Yield of Diagnostic Tests and Management of Crofelemer for Chronic Idiopathic Diarrhea In Non-HIV Patients: A Pilot Study

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Yield of Diagnostic Tests and Management of Crofelemer for Chronic Idiopathic Diarrhea In Non-HIV Patients: A Pilot Study

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Study Population

Males and females between age 18-75 years with chronic functional diarrhea (defined as 3 non-bloody loose stools per day or more than 20 non-bloody loose stools per week for ≥ 4 weeks) without an obvious cause after evaluation for organic causes presenting to Ertan Digestive Diseases Center (EDDC) in Houston.

Sample Size

Up to 100 Subjects

Study Duration

Approximately one year from institutional review board (IRB) approval

Subject Duration

Approximately 3 to 4 months per subject

Tentative Dates of Study

Estimated commencement date of the study: Nov 2019

Estimated completion date of the study: May 2021

Type of Study

Pilot Study; Non-Blinded Clinical Trial

Amount of Product Required

2 tablets x 28 days x 25 patients = 1,400 crofelemer tablets

No placebo needed. The drug will be used solely to conduct the study and all safety and regulatory reporting obligations will be followed. Any unused drug will be returned to Napo Pharmaceuticals within 90 days of study completion.

Background and Rationale

Chronic Diarrhea and Epidemiology

Chronic diarrhea is a common complaint of patients presenting to family practitioners, internists and is one of the most common reasons for referral to gastroenterologists. It is estimated that the prevalence of chronic idiopathic diarrhea in developed countries (including the US) is approximately 3-5% [1-3]. It has a significant negative effect on health-related quality of life (HRQOL) and causes high economic burden on patients and society. The American Gastrointestinal Association Burden of Illness study showed that the estimated annual direct and indirect costs associated with chronic diarrhea is up to $524 million per year and $136 million per year, respectively [3].

Diagnostic Evaluation of Chronic Diarrhea

There are many causes of chronic diarrhea known to man and several algorithms have been created for the evaluation chronic diarrhea [2-4]. Over the last 10 years, additional diagnostic tools have become available that may increase the identification of heretofore unappreciated causes of chronic diarrhea. In addition to traditional stool analyses and lower gastrointestinal endoscopy, breath testing for specific carbohydrate maldigestion, stool multiplex examinations for gastrointestinal infection, and assays for carbohydrate and bile acid malabsorption have become available in routine clinical practice. As a consequence, clinical awareness of the conditions diagnosed by these emerging assays has increased, but prevalence values for these conditions and the relative importance of their contributions to the symptoms of chronic diarrhea remain unknown. For instance, recent estimates have placed the prevalence of bile acid malabsorption (BAM) in patients with irritable bowel syndrome (IBS) with diarrhea between 25-50%. Up until recently, there has been no diagnostic test available outside research institutions for BAM and treatment for this condition has been empiric bile acid sequestrant therapy, which can interfere with the absorption of other medications. The availability of the serum 7C4 test for BAM may be an important development in the management of patients with chronic diarrhea, but outcomes data are lacking.

Congenital sucrase-isomaltase enzyme deficiency (CSID) is an often unrecognized, autosomal recessive disorder with wide phenotypic heterogeneity with symptoms such as chronic diarrhea, bloating, abdominal pain, and flatulence that are non-specific and commonly associated with other digestive disorders. This results from maldigestion of sucrose and starches in the diet, release of water secondary to high intraluminal osmolality, and subsequent bacterial fermentation [5]. Recent work has shed some light on the hypothesis that CSID may be more prevalent than we previously believed with estimates ranging from 9.3% to 21% [6,7]. Demonstration of normal

duodenal or jejunal mucosal histology and low to absent sucrase activity detected by enzyme assay remains the gold standard for diagnosis of CSID [8-11]. An evolution of the H_2 BT introduced in the early 1970's was the measurement of isotope-labeled CO_2 in breath using ^{13}C or ^{14}C [12]. These tests depend on measurement of changes in isotope labeled breath via infrared mass-dispersion spectrophotometry which is simple and has a short turnaround time [13-15]. Since the introduction of mass spectrometers for the detection of the stable isotope of ^{13}C in expired air the BT technique has been adapted for the study of malabsorption with collection systems that are well tolerated and widely reproducible. ^{13}C Breath testing is a non-invasive, 90-minute test that can be easily administered by the patient at home. An 8 hour fast is required after which the patient collects a baseline sample and then 20 gram of ^{13}C Sucrose is administered orally. The patient collects breath samples 30 minutes apart by blowing through a straw into labeled, screw-cap glass tubes. These tubes are then mailed to the analyzing lab and results are obtained within 24 hours.

Management of Chronic Diarrhea

Despite the advances in the medical field, in a substantial number of cases, no organic or functional etiology can be determined. In those circumstances and in cases where no specific treatment is available or specific treatment fails to affect the cure, symptomatic treatment of diarrhea remains the mainstay of management. Variable success has been seen with pharmacological agents including anti-secretory (octreotide), anti-motility (loperamide and diphenoxylate atropine), and adsorbent medications along with adjunctive non-pharmacologic measures such as dietary modifications (fiber supplements like psyllium or absorbents like kaolin) [2].

About Crofelemer

Crofelemer is a novel compound isolated from the plant *Croton lechleri* (family *Euphorbiaceae*) found in the western Amazonian regions of South America. (Attachment 6) This naturally occurring extract is an acid-labile, proanthrocyanidin oligomer found in the red latex of the plant [16]. Native populations of South America have used the sap of the plant for self-treatment of chronic diarrhea for many years. Crofelemer is primarily composed of (+)–catechin, (–)–epicatechin, (+)–gallocatechin, and (–)–epigallocatechin monomer units linked in random sequence (Figure 1).

The mechanism of action of crofelemer is through dual inhibition cyclic adenosine monophosphate (cAMP)-stimulated cystic fibrosis transmembrane conductance regulator (CFTR) chloride ion (Cl) channel, and the calcium-activated Cl channels (CaCC) at the luminal membrane of enterocytes [17,18]. This structurally unrelated inhibition

of intestinal chloride channels normalizes the flow of Cl and water in the GI tract, leading to anti-secretory effects of crofelemer. Systemic absorption is minimal and concentrations of crofelemer in plasma remained below the level of quantitation (50 ng/mL) in studies. There are no active metabolites identified and the route of elimination is unknown.

Previously, crofelemer has been investigated for the treatment of several types of chronic diarrhea, including traveler's diarrhea [19], AIDS-associated diarrhea [20], and infectious diarrhea such as cholera [21]. Crofelemer has also been studied in patients with diarrhea-predominant IBS (IBS-D) [22]. Crofelemer has also been evaluated as a topical application in patients with AIDS for the treatment of recurrent genital and perianal herpes lesions.
Due to its large chemical structure, crofelemer has minimal systemic absorption when given orally, irrespective of concomitant food intake or duration of exposure. It has demonstrated a good safety profile and is well tolerated in current published studies [23]. In a study performed in 2002 on 184 travelers returning from Mexico, Jamaica, and the United States-Mexico border, De Cesare et al. demonstrated a 21% reduction in the duration of traveler's diarrhea in more than 90% of the individuals with crofelemer [19]. Holodniy et. al conducted a multicenter, phase II, randomized, double blind, placebo-controlled study [20]. 26 patients with AIDS received a 4-day course of crofelemer with marked reduction in stool frequency and stool weight compared to placebo. Crofelemer has also been efficacious in reducing pain and discomfort in female patients with IBS-D. This was shown by Mangel et al. in a placebo-controlled trial in 2008 [22]. The phase 3 ADVENT trial lead by McArthur et al. used a 2-stage design [23]. The first stage included a placebo-controlled phase with approximately 200 HIV-seropositive patients on HAART therapy, randomized to receive crofelemer 125 mg, 250 mg, or 500 mg or placebo twice daily. After a responsiveness analysis, crofelemer 125mg twice daily was used in a placebo controlled second stage trial. Clinical response was defined as ≤2 watery stools per week during ≥2 of the 4 weeks of the placebo-controlled phase. Crofelemer provided a 17.6% response rate compared to only 8.0% in the placebo group. It decreased the number of daily watery bowel movements and daily stool consistency score, but was ineffective in controlling urgency, abdominal pain, and incontinence. Both clinical trial stages were followed by 20-week open label trial with weekly response-assessment. In this trial the placebo-response rate rose for weekly responders to 56%. More pronounced crofelemer treatment effects were observed in patients with diarrhea of greater severity (≥2 watery stools per day) or duration (>2 years) or who had used multiple (≥2) antidiarrheal medications prior to the study.

Formerly known as Fulyzaq, crofelemer was approved by US-FDA in December 2012 for symptomatic treatment of HIV-related diarrhea in the dose of 125mg tablets taken two times a day [24]. It was the first botanical therapy to receive FDA approval and is now marketed under the name of Mytesi®. The most common adverse reactions for crofelemer that occurred in at least 2% of patients in the ADVENT trial at a higher incidence than placebo were upper respiratory tract infection, bronchitis, dry cough, flatulence and increased bilirubin [23](Table 1). Adverse reactions that occurred in between 1% and 2% of patients taking a 250 mg daily dose of crofelemer were abdominal pain, acne, increased aspartate aminotransferase, increased conjugated bilirubin, increased unconjugated blood bilirubin, constipation, depression, dermatitis, dizziness, dry mouth, dyspepsia, gastroenteritis, herpes zoster, nephrolithiasis, pain in extremity, pollakiuria, procedural pain, seasonal allergy, sinusitis and decreased white blood cell count.

There are no absolute contraindications reported for crofelemer use. It is a white, oval, enteric-coated 125 mg delayed-release tablet. The inactive ingredients of crofelemer are - microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The coating ingredients are - ethylacrylate and methylacrylate copolymer dispersion, talc, triethyl citrate, and white dispersion, which contains xanthan gum, titanium dioxide, propyl paraben, and methyl paraben. Since there is no known relation between food intake and drug administration, crofelemer can be taken with or without meal. However, it should not be crushed or chewed and is intended to be swallowed whole. It is marketed as a bottle of 60 tablets and should be stored at 20°C-25°C (68°F-77°F); excursions are permitted between 15°C-30°C (59°F-86°F) (Attachment 6 and 7).

With the increasing interest in discovering uses of crofelemer in other spectrum of diarrheal disease, objective of this study will be to evaluate the efficacy of crofelemer in non-HIV patients with chronic idiopathic diarrhea. With most patients relying on anti-motility agents or other adjunct therapies with variable success, there is a promise in crofelemer for future studies.

Chronic Diarrhea and Health-Related Quality of Life

Chronic diarrhea can result in a decline in nutritional status and subsequent decline in functional status and overall quality of life. HRQOL is a multidimensional construct that consists of three broad domains − physical, psychological, and social functioning − that are affected by one's disease and/or treatment [25]. The measures of

quality of life may be influenced by factors unrelated to the health status of the patient including change in their expectations and aspirations as circumstances change, values patients place on life, their risk aversion, or their attitude towards certain type of medical intervention [26]. Understanding how chronic diarrhea affects HRQOL is still very limited and restricted to specific population studies largely focusing on people living with AIDS and IBS [27-29]. There is no HRQOL questionnaire specifically developed, or validated for, chronic idiopathic diarrhea. Short-Form 36 (SF-36) is a generic questionnaire developed in the early 1990's to evaluate HRQOL in illness and make comparisons with the background population or between different diseases. It is a self-administered, general questionnaire comprising 36 items, which is well validated and accepted. Thirty-five of the items are grouped into eight scales: physical function (PF), role limitations due to physical disability (RP), bodily pain (BP), general health perception (GH), vitality (VT), social function (SF), role limitation due to emotional problems (RE), and mental health (MH). The results are presented as scale scores ranging from 0 (worst possible health state) to 100 (best possible health state) following the standard SF-36 scoring algorithm [30-32]. With our study, we aim to shed some light on the perception of health and quality of life in patients with chronic idiopathic diarrhea. In addition, we will also look at any change in that perception after administration of crofelemer for 4 weeks.

Objectives

Primary Objective – Assess the efficacy of crofelemer in adult, non-HIV patients with idiopathic chronic diarrhea

Secondary Objectives -

1. Determine the prevalence of identifiable causes of chronic diarrhea in a non-HIV patients
2. Assess the diagnostic yield, in terms of identification of treatable etiologies, of commercially available diagnostic evaluations in adult, non-HIV patients with chronic idiopathic diarrhea; i.e., evaluate which tests, among the standard diagnostic tests commonly conducted as part of the evaluation of chronic idiopathic diarrhea, are most likely to identify a treatable cause of the diarrhea.
3. Assess the usefulness of CSID testing in adults with chronic idiopathic diarrhea via sucrase enzyme level testing on small intestinal biopsies, and ^{13}C-SBT.
4. Analyze the relationship between chronic idiopathic diarrhea and health-related quality of life and assess the impact of crofelemer treatment on health-related quality of life

Details of the Study

Definition of Chronic Diarrhea - Persistent increase in bowel movement frequency (≥ 3 bowel movements per day or ≥ 20 bowel movements per week) **AND** decrease in consistency of >50% stools (liquid or watery-Bristol Stool Form Scale type 6 or 7) for more than 4 weeks [33].

Outcome measures

Primary Response to crofelemer- A 50% decrease in mean stool count per week by the end of week 4

Secondary Responses to crofelemer- An improvement (decrease) in stool consistency by more than 2 levels in the Bristol stool scale (Figure 2) [34,35].

2. Changes in HRQOL at T0 and at T+4 weeks

3. Descriptive analysis of the frequency of identified etiologies of chronic diarrhea and the frequency of abnormal diagnostic test results leading to the identification of those etiologies

Treatment Failure/Non-responder -

1. Failure to meet the primary response definition
2. Medication non-compliance: Subjects who missed more than a total of four doses over the 4-week course.
3. Subjects who fail to record at least 80% of the daily symptom diary.

Inclusion Criteria

Males and females between age 18-75 years with chronic diarrhea (defined as 3 non-bloody loose stools per day or more than 20 non-bloody loose stools per week for more ≥ 4 weeks) and Bristol Stool Form Scale for stool consistency of 6/7 with >50% stool without an obvious cause after evaluation for organic etiologies. Patients of all ethnicities will be included in the study.

Exclusion Criteria

Since the study focuses on chronic idiopathic diarrhea, subjects who may have other organic pathologies or co-morbidities that may explain the cause of diarrhea will be excluded.

1. Hematochezia (potentially related to an organic cause).
2. Subjects less than 18 years of age more than 75 years of age (safety and effectiveness of crofelemer has not been established in these age groups).
3. Pregnant females (crofelemer is a Category C drug due to lack of well-controlled studies to study its effects in this population).

4. Lactating females (it is unknown if crofelemer is excreted in the human milk and thus may have unknown adverse effects on the nursing infants).
5. HIV positive individuals.
6. Persons within ability to provide consent and understand the study
7. Persons with history of alcohol abuse or binge drinking.
8. Persons with history of surgical bowel resection or bariatric surgery in the past 12 months.
9. Persons who have undergone cholecystectomy (open or laparoscopic) in the past 3 months.
10. Persons receiving antibiotics currently or have received antimicrobials in the past 4 weeks.
11. Persons with end-organ failures including end-stage renal disease, end-stage liver disease, or severe heart failure.
12. Persons with metastatic hematologic and oncologic malignancies.
13. Persons receiving chemo-radiation or immune-modulators for oncologic or rheumatologic conditions.
14. Persons with any other known organic gastrointestinal or non-gastrointestinal disease process in which diarrhea is a recognized clinical feature.
15. Gluten free diet for previous 3 months and refusal to ingest gluten.

Recruitment strategy

1. Prospective recruitment of patients referred to the Gastroenterology division of UTHealth/MHHS for evaluation and management of chronic diarrhea.
2. Furthermore, presentations will be given to faculty members in the Department of Gastroenterology, Hepatology and Nutrition and Internal Medicine at UTHealth/MHHS to discuss the study and facilitate recruitment of subjects.
3. Inclusion of study criteria and description of study procedures on the research page for the UTHealth/MHHS Gastroenterology Division.
4. Poster advertisements at UTHealth/MHHS bulletin boards with contact information.

Phases of the study

1. Screening period of 4-8 weeks for each patient to undergo diagnostic evaluation to determine eligibility to participate in the study
2. Treatment period of 4 weeks for collection of efficacy data on crofelemer

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3. Post-Treatment follow-up for drug efficacy, safety assessment, and overall quality of life analysis

Based on estimated prevalence of identifiable causes of chronic diarrhea in approximately 50% of adult patients and an estimated non-eligibility prevalence of up to 75% of prospective patients, to enroll 25 patients who meet the eligibility criteria for the study, we are estimating that approximately 100 patients will be required to undergo evaluation for this pilot study. This will be achieved over a period of 12-18 months starting from Fall 2019.

Since this is a pilot study with limited data available of the effect of the drug on the specified population, a sample size of 25 subjects is considered safe and feasible to inform potential future randomized controlled trials.

Criteria for termination of trial:

1. Severe unanticipated adverse effects of the drug in the participants
2. Inability to enroll stipulated number of participants over the anticipated study time
3. Withdrawal of more than 50% of the selected subjects from the study. Please note that subjects may withdraw voluntarily from the study at any time of the subject duration. He/she will be required to write a written request addressed to the PI, explaining the reason for withdrawal. New subjects will be enrolled to the study after the screening period, if possible during the total study duration.
4. Enrollment of 25 subjects into the treatment phase or 100 patients in the diagnostic phase, whichever occurs first.

Number of visits/encounters

Four clinic visits at EDDC

1. Pre-screening assessment of subjects (4-8 weeks prior to treatment phase)
2. Discussion of the results of diagnostic tests and evaluations; initiation of treatment with crofelemer 125 mg tablets twice daily (BID) (Day 1) (Attachment 7)
3. Mid-study follow-up (Day 14) for symptomatic evaluation of diarrhea and any adverse events
4. Final post-treatment follow-up on Day 29 **OR** the first business day after completion of treatment

PHASE 1: SCREENING PERIOD

A careful, detailed and comprehensive medical, surgical, and social history will be obtained to categorize the diarrhea and rule out obvious organic causes of diarrhea. All of these diagnostic tests are considered standard of care for the evaluation of chronic idiopathic diarrhea.

The order in which these investigations will be performed will be tailored on a case-to-case basis (patient education for each test is added as an attachment and mentioned in parenthesis)–

1. Complete Blood Count (CBC)
2. Comprehensive Metabolic Panel (CMP)
3. HIV Screening – To screen patients for the study as our study focuses on non-HIV patients only (if not done in previous 6 months)
4. Esophagogastroduodenoscopy (Attachment 8) and Colonoscopy (Attachment 9)– (performed by PI) with random and (if required by endoscopic findings) targeted biopsies of the UGI (duodenum) and LGI (colon) tract mucosa sent to the department of pathology for analysis as well testing for CSID (duodenal biopsies)
5. Stool multiplex panel for the following gastrointestinal pathogens:

Campylobacter

Cryptosporidium

E. coli O157

Enterotoxigenic E.coli (ETEC)

Shiga Toxin-producing E. coli (STEC)

Giardia lamblia

Norovirus GI/GII

Rotavirus A

Salmonella

Shigella

Adenovirus 40/41

Entamoeba histolytica

Vibrio cholera

Yersinia enterocolitica

Clostridium difficile

6. Urine Pregnancy Test when clinically indicated
7. Thyroid Panel: Thyroid stimulating hormone and free T4

8. Tissue transglutaminase and IgA
9. C-reactive protein
10. Serum 7C4
11. Gastrin Level
12. Calcitonin Level
13. VIP Level
14. Stool osmolality
15. Stool Qualitative Stool Fat
16. Stool Reducing Substances
17. Stool calprotectin
18. Stool elastase
19. Lactulose Hydrogen Breath Test
20. ^{13}C-Sucrose Breath Test
21. HRQOL (SF-36) baseline - This is a questionnaire that consists of 36 questions and asks subjects' views about their health. Subjects will fill this form two times during the total duration of study – at the initial visit prior to starting treatment and once at the end at the post-treatment follow-up (Attachment 5a and 5b).

We estimate that it may take from 4 weeks up to 8 weeks to obtain and complete all the above-mentioned tests. Patients will be updated by a call from the study coordinator to discuss the results and scheduled the pre-treatment clinic visit.

Diagnostic tests will be denoted as normal, abnormal, or unable to be performed (in the event of insufficient sample, non-compliance, or lab error). Descriptive statistics will be used to denote the percentage of patients with any abnormal diagnostic tests and the frequency of abnormal results for each test, relative to other diagnostic tests, will be computed and recorded for the cohort.

In accordance with good clinical and standard practice, abnormal tests will be evaluated and acted upon as indicated. Any diagnosis of a causative medical condition identified as a result of the standardized diagnostic evaluation will be recorded, as will patient response to appropriate therapy for any identified medical conditions, if any.

PHASE 2: TREATMENT PERIOD

Consecutive patients completing the diagnostic phase who are not identified as having a proven etiology of their chronic diarrhea symptoms will be invited to participate in the treatment phase. With the evidence supporting 125 mg BID dosing of crofelemer as the appropriate dose for response as shown by the ADVENT study, we will be administering the same dose of 125 mg tablets taken by mouth twice daily for our subjects.

We will provide the subjects with a total of 56 tablets for the 28-day course. An IND has not been sought for this study because the study meets the exemption criteria as stated in 21 CFR 312.2(b): investigations using a marketed drug or biologic do not require submission of an IND if all six conditions below are met:

1. It is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug.
2. It is not intended to support a significant change in the advertising for the product.
3. It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug.
4. It is conducted in compliance with the requirements for Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and informed consent.
5. It is conducted in compliance with the requirements concerning the promotion and sale of drugs.
6. It does not intend to invoke 21 CFR 50.24 (exception from informed consent for emergency research).

As there is effect of food intake on the drug's absorption, it can be taken with or without meal. Subjects will be advised to remain on a regular diet and limit major dietary modifications during the study period. Patients will be advised to follow their regular routine including average level of daily activity and there are no restrictions to travel with emphasis on compliance with the medication. Women of childbearing age will be advised to use at least one method of contraception including barrier method, hormonal therapies with pills, implants or IUDs. In case, a

subject misses a period or has a positive home urine pregnancy test, she will be advised to call the study coordinator or PI's office immediately.

Use of rescue medications i.e. loperamide will be allowed in order to prevent hesitation of participants to enter the study. However, the use will be monitored and limited to fourteen 2mg doses per week.

Symptom Diary maintenance has been used previously for IBS-D studies [62]. This not only improves compliance and accurate data collection, but also provides a sense of control to the patient as a participant in the study. Therefore, each subject will be asked to maintain a Daily Symptom Diary with the following information (Attachment 3) -

1. Time of bowel movements per 24-hour period (midnight to midnight)
2. Number of loose stools per 24-hour period
3. Consistency of each bowel movement (according to Bristol Stool Form Scale) (Figure 2)
4. Presence of urgency with each bowel movement (0-4 VAS scale; 0-none, 1-mild, 2-moderate, 3-severe, 4-incontinence)
5. Supportive Anti-diarrheal medication taken (Yes/No)
6. Dose of supportive anti-diarrheal medication taken
7. Number of Anti-diarrheal medications taken per 24-hour period
8. Daily time of administration of crofelemer (AM/PM)
9. Any other new symptoms noted

Participants will be provided with the Daily Symptom Diary on their second visit, prior to treatment initiation. It will be a notebook with the above questions printed on each page with a total of 30 entries and 5 extra pages in the back for any other information that the participant may wish to include (Attachment 3). The completeness of entries and pattern of symptoms will be assessed on the subsequent visits on Day 14 and Day 29. All information will then be noted and uploaded to the study database subsequently. Participants will need to have at least 80% completed entries i.e. 22 diary entries throughout the study period. Any missing entry will be considered as no bowel movements for that day. Any subject with insufficient data entry of less than 22 entries will be categorized a non-responder. No patient identifiers will be included in the diary, other than subject number that corresponds to the master study

enrollment log, which will be maintained electronically. Patients will be given sequential study ID numbers (1 up to 100) upon enrollment into the study.

PHASE 3: POST-TREATMENT FOLLOW-UP

A post-treatment follow-up visit would be scheduled with the PI on Day 29 or the first business day after completion of the crofelemer course. The following variables will be obtained and analyzed for the study -

1. Age (in years)
2. Gender (Male/Female/Other)
3. Ethnicity (Caucasian/Hispanic/African American/Native American/Asian/Other)
4. BMI (in kg/m^2)
5. Number of weeks/years of diarrhea fulfilling entry criteria
6. Number of stools per day (Day 0)
7. Number of stools per day (Day 14)
8. Number of stools per day (Day 28)
9. Total number of stools per week (Week 1, 2, 3, and 4)
10. Average consistency of stools (Day 0)
11. Average consistency of stools (Day 14)
12. Average consistency of stools (Day 28)
13. Previous use of other anti-diarrheal agents (Yes/No)
14. Average number of anti-diarrheal agents used per week (Day 0)
15. Average number of anti-diarrheal agents used per week (Day 14)
16. Average number of anti-diarrheal agents used per week (Day 28)
17. Abdominal Pain yes or no and scored from 0 to 10 (0-no pain, 10-worst abdominal pain imaginable)
18. Urgency (according to 0-4 VAS scale)
19. Fecal Incontinence (Yes/No)
20. Other comorbid diagnoses
21. Concomitant medications and dosing
22. HRQOL (SF-36) Post-treatment (Attachment 5b)

Data and Safety Monitoring

Adverse Events Reporting – Adverse events are not expected. However, in the event of any unanticipated medical occurrence in a subject directly caused by the drug, it is the responsibility of the Investigator to record all relevant information regarding the medical occurrence on the Sample Collection Study Incident Case Report Form and provide it to the IRB and study sponsors promptly. The Investigator will be responsible for the proper reporting of any potential adverse events (AE) or serious adverse events (SAE) (as defined by general medical standards) to the appropriate authorities. AEs/SAEs related to medication treatment(s) will be reported directly to the manufacturer of the medication product. The investigator will be responsible for ensuring that adequate medical care is provided to a subject for any untoward medical occurrence resulting from this clinical protocol.

Statistics

Since this is a pilot study, simple descriptive statistics will be used to denote outcomes and findings from diagnostic evaluations and treatment. For the diagnostic outcomes, this will include the prevalence of organic gastrointestinal disorders identified as a result of diagnostic testing. For the treatment outcomes, responder and non-responder rates will be described as well as the incidence of adverse effects. Changes in HRQOL will be described in standard fashion.

Ethics

1. IRB approval will be sought from CPHS for initiation of the study. The protocol and related documents will be submitted for review to the UTHealth institutional ethics committee.
2. A written informed consent will be obtained from the participants prior to initiation of the study. Consent will be made available in English.
3. All participants will be provided with the study coordinator's office phone number and fax number for correspondence and answering any queries regarding the study, treatment or any other concerns.

Data handling and record keeping

1. Data will be collected through accessing the individual participant's electronic medical records in the Memorial Hermann Hospital Care4 (inpatient) and UTHealth AllScripts (outpatient) and recorded in the password-protected database electronically.

2. All identifying personal health information will be kept confidential as per HIPAA compliance requirements.
3. Source documents will be accessed only by the principal and co-investigator and will be used solely for the purpose of this study. The records will be accessible for inspection and copying by authorized authorities.
4. All data will be stored electronically in a PIN-protected USB drive and data transfer will be performed through encrypted emails between investigators and staff (if necessary) using institutional email addresses.
5. Patient diaries will be maintained by the patient until the end of study and will be turned in at the end of study to the investigators for abstracting into the study database. Once abstracted, the diaries will be stored with any other had copy study materials in a secured storage container in a locked room maintained by study coordinator personnel.
6. We will share de-identified demographics and results of CSID testing with investigators from the University of Michigan who are performing a similar study aimed and determining the prevalence of CSID. (Attachment 11)

Quality control and assurance

1. The investigators will meet every month to review the data collected and assess the progress of the project.
2. Study sponsors will be provided with a quarterly report of the progress of the ongoing research including adverse events (if any).

Publication Plan

1. We plan to publish the results of the study in an internationally recognized scientific journal.
2. Napo pharmaceuticals will be provided with the finalized manuscript prior to submission as part of the Grant Agreement.
3. We will make the results of the study available to the participants within 8 weeks of final analyses. It will either be handed to them on their next routine follow up or sent to them by mail, whichever is earlier.

Funding

1. [redacted]
2. The remainder of the diagnostic evaluations are considered standard of care and patients will be billed through their insurance in accordance with standard operating procedures for these tests and procedures.

3. Pre-authorization for insurance coverage for these tests will be sought to ensure that you will not be billed later because test was done but insurance later informed you that the test wasn't covered. If specific tests or evaluations are not covered by insurance/Medicare, patients will be given the choice of not undergoing that testing or covering the cost out of pocket.

Conflicts of Interest

The authors disclose no conflicts of interest.

Limitations of the study

1. Participants will not be monitored as inpatients during the study period. This introduces the possibility of confounding factors including variation in diets and excessive use of other rescue medications for symptomatic relief
2. Small sample size of 25 patients for the pilot treatment (crofelemer) arm
3. Short follow up period of 4 weeks to assess effects of the crofelemer will limit any longer-term observations or conclusions regarding chronic therapy with this medication

Based on the results of this pilot study, a randomized control multi-center clinical trial may be warranted with a larger cohort and longer treatment and follow up duration. We are hoping that this study would set up a base for future investigators to explore the potential uses of crofelemer from chronic idiopathic diarrhea given the prevalence of the condition and the absence of FDA approved therapies.

Attachments

1. Curriculum Vitae of the Principal Investigator
2. Written Informed Consent Form to participate in the clinical trial with HIPAA authorization
3. Template of Sample Entry of Daily Symptom Diary
4. Written Informed Consent Form Esophagoduodenoscopy and Colonoscopy
5. SF-36: Health-related Quality of Life Questionnaire Form Pre-Treatment Survey (5a) and Post-Treatment Survey (5b)
6. Crofelemer Package Insert
7. Patient Education Sheet on Crofelemer
8. Patient Education Sheet on Esophagogastroduodenoscopy procedure

9. Patient Education Sheet on Colonoscopy procedure
10. University of Michigan CSID Protocol

Figure 1. A Chemical Structure of crofelemer.

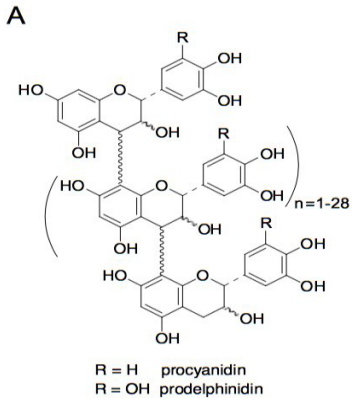

Figure 2. Bristol Stool Scale Chart (Reproduced by permission of the late Dr K W Heaton, Reader in Medicine at the University of Bristol. © 2000 Norgine Pharmaceuticals Ltd.) [61]

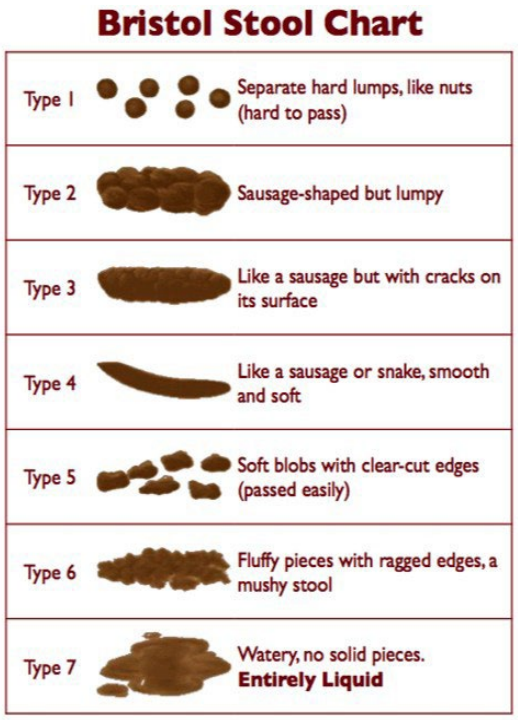

Figure 3. Schematic Design of the Study

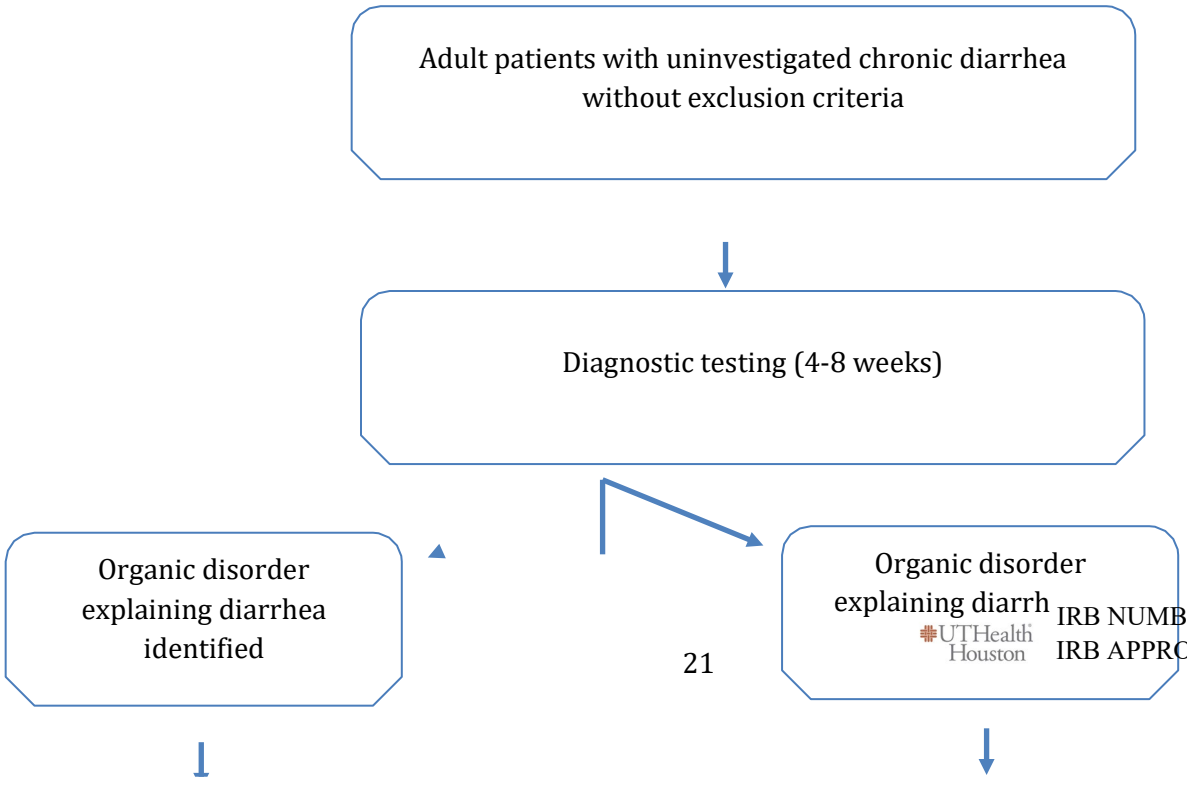

Table 1. Adverse Reactions Occurring in at Least 2% of Patients in the 125 mg Twice Daily Group

Adverse Reaction	Crofelemer 125 mg BID*N = 229 n(%)	Placebo N = 274 n(%)
Upper respiratory tract infection	13 (5.7)	4 (1.5)
Bronchitis	9 (3.9)	0
Cough	8 (3.5)	3 (1.1)

Flatulence	7 (3.1)	3 (1.1)
Increased bilirubin	7 (3.1)	3 (1.1)
Nausea	6 (2.6)	4 (1.5)
Back pain	6 (2.6)	4 (1.5)
Arthralgia	6 (2.6)	0
Urinary tract infection	5 (2.2)	2 (0.7)
Nasopharyngitis	5 (2.2)	2 (0.7)
Musculoskeletal pain	5 (2.2)	1 (0.4)
Hemorrhoids	5 (2.2)	0
Giardiasis	5 (2.2)	0
Anxiety	5 (2.2)	1 (0.4)
Increased alanine aminotransferase	5 (2.2)	3 (1.1)
Abdominal distension	5 (2.2)	1 (0.4)
* Twice daily		

Abbreviations

AE - Adverse Event

BAM - Bile Acid Malabsorption

BID - Twice Daily

BSS - Bristol Stool Scale

^{13}C-SBT - ^{13}C-Sucrose Breath Test

CSID - Congenital Sucrase-Isomaltase Deficiency

EDDC - Ertan Digestive Disease Center

EGD - Esophagoduodenoscopy

FDA - Food and Drug Association

H_2 BT - Hydrogen Breath Testing

HRQOL - Health-related Quality of Life

IBS - Irritable Bowel Syndrome

IRB - Institutional Review Board

MGAM - Maltase-Glucoamylase Complex

PI - Principal Investigator

QOL - Quality of life

SI - Sucrase-Isomaltase

UTHealth/MHHS - University of Texas Health Science Center at Houston/ Memorial Hermann Healthcare System

VIP - Vasoactive Inhibitory Peptide

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