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PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	**Crofelemer for functional diarrhea**
Principal Investigator	**Anthony Lembo, MD**

B1. PURPOSE OF PROTOCOL

The primary objectives of this study are:

- To evaluate the clinical response of patients with diarrhea to crofelemer relative to placebo.
- To evaluate the overall safety and tolerability of croflemer in the treatment of diarrhea.

The secondary objective of this study is assess whether improvement in bowel function with crofelemer is more effective in subjects without evidence of bile acid malabsorption (i.e., elevated C4 level).

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Irritable bowel syndrome (IBS) is a gastrointestinal condition defined by abdominal pain and altered bowel habits in the absence of another disease that can account for these symptoms (1). IBS is the most commonly diagnosed gastrointestinal condition and has a population prevalence of up to 12% in North America (1–3). IBS is more prevalent in women than in men (4). Depending on diagnostic criteria and study methodology, anywhere from 0.8-50% of IBS patients in the United States suffer from the diarrhea-predominant IBS subtype (IBS-D), in which altered bowel habits are most frequently diarrhea (5). Patients with IBS-D and IBS in general report significantly reduced quality of life, higher indirect costs, and greater impairments in daily and work activities (6–10). Limited medication options are available for treatment of diarrhea symptoms associated with IBS-D.

Crofelemer is a potent antisecretory agent and has promising therapeutic properties for functional diarrhea patients. Crofelemer is an active compound extracted from the latex of the Western South American plant *Croton lechleri*. The latex has been used for medicinal purposes for centuries by indigenous peoples, with its active properties attributable to the crofelemer compound (11). Crofelemer has an inhibitory effect on cAMP-mediated secretion of chloride ions in T84 and Caco-2 epithelial cells, resulting in antisecretory effects in the colon that may alleviate diarrhea and related symptoms (12). Crofelemer has been shown to improve traveler's diarrhea and HIV-associated diarrhea (13,14). It's applicability to symptoms of functional diarrhea is still unclear.

In a Phase II randomized trial, Mangel & Chaturvedi observed the effects of crofelemer in the setting of IBS-D (15). While they did not meet the primary endpoint of altering stool consistency in IBS-D patients, they did find upon further analysis that crofelemer significantly reduced the number of pain- and discomfort-free days in female patients with IBS-D. This study warrants further investigation of the effects of crofelemer in treating symptoms of functional diarrhea.

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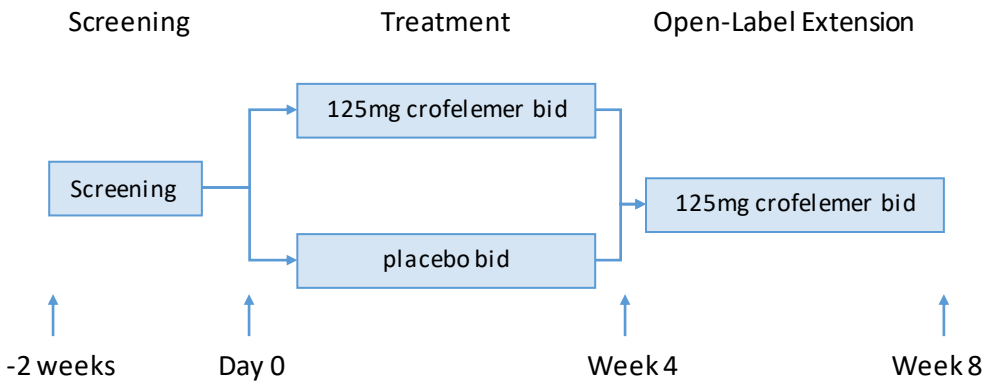
B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

This is a randomized, double-blind, placebo-controlled, parallel group, study is designed to evaluate the efficacy and safety of orally administered crofelemer in patients with diarrhea. The study will consist of a 2-week screening phase, a 4-week double-blind treatment phase, followed by a 4 week open-label extension for both groups.



Visit 1

- Informed Consent
- Baseline demographics, medical and treatment history
- Baseline questionnaires via RedCap
- Vitals (height, weight, blood pressure, temperature, heart rate)
- Blood draw for bile acid malabsorption (BAM); mast cell activation, i.e C4, tryptase, histamine; and storing of blood for future studies. BAM is a send-out lab performed by Prometheus Labs. Mast cell activation will be done at a research laboratory at BIDMC.
- Subjects meeting the inclusion and exclusion criteria will enter a screening period of up to 2 weeks during which time subjects will complete daily diary assessment of their bowel symptoms including bowel frequency and use of loperamide via RedCap.
- At the conclusion of the screening period, subjects will be evaluated to determine if they met study entry criteria related to diary compliance, loperamide rescue medication use, and stool consistency (i.e., Bristol Stool Score).

Visit 2 (Day 0)

- Adverse event assessment
- Vitals (weight, blood pressure, temperature, heart rate)
- Subjects who meet all conditions for study entry will be randomized into the 4-week double-blind treatment phase. Subjects will be randomized (1:1) to receive crofelemer 125 mg BID or placebo BID for 4 weeks. Approximately 80 patients will be randomly assigned (in a 1:1 ratio) to 125mg crofelemer bid vs. placebo.
- Subjects will continue to complete daily diary assessments of their bowel symptoms and use of loperamide during the 4-week treatment period via RedCap.

Visit 3 (Week 4)

- Adverse event assessment

- Vitals (weight, blood pressure, temperature, heart rate)
- Blood draw for mast cell activation, i.e C4, tryptase, histamine; and storing of blood for future studies
- Subjects will return their unused study drug to the study team for IP accountability.
- Subjects completing the 4 week double-blind treatment phase will be eligible to enter an open-label extension for 4 weeks during which all subjects will receive crofelemer 125 mg BID.
- Subjects will continue to complete daily diary assessments of their bowel symptoms and use of loperamide during the 4-week treatment period via RedCap.

Visit 4 (Week 8)

- Adverse event assessment
- Vitals (weight, blood pressure, temperature, heart rate)
- Subjects will return their unused study drug to the study team for IP accountability

Concomitant Medications

Subjects will be allowed and advised to continue with their current diarrhea treatments as long as it was at a stable dose for 30 days prior to randomization.

Protected Health Information

As the study is not industry-sponsored, no protected health information will be provided to any outside sources, excluding Prometheus Laboratories which is BIDMC's send out for BAM.

Questionnaires/Efficacy Assessments

Throughout the study subjects will be required to access their electronic diary every day via RedCap, preferably at the same time each day, to record bowel symptoms and rescue medication use.

- Bristol Stool Score (BSS)
  Patients will be asked to rate the BSS most representative of the past 24 hours. The patient-reported BSS consistency score is based on a 1 to 7 scale where 1 corresponds to a hard stool and 7 corresponds to watery diarrhea.
- Frequency, Urgency and Incontinence
  Patients will be asked to record the number of bowel movements, number of incontinence episodes and the number of urgency episodes over the past 24 hours.
- Diarrhea - Adequate Relief
  Once per week patients will be asked whether they have experienced adequate relief of their diarrheal symptoms. The IBS-adequate relief (IBS-AR) score is a dichotomous single item used to assess adequate relief of IBS symptoms.
- Diarrhea - Quality of Life
  Patients will be asked to assess the impact of their IBS-like symptoms on their quality of life using the IBS-Quality of Life instrument (Patrick et al, 1998). The IBS-QoL will be completed at the study center at all visits. The IBS-QoL will be completed at the beginning of the applicable study visits before all other evaluations, especially discussion of AEs or the patient's medical condition.
- Worst Abdominal Pain Score
  Patients will be asked to rate their worst abdominal pain in the past 24 hours. The patient-reported worst abdominal pain will be recorded on a 0 to 10 scale, where 0 corresponds to no pain and 10 corresponds to worst imaginable pain.
- Abdominal Discomfort Score
  Patients will be asked to rate their abdominal discomfort in the past 24 hours. The patient-reported abdominal discomfort will be recorded on a 0 to 10 scale, where 0 corresponds to no discomfort and 10 corresponds to worst imaginable discomfort.
- Abdominal Bloating Score

Patients will be asked to rate their abdominal bloating in the past 24 hours. The patient-reported abdominal bloating will be recorded on a 0 to 10 scale, where 0 corresponds to no bloating and 10 corresponds to worst imaginable bloating.

Rescue Medication for Uncontrolled Diarrhea

Subjects will be allowed to take loperamide rescue medication for the acute treatment of uncontrolled diarrhea. Loperamide at a unit dose of 2 -4 mg may be taken once approximately every 6 hours with the following guidelines:

- No more than 4 unit doses over a continuous 24-hour time period (8 mg/day)
- No more than 7 unit doses over a continuous 48 hour time period (14 mg over 2 days)
- No more than 11 unit doses over a continuous 7-day time period

Loperamide will not be provided to the subjects by the study team as it is standard of care for functional diarrhea.

Blood Collection

Any blood that is remaining after the analysis is completed will be stored frozen indefinitely at BIMDC for use in future studies. The sample will remain de-identified, but be labeled with the unique subject code. Information related to the subject's diagnosis, treatment, and study results will be retained and possibly used in future analysis and more information becomes identified regarding functional bowel disorders. PHI related to the stored samples will not be used in the future analysis and will be kept on BIDMC's secure server. Any samples that may be shared with collaborators will contain the subject code, but will not have any identifiable information or PHI.

Placebo Tablets

Placebo tablets are matching film-coated [white] tablets that contain standard FDA approved excipients that are used for Mytesi tablets and are identical in size, shape and weight. They will be provided and produced by the manufacturer of Mytesi (crofelemer).

B. Statistical Considerations

Sample Size Justification:

This study aims to recruit 120 subjects until 80 subjects are enrolled. This sample size is based on a 85% power calculation assuming placebo response is 40%.

Data Analysis:

All continuous variables will be tested for normality using the Shapiro-Wilk test. Normally distributed continuous data will be presented as mean ($\pm$ SD) and will be compared pre-and post- interventions using paired Student's t-test. Continuous data which are not normally distributed will be presented as median (range) and compared using Wilcoxon signed-rank test. Proportions will be expressed as percentages and compared using chi-square test or fisher exact test as appropriate.

C. Subject Selection

Inclusion Criteria

1. Patient is a man or woman aged 18 to 65 years, inclusive, at Screening.
2. Patient has functional diarrhea defined by the Rome IV criteria as loose (mushy) or watery stools ≥25% and hard or lumpy stools <25% of bowel movements
3. Patient has had a colonoscopy performed:
    a. Within 10 years prior to Prescreening if patient is at least 50 years of age (alternatively, a flexible sigmoidoscopy, double contrast barium enema, or CT colonography within the past 5

years is acceptable [see recommendations of the American Cancer Society])
   b. Since the onset (if applicable) of any of the following alarm features for patients of any age (see Spiller and Thompson, 2010 – i.e. Patient has documented weight loss within the past 6 months; Patient has nocturnal symptoms; Patient has a familial history of colon cancer; or patient has blood mixed with their stool (excluding any blood from hemorrhoids).
4. Patient has an average daily stool consistency score (BSS) of ≥5.0 on days without the use of an anti-diarrheal and at least 3 days with a BSS score ≥5 on a 1 to 7 scale over the week prior to randomization.
5. Patient has completed the daily diary on at least 6 of the 7 days during the week prior to randomization AND at least 11 of the 14 days during the 2 weeks prior to randomization.
6. Patient has not used loperamide rescue medication more than 4 days during the screening period.
7. Patient is not planning to change his/her usual diet and lifestyle during the course of the study.
8. Patient is willing to be compliant with study procedures including completing the daily diary during the screening period and throughout the study.
9. Patient must sign an informed consent document before the initiation of any study-related procedures indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

<u>Exclusion Criteria</u>

1. Patient has a history of inflammatory or immune-mediated GI disorders including inflammatory bowel disease (ie, Crohn's disease, ulcerative colitis, microscopic colitis) and celiac disease.
2. Patient has a predominant symptom of abdominal pain.
3. Patient has a history of diverticulitis within 3 months prior to screening. Patients with a history of diverticulosis are candidates for the study.
4. Patient has a history of intestinal obstruction, stricture, toxic megacolon, GI perforation, fecal impaction, gastric banding, bariatric surgery, adhesions, ischemic colitis, or impaired intestinal circulation (eg, aortoiliac disease).
5. Patient has any of the following surgical history:
   a. Any abdominal surgery within the 3 months prior to screening; or
   b. Patient has a history of major gastric, hepatic, pancreatic, or intestinal surgery (appendectomy, cholecystectomy, hemorrhoidectomy, or polypectomy greater than 3 months are allowed). For the purposes of this study, laparoscopic surgeries without complication are considered minor and non-exclusionary, provided the condition for which the surgery was performed was not exclusionary.
6. Patient has an unstable renal, hepatic, metabolic, or hematologic condition.
7. Patient has a history of human immunodeficiency virus infection.
8. Patient has a history of DSM-IV-TR-defined substance dependency, excluding nicotine and caffeine, within 2 years prior to Prescreening.
9. Patient has a history of alcohol abuse as defined by DSM-IV-TR, binge drinking as defined by the National Institutes on Alcohol Abuse and Alcoholism, or any medical treatment for alcohol-related co-morbidities, within 5 years prior to Prescreening. Recovered alcoholics who have not consumed alcohol over the 5 years prior to Prescreening are candidates for the study.
10. Patient has current (within 14 days of randomization) or expected use of any narcotic or opioid containing agents, tramadol
11. Patient is unable to swallow solid, oral dosage forms whole with the aid of liquid (patients may not chew, divide, dissolve, or crush the study drug).
12. Patient has received an investigational drug or used an investigational medical device within 30 days prior to randomization.
13. Patient has a known pregnancy or is breastfeeding.

B4. POSSIBLE BENEFITS

Subjects may experience improvement in their functional diarrhea symptoms.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Safety
Possible risks of crofelemer include upper respiratory tract infection, bronchitis, cough, flatulence, increased bilirubin, nausea, back pain, arthralgia, UTI, nasopharyngitis, musculoskeletal pain, hemorrhoids, giardiasis, anxiety, increased alanine aminotransferase, abdominal distention.

There is a possible risk of loss of confidentiality, however every effort will be made to ensure patient confidentiality which includes but is not limited to only discussing medical information in a private clinical setting and collecting information necessary to accomplish the research purpose. Physical data will be kept in a locked room that only the research team have access to. Electronic data will be kept on the secure server with access granted only to the individuals on the research staff.

The risk/benefit ratio of the study is favorable for the patient due to the limited options for treating functional diarrhea.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment
Patients will be identified in the following ways:

- Clinical practice of the Center for Functional Bowel Disorders and GI Motility at BIDMC
- GI referrals from BIDMC
- Review of medical records, data repositories, and appointment logs
- Clinical Query 2
- Advertisements

Potential study participants (obtained from the means listed above) will be contacted by phone and a brief phone screening will be initiated to assess subject's eligibility before scheduling the office visit.

Potential study participants identified through Clinical Query 2 or appointment logs will be mailed a letter or postcard with opt-in information.

Consent
During the screening visit the Investigator will fully explain the purpose of the study to the patient and all questions and concerns regarding the study will be addressed as well (informed consent process) in a private area in the Division of Gastroenterology.

B7. STUDY LOCATION

Privacy
Every effort will be made to ensure the patient's privacy which includes but is not limited to only discussing medical information in a private clinical setting and collecting information necessary to accomplish the research purpose.

Physical Setting
Study visits will be conducted in the Division of Gastroenterology

B8. DATA SECURITY

Physical data will be kept in a locked room that only the research team has access to. Electronic data will be kept on BIDMC server.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

B10 Dissemination of Research Results

Subjects will be thanked for their participation following their participation in the study and informed of the possibility of future publications.