Reduce Crohn's-Associated Diarrhea With Sodium Channel Therapy

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A randomized, double blind, placebo-controlled, crossover study of ranolazine for the treatment of Crohn's Disease-associated diarrhea

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REACT

REduce Crohn's-Associated Diarrhea with Sodium Channel Therapy

Contents

1 PROTOCOL SYNOPSIS

Sponsor	Vanderbilt University Medical Center
Protocol Title	A randomized, double blind, placebo-controlled, crossover study of ranolazine for the treatment of Crohn's Disease-associated diarrhea
Phase of Development	Phase 2 Pilot
Study drug and Mechanism	Ranolazine, sodium channel inhibitor
Treatment Schedule Dose/Route	Ranolazine and placebo will be dispensed as 500 mg oral tablets. The full dose is 500 mg twice per day for a total of 12 weeks.
Objectives	Primary: Demonstrate the efficacy of ranolazine compared to placebo in reducing CD-associated diarrhea Secondary: Demonstrate the efficacy of ranolazine compared to placebo in improving quality of life Exploratory: Explore the longitudinal effects of ranolazine on loose stool frequency Safety: Demonstrate the safety and tolerability of ranolazine when given in combination with other standard CD treatments
Endpoints	Primary endpoint: Mean change in daily number of loose stools Secondary endpoints: Mean change in CDAI score; Mean change in SIBDQ score; Mean change in PHQ-8 score; Mean change in HBI score. Exploratory endpoints: Time to 50% reduction in daily number of loose stools. Safety endpoints: Rate of treatment emergent adverse effects.
Trial Design	This will be a single-site, placebo-controlled, randomized, crossover study to evaluate the efficacy, safety, and tolerability of ranolazine for the treatment of Crohn's Disease-associated diarrhea.
Number of Patients	20 (10 in remission and 10 with active inflammation)
Duration of Therapy	12 weeks ranolazine and 12 weeks placebo
Duration of Follow-up	12 weeks
Patient Selection	The study will include subgroup analyses in two distinct patient groups: Arm 1) Crohn's Disease in remission, defined as endoscopic or radiographic findings consistent with controlled Crohn's in the past 2 years BUT still experiencing symptoms (e.g., diarrhea, abdominal pain)

	Arm 2) Active Crohn's Disease, defined as endoscopic or radiographic findings consistent with active Crohn's in the past 2 years AND have been on a stable dose of standard medication for at least one month prior to enrollment. Inclusion Criteria: 1. Meet diagnostic criteria for Crohn's Disease with active diarrhea 2. Have greater than three loose stools per day Exclusion Criteria: 1. Male and female subjects <18 years of age 2. Significant change in medication including prednisone, antidepressant medications, or stimulants within the last 4 weeks a. Allowances include: Rectal hydrocortisone, rectal mesalamine, addition of prednisone (up to 20mg) for flares, etc. 3. Regular (daily) use of opioids or other drugs of abuse including heavy alcohol or marijuana use 4. Severe psychiatric disease including schizophrenia, psychosis, suicidal depression 5. Previous use of ranolazine within 2 months prior to enrollment 6. Prior use of ranolazine which was discontinued for safety or tolerability 7. Metabolic derangement defined as liver function tests >3x upper limit of normal or severe renal disease defined as calculated creatinine clearance <30 mL/min 8. Have liver cirrhosis 9. Concurrent use of strong CYP3A inhibitors or inducers: ketoconazole, itraconazole, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir, rifampin, rifapentine, phenobarbital, phenytoin, clarithromycin, St Johns Wart, digoxin 10. A family history of (or congenital) long QT syndrome or known acquired QT interval prolongation 11. Inability or refusal to give informed consent for any reason including a diagnosis of dementia or cognitive impairment 12. Patients who are pregnant or breastfeeding 13. Patients who are enrolled in other investigational drug studies or who have taken investigational drugs within 30 days before enrollment 14. Other factors which in the opinion of the investigator could potentially impact the study outcomes (e.g., underlying disease, medications, history) or prevent the participant from completing the protocol (poor compliance or unpredictable schedule)

Study Assessments	1. Daily number of loose stools 2. Crohn's Disease Activity Index (CDAI) 3. Short Inflammatory Bowel Disease Questionnaire (SBDQ) 4. Harvey Bradshaw Index (HBI) 5. Patient Health Questionnaire (PHQ-8)

2 SCHEMA

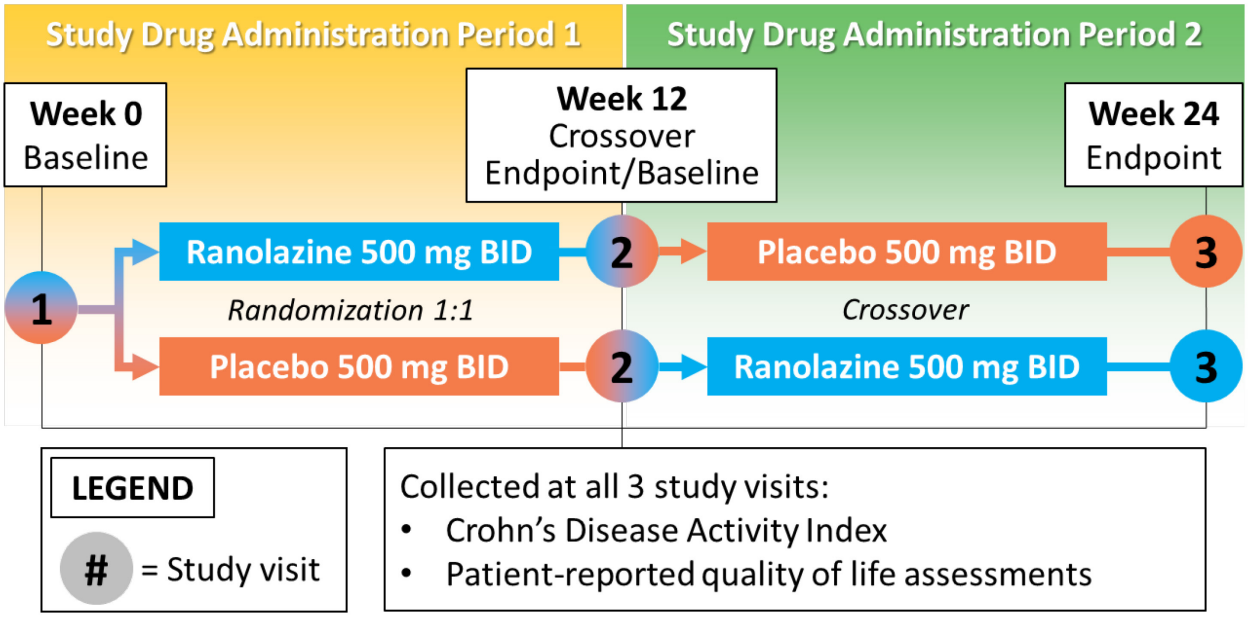

Figure 1. Clinical trial schematic

3 BACKGROUND AND RATIONALE

3.1 Crohn's Disease

Crohn's Disease (CD) is an idiopathic inflammatory disorder of unknown etiology with genetic, immunologic, and environmental influences. CD can affect any part of the gastrointestinal (GI) tract affecting some areas of the GI tract and leaving others untouched. The pathology of CD is characterized by transmural infiltration of lymphocytes and macrophages, granulomas, fissuring ulceration, and submucosal fibrosis. The transmural inflammatory process of CD predisposes patients to the formation of fistulas and it has been estimated that approximately 35% of patients will have at least 1 fistula during the course of their disease.[1] CD patients experience a lifelong cycle of a relapsing-and-remitting disease course requiring frequent corticosteroids, and/or escalation in immunosuppressive treatment; approximately half of patients will require surgery

within 10 years of diagnosis.[2] Even patients who achieve remission can experience persistent, refractory diarrhea or other symptoms such as abdominal pain, significantly affecting their quality of life and ability to work. Over 780,000 Americans are affected by CD and the worldwide incidence has been steadily increasing.[3,4]

The current standard of care for patients with CD is individualized and based on disease location, disease severity, disease-associated complications, and future disease prognosis. Therapeutic approaches are a sequential continuum to treat "acute disease" or "induce clinical remission," and then to "maintain response/remission," the overall treatment goal being to control inflammation and symptoms arising from active inflammation. Medical therapy used to treat CD includes the categories of 5-aminosalicylates (5-ASA), antibiotics, corticosteroids, immunomodulators, and biologics (the anti-TNF agents infliximab, adalimumab, certolizumab pegol; agents targeting leukocyte trafficking, including vedolizumab, natalizumab; and the anti-p40 (anti-IL-12/23) antibody, ustekinumab). Diarrhea and/or abdominal pain that is not responsive to standard therapies may be treated with lomotil or other opioids which have significant side effects and risk. Despite significant medical advancements in the treatment of CD, there remains a considerable unmet medical need for safe, effective, oral treatments for CD.

3.2 PheWAS in Drug Repurposing and Discovery

PheWAS is a method that explores the association between single nucleotide polymorphisms (SNPs) and diseases across the human phenome. This approach has been used to identify phenotypes associated with SNPs in various genes, including those producing proteins selectively targeted by FDA approved drugs. PheWAS leverages Vanderbilt's informatics and data mining expertise combined with robust de-identified health records with associated genomic data in BioVU (>250,000 human DNA samples as of May 2019). A PheWAS was performed in a disease-agnostic cohort of 28,000 BioVU patients in order to identify potential novel genotype-phenotype associations related to the SNPs in *SCN5A*. The effect of carrying at least one minor allele in this SNP on the presence of having various medical diagnoses (phenotypes) as defined by PheWAS codes derived from ICD-9 billing codes in the electronic health record (EHR) has been evaluated.

Using this precision drug repurposing method that leverages natural human genetic variation as a proxy for – and method of more accurately predicting – the physiologic effects of therapies in humans,[5] ranolazine was identified as a possible new therapy for CD. A variant (P2006A) in the *SCN5A* gene, which encodes the sodium channel protein type 5 subunit alpha ($Na_v1.5$), significantly increases persistent sodium currents, functioning as a natural gain of function variant or 'agonist.' Sodium channels play a major role in signaling the start of each heartbeat, coordinating the contractions of the heart chambers, and maintaining a normal heart rhythm.[6] A phenome-wide association study (PheWAS) uncovered a significant association between the P2006A variant and increased risk for heart palpitations (OR=4.2, *P*=0.0006), which is expected given ranolazine's known effects. Using this association as an 'anchor' in the dataset, phenotypes with a risk-causing OR >1 are possible new indications for ranolazine, which is a $Na_v1.5$ *antagonist.* PheWAS data show a potential new indication for CD (OR=4.9, *P*=0.005).

3.3 Sodium Channels and Gastrointestinal Function

Human gastrointestinal $Na_v1.5$ is structurally homologous to its cardiac equivalent and bears strong electrophysiological, mechanosensitive, and pharmacological similarities.[7] Ranolazine

blocks both peak amplitude and mechanosensitivity of Na(+) current in human colon smooth muscle cells (SMCs) and decreases contractility of human colon muscle strips. Some have concluded that this provides a likely mechanistic explanation for ranolazine-induced constipation observed in some angina patients.[8] Patients with *SCN5A* channelopathies and known cardiac arrhythmias also have an increased prevalence of functional GI disease.[7]

3.4 Investigational Agent – Ranolazine

Ranolazine, sold under the trade name Ranexa® by Gilead Sciences, received FDA approval in 2006 for chronic angina. Ranolazine is currently under investigation for several other CVD- and diabetes-related indications.[9] The lower end of the FDA-approved dose for chronic angina, 500 mg twice daily, will be used in this trial (1000 mg twice daily is also FDA approved for chronic angina). Ranolazine will be dispensed as 500 mg oral tablets, purchased and encapsulated by IDS, who will also compound matching placebo. When used properly and not concurrently with contraindicated drugs outlined in the exclusion criteria, ranolazine has been shown to be safe and well-tolerated. Ranolazine's safety profile has been established by extensive clinical experience. The most common side effects include dizziness, nausea, constipation, and headache; less than 2% of patients experience these side effects.[10,11]

3.5 Rationale for Study Design

Ranolazine may improve Crohn's Disease symptoms by acting on one of more interrelated pathways (see **Figure 2**):

Ranolazine may reduce inflammation: Transmural inflammation of the gastrointestinal tract is considered a hallmark of CD and is implicated in endothelial dysfunction and gut dysmotility, both described below. Given the ability of inflammation to induce channelopathies in the GI smooth muscle, some have proposed that clinical symptoms of gut disorders such as inflammatory bowel syndrome may be regulated at the level of the ion channel.[12] Clinical and experimental data also suggest that changes in sodium channels may play a role in inflammatory pain and therefore, sodium channel blockers like ranolazine may have some therapeutic potential.[13] There is some evidence suggesting that ranolazine may have an effect on inflammatory biomarkers.[14,15] Specific examples of anti-inflammatory effects observed with use of ranolazine include: attenuation of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) in a rat model of congestive heart failure;[16] significant decrease in the pro-inflammatory cytokines IL-1β and TNFα, and a significant increase in anti-inflammatory PPAR-ɣ expression in cultured rat astrocytes;[15,17] and stimulation of myogenesis and with concurrent reduction in measures of a pro-oxidant inflammation/oxidative condition in murine myoblastic cells.[18] Further, among individuals with stable coronary artery disease treated with ranolazine, investigators observed anti-inflammatory effects including reduced C reactive protein and asymmetric dimethylarginine.[14] More broadly, sodium channel blockade itself has been shown to have effects concordant with decreased inflammation, with phenytoin reducing by approximately 50% the release of several pro-inflammatory cytokines (IL-

1α, IL-1β, TNF-α) in lipopolysaccharide-stimulated microglia, with smaller but similar decreases observed with another sodium channel inhibitor, TTX.[19]

Ranolazine may reduce endothelial dysfunction: Endothelial dysfunction occurs when there is impairment in homeostatic functions of endothelium, ranging from control of vascular tone and leukocyte trafficking to surveillance of platelet adhesion and thrombus formation.[20] A growing body of evidence suggests the involvement of intestinal microvascular endothelial cells, a non-immune cell lineage, in the pathway to the development and maintenance of IBD. Changes in endothelial structure and function, mediated by a complex network of chemokines, cytokines and inflammatory growth factors, are a distinctive feature of active disease and their magnitude is related to disease severity.[20,21] In addition, it has been shown that human intestinal microvessels taken from chronically inflamed IBD mucosal tracts exhibit endothelial dysfunction with significant impairment of endothelium-dependent vasodilation.[20,22] Endothelial dysfunction has been evaluated in IBD patients using brachial artery flow-mediated vasodilatation (FMD), a well-established measure of endothelial function; significantly lower FMD in IBD patients compared to controls has been found, suggesting endothelial dysfunction as one etiological factor of IBD.[20,23] A strong and independent association between endothelial dysfunction and the risk for future cardiovascular disease (CVD) has been established in the literature;[20,24] IBD is also a risk factor for CVD, suggesting endothelial dysfunction is a shared mechanism in both IBD and CVD.[25] A crossover study of coronary artery disease patients found that ranolazine improved endothelial-dependent vasodilatation, a marker of endothelial dysfunction.[14] Given this evidence, ranolazine may improve endothelial function in CD patients, which could lead to reduction of CD symptoms.

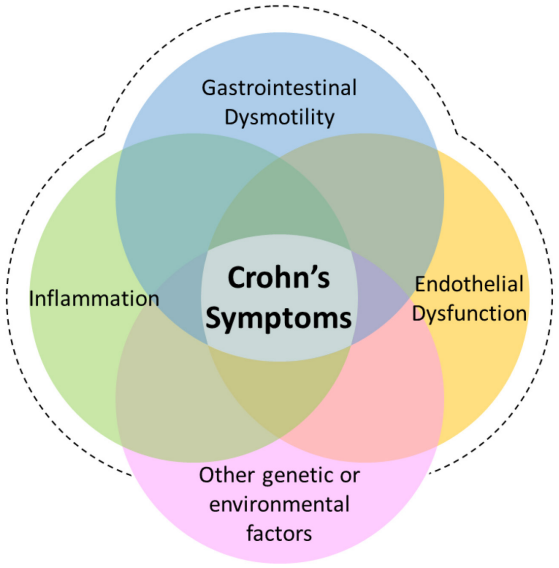

Figure 2. Interrelated pathways contributing to Crohn's Disease symptoms that may be affected by ranolazine.

Ranolazine may restore normal, coordinated gut motility: Gastrointestinal motility results from coordinated interaction of multiple cooperating mechanisms and is modulated by the enteric nervous system. Both interstitial cells of Cajal (ICC) and intestinal smooth muscle cells (SMCs) serve a fundamental role in normal gastrointestinal motility and express the sodium channel alpha subunit $Na_V1.5$, which is targeted by ranolazine. ICC are ubiquitously present in the human gastrointestinal tract and generate pacemaker activity through slow electrical waves. They are electrically coupled to SMCs via gap junctions ensuring coordinated GI motility.[26] GI dysmotility is a feature of CD and is interrelated with the other features of the disease. For example, multiple studies have shown inflammatory effects to be correlated with reduced intestinal motility; studies using MR enterography have found a significant difference in terminal ileum motility in patients with small bowel CD compared with healthy subjects,[27] and when comparing inflamed and non-inflamed small bowel segments of CD patients.[28] Hypermotility and gastrointestinal lesions also

have a close relationship. The collective results of several rat studies indicate that intestinal hypermotility with its high-amplitude contractions likely disrupts the mucus layer of the intestines, interrupting the host defense barrier, exposing the luminal contents to the epithelium and allowing bacterial invasion of the mucosa, which then triggers an inflammatory response.[29–38] Instances of severe gastrointestinal dysmotility have been reported in CD patients without clinically active disease (no active inflammation or mechanical obstruction) as well.[39] Given this evidence, ranolazine may reset and maintain the calibration and synchronicity of the gut's motility mechanism, resulting in a reduction of Crohn's-associated diarrhea or other symptoms that impact quality of life.

4 STUDY OBJECTIVES AND ENDPOINTS

The safety, tolerability, and efficacy of ranolazine given in combination with standard CD treatments will be assessed as outlined in the endpoints below.

Primary endpoint:

- Mean change in daily number of loose stools

Secondary endpoints:

- Mean change in CDAI score
- Mean change in SIBDQ score
- Mean change in PHQ-8 score
- Mean change in HBI score

Exploratory endpoints:

- Time to 50% reduction in daily number of loose stools

Safety endpoints:

- Rate of treatment emergent adverse effects

	Objective	Outcome(s)
Primary	Demonstrate the efficacy of ranolazine compared to placebo in reducing CD-associated diarrhea and other symptoms	CDAI, Daily # loose stools, HBI
Secondary	Demonstrate the efficacy of ranolazine compared to placebo in improving quality of life	SIBDQ, PHQ-8
Exploratory	Explore the longitudinal effects of ranolazine on loose stool frequency	Daily # loose stools
Safety	Demonstrate the safety and tolerability of ranolazine when given in combination with other standard CD treatments	Adverse events

Table 1. Clinical trial objectives

The crossover design was selected to yield a more efficient comparison of a treatment that aims to alleviate symptoms. Given the short, seven-hour half-life of ranolazine, the scientific value of adding an extra study visit to account for a 1.5-3 day washout was outweighed by the extra burden placed on patients. All patients will be able to continue their standard medication throughout the duration of the study.

5 PARTICIPANT SELECTION

5.1 Recruitment and Screening

The primary recruitment strategy is to recruit all 20 patients directly from the ~5000 patients currently seen at the Vanderbilt IBD Center. Throughout the enrollment period, a dedicated clinical research coordinator will review EHRs of patients who have upcoming routine clinic visits to identify those who meet eligibility criteria. These patients will be flagged for recruitment and be presented the study during a routine visit. Patients who express interest will then meet with the clinical research coordinator immediately after their routine visit to receive more information about the study and for further screening, which entails an in-depth review of current medications and comorbidities. Those who meet eligibility criteria will have the opportunity to consent and enroll in the study. Enrolled participants will complete clinical assessments, provide urine for pregnancy testing (limited to women of childbearing potential), and be randomized to their treatment sequence. Their next study visit will be scheduled, and they will be sent home with study medication.

Other recruitment methods may include:

MyResearchAtVanderbilt (MRAV) was a participant repository recruitment tool available to Vanderbilt researchers that reached over 18,000 My Health at Vanderbilt users that previously confirmed they would like to be contacted directly for research. This repository provided investigators a forum for advertising to volunteers for a specific study. Email notifications are limited to IRB approved language, describe study specifics and provide contact information (**Appendix A**). To utilize this initiative, investigators complete a MRAV Access Request that is reviewed to ensure the recruitment tool and requested number of contacts are appropriate.

In our prior study (IRB #191478), the above resource was leveraged to identify patients with Crohn's disease. A patient survey was sent to 342 patients who met the definition of Crohn's disease according to a validated Crohn's phenotype algorithm based on a combination of ICD billing codes and medications in their medical record. A total of 69 patients responded to the survey, and 64 of those patients agreed to be contacted for a future study. We have medical record numbers for those respondents. The study coordinator will pre-screen these patients via review of their medical records to determine if any meet the study criteria. Individuals who are eligible for the study will be contacted via phone for further screening.

Provider Sponsored Emails from the Principal Investigator may be used to recruit additional VUMC patients (**Appendix B**). Emails will be sent to VUMC patients not in MRAV, identified using Vanderbilt's Research Derivative (a database of clinical and related data derived from the Medical Center's clinical systems and restructured for research[40]), who have 2 or more Crohn's Disease diagnostic codes, and an e-mail address within their EHR though the Data Coordinating Core (DCC).

Both the MRAV/MHAV email and the provider sponsored email will include links to a REDCap screening survey (**Appendix C**).

Flyers will also be used as an additional recruitment tool. They will be placed in clinic locations around Tennessee including but not limited to Davidson and Williamson counties (**Appendix D**).

Public-Facing Study Website landing page is another recruitment tool that will be used. It provides an overview of the study and contact information for the study coordinator, and it will be available at: https://drugrepurposing.org/react/. This landing page (**Appendix E**) will be on the Vanderbilt Institute for Clinical and Translational Research (VICTR) drug repurposing website (https://drugrepurposing.org) and maintained by Meghan Vance, Associate Program Manager, and Jessica Abner, Project Manager. The purpose of this website is to provide visitors with an overview of the clinical trial, with the overall goal of raising awareness about the study.

5.2 Inclusion Criteria

The study will include two distinct patient groups:

Arm 1) Crohn's Disease in remission, defined as endoscopic or radiographic findings consistent with controlled Crohn's in the past 2 years BUT still experiencing symptoms (e.g., diarrhea, abdominal pain)

Arm 2) Active Crohn's Disease, defined as endoscopic or radiographic findings consistent with active Crohn's in the past 2 years.

Inclusion Criteria:

1. Meet diagnostic criteria for Crohn's Disease with active diarrhea (≥3 loose stools per day on average)

5.3 Exclusion Criteria

Exclusion Criteria:

1. Male and female subjects <18 years of age
2. Significant change in medication including prednisone, antidepressant medications, or stimulants within the last 4 weeks
    a. Allowances include: Rectal hydrocortisone, rectal mesalamine, addition of prednisone (up to 20mg) for flares, etc.
3. Regular (daily) use of opioids or other drugs of abuse including heavy alcohol or marijuana use
4. Severe psychiatric disease including schizophrenia, psychosis, suicidal depression
5. Previous use of ranolazine within 2 months prior to enrollment
6. Prior use of ranolazine which was discontinued for safety or tolerability
7. Metabolic derangement defined as liver function tests >3x upper limit of normal or severe renal disease defined as calculated creatinine clearance <30 mL/min
8. Have liver cirrhosis
9. Concurrent use of strong CYP3A inhibitors or inducers: ketoconazole, itraconazole, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir, rifampin, rifapentine, phenobarbital, phenytoin, clarithromycin, St Johns Wart, digoxin
10. A family history of (or congenital) long QT syndrome or known acquired QT interval prolongation
11. Inability or refusal to give informed consent for any reason including a diagnosis of dementia or cognitive impairment

12. Patients who are pregnant or breastfeeding
13. Patients who are enrolled in other investigational drug studies or who have taken investigational drugs within 30 days before enrollment
14. Other factors which in the opinion of the investigator could potentially impact the study outcomes (e.g., underlying disease, medications, history) or prevent the participant from completing the protocol (poor compliance or unpredictable schedule)

6 TABLE OF EVENTS

	Pre-Enrollment	**Period 1**		**Crossover**	**Period 2**	
	Day -7-0	**Day 0**	**Days 1-83**	**Day 84**	**Days 85-167**	**Day 168**
Procedure/ Assessment	Prescreen patients with upcoming SOC appts	**Visit 1** Screen, enroll, randomize/ Period 1 baseline	*Daily text message and paper diary data collection*	**Visit 2** Period 1 endpoint/ Period 2 baseline	*Daily text message and paper diary data collection*	**Visit 3** Period 2 endpoint
EMR review	X					
Informed consent		X				
Medical history		X		X		X
Physical exam including vital signs		X		X		X
Concomitant meds		X		X		X
Urine pregnancy test		X		X		
Crohn's Disease Activity Index (CDAI)		X		X		X
Short Inflammatory Bowel Disease Questionnaire (SIBDQ)		X		X		X
Patient Health Questionnaire-8 (PHQ-8)		X		X		X
Harvey Bradshaw Index (HBI)		X		X		X
Randomization 1:1		X				
Start study drug		X		X		
Assess medication compliance				X		X
Daily number of loose stools		X	X	X	X	X
Adverse event monitoring		X	X	X	X	X

7 PROCEDURES

7.1 Overview

Patients will be enrolled in the study for a total of 24 weeks. Patients entering the clinic for a routine visit will be recruited, consented, enrolled, and randomized at that same visit. They will undergo eligibility screening and be sent home with investigational medication. They will return at the end of the first 12-week study drug administration period for a mid-point study visit at which they will provide Period 1 endpoint/Period 2 baseline measurements and crossover to the second study drug administration period. As during the first administration period, they will return for the third and final study visit at the end of the second 12-week study drug administration period (Week 24/Day 168). Alternatively, patients can decide to participate in the study through virtual visits. The same timeline will be followed. Participants will be sent a blood pressure cuff and given instructions (**Appendix F**) to take their own measurements. Between study visits, the study coordinator will call or text participants with reminders about study visits and the completion of the daily survey.

7.2 Randomization Procedures

Participants will be allocated to treatment sequence (ranolazine first/placebo second or vice versa) using a block randomization module in REDCap. Equal numbers of participants will randomized to the ranolazine-first and placebo-first groups. Participants will also be stratified based on remission status so that equal numbers of participants are enrolled in Arms 1 and 2. Only the IDS team members and biostatisticians will have access to the randomization module.

7.3 Agent Administration and Duration of Treatment

The investigator will instruct all patients to take the study drug exactly as specified in the protocol. The study team will assess medication compliance at each study visit. Ranolazine and placebo will be dispensed as 500 mg tablets, encapsulated by IDS. The full dose is 500 mg twice per day. Patients will be given a sufficient number of capsules to last until the next visit. All patients will take ranolazine and placebo, each for 12 weeks. Patients may contact the study team if experiencing side effects and receive instructions about how to reduce their dose to 500 mg BID.

Study drugs should be taken at approximately the same time each day, preferably in the morning and evening, and no earlier than 1 hour and no later than 4 hours after the scheduled time. Each dose of ranolazine should be taken with a glass of water. Ranolazine may be dosed with or without food. Ranolazine capsules should never be chewed, cut, or crushed. The entire contents of the ranolazine capsules should be consumed; the dose should not be divided.

If a dose is missed (i.e., not taken within 4 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

Patients will also be given instructions for self-administration as to the number and strength of the capsules to take. Patients will be instructed to bring all unused capsules to each study visit for assessment of compliance and medication disposal.

7.4 Safety Assessments

7.4.1 Urine Sample Collection

Urine will be collected from female participants of childbearing potential during study visits 1-2 for a urine pregnancy test. The study team will provide over the counter pregnancy tests for participants who decide to participate in the study remotely. These tests will be shipped to potential participants to confirm eligibility. Pregnancy is an exclusion criterion for this study.

7.5 Efficacy Assessments

7.5.1 Crohn's Disease Activity Index (CDAI)

The CDAI, considered the 'gold standard' for defining clinical endpoints in CD trials, is an assessment predominantly used in research settings to quantify CD symptoms. The CDAI is a composite score ranging from 0 to approximately 600, with higher scores indicating greater disease activity. The 8 components used to assess the CDAI and their weighting factors are noted in **Table 2**.[41] Since blood draws will not be performed as part of this study, the hematocrit component of the CDAI will not be assessed.

Clinical or Laboratory Variable	Weighting
Number of liquid or soft stools each day for 7 days	x 2
Abdominal pain (graded 0-3 on severity) each day for 7 days	x 5
General well-being, from 0 (well) to 4 (terrible) daily for 7 days	x 7
Presence of extraintestinal complications	x 20
Taking diphenoxylate/atropine, loperamide, or opiates for diarrhea	x 30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	x 10
Hematocrit of <0.47 in men and <0.42 in women	x 6
% deviation from standard weight	x 1

Table 2. CDAI components and weighting

Clinical remission based on CDAI score is defined as a CDAI score of <150. Clinical response is defined as CDAI reduction from baseline of ≥100 points or CDAI score <150. Clinical remission based on abdominal pain and stool frequency is defined as an average stool frequency score ≤3 with a stool frequency no worse than baseline and an average abdominal pain score ≤1.

7.5.2 Electronic data collection

We will collect data directly from patients using MyCap or, if installation and use of an app is not possible, through a paper version. MyCap is a secure mobile application developed by the REDCap team at Vanderbilt and integrated into the REDCap database system. Participants install the application on their personal device. All interaction with the app is secure and requires the user to enter a 6-digit pin. Once a patient has consented, they join a study for data collection by scanning a unique QR code. Then, patients receive a notification each day to answer questions about their number of loose stools and antidiarrheal medication use. This provides the capacity for collecting patient reported outcomes in a secure and robust manner. If patients are unable to use this application or unwilling to install it, they will be provided with a paper version of the

questionnaire. This minimizes loss to follow up and maximizes the efficiency of the study. Research teams have had great success using REDCap-based mobile data collection for multiple studies including collection of data about quality of life and exercise after heart surgery (NCT03270124), pain reporting in sickle cell disease (NCT03629678), and pain using a visual analog scale (VAS) during an interventional drug study (NCT03865940).

7.5.3 Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

The SIBDQ is a 10-item shortened version of the original 32-item IBDQ. The SIBDQ measures quality of life in four domains: bowel symptoms, emotional health, systemic symptoms, and social function.[42]

7.5.4 Patient Health Questionnaire (PHQ-8)

The PHQ-8 is a 8-item module that screens for the presence and severity of depression and can be used to make a depression diagnosis using DSM-IV criteria.[43]

7.5.5 Harvey Bradshaw Index (HBI)

The Harvey-Bradshaw index (Harvey-Bradshaw Index - HBI) was conceived in 1980 as a simplified version of the CDAI to foster a systematic collection of clinical data related to Crohn's disease. The index considers five parameters, exclusively clinical (patient well-being, abdominal pain, number of liquid or soft stools, abdominal mass, complications). For each parameter a specific score is assigned.[44]

8 DESCRIPTION OF STUDY TREATMENT

8.1 Description of Study Drug

The study drug, 500 mg extended release generic ranolazine tablets, will be obtained by Vanderbilt's Investigational Drug Service (IDS). IDS will over-encapsulate ranolazine tablets at the IDS pharmacy. The tablet will be covered with microcrystalline cellulose in the capsule. The matching placebo manufactured for this study will be identical in appearance and will also be compounded at IDS. Ranolazine and placebo can be stored at room temperature for up to 6 months.

8.2 Study Drug Accountability and Disposal

Investigational drug should not be used for purposes other than as defined in this protocol.

The Principal Investigator will provide study drug only to the identified subjects of this study, according to the procedures described in this study protocol. All supplies of study drug will be accounted for in accordance with Good Clinical Practice. Both the Investigational Drug Service and the Principal Investigator will maintain accurate records of the disposition of all investigational supplies received during the study. The records should include the amounts and dates that the clinical drug supplies were received, dispensed to the subject, and returned by the subject.

8.3 Study Drug Compliance

It is the Principal Investigator's responsibility to ensure that subjects are correctly instructed on how to take their study drug, and that each subject is fully compliant with his/her assigned dosing regimen. The study coordinator will assess medication compliance at each study visit. Subjects will be asked to return all unused study drug at the end of the study. The study drug should be dispensed by the Principal Investigator, or by a qualified individual under the Principal Investigator's supervision.

At each visit, previously dispensed study drug capsules will be collected by the Principal Investigator, or by a qualified individual under the investigator's supervision, and compliance assessed. Subjects exhibiting poor compliance, i.e. 2 or more missed medication days in 1 week, as assessed by medication counts at each visit, should be counseled on the importance of good compliance to the study dosing regimen. Subjects who are persistently noncompliant (<80% or >120%) may be removed from the study.

9 CONCOMITANT MEDICATIONS AND PROCEDURES

9.1 Permitted Concomitant Medications and Procedures

Any medication that is considered necessary for the subject's health and is not expected to interfere with the evaluation of or interact with ranolazine may be continued during the study. All patients must remain on a stable dose of their standard Crohn's Disease medications throughout the course of the study. Use of antidiarrheals such as loperamide is permitted and will be tracked.

9.2 Prohibited Concomitant Medications and Procedures

Prohibited concomitant medications are listed in the exclusion criteria.

10 STATISTICAL CONSIDERATIONS

10.1 Overview

The hypothesis to be tested in this study is that sodium channel dysfunction may contribute to diarrhea among Crohn's Disease patients, and that inhibition of sodium currents may be beneficial. Our overall goal is to conduct an exploratory clinical trial of the sodium channel blocker, ranolazine, in a population of Crohn's Disease patients who are experiencing persistent diarrhea.

10.2 Study Population Definitions

The following analysis populations will be used in the statistical analysis:

- Intent-to-treat (ITT): The ITT analysis population will consist of all randomized subjects from the screened analysis population who receive at least one dose of study medication. Outcomes for the subjects in the ITT analysis population will be analyzed according to actual treatment received during the study drug administration period when the outcome measure was collected. The primary analysis population for all efficacy endpoints will be the ITT analysis population.
- Safety: The safety analysis population is defined as all subjects who are randomized and receive at least one dose of study medication, analyzed by actual treatment received.
- Per-protocol (PP): The PP population will consist of all patients in the ITT population who adhere to the protocol. This population will be used in sensitivity analyses of the primary and key secondary endpoints to evaluate the influence of major protocol violators and protocol deviators on the primary results.

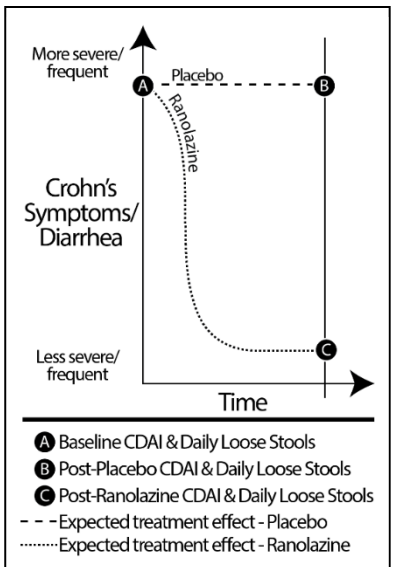

Figure 3. Potential effect of ranolazine on Crohn's symptoms

10.3 Statistical Methods

We will test for differences in the average effect of treatment for each proposed outcome using separate paired t-tests. For subjects randomized to receive ranolazine first, we will compare the response at the end of Period 1 (Visit 2) to the response at the end of Period 2 (Visit 3); for subjects randomized to receive placebo first, we will compare Visit 3 to Visit 2. Results will be expressed as the mean effect of treatment with corresponding 95% confidence intervals. We will use semi-parametric approaches to adjust for multiple comparisons among correlated hypotheses and anticipate that randomization and the paired analysis approach will mitigate confounding.

To utilize the longitudinal data collected at multiple visits and test hypotheses related to the timing of treatment effectiveness, we will also generalize the paired t-test to a regression model framework. Separate longitudinal regression models will be estimated that include fixed effects of time, treatment-group indicator, and the time by treatment indicator interaction. To account for correlation arising from taking repeated measurements on the same subject over time, we will use either random effects (continuous outcomes) or generalized estimating equations with the robust Huber-White sandwich estimator clustering on subject identifier (binary, ordinal, count outcomes). For outcomes measured at visits 1-3, time will be modeled as a factor (categorical) variables, and for diary data collected daily, we will flexibly model time using regression splines. These models will allow us to estimate the changing effect of treatment over time. We will use the diary data to evaluate compliance and model changes in the number of stools per day over time. While our primary analysis will be intent to treat, we will consider secondary analyses to determine if rate of compliance modifies the effect of treatment. For the number of stool per day analysis, a Poisson longitudinal regression model will allow us to estimate the quantities described in **Figure 3** including to time to symptom reduction and time to symptom recurrence after treatment discontinuation.

Power and sample size. We plan to enroll 20 total subjects (10 in each arm). Based on potential 20% dropout rate, we are aiming to have 16 or more completers for this study. We used previously

published[42] and preliminary data collected at Vanderbilt to estimate the standard deviation of the difference based on the standard deviation of the outcome and intraclass correlation. Accounting for multiple comparisons at a significance level of 0.05, we will have 80% power to detect changes of 63, 9.4, and 4.1 points for the CDAI, SIBDQ, and PHQ-8 outcomes. Using a rate of 3 loose stools per day, we will have 80% power to detect a reduction of 1.05 stools per day, or 7.35 per week (primary endpoint).

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event

An AE is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment”. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

AEs include any of the following:

- Worsening (change in nature, severity or frequency) of conditions present at the onset of the trial
- Subject deterioration due to the primary illness
- Intercurrent illnesses
- Drug interactions
- Events related or possibly related to concomitant medications
- Abnormal laboratory values or changes of vital signs, as well as significant shifts from baseline within the range of normal, which the Investigator considers to be clinically significant

CD relapse and related symptoms will be monitored as study endpoints and thus will not be recorded as AEs.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered the AE rather than the procedure itself.

Abuse, withdrawal, sensitivity or toxicity to a study drug should be reported as an AE. Overdose, accidental or intentional, that are associated with an AE should be reported on the eCRF. Any sequela of an accidental or intentional overdose of a study drug should be reported as an SAE on the AE eCRF. The overdose resulting from in the SAE should be identified as the cause of the event on the SAE Report Form and eCRF but should not be reported as an SAE itself.

11.1.2 Serious Adverse Event

During clinical investigations, serious AEs may occur. If the event is suspected to be drug-related, the event may be significant enough to lead to important changes in the way the medicinal product

is developed (*e.g.*, change in dose, population, needed monitoring, consent forms). This is particularly true for reactions, which, in their most severe forms, threaten life or function. A serious AE (SAE) or serious adverse drug experience (SADE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening. 'Life-threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E6).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity (as per reporter's opinion)
- Is a congenital anomaly/birth defect
- Is another medically important condition. Important medical conditions that may not result in death, be life-threatening or require hospitalization may be considered as SAEs or SADEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse [Code of Federal Regulations Title 21, Volume 5, 21CFR312.32, revised April 1, 2006].

11.1.2.1 Assigning Relationship of Serious Adverse Event to Study Drug (Causality)

The Principal Investigator will determine the relationship of each SAE to study drug (i.e., causality) by using the classification criteria 'not related', 'possibly related', or 'probably related'. Descriptions of the three classification categories are as follows:

Not Related (must include at least the first two features)

- It does not follow a reasonable temporal sequence from administration of the drug.
- It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It does not follow a known pattern to the suspected drug.
- It does not reappear or worsen when the drug is re-administered.

Possibly Related (must include at least the first two features)

- It follows a reasonable temporal sequence from administration of the drug.
- It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It follows a known response pattern to the suspected drug.

Probably Related (must include at least the first 3 features)

- It follows a reasonable temporal sequence from administration of the drug.

- It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It disappears or decreases on cessation or reduction of dose. there are exceptions when an AE does not disappear upon discontinuation of the drug (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia).
- It follows a known pattern of response to the suspected drug.

Related (must include all of the following features)

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It disappears or decreases on cessation or reduction of dose. there are exceptions when an AE does not disappear upon discontinuation of the drug (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia.
- It follows a known pattern of response to the suspected drug.
- It reappears or worsens if the drug is re-administered.

All efforts should be made to classify the SAE according to the above categories. After initiation of study drug, all SAEs, regardless of relationship to study drug, will be recorded until the subject completes his or her last study visit.

11.1.3 Adverse Drug Reaction

In the pre-approval clinical experience with a new medicinal product or its new usage, particularly as the therapeutic dose(s) may not be established, an adverse drug reaction is defined as: All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADR).

11.1.4 Unexpected Adverse Drug Reaction

An unexpected ADR is: An adverse drug reaction, the nature or severity of which is not consistent with the applicable product information, also known as reference safety information. The reference safety information is the package insert.

11.2 Monitoring, Recording, and Reporting of Adverse Events

Serious adverse events related to the use of the study drug (ranolazine) are not expected to occur based on extensive previous human experience. Since ranolazine is a marketed drug with a well-established safety profile, non-serious adverse events will not be subject to expedited reporting for this study. For both AEs and SAEs, the Principal Investigator will provide a record of the start and stop dates of the event, the action taken with study drug as a result of an AE or SAE as applicable (e.g., discontinuation, interruption, or dose reduction of study drug, as appropriate), whether any concomitant and/or additional treatments were given for the event, and the outcome

of the event. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

The study team will review all AE at their regular team meetings. AE will be reported to the IRB during annual review.

Our procedures for reporting the serious adverse events will be as follows: 1. SAEs will be recorded in the patient's study chart and reported to the Principal Investigator within 24 hours of the study team's awareness of the occurrence by email or text message and will be reported to Vanderbilt's IRB according to IRB policies (5 working days). The Principal Investigator will be responsible for systematically reviewing SAEs, assigning causality, and evaluating relatedness of each event. The Principal Investigator will determine if any necessary actions need to occur as result of the event in order to increase the safety of the protocol.

11.3 Pregnancy

Pregnancy in itself is not regarded as an AE unless there is suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Pregnancies or suspected pregnancies, i.e. positive pregnancy test in a female subject of childbearing potential regardless of disease state, occurring while the subject is on study drug, or within 30 to 45 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of study drug to the Principal Investigator.

12 DISCONTINUATIONS

12.1 Criteria for Removal from Study

Participants will be removed from study treatment when any of the criteria listed in the next section applies. All patients who initiate protocol treatment will be included in the safety analysis, and all patients who initiate protocol treatment and receive the full 24 weeks of treatment (12 weeks ranolazine and 12 weeks placebo) will be included in overall evaluation of response. All reasons for discontinuation of therapy should be documented clearly in the medical record.

12.2 Discontinuation of Treatment

The reasons for discontinuation or protocol treatment include, but are not limited to:

- Non-compliance with the study protocol, including, but not limited to not attending the scheduled visits. The PI will determine when non-compliance should lead to removal from study. Note: These patients will still be included in the overall evaluation of safety.
- Unacceptable major toxicity. Note: These patients will still be included in the overall evaluation of safety.

- Intercurrent illness or condition that would, in the judgment of the treating investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment
- At subject's own request. Note: The reason for discontinuation from the study must be documented. These patients will be included in the overall evaluation of safety and response if the full protocol therapy was administered prior to withdrawal.
- Study is closed for any reason (e.g. new information shows that the patient's welfare would be at risk if she continued study treatment)
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator

12.3 Replacement of Patients Who Discontinue Early

The study intends that patients will complete the full 24 weeks of study drug administration. If a patient discontinues study treatment for reasons clearly not related to study treatment, after completing fewer than the full 24-week course of study drug, then that patient will be considered not evaluable for efficacy analysis (will still be included in the safety analysis though) and may be replaced with a new patient.

12.4 Withdrawal from Study

Subjects may voluntarily withdraw from the study at any time. The Principal Investigator will provide written explanation in the source documentation to be entered on the appropriate eCRF page describing the reason for discontinuation. No study data from patients who withdraw consent at any time will be used in analysis.

The criteria for enrollment are to be followed explicitly.

Reasons for discontinuation include, but are not limited to, the following:

- Physician decision: The Principal Investigator must discontinue study drug if is determined that it is not safe or in the subject's best interest to receive further treatment.
- Noncompliance with study drug: A subject may be discontinued from the study for failure to comply with the dosing regimen as specified by the protocol.
- Noncompliance with protocol/protocol deviation: A subject fails to follow protocol procedures, or other event or decision that stands in contrast to the guidelines set in the protocol.
- Adverse event: A subject must be discontinued from study drug if, in the judgment of the Principal Investigator or if specified in the protocol, the subject develops an AE such as an intercurrent illness or complication that justifies discontinuation from study drug.

13 REGULATORY CONSIDERATIONS

13.1 Investigational New Drug (IND)

According to the guidance published by the FDA (as outlined in § 312.2(b)(1)) clinical investigations of **marketed** drugs are exempt from the IND requirements if all of the below criteria are met; notes on this study are included:

1. The drug product is lawfully marketed in the United States
    a. Ranolazine is FDA approved for chronic angina. We are proposing to test this lawfully marketed drug product for a new indication.
2. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
    a. Data resulting from this small-scale pilot trial in 20 adults will be used to support the next phase of development (e.g., preliminary data for future grant proposals, informing the design of future trials, attracting commercial interest) and will NOT be reported to the FDA in direct support of a new indication/label change.
3. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising of the drug.
    a. Data resulting from this small-scale pilot trial in 20 adults will not be used to support any change in advertising. See notes above on #2 for detail about how resulting data will be used.
4. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreased the acceptability of the risk) associated with the use of the drug product.
    a. This investigation will use the FDA approved dose and route of administration for ranolazine. Ranolazine has a good safety profile and its use in the Crohn's patient population is not anticipated to significantly increase risk.
5. The investigation is conducted in compliance with the requirement for review by an IRB and with the requirements for informed consent.
    a. A full clinical protocol, informed consent document, and other materials will be submitted to the VUMC Human Research Protections Program in order to obtain IRB approval to conduct this trial at VUMC. If the IRB requests that an IND is filed, one will be filed with the FDA, and the 'may proceed' letter will be submitted to the IRB in order to gain approval to conduct the trial at VUMC.
6. The investigation is not intended to promote or commercialize the drug product.
    a. Data resulting from this small-scale pilot trial in 20 adults is not intended to promote or commercialize the drug product. See notes above on #2 for detail about how resulting data will be used.

13.2 Good Clinical Practice

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations)
- Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996)

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice to which it conforms.

13.3 Privacy/Confidentiality

Data will be maintained in paper and computer files that will be locked and password-protected. Only the study team will have access to identifying information. Information will be maintained indefinitely by the Principal Investigator.

13.4 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards. Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to implementation at that institution.

13.5 Compliance with Trial Registration and Results Posting Requirements

This study will be registered with clinicaltrials.gov prior to initiation of enrollment of study subjects.

14 DATA AND SAFETY MONITORING

14.1 Overall Framework

The Principal Investigator, study coordinator, and clinical research data monitor will be responsible for real-time monitoring of all trial-related activities. They will assure that the study is conducted according to Good Clinical Practice Guidelines and according to FDA requirements. The study team will meet monthly to review recruitment, enrollment, retention, status of each participant currently enrolled, adverse events. Targets will be established for enrollment and completion and reviewed at each meeting where strategies will be discussed to assure that the study is on track. Adverse and serious adverse events reports will be monitored in real-time by the Principal Investigator, study coordinator, and project manager. All final data will be stored on case report forms in REDCap with all source documents uploaded into REDCap then shredded.

14.2 Data Management and Reporting

All study data, including those captured from the EHR and other hospital databases, will be transferred into the study database via standardized electronic case report forms (eCRFs) which will reside in a centralized REDCap database located on Vanderbilt's secure servers. REDCap is a secure, web-based application for building and managing online databases. Vanderbilt University Medical Center, with collaboration from a consortium of institutional partners, including the Vanderbilt Institute for Clinical and Translation Research (VICTR) Informatics Core, developed and manages a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. Data will be accessed via password protected and secured Web-based interface for data entry and data cleaning. REDCap contains an audit trail for tracking all activities within the system. REDCap servers are housed in a local data center at Vanderbilt and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA Security guidelines and is recommended by both the Vanderbilt University Privacy Office and Institutional Review Board. REDCap has been disseminated for use locally at other institutions and currently supports more than 3,700 academic/non-profit consortium partners and over 1 million research end-users (www.project-redcap.org).

In addition to the subject database, which will include all study participant data, REDCap will also be used for a regulatory and monitoring database.

To ensure data is accurately and completely collected during the study, periodic monitoring will occur by the Project Manager to ensure the study protocol is being followed, protocol changes have been implemented appropriately, data are being captured per protocol, and are accurate, complete, and current for study subjects. Per best practice guidelines, the monitor will compare a representative number of subject records and other supporting documents with the investigator's reports. Specifically, monitoring activities will include:

[1] A **Technical Review** annually which will consist of the clinical research data monitor examining the quality and accuracy of data, regulatory documents, and other essential documents. Data quality and accuracy will be reviewed through a CRF data and source document review. Regulatory Document Review will consist of a review of IRB approvals, informed consents, critical documents, and protocols/amendments.

[2] The **Scientific Review** will occur annually and will consist of a review of the study's organizational structure, patient recruitment, staff training, and quality control procedures by the clinical research data monitor. Monitoring progress reports will be submitted to the IRB as requested and/or required. This review will serve as a method for identifying systematic problems and provide a means in which to institute resolution and follow-up and therefore increase data quality.

14.3 Source Verification

All data entered into the REDCap system must come from an original source. Study coordinators will upload all related source documents and medical records that contain information (including Protected Health Information for verification purposes) used in completing the eCRFs into the secure REDCap system. If original source is given verbally and/or if study procedures were documented outside of the medical record, an original source document must be created (which includes applicable signatures and dates) that provides an accurate account of the information

that was exchanged. All applicable study source documentation will be uploaded into REDCap for monitoring purposes then shredded.

14.4 Meetings

Study initiation meeting: Once IRB approval is received, an in-person study initiation team meeting will be scheduled by the Project Manager. During this meeting, the study team will review the following with the Principal Investigator:

- Overall study goals and obligations
- Protocol procedures, with particular attention to inclusion/exclusion criteria, enrollment goals, adverse events, and GCP compliance
- Presentation of the REDCap databases
- Informed consent procedure
- AE/SAE reporting
- CRF completion and error/correction/need for adequate source documentation
- Maintenance of the regulatory binder and site visit log, both maintained electronically in REDCap
- Any other issue as deemed important to the conduct of the study

Monthly study team meetings: These meetings will include the Principal Investigator, Study Coordinator, Statistician, Clinical Research Data Monitor, Project Manager, and relevant staff from the Gastroenterology Clinical Research Enterprise (GICRE) to review adverse events and unanticipated problems. Determinations will be made whether adverse events and unanticipated problems are related to the study. The team will discuss if any change in risk to the patients is present that would require a change to the informed consent document.

14.5 Frequency of Monitoring

- Real-time: AE/SAE monitoring by the Principal Investigator and Study Coordinator
- Monthly: Study team meetings including the Principal Investigator, Study Coordinator, Statistician, Project Manager, and relevant GICRE staff
- Annual: Institutional IRB

14.6 Individual or Group Responsible for Monitoring

Responsibility for monitoring will occur at multiple levels. The Principal Investigator will ultimately be responsible for assuring that all aspects of study conduct comply with GCP guidelines and all regulatory body guidelines. The institutional IRB will conduct annual reviews of the study.

14.7 Process for AE, UP and SAE Reporting

Information on AE will be collected by the study coordinator or other members of the study team at each interaction and recorded on case report forms in REDCap. Interactions occur at each of the three study visits (Days 0, 84, 168) and during telephone/email interactions. AE will be reviewed at each study team meeting with annual reporting to the IRB. UP will be reviewed at

each study team meeting and the relationship to the study will be determined. The team will discuss if any change in risk to the patients is present that would require a change to the informed consent document. Any SAE will be reported to the Principal Investigator within 24 hours of when the study team becomes aware that the SAE occurred. There will be a preliminary determination of whether the SAE is study related or not. The study team will report the SAE to the institutional IRB.

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16 APPENDIX A: MRAV EMAIL

RE: MyResearch: Study on Crohn's Disease Symptoms

From: myresearch@vanderbilt.edu

Hello,

In a survey sent to My Health at Vanderbilt users you agreed to be contacted directly to receive information about research studies. Below is a description of a research study at Vanderbilt that could possibly match your health profile.

We are conducting a research study on Crohn's Disease in order to better understand the disease and possible new ways to treat it. The purpose of this study is to learn more about the treatment of diarrhea in patients with Crohn's and to test whether a drug called ranolazine is able to reduce or improve those symptoms over the course of three months.

The study will involve three study visits over the course of six months at the IBD Clinic at Vanderbilt or through virtual visits. Each visit will last 2-3 hours and will include a number of clinical assessments.

If you are eligible and choose to participate, you will be compensated upon study completion.

Whether or not you participate in this study, your care will continue as usual. Your participation is voluntary. Our screening process includes a review of your Vanderbilt medical record. If you are interested in participating, please follow this link to complete a pre-screening survey.

If our study team determines that you are potentially eligible, you will be contacted by our research coordinator, Erin Landry, who can provide more information and schedule a study visit.

Thank you in advance for your participation!

Dawn Beaulieu, MD
Associate Professor of Medicine
Division of Gastroenterology, Hepatology and Nutrition
Vanderbilt University Medical Center

17 APPENDIX B: PROVIDER SPONSORED EMAIL

RE: Study on Crohn's Disease Symptoms

Hi [insert name of CD patient/caregiver],

We are conducting a research study on Crohn's Disease in order to better understand the disease and possible new ways to treat it. The purpose of this study is to learn more about the treatment of diarrhea in patients with Crohn's and to test whether a drug called ranolazine is able to reduce or improve those symptoms over the course of three months.

The study will involve three study visits over the course of six months at the IBD Clinic at Vanderbilt or through virtual visits. Each visit will last 2-3 hours and you will undergo a number of clinical assessments.

If you are eligible and choose to participate, you will be compensated upon study completion.

Whether or not you participate in this study, your care will continue as usual. Your participation is voluntary. Our screening process includes a review of your Vanderbilt medical record. If you are interested in participating, please follow this link to complete a pre-screening survey.

If our study team determines that you are potentially eligible, you will be contacted by our research coordinator, Erin Landry, who can provide more information and schedule a study visit.

Thank you in advance for your participation!

Dawn Beaulieu, MD
Associate Professor of Medicine
Division of Gastroenterology, Hepatology and Nutrition
Vanderbilt University Medical Center

18 APPENDIX C: PRE-SCREENING SURVEY

Pre-Screening Survey

Record ID	_____

We are conducting a research study on Crohn's Disease in order to better understand the disease and possible new ways to treat it. The purpose of this study is to learn more about the treatment of diarrhea in patients with Crohn's and to test whether a drug called ranolazine is able to reduce or improve those symptoms.

To determine whether you may be eligible for this study, please complete the survey below.

If our study team determines that you are potentially eligible, you can choose to provide your name and contact information if you would like to receive more information about the study.

Thank you!

When was your Crohn's diagnosed?	_____
Who diagnosed your Crohn's?	_____
Who is your gastroenterologist?	_____
If you don't have a gastroenterologist, who is currently treating your Crohn's?	_____
When was your last colonoscopy?	_____ (rough estimate of date is acceptable)
Is your Crohn's currently in remission?	◯ Yes ◯ No ◯ Not sure
On average, do you experience diarrhea 3 or more times per day?	◯ Yes ◯ No ◯ Not sure
Are you pregnant or breastfeeding?	◯ Yes ◯ No ◯ N/A
Do you regularly use opioids or other drugs of abuse including heavy alcohol or marijuana use?	◯ Yes ◯ No
Do you have any severe psychiatric disease such as schizophrenia, psychosis, or suicidal depression?	◯ Yes ◯ No

Based on the information you provided, you may be eligible for this study.

◯ Yes
◯ No

Would you like to receive additional information about the study via phone and/or email?

Your name:

_____
(first and last)

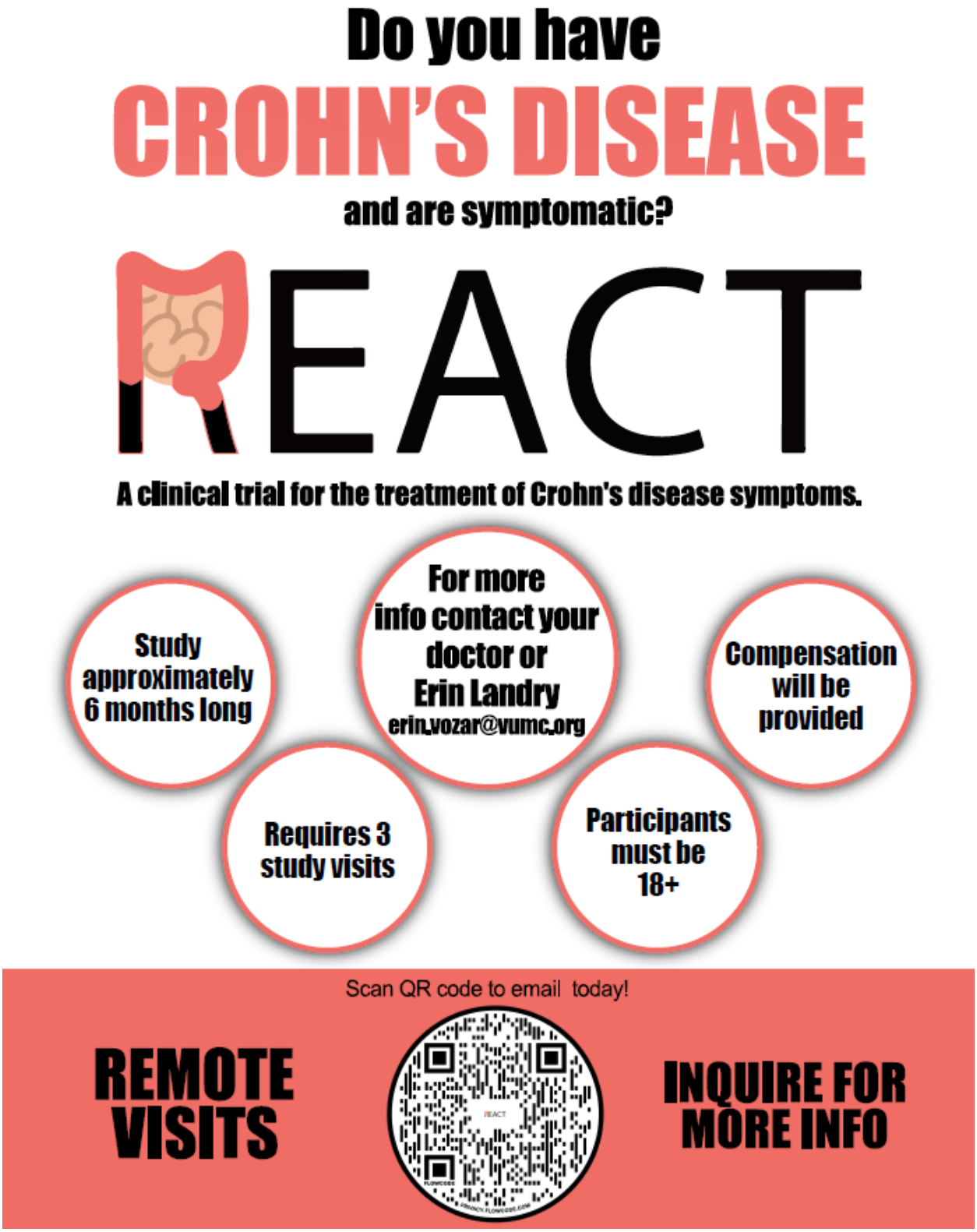
Email:

_____
(optional)

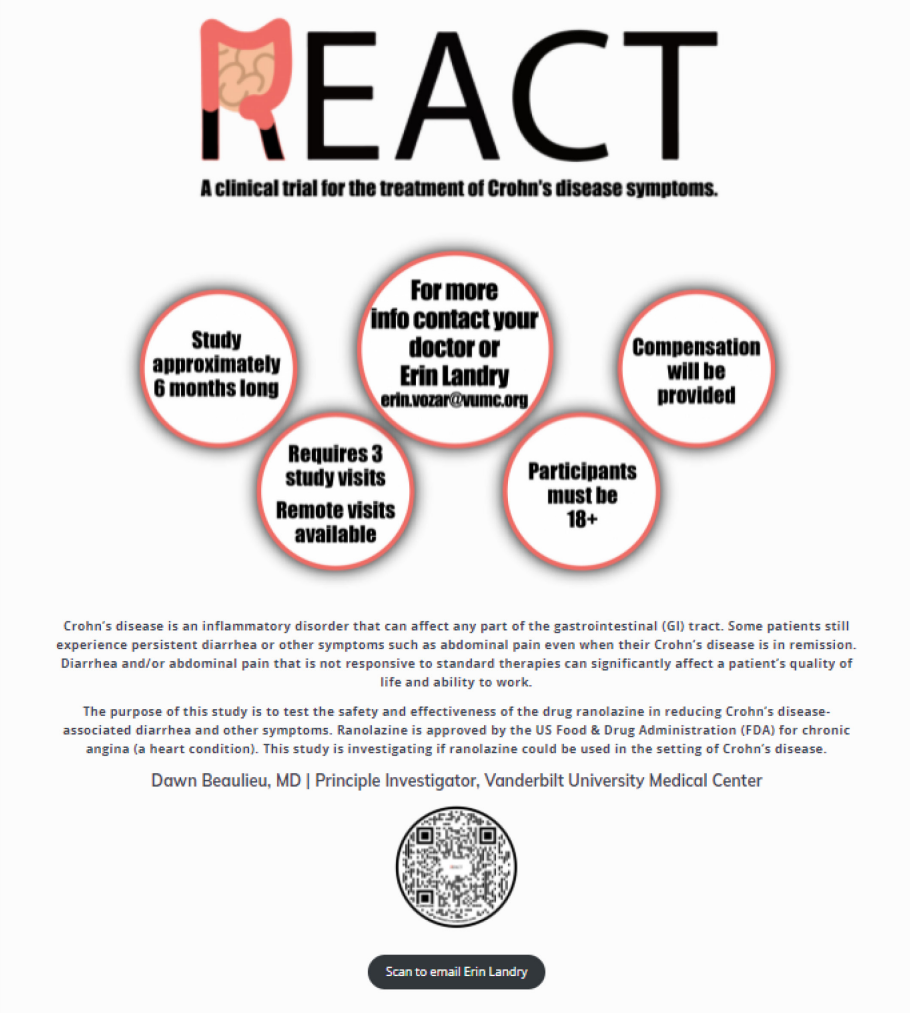
Phone number:

_____
(optional)

19 APPENDIX D: RECRUITMENT FLYER

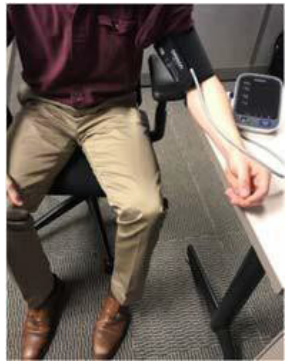


20 APPENDIX E: STUDY WEBSITE LANDING PAGE



21 APPENDIX F: INSTRUCTIONS FOR BLOOD PRESSURE MONITOR

INSTRUCTIONS FOR AT-HOME BLOOD PRESSURE READINGS



1. Remove any tight clothing from your arm for blood pressure measurement (left arm preferred unless there is a reason not to use the left arm).
2. Sit upright in a chair with both feet uncrossed and flat on the ground; do not talk during the recording.
3. Place cuff around your arm at the same level as your heart and secure Velcro fastener.
4. Press 'Start' Button and remain as still as possible during the recording
5. 1 blood pressure measurement will be taken automatically.
6. Record the blood pressure on the next page.
7. Blood pressure should be measured 7 days after hospital discharge. The study team will let you know what days after this, if any, you should repeat your blood pressure.

Display/Messages for Blood Pressure Monitor

Problem	Explanation	Solution
LCD shows low battery symbol	Low Battery	Change all the batteries
LCD shows "Er 0"	Pressure system is unstable before measurementе	Try again without moving
LCD shows "Er 1"	Fail to detect systolic pressure	
LCD shows "Er 2"	Fail to detect diastolic pressure	
LCD shows "Er 3"	Pneumatic system blocked or cuff is tootight during inflation	Apply the cuff correctlyand try again
LCD shows "Er 4"	Pneumatic system leakage or cuff is too loose during inflation	
LCD shows "Er 5"	Cuff pressure above 300mmHg	Measure again after 5 minutes. If the error is stillthere, please contact yourlocal iHealth distributor
LCD shows "Er 6"	More than 3 minutes with cuff pressure above 15 mmHg	
LCD shows "Er 7"	EEPROM accessing error	
LCD shows "Er 8"	Device parameter checking error	
LCD shows "Er A"	Pressure sensor parameter erroron	
No response when you pressbutton or install batterypiles	Incorrect operation or strongelectromagnetic interference.	Take out the batteries, waitfive minutes and then reinstall batteries

Movement during a measurement or an error will result in an additional reading. In this case, the monitor will deflate and retake a replacement measurement. An error display (see table) could appear on the screen to indicate the cause of the error, however the monitor will immediately proceed to an additional recording.

Please avoid taking any medications, drinking alcohol or caffeine, eating, smoking or exercising at *least 30 minutes prior* to taking your blood pressure.

Record your blood pressure here:

Date of blood pressure___/___/___Blood pressure____/____Please measure your blood pressure prior to the study team calling you.

If you have any issues/questions with your blood pressure monitor, please email Erin Landry at erin.vozar@vumc.org for assistance.

22 APPENDIX G: CROHN'S DISEASE ACTIVITY INDEX

Variable	Description	Scoring	Multiplier
No. liquid stools	Sum of 7 days		×2
Abdominal pain	Sum of 7 days ratings	0 = none 1 = mild 2 = moderate 3 = severe	×5
General well-being	Sum of 7 days ratings	0 = generally well 1 = slightly under par 2 = poor 3 = very poor 4 = terrible	×7
Extraintestinal complications	No. listed complications	Arthritis or arthralgia; iritis or uveitis; erythema nodosum; pyoderma gangrenosum; aphthous stomatitis; anal fissure, fistula, or abscess; fever >37.8° C	×20
Antidiarrheal drugs	Use in previous 7 days	0 = no 1 = yes	×30
Abdominal mass		0 = no 2 = questionable 5 = definite	×10
Hematocrit (Hct)	Expected – observed Hct	Males: 47 – observed Females: 42 – observed	×6
Body weight	Ideal/observed ratio	[1 – (ideal/observed)] × 100	×1 (not <–10)

From Best WR, Becktel JM, Singleton JW, et al: Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 70:439–444, 1976.

23 APPENDIX H: MYCAP QUESTIONNAIRE

Confidential

Daily Survey

Please complete the survey below.

Thank you!

Please enter today's date:

_____

Please enter the number of loose stools you had today.

_____

Types 5, 6, and 7 on the Bristol Stool Chart count as loose stools.

Did you use any antidiarrheal medication today such as Immodium/loperamide?

- ○ Yes
- ○ No

Please enter the name and quantity of antidiarrheal medication you used.

_____

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy consistency
Type 7		Liquid consistency with no solid pieces

REACT
REduce Crohn's-Associated Diarrhea with Sodium Channel Therapy

24 APPENDIX I: SHORT INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE

Confidential

REACT Study Database
Page 1

SIBDQ

Record ID _____

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.

How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks?	◯ All of the time ◯ Most of the time ◯ A good bit of the time ◯ Some of the time ◯ A little of the time ◯ Hardly any of the time ◯ None of the time
How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem?	◯ All of the time ◯ Most of the time ◯ A good bit of the time ◯ Some of the time ◯ A little of the time ◯ Hardly any of the time ◯ None of the time
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?	◯ A great deal of difficulty; activities made impossible ◯ A lot of difficulty ◯ A fair bit of difficulty ◯ Some difficulty ◯ A little difficulty ◯ Hardly any difficulty ◯ No difficulty; the bowel problems did not limit activities
How often during the last 2 weeks have you been troubled by pain in the abdomen?	◯ All of the time ◯ Most of the time ◯ A good bit of the time ◯ Some of the time ◯ A little of the time ◯ Hardly any of the time ◯ None of the time
How often during the last 2 weeks have you felt depressed or discouraged?	◯ All of the time ◯ Most of the time ◯ A good bit of the time ◯ Some of the time ◯ A little of the time ◯ Hardly any of the time ◯ None of the time

01/04/2021 10:32am projectredcap.org REDCap

25 APPENDIX J: PATIENT HEATLH QUESTIONNAIRE-8

Confidential

Patient Health Questionnaire-8

Record ID _____

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	○	○	○	○
Feeling down, depressed, or hopeless	○	○	○	○
Trouble falling or staying asleep, or sleeping to much	○	○	○	○
Feeling tired or having little energy	○	○	○	○
Poor appetite or overeating	○	○	○	○
Feeling bad about yourself_or that you are a failure or have let yourself or your family down	○	○	○	○
Trouble concentrating on things, such as reading the newspaper or watching television	○	○	○	○
Moving or speaking so slowly that other people could have noticed. Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual	○	○	○	○

If you checked off any of the problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- ○ Not difficult at all
- ○ Somewhat difficult
- ○ Very difficult
- ○ Extremely difficult

Total _____

Minimal Depression

Mild Depression

Moderate Depression

Moderatley Severe Depression

Severe Depression

01/04/2021 10:25am projectredcap.org REDCap

26 APPENDIX K: HARVEY BRADSHAW INDEX

Parameter	Input and score
1. Patient well-being (previous day)	0 = very well 1 = slightly below par 2 = poor 3 = very poor 4 = terrible
2. Abdominal pain (previous day)	0 = none 1 = mild 2 = moderate 3 = severe
3. Number of liquid or soft stools (previous day)	blank field possibility to insert an integer, from 1 to 25
4. Abdominal mass	0 = none 1 = dubious 2 = definite 3 = definite and tender
5. Complications	No (0 points) Yes (drop-down menu with multiple selection; each selected complication is counted with 1 point) arthralgia uveitis erythema nodosum aphthous ulcer pyoderma gangrenosum anal fissures appearance of a new fistula abscess

Calculation formula: sum of the scores of all 5 parameters.
A score below 5 is generally considered as clinical remission. A reduction of 3 points is considered as relevant to define clinical response.