate agreement with study centers.

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Appendix 1. SES-CD and SEMA-CD Scores

Scoring of the Simple Endoscopic Score for Crohn's Disease (SES-CD)

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

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

Adapted from: Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505-12.

Scoring of the Simplified Endoscopic Mucosal Assessment for Crohn's Disease (SEMA-CD)

Points	Ileum	Colon	Description	
0	○Endoscopic remission	○Endoscopic remission	Normal	
1	○Minimal disease	○Minimal disease	No more than a few aphthous ulcers Otherwise normal	
2	○Mild disease	○Mild disease	Scattered aphthous ulcers or small ulcers No large ulcers (i.e. no ulcers >2cm) Narrowing, ok if it can be passed	
3	○Moderate disease	○Moderate disease	Scattered large ulcers or widespread small ulcers Multiple passable stenoses No nonpassable stricture or visible fistulas	
4	○Severe disease	○Severe disease	Widespread large ulcers Nonpassable stricture or visible fistula	
-	○Not assessed	○Not assessed		
Colonic segments involved	❑ Ascending	❑ Transverse	❑ Descending	❑ Rectum

Note: Strictures of the ileocecal valve should be considered in the *ileum* score. Nonintubation of ileum, without stricture should be considered "not assessed."

Source: Adler J, Eder SJ, Gebremariam A, et al. Development and testing of a new Simplified Endoscopic Mucosal Assessment for Crohn's Disease: the SEMA-CD. Inflamm Bowel Dis. 2021;27(10):1585-1592. doi:10.1093/ibd/izaa307

Appendix 2. Mayo Endoscopic Subscore

Endoscopic Findings
0 Normal or inactive disease
1 Mild disease (erythema, decreased vascular pattern, no friability)
2 Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 Severe (spontaneous bleeding, ulceration)

Source: Food and Drug Administration, Center for Drug Evaluation and Research. Draft guidance: ulcerative colitis: clinical trial endpoints. guidance for industry. 2016.

Appendix 3. PRO2 UC and PRO2 CD

Note: Study participants will complete the PRO2 utilizing a 3-day recall period (excluding days of bowel preparation and ileocolonoscopy, if applicable).

PRO2 UC

Stool frequency 0 Normal number of stools for this subject 1 1 to 2 stools more than normal 2 3 to 4 stools more than normal 3 5 or more stools more than normal
Rectal bleeding 0 No blood seen 1 Streaks of blood with stool less than half the time 2 Obvious blood (more than just streaks) or streaks of blood with stool most of the time 3 Blood alone passed

Source: Schroeder, et al. N Engl J Med. 1987; US FDA. Ulcerative colitis: clinical trial endpoints. Guidance for industry (Draft Guidance). 2016.

PRO2 CD

Enter all values legibly using a black ballpoint pen	**Day 1** **Date:**	**Day 2** **Date:**	**Day 3** **Date:**	**Mean of 3 days**
Number of liquid or very soft stools				
Daily abdominal pain rating (0 = none, 1 = mild, 2 = moderate, 3 = severe)				

Source: Khanna R, Zou G, D'Haens G, Feagan BG, Sandborn WJ, Vandervoort MK, et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. Aliment Pharmacol Ther. 2015 Jan;41(1):77-86. doi:10.1111/apt.13001

Appendix 4. Prevalence Patterns of Endoscopic Activity in Patients with IBD by PRO Patterns

Prevalence patterns of endoscopic activity in patients with Crohn's disease and ulcerative colitis by patient-reported outcomes (PRO) patterns, based on post-hoc analysis of clinical trials of TIMs in IBD. The definitions of PRO and endoscopic activity presented here are the same as the ones being used in the proposed trial

Crohn's disease	Endoscopic activity (based on SES-CD)		
PRO2-CD	Remission (SES-CD <3)	Mild (SES-CD 3-6)	Moderate-severe (SES-CD >6)
Remission	29%	18%	**53%**
Mild	27%	21%	52%
Moderate-severe	20%	14%	66%
Ulcerative colitis	**Endoscopic activity (based on Mayo endoscopy score)**		
PRO2-UC	Remission (MES 0)	Mild (MES 1)	Moderate-severe (MES 2 or 3)
Remission	25%	52%	**23%**
Mild	6%	32%	62%
Moderate-severe	1%	10%	89%

Source: Dulai, et al. Aliment Pharmacol Ther. 2020.

Appendix 5. Short Quality of Life Questionnaire for Inflammatory Bowel Disease

SIBDQ

SHORT QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (SIBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from (Systemic)

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

2. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from (Social)

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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SIBDQ

3. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from
(Social)

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

4. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from
(Bowel)

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from
(Emotional)

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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SIBDQ

6. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from
(Bowel)

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

7. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from
(Systemic)

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

8. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from
(Emotional)

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

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SIBDQ

9. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from
(Bowel)

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from
(Emotional)

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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Appendix 6. IBD-Control

IBD-Control

The Inflammatory Bowel Disease Control Questionnaire

1	**Do you believe that:**			
	a. Your IBD has been well controlled in the past *two weeks*?	Yes ☐	No ☐	Not sure ☐
	b. Your *current treatment* is useful in controlling your IBD? (If you are not taking any treatment, please tick this box ☐)	Yes ☐	No ☐	Not sure ☐
2	**Over the past *two weeks*, have your bowel symptoms been getting worse, getting better or not changed?**	Better ☐	No change ☐	Worse ☐
3	**In the past two weeks, did you:**			
	a. Miss any planned activities because of IBD? (e.g. attending school/college, going to work or a social event)	Yes ☐	No ☐	Not sure ☐
	b. Wake up at night because of symptoms of IBD?	Yes ☐	No ☐	Not sure ☐
	c. Suffer from significant pain or discomfort?	Yes ☐	No ☐	Not sure ☐
	d. Often feel lacking in energy (fatigued) (by 'often' we mean more than half of the time)	Yes ☐	No ☐	Not sure ☐
	e. Feel anxious or depressed because of your IBD?	Yes ☐	No ☐	Not sure ☐
	f. Think you needed a change to your treatment?	Yes ☐	No ☐	Not sure ☐
4	**At your next clinic visit, would you like to discuss:**			
	a. Alternative types of drug for controlling IBD	Yes ☐	No ☐	Not sure ☐
	b. Ways to adjust your own treatment	Yes ☐	No ☐	Not sure ☐
	c. Side effects or difficulties with using your medicines	Yes ☐	No ☐	Not sure ☐
	d. New symptoms that have developed since your last visit	Yes ☐	No ☐	Not sure ☐
5	**How would you rate the OVERALL control of your IBD in the past two weeks?** Please draw a vertical line (|) on the scale below			



Appendix 7. PROMIS-7 – Fatigue Short Form 7a

PROMIS® Item Bank v.1.0 - Fatigue -Short Form 7a

Fatigue - Short Form 7a

Please respond to each question by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
FATEXP40	How often did you feel tired?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	How often did you experience extreme exhaustion?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	How often did you run out of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	How often did your fatigue limit you at work (include work at home)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	How often were you too tired to think clearly?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	How often were you too tired to take a bath or shower?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	How often did you have enough energy to exercise strenuously?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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Appendix 8. IBD-DI-SR

Please answer the following questions about your IBD and your health. Please think about the LAST WEEK, take both good and bad days into account.

1. In general how would you rate your health today?

○ Very good ○ Good ○ Moderate ○ Bad ○ Very Bad

2. Have you been diagnosed by a doctor as having arthritis? ○ Yes ○ No

3. Do you have problems with joint pains? ○ Yes ○ No

4. How many liquid or very loose stools (bowel movements) did you have in the last week?

(Please give an approximate number.) _____

Please choose the best answer choice to the questions in the following table:

IN THE LAST WEEK	None	Mild	Moderate	Severe	Extreme
… how much of a problem did you have with sleeping, such as falling asleep, waking up frequently during the night, or waking up too early in the morning?	○	○	○	○	○
… how much of a problem did you have due to not feeling rested and refreshed during the day (e.g. feeling tired, not having energy)?	○	○	○	○	○
… how much of a problem did you have with feeling sad, low or depressed?	○	○	○	○	○
… how much of a problem did you have with worry or anxiety?	○	○	○	○	○
… how much of a problem did you have with the way your body or body parts looked?	○	○	○	○	○
… how much of a problem did you have with stomach or abdominal pain?	○	○	○	○	○
IN THE LAST WEEK	None	Mild	Moderate	Severe	Extreme
… how much difficulty did you have coordinating and managing defecation including choosing and getting to an appropriate place for defecation and cleaning yourself after defecation?	○	○	○	○	○
… how much difficulty did you have looking after your health, including maintaining a balanced diet?	○	○	○	○	○
… how much difficulty did you have with personal relationships?	○	○	○	○	○
… how much difficulty did you have with participation in the community?	○	○	○	○	○
… how much difficulty did you have with work	○	○	○	○	○

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Appendix 9. Treatment Burden Questionnaire

Treatment Burden Questionnaire

(English version)

Authors: Viet –Thi Tran and Philippe Ravaud

METHODS Team, Unit 1153, INSERM, Paris, France

References

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http://www.biomedcentral.com/1741-7015/12/109

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Inserm

Take a moment and consider everything you have to do to take care of your health. Please rate the burden or problem associated with each of the following items.

1. How would you rate the problems related to :

A. The taste, shape or size of your tablets and/or **the annoyances** caused by your injections (for example: pain, bleeding, bruising or scars)?

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

B. The number of times you should take your medication daily?

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

C. The **efforts you make not to forget to take your medications** (for example: managing your treatment when you are away from home, preparing and using pillboxes…)

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

D. The necessary precautions when taking your medication (for example: taking them at specific times of the day or meals, not being able to do certain things after taking medications such as driving or lying down…)

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

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2. Regarding your medical follow-up, how would you rate the problems related to :

A. **Lab tests and other exams** (for example: blood tests or radiology): frequency, time spent and associated nuisances or inconveniences

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

B. **Self-monitoring** (for example: taking your blood pressure or checking your blood sugar) : frequency, time spent and associated nuisances or inconveniences

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

C. **Doctor visits and other appointments**: frequency and time spent for these visits and difficulties finding healthcare providers

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

D. The difficulties you could have in your **relationships with healthcare providers** (for example: feeling not listened to enough or not taken seriously)

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

E. **Arranging medical appointments** (doctor visits, lab tests and other exams) and **reorganizing your schedule** around these appointments

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

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How would you rate:

3. The **administrative burden** related to healthcare (for example: all you have to do for hospitalizations, reimbursements and/or obtaining social services)?

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

4. **The financial burden** associated with your healthcare (for example: out of pocket expenses or expenses not covered by insurance)?

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

5. The burden related to **dietary changes** (for example: avoiding certain foods or alcohol, having to quit smoking...)?

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

6. The burden related to **doctors' recommendations to practice physical activity** (for example: walking, jogging, swimming…)?

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

7. How does your healthcare impact **your relationships with others** (for example: needing assistance in everyday life, being ashamed to take your medication…)?

Does not apply ☐	Not a problem	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Big problem

8. 'The need for medical healthcare on a regular basis **reminds me of my health problems**'

Not at all	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	All the time

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Appendix 10. Treatment Satisfaction Questionnaire for Medication

TSQM *(Version II)*

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it.* For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat the condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

☐1 Yes
☐0 No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied

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☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(5) Not Applicable

5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(5) Not Applicable

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(5) Not Applicable

7. How satisfied or dissatisfied are you with how easy the medication is to use?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

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9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

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Appendix 11. Costs for Patients Questionnaire

Date: …-…-…

Subject No: _____
Code:_____

COSTS FOR PATIENTS QUESTIONNAIRE (CoPaQ)

The purpose of this questionnaire is to assess your expenses as a result of your state of health. It is divided into three sections and should take you 10 to 15 minutes to complete. Some of the items may not apply to your situation. When answering, please only consider the period ranging from ..... to ..... All your information will remain confidential.

All listed costs or expenses must be associated with your **Ulcerative Colitis or Crohn's Disease** as it relates to your daily life, or be directly linked with the use of health care services needed to treat your condition for the period ranging from ..... to ..... You should only take into account the amounts you need to cover yourself, specifically the net amount. Do not include in your answers any portion of the costs reimbursed by your insurance. For some of the questions, you may have more than one answer.

Section A. Costs for Patients Questionnaire

1- Costs you need to cover, i.e. the net amount you have to pay (and not the portion reimbursed by your insurer)

1.1. Did you travel to a health center (e.g. hospital, family medicine group, physiotherapy clinic) to receive health care services, or for consultations?

☐ Yes ☐ No

If no, please go to question 1.7

1.2. What means of transportation did you use to get to the health center or to your consultations?

☐ Public transit (bus, metro/subway)

☐ Taxi or Rideshare (Uber, Lyft, etc.)

☐ Your personal vehicle

☐ Other means of transportation (on foot, by bicycle, personal vehicle of the person who went with you)
.....

1.3. On average, how many miles (round trip) did you travel to get to the health center or foryour consultations? ..... mile(s) per visit.
Number of visits during the reference period: .....

1.4. Did you ever pay for parking during your visits?

☐ Yes ☐ No

If yes, please provide the total number of visits and the net amount paid for all your parking needs: ……visit(s); $……..

1.5. On average, how long was your waiting time in the clinic?
……hour(s) .....minutes

1.6. When travelling to the health center or to consultations, did you pay for accommodation?

☐ Yes ☐ No

If yes, please provide the total number of visits and the net amount paid for all your accommodations: ……visit(s); $ ……..

1.7. Did you ever pay any portion "out of pocket" for your prescribed medication that was not reimbursed?

☐ Yes ☐ No

If yes, please provide the net amount you paid: $……

1.8. Did you pay for non-prescribed medication or dietary supplements (e.g. aspirin, natural products)?

☐ Yes ☐ No

If yes, please provide the net amount you paid: $……..

1.9. Did you incur expenses for home care services (e.g. rehabilitation, etc.)?

☐ Yes ☐ No

If yes, please provide the net amount you paid: $.....Please provide the type of expenses……..

1.10 Did you incur expenses for the purchase of any medical devices (e.g., blood pressure monitor, blood glucose monitor, walker, wheelchair, raised toilet seat, protective underwear, shower rails)?

☐ Yes ☐ No

If yes, please provide the net amount you paid: $..... Please provide the type of expenses……..

1.11 Did you renovate your home in order to better accommodate your condition?

☐ Yes ☐ No

If yes, please provide the net amount you paid: $……..

1.12 Did you pay for any tests or examinations performed during or following any of your consultations (e.g., blood tests, X-rays)?

☐ Yes ☐ No

If yes, please provide the net amount you paid: $……..

1.13 Did you pay for any additional non-medical services during or following your consultations (e.g., insurance forms, sending photocopies, doctor's certificate)?

☐ Yes ☐ No

If yes, please provide the net amount you paid: $……..

1.14 Did you pay for any non-medical care services (e.g. physiotherapy, occupational therapy, psychology, osteopathic treatments, massage therapy, dentistry or optometry)?

☐ Yes ☐ No

If yes, please provide the net amount you paid: $……..

1.15 Did you pay for someone to care for your dependents during any of your consultations (e.g., childcare)?

☐ Yes ☐ No

If yes, please provide the net amount you paid: $……..

1.16 Did you incur other expenses (e.g., food services, any specific meals related to accessing health care services)?

☐ Yes ☐ No

If yes, please provide the net amount you paid during this period: $ ..... Please provide the type of expenses……..

2. Average time spent (or required) to access medical services

2.1. How much time did you spend travelling to and from the health center or for your consultations (round trip)? ..... hour(s) .....minutes

2.2. Approximately how long did you need to wait to receive medical services (e.g., over the phone, or to schedule an appointment at the clinic prior to your consultation)? ……..hour(s) .....minutes

3. Costs related to your job

3.1. Have you suffered a loss of income?

☐ Yes ☐ No

If no, please go to question 4.1.

If yes, for what reason? (List all that apply to you)

☐ Short- or long-term decrease in salary as a result of missing work

☐ As a result of receiving a claim for employment insurance

☐ Reduced working hours per week (e.g., working 4 days/week)

☐ Limited career advancement or salary increase (e.g., cannot request or accept a promotion)

☐ Other (specify .....)

3.2. What is your rough estimate (net amount) of the incurred loss of income?

$ _____ ☐ Difficult to evaluate

4. Financial stress caused by your state of health

4.1. I feel financially stressed due to my state of health:

☐ Not at all

☐ A little bit

☐ Somewhat

☐ Quite a bit

☐ Very much

5. Net costs for the caregiver (i.e., the person who regularly devotes time to help you with your daily activities) or the person who accompanies you, if any

5.1. Did a caregiver or anyone else accompany you to your consultations at the health center?

☐ Yes, all the time

☐ Yes, very often

☐ Yes, half of the time

☐ Yes, sometimes

☐ No, never

If "No, never", please go to section B

5.2. Did you travel together to the health center?

☐ Yes ☐ No

If yes, please go to question 5.5

If no, please specify the means of transportation used by the caregiver or the person accompanying you.

☐ Bus/metro/subway ☐ Taxi/Rideshare ☐ Personal vehicle ☐ Other

5.3. On average, how much time and how many miles (round trip) did this person travel to get to the health center for each one of your visits?
……hour(s)……minutes .....mile(s)

5.4. Did this person pay for parking?

☐ Yes ☐ No ☐ I do not know

If yes, please provide the net amount paid: $……

5.5. Did the caregiver or the person accompanying you pay for any accommodations while accompanying you to the health center or to your consultations?

☐ Yes ☐ No

If yes, please provide the net amount paid: $……

5.6. Did your caregiver or the person accompanying you receive any training in order to assist you?

☐ Yes ☐ No ☐ I do not know

If yes, please provide the net amount paid: $ .....and the duration of the training ……hour(s) .....minutes

5.7. Did your caregiver or the person accompanying you incur any other expenses while accompanying you?

☐ Yes ☐ No ☐ I do not know

If yes, please provide the net amount paid: $……Please provide the type of expenses……..

5.8. How long is the estimated waiting time experienced by your caregiver or the person accompanying you during your medical consultations?
……..hour(s) .....minutes

6. Time spent by your caregiver or the person accompanying you not directly related to medical services

6.1. Approximately how much time in total (round trip) do you estimate your caregiver or the person accompanying you spent travelling with you to get to your non-medical consultations (e.g., massage therapy, chiropractic, naturopath)?
……..hour(s) .....minutes

6.2. How long is the estimated waiting time experienced by your caregiver or the person accompanying you during your non-medical consultations (e.g., massage therapy, chiropractic, naturopath)? ……..hour(s)..... minutes

6.3. What is the estimated average time per week your caregiver or the person accompanying you spends performing various tasks (e.g., housework, home care)?
……..hour(s) .....minutes per week

Section B. Sociodemographic and Health Questions

1. **Are you:**

☐ Man ☐ Woman ☐ Other…….

2. **Highest level of education completed:**

☐ Less than a high school diploma
☐ High School Diploma/GED
☐ Some college, no degree
☐ Associate's degree
☐ Bachelor's Degree
☐ Master's Degree
☐ Professional Degree (JD, MD, DDS, etc.)
☐ Doctoral (PhD)
Other: ……..

3. **Do you have a paid job?**

☐ Yes ☐ No

If not, which of the following best describes your situation?

☐ I cannot work at a paid job because of health problems. (If you had a paid job before, please specify your occupation and the position you held: Occupation …… ...
……period ranging from ……to.....)

☐ Other reasons (e.g., looking for work, unpaid job, retired)

4. **Are you:**

☐ Married ☐ Separated
☐ In a relationship ☐ Divorced
☐ Single ☐ Widowed

5. **How many people live in your household?**

☐ I live alone ☐ I live with one or more individuals

6. **Are there any children in your household?**

☐ Yes, the age of the youngest child living in the household is..... months/ years

☐ No

7. **Do you live in a rural or urban area?**

☐ Rural area ☐ Urban area

8. **What is your approximate gross annual income? Check the income category that applies to you.**

☐ < $5,000	☐ $25,000-29,999	☐ $50,000-59,999	☐ $90,000-99,999
☐ $5,000-9,999	☐ $30,000-34,999	☐ $60,000-69,999	☐ $100,000-124,999
☐ $10,000-14,999	☐ $35,000-39,999	☐ $70,000-79,999	☐ $125,000-149,999
☐ $15,000-19,999	☐ $40,000-44,999	☐ $80,000-89,999	☐ ≥ $150,000
☐ $20,000-24,999	☐ $45,000-49,999		

9- **What is your age group? Check the group that applies to you.**

☐ 18-24 years	☐ 55-64 years
☐ 25-34 years	☐ 65-74 years
☐ 35-44 years	☐ 75-84 years
☐ 45-54 years	☐ 85 years or more

Section C. Acknowledgements and Comments Page

Thank you for completing this questionnaire. If you have any comments, please provide them below.

QUOTIENT-Protocol-04Dec2025-V05

Final Audit Report 2025-12-13

Created:	2025-12-10
By:	Kathleen Pillsbury (kathleen.pillsbury@robartsinc.com)
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