Rifaximin on Visceral Hypersensitivity

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Investigator-Initiated Study Proposal

Rifaximin on Visceral Hypersensitivity

Protocol ID: 49509

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1.0 INTRODUCTION

1.1 Background and Scientific Rationale

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders, with a global prevalence of 11% according to a recent meta-analysis [1]. Patients with IBS visit the doctor more frequently, consume more medications, and use more diagnostic tests, such that the total costs of managing IBS in the United States in excess of $30 billion per year, including indirect costs relating to loss of productivity of more than $20 billion [2]. IBS manifests itself in 3 major forms; diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), and mixed (IBS-M) [3], and is predominantly characterized by symptoms of abdominal pain, changes in stool frequency and consistency, and abdominal bloating [4].The diagnosis of IBS involves the identification of these key clinical symptoms [5, 6]. Abdominal pain/discomfort (i.e. visceral hypersensitivity) is present in all patients and remains the most therapy-resistant symptom in IBS. Apart from abdominal pain, which is measured subjectively using visual scales, several studies have shown a significant increase in rectal sensitivity, which is measured objectively using an inflatable balloon. Hence, drugs which are shown to have objective effects on visceral hypersensitivity are crucial in the management of IBS.

Over the last decade, our group has demonstrated that small intestinal bacterial overgrowth (SIBO) may play a significant role in IBS [7-11]. SIBO is a condition in which there is an increase in the number of bacteria in the small bowel [12-14], and typically includes an overgrowth of coliform bacteria which are normally found in the colon [15]. These are predominantly gram-negative aerobes and anaerobic species that produce gas during fermentation of carbohydrates [15, 16], and the SIBO hypothesis proposes that it is this expansion of bacteria in the small bowel that leads to IBS symptoms including bloating, abdominal discomfort and changes in stool form [17]. Two separate studies using cultures of small bowel aspirates have now confirmed that IBS subjects have higher coliform counts in the small bowel than non-IBS subjects [15, 18]. Significantly, 60% of IBS-D subjects were found to meet the definition of SIBO [18].

1.2 Current Standard Therapy

Currently, three drugs for IBS-D (rifaximin, alosetron and eluxadoline) and two (linaclotide and lubiprostone) for IBS-C are approved by FDA [19]. While these drugs have shown to decrease abdominal pain based on subjective scales in their respective clinical trials, there is very little data to substantiate objective changes in visceral hypersensitivity. While rifaximin is an

antibiotic, the exact underlying mechanism of action for rifaximin in reducing the pain component of IBS remains unknown. However, rifaximin is the only medication that has been shown in randomized controlled trials to decrease abdominal discomfort in all subtypes of IBS. This suggests that rifaximin, unlike other approved medications, addresses the underlying pathophysiology of IBS rather than simply targeting symptom relief.

Given the role of altered bacterial populations in IBS, a number of randomized controlled trials have been conducted examining the utility of antibiotics in treating IBS [20-23]. All of these controlled trials have demonstrated significant success with antibiotic therapy. The two principal antibiotics studied to date are neomycin [8] and rifaximin (Xifaxan) [21, 24, 25]. While neomycin was a successful therapy for IBS, it was disappointing in its ability to normalize the lactulose breath test (LBT) [8]. In contrast rifaximin, a non-absorbed antibiotic (99.6% retained in the GI tract), has been shown to normalize the LBT in 70% of subjects [26]. The most recent phase III randomized controlled trial of rifaximin demonstrated three important findings [23]:

First, rifaximin was effective in improving the primary endpoint (adequate relief of global IBS symptoms and newer FDA endpoints for IBS) compared to placebo. Second, rifaximin treatment resulted in significantly greater improvement in all major IBS symptoms (abdominal pain, bloating, and stool consistency). Third, the drug had a durable effect for over 3 months after the cessation of therapy[23].

1.3 Rationale for the Study

Currently in clinical practice and research, visceral sensitivity can be objectively, safely, easily and reliably measured using an inflatable rectal balloon attached to a barometer. We hypothesize that rifaximin is effective in decreasing rectal visceral hypersensitivity in IBS patients. In this study, we propose to test this hypothesis. Moreover, we will explore whether this effect is mediated by SIBO and accompanied by improvement in breath test results.

2.0 OBJECTIVE

The primary objective of this study is to assess the effect of rifaximin in decreasing rectal hypersensitivity in patients with IBS-M and IBS-D. The secondary objective of this study is to assess the role of SIBO in rectal sensitivity.

3.0 STUDY DESIGN

3.1 Program Type/Scope of Trial/Clinical Design

The proposed study is a prospective clinical trial to determine whether Xifaxan can decrease rectal visceral hypersensitivity in diarrhea-predominant and mixed type IBS patients.

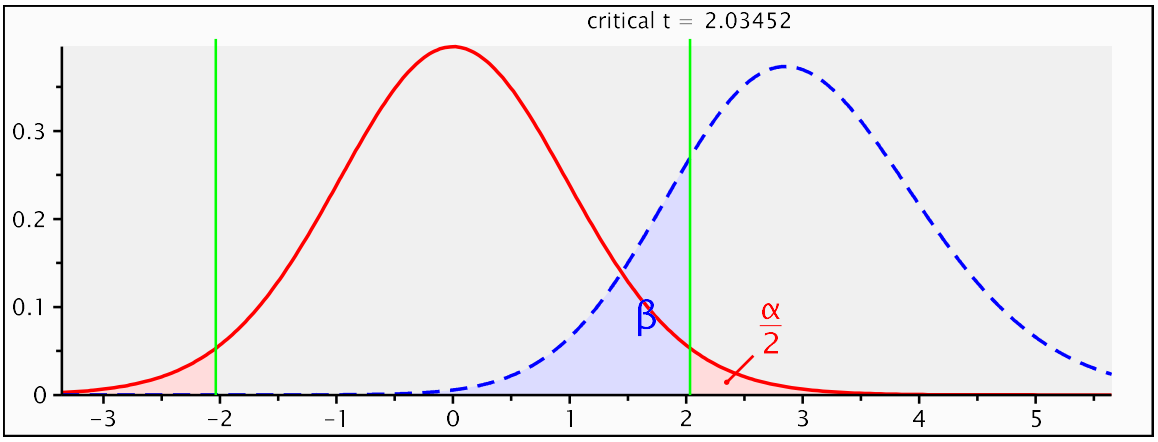
IBS-D and IBS-M patients will undergo baseline rectal sensitivity testing. Patients will then receive rifaximin 550 mg by mouth three times daily for 14 days. On day 15, patients will undergo repeat rectal sensitivity testing.

3.2 Study Population/Demographics/Disorder

Adult patients (age 18-75) with IBS-D or IBS-M (diagnosed based on Rome IV criteria [27]) will be assessed for eligibility to participate in this study. Potential subjects will be identified and recruited through the GI Motility Clinic at Cedars-Sinai Medical Center.

3.3 Number of Subjects (Statistical Justification)

We are planning a study of a continuous response variable before and after therapy. In our previous study of 122 patients, we showed that the rectal balloon volume to cause the sensation of urge to defecate had a mean of 87 cc and standard deviation of 42 cc [28]. We consider a 20 cc increase in threshold of urge to defecate to be clinically significant. The effect size associated with this assumption is 0.50. We need to study 34 subjects be able to reject the null hypothesis that the rectal sensitivity after rifaximin is equal with probability (power) of 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. As this is a 4 month follow up study, we expect a 15% dropout rate based on our previous clinical experience. Therefore, we will need to consent 40 subjects to achieve our statistical goals. Statistical analysis will be performed using STATA ver 14.0. Paired t test will be used to assess the primary outcome of interest and selected secondary outcomes. Logistic regression will be used to assess the determinants of responders (improvement of 20 cc in rectal volume to cause urge).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4.0 ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

- Male or female subjects aged 18-75 years old inclusive
- Meet Rome IV criteria for IBS-D or IBS-M
- Subjects should report urgency with bowel movement at least once a week
- If subjects are ≥50 years old, a colonoscopy must have been completed within the past 5 years
- Subjects are capable of understanding the requirements of the study, are willing to comply with all the study procedures, and are willing to attend all study visits.
- Agree to use an acceptable method of contraception throughout their participation in the study. Acceptable methods of contraception include:
    - double barrier methods (condom with spermicidal jelly or a diaphragm with spermicide),
    - hormonal methods (e. g. oral contraceptives, patches or medroxyprogesterone acetate), or
    - an intrauterine device (IUD) with a documented failure rate of less than 1% per year.
    - Abstinence or partner(s) with a vasectomy may be considered an acceptable method of contraception at the discretion of the investigator.
    - All subjects will provide Institutional Review Board (IRB)-approved informed written consent prior to beginning any study-related activities

NOTE: Female subjects who have been surgically sterilized (e.g. hysterectomy or bilateral tubal ligation) or who are postmenopausal (total cessation of menses for >1 year) will not be considered “females of childbearing potential”.

4.2 Exclusion Criteria

- Treatment with antibiotics or Xifaxan in the last two months
- Subjects with history of intestinal surgery (except appendectomy or cholecystectomy)
- Subjects with known pelvic floor dysfunction
- Pregnancy

- Nursing mothers
- Poorly controlled/uncontrolled significant medical condition that would interfere with study procedures
- History of bowel obstruction
- History of celiac disease
- History of inflammatory bowel disease
- Cirrhosis
- IBS-C/chronic idiopathic constipation
- Poorly controlled diabetes (hemoglobin A1c >8.0% for ≥1 year) [29]
- History of anorectal radiation/surgery
- History of prostatitis
- Known allergy or hypersensitivity to rifaximin or rifamycin
- Current treatment with eluxadoline or opiates

NOTE: Development of any of the exclusion criteria during the study will be considered a basis for subject discontinuation.

5.0 INVESTIGATIONAL PRODUCT

5.1 Formulation and Supply

Xifaxan will be supplied by Salix pharmaceuticals. Xifaxan is approved by FDA to be used in patients with IBS-D, hepatic encephalopathy and *E. coli*-associated traveler's diarrhea.

5.2 Packaging

On day 0 (see section 6.0 – Study Procedures and Regimens), subjects will be provided medication packs sufficient for 14 days.

For all study investigational product, a system of investigational product numbering in accordance with all requirements of current Good Manufacturing Practice (GMP) will be used. This will ensure that for each subject, any measured quantity of study investigational product can be identified and traced back to the original pack of medication.

Lists linking all numbering levels will be maintained by the institutions in charge of investigational product packaging including the Sponsor.

5.3 Labeling

Each pack will bear a label which includes, but is not limited to, the following information:

- Product: Xifaxan
- Kit Number
- Quantity
- Instructions for taking product
- Storage conditions: Store packets/kit at 20-25°C (68-77°F): excursions permitted between 15-30°C (59-86°F)
- Manufacturer

In addition, each kit label will contain an area for the site to write the following information:

- Subject initials
- Subject ID Number
- Date Dispensed

- Date Returned

5.4 Storage and Handling

All investigational product will be kept in a locked area with limited access to study staff only. The locked area will be maintained under controlled temperature conditions at 20-25°C (68-77°F); excursions are permitted to 15-30°C (59-86°F).

5.5 Rationale for Xifaxan dose selection

Currently, Xifaxan is approved for treatment of IBS-D. The dosing is 550 mg PO TID for 14 days. In addition, two 14-day retreatment courses of Xifaxan is allowed by FDA if the patient does not respond to initial therapy. We have designed our study so that subjects will receive one standard 14-day course of Xifaxan during the study. This is less than the three courses of Xifaxan allowable for IBS-D patients per the FDA.

6.0 STUDY PROCEDURES AND REGIMENS

6.1 Subject identification and recruitment

Potential subjects with IBS-D and IBS-M will be identified through the GI Motility Clinic at Cedars-Sinai Medical Center and assessed for eligibility to participate in this study.

6.2 Therapy phase

If patients meet the inclusion criteria and provide informed written consent, they will:

Visit 1: Day -7

- Undergo a urine pregnancy test (if a woman of childbearing potential)
- Complete a baseline symptom questionnaire (see Appendix 1). This can either be filled online using REDCap, a secure, web-based application for building and managing online surveys and databases with which Cedars-Sinai is partnered, or completed in paper format
- Present fasting for a full lactulose breath test (see Appendix 2)
- Up to 60 cc of exhaled breath gas at baseline and 120 minutes of testing will be stored for additional testing by mass spectroscopy (Exetainer® 12ml flat-bottom vacuumed vials, LabCo, UK).
- Subjects will be given a stool diary (see Appendix 3) and asked to complete this at home over the next 7 days, using the Bristol Stool Chart (see Appendix 4) as a visual aid
- Patient will undergo a rectal sensitivity assessment (Appendix 5)

Day -7 to Day 0

- Complete a 7-day baseline stool and symptom diary (see Appendix 3) using the Bristol Stool Chart (see Appendix 4)

Visit 2: Day 0

- A 14-day supply of Xifaxan will be provided to the patient

Each subject will be instructed by the investigator or his representative on the proper self-administration, handling and storage of the product. Each subject will be instructed to take Xifaxan 550 mg PO TID for 14 days. For the purpose of accountability, all unused

packets from each kit dispensed to the subject should be returned to the site at each visit. In order to maintain compliance with federal regulations, records of the disposition of drug will include: dates dispensed, quantity, use by the subject and dates of returns.

Day 0 to Day 14

- Subjects will complete weekly symptom questionnaires (see Appendix 6) at home, beginning on Days 0 and 7. Again, these can either be filled online using REDCap, or completed in paper format
- Subjects will complete a Daily Stool Diary (see Appendix 3)

Visit 2: Day 15

- Subject will undergo a rectal sensitivity assessment (Appendix 5)
- Subject will undergo an LBT
- Up to 60 cc of exhaled breath gas at baseline and 120 minutes of testing will be stored for additional testing by mass spectroscopy (Exetainer® 12ml flat bottom vials, LabCo, UK).

6.3 Study Flowchart

6.4 Study Duration

The study duration will be approximately 1 year. Each subject will be involved in the study for 3 weeks (see Study Flowchart).

6.5 Medications Not Permitted

The following medications may not be taken while on this study:

- Opiates or new pain modulating medications
- Eluxadoline

7.0 OUTCOME MEASURES

7.1 Primary Outcome Measure

The primary outcome of the study is the mean change in the balloon volume that leads to first urge to defecate. A 100-mm visual analogue scale with verbal descriptors (0=no sensation, 20=first sensation, 40=first sense of urge, 60=normal urge to defecate, 80=severe urge to defecate, and 100=discomfort/pain) will be used to score evoked sensations [30].

7.2 Secondary Outcome Measures

Secondary outcome measures will include:

- mean change in the balloon pressure and volume that leads to first urge to defecate
- mean change in the balloon pressure and volume that leads to severe urge to defecate
- mean change in the balloon pressure and volume that leads to severe urge to defecate
- mean change in the balloon pressure and volume that leads to severe urge to defecate
- mean change in the balloon pressure and volume that leads to first sensation
- mean change in the balloon pressure and volume that leads to first sensation
- mean change in the balloon pressure and volume that leads to first sensation
- Association of urgency symptom and rectal sensitivity testing
- Normalization of LBT as a predictor of improvement of rectal hypersensitivity

8.0 SIDE EFFECTS

All side effects will be captured, evaluated and categorized as follows:

- An Adverse Event (AE) will be a side effect that is an event reported by the subject that is deemed related to Xifaxan but may or may not prevent continuation of the trial (examples include body aches, loose stool)
- A Serious Adverse Event (SAE) will be an event report by a subject during the trial may or may not be deemed related to Xifaxan that forces discontinuation of the trial (examples include anaphylaxis, etc.).

All side effects will be reported to a data safety monitor who is independent of the study.

The assessment of the relationship of an AE to the administration of the study medical food supplement is a clinical decision based on all available information at the time of the completion of the source documentation of the AE or of the SAE form, if applicable.

An assessment of “Not” or “Unlikely” would include (Note: “Unlikely” is considered not related to the study medical food supplement):

- The existence of a clear alternative explanation, e.g., mechanical bleeding at surgical site; or
- Non-plausibility, e.g., the subject is struck by an automobile when there is no indication that the study medical food supplement caused disorientation that may have caused the event; cancer developing a few days after the first therapy administration.

An assessment of “Possible” or “Related” indicates that there is a reasonable suspicion that the AE is associated with the use of the study medical food supplement.

Factors to be considered in assessing the relationship of the AE to the study medical food supplement include:

- The temporal sequence from administration of the study medical food supplement: The event should occur after the therapy is given. The length of time from therapy exposure to event should be evaluated in the clinical context of the event.
- Recovery of discontinuation (de-challenge), recurrence on re-introduction (re-challenge): Subject’s response after discontinuation of the study medical food supplement (de-challenge), or response after re-introduction of the study medical

food supplement (re-challenge) should be considered in the view of the usual clinical course of the event in question.

- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other therapies the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- Concurrent study procedures: Study procedures should also be considered as possible causes of an AE. Invasive procedures such as biopsies have their own profile of expected AEs and the Investigator should consider these.

The Investigator will make a separate and independent assessment of every AE's relationship not just to the study the study medical food supplement, but also to the subject's pre-existing medical condition(s).

The severity of AEs should be graded as follows:

- Mild – usually transient in nature and generally not interfering with normal activities
- Moderate – sufficiently discomforting to interfere with normal activities
- Severe – prevents normal activities

8.1 Clinical criteria for withdrawing an individual subject from the study

Clinical criteria for withdrawing an individual subject from the study are as follows:

- Subject chooses to withdraw
- The occurrence of an adverse event, which, in the judgment of the Investigator or independent monitor, suggests an unacceptable risk to the subject
- Pregnancy
- Investigator discretion
- Subject noncompliance

8.2 Criteria for stopping or changing the study protocol

Criteria for stopping or changing the study protocol due to safety concerns are as follows:

- Should the investigator, independent monitor, the FDA, or local regulatory authorities become aware of conditions arising during the conduct of this study that may warrant the cessation of the study, such action may be taken. Prior to such action, consultation between the investigator, and, as appropriate, the FDA and/or local regulatory authorities will take place

- If there are >2 subjects with serious adverse events, the independent study monitor will examine and audit the cases and determine the relevance to the assigned study medical food supplement and whether the trial should continue or if there are grounds for discontinuing the study

8.3 Follow-up of AEs and SAEs

All AEs and SAEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. The investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

8.4 Prompt Reporting of SAEs to Salix Pharmaceuticals.

Serious adverse events must be reported promptly to Salix pharmaceuticals. once the investigator determines that the event meets the protocol definition of an SAE.

Prompt reporting of a SAE requires:

- Completion and transmission of SAE information to Salix pharmaceuticals. within 24 hours of the investigator's knowledge of the event. The SAE It is very important that the investigator provide his/her assessment of causality to investigational product at the time of initial reporting of the SAE. SAE information should include at a minimum:
    - AE description (diagnosis)
    - Onset Date

- Resolution date
- Duration
- Seriousness (Fatal, Life Threatening, Hospitalization require or prolonged, Congenital anomaly, Disabling/Incapacitating, Other – describe)
- Contributing factors (underlying disease being studied, concurrent illness – specify if yes, concurrent therapy – specify if yes, other - describe)
- List relevant medical conditions (past or current), include onset and resolution dates if known
- List any medications taken to treat this SAE
- Provide any relevant diagnostic procedures and laboratory results
- Add a narrative/comments providing a textual description of the SAE including chronological presentation and evaluation of the SAE, associated signs and symptoms, treatment of the SAE and outcome of the SAE.

Prompt reporting of additional information for previously reported SAEs should follow the same reporting timeframe as initial reports.

8.5 Pregnancy Reporting

Pregnancies detected during study conduct should be promptly reported to Salix pharmaceuticals as soon as the investigator is notified. should be notified via fax of any updates on the status of the pregnancy as soon as the information becomes available by update and/or amendment of the initial pregnancy reporting form. Pregnancies will be followed to term and information will be collected on the pregnancy outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, abnormalities, or complications.

9.0 AUDITS

At its discretion, Salix pharmaceuticals may conduct a quality assurance audit of this study. If such an audit occurs, the investigator agrees to allow the auditor direct access to all relevant documents and to schedule his/her time and the time of his/her staff to permit meetings with the auditor to discuss findings and any relevant issues.

In addition, regulatory agencies may conduct a regulatory inspection of this study. If such an inspection occurs, the investigator agrees to allow the inspector direct access to all relevant documents and to schedule his/her time and the time of his/her staff to permit meetings with the auditor to discuss findings and any relevant issues.

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11.0 SUPPORT REQUESTED (STUDY BUDGET)

Labor	Cost	SubTotals
1. Principal Investigator with fringe (1% effort)	$ 3,248	
2. Co-Investigator with fringe (3% effort)	$ 9,901	
3. Study Coordinator with fringe (19.5% effort)	$ 14,120	$ 27,269
Other Direct Costs		
1. Lactulose breath tests	$ 11,855	
2. Rectal sensitivity tests	$ 22,902	
3. Pharmacy dispensing fees	$ 1,200	
4. IRB fees (overhead not applicable)	$ 3,000	
5. Pharmacy startup fee	$ 1,500	
6. Pharmacy closeout fee	$ 500	
7. Patient compensation ($80 per visit x 80 visits)	$ 6,400	
8. Pregnancy tests (for exclusion criteria)*	$ 173	$ 47,530
Direct Cost Total		**$ 74,799**
Overhead (30%, no overhead on IRB fees)		$ 21,540
Total Initial Budget		**$ 96,339**
Additional Annual Invoiceable Costs**		
1. IRB Continuing Expedited Review Fee (overhead not applicable) † or	$ 750	**$ 750**
2. IRB Continuing Full Committee Review Fee (overhead not applicable) †	$ 1,500	**$ 1,500**
3. Pharmacy Annual Renewal Fee (inclusive of 30% overhead)	$ 975	**$ 975**
Total Study Costs (including one (1) Pharmacy Renewal at $975 including overhead and One IRB Continuing renewal at the maximum $1,500 fee).		**$ 98,814**

* Assuming 50% of subjects are females of childbearing age
** Paid only if study extends into second year
† Either the $750 Continuing Review fee or the $1500 Continuing Review fee may be charged at annual renewal depending on the type of review the IRB does, but both fees won't be charged for the same review.

Labor	Cost	Sub-Totals

1. Principal Investigator with fringe (1% effort)	$	3,248		
2. Co-Investigator with fringe (3% effort)	$	9,901		
3. Study Coordinator with fringe (19.5% effort)	$	14,120	$	27,269
Other Direct Costs				
1. Lactulose breath tests	$	11,855		
2. Rectal sensitivity tests	$	22,902		
3. Pharmacy dispensing fees	$	1,200		
4. IRB fees (overhead not applicable)	$	3,000		
5. Pharmacy startup fee	$	1,500		
6. Pharmacy closeout fee	$	500		
7. Patient compensation ($80 per visit x 80 visits)	$	6,400		
8. Pregnancy tests (for exclusion criteria)*	$	173	$	47,530
Direct Cost Total			**$**	**74,799**
Overhead (30%, no overhead on IRB fees)			$	21,540
Total Initial Budget			**$**	**96,339**
Additional Annual Invoiceable Costs**				
4. IRB Continuing Expedited Review Fee (overhead not applicable) † or	$	750	**$**	**750**
5. IRB Continuing Full Committee Review Fee (overhead not applicable) †	$	1,500	**$**	**1,500**
6. Pharmacy Annual Renewal Fee (inclusive of 30% overhead)	$	975	**$**	**975**
Total Study Costs (including one (1) Pharmacy Renewal at $975 including overhead and One IRB Continuing renewal at the maximum $1,500 fee).			**$**	**98,814**

* Assuming 50% of subjects are females of childbearing age
** Paid only if study extends into second year
† Either the $750 Continuing Review fee or the $1500 Continuing Review fee may be charged at annual renewal depending on the type of review the IRB does, but both fees won't be charged for the same review.

Appendix 1: Baseline Questionnaire

Patient Code: _____

SECTION 1: DEMOGRAPHICS

1. Date:_____
2. Age: _____
3. Sex: _____
4. Height: _____
5. Weight (lbs): _____

SECTION 2: PAST MEDICAL AND SURGICAL HISTORY

1. In the following chart answer yes or no to the surgeries listed and list any other previous surgical procedures you have had:

PLEASE PRINT CLEARLY

Type of Surgery	Circle YES or NO	Problem (symptoms)	Date of Surgery
1. Appendix removal	YES NO		
2. Tonsils removal	YES NO		
3. Gastric Bypass	YES NO		
4.			
5.			
6.			
7.			
8.			
9.			
10.			

(If more than 10 surgical procedures…continue on reverse of this page)

2. Please indicate if you have ever been told you have any of the following diagnoses:

Diagnosis	Indicate "X" if you have been told you had the diagnosis	If yes, when was it diagnosed?
1. Irritable bowel		
2. Crohn's Disease		
3. Ulcerative Colitis		
4. Fibromyalgia		
5. Gastroesophageal reflux disease		
6. Diabetes (Type I)		
7. Diabetes (Type II)		

FOR WOMEN ONLY:

Do you have a history of difficultly getting pregnant? YES NO

Do you have irregular periods? YES NO

Have you ever been diagnosed with polycystic ovary syndrome (PCOS)? YES NO

SECTION 3: MEDICATIONS

1. List the medications that you are on currently:

PLEASE PRINT CLEARLY

Medication	Dose	For what problem	Approximate start date
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			

(If more than 10…continue on reverse of this page)

2. List any antibiotics other than rifaximin you have taken in the last 6 months:

Antibiotic	Dates taken	Why taken?
1.		
2.		
3.		
4.		
5.		

SECTION 4: SOCIAL HISTORY

1. Do you or did you ever smoke? YES NO
   If "YES", when did you start….. **_____**
   and when did you quit…_____

2. Do you drink alcohol? YES NO
   If "YES", you drink _____ glasses of _____ (type of alcohol)
   every _____ (day/week/month)

3. Were you breastfed as a child? YES NO Unknown
   If "YES", for how long _____?

SECTION 5: TRAVEL HISTORY

1. In the following chart, list the places outside of the US you have traveled:

Location Traveled	Date	Did you experience excessive Diarrhea on this trip?
1.		YES NO
2.		YES NO
3.		YES NO
4.		YES NO
5.		YES NO
6.		YES NO
7.		YES NO
8.		YES NO
9.		YES NO
10.		YES NO

(If more than 10…continue on reverse of this page)

SECTION 6: DIETARY CHANGES

1. Please list any recent changes you have made to your diet:

Date started	Type of Change	Date discontinued (if applicable)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		

Appendix 2: Lactulose Breath Test

Preparation for the Test:

Subjects will not be allowed to consume any heavy protein or legumes on the night before the test.

Subjects will fast beginning at 7 pm on the previous evening to guarantee a 12 hour fast. Only water will be allowed until midnight before the test. Subjects cannot chew gum during this time of fasting.

All subjects will be asked to brush their teeth or use mouthwash (not swallowed) and refrain from smoking cigarettes on the morning of the test.

Test Administration:

All subjects will provide a baseline end expiratory breath sample at the start of the test.

They will then be provided a syrup containing 10 g of lactulose syrup after which breath samples will be collected every 15 minutes exactly for 120 minutes.

Sample Analysis:

Samples will be analyzed using a gas chromatograph capable of measuring hydrogen (H_2), methane (CH_4) and carbon dioxide (CO_2). The CO_2 will be used to correct for alveolar sampling error. The H_2 and CH_4 will be plotted on a graph with time on the x-axis and gas concentration in ppm on the y-axis.

Appendix 3: Stool Diary

See next page.

Daily Diary **Subject Number:** _____

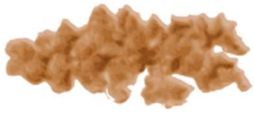
If you had no bowel movements today, please check this box: ☐ no bowel movements today.

Date: _ _ / _ _ / 20 _ _	**Describe the consistency of bowel movement** **1** hard lumps **2** lumpy sausage **3** cracked sausage **4** smooth sausage **5** soft lumps **6** mushy **7** watery	**Describe the Ease of Passage of bowel movement** **1** no straining needed **2** mild straining **3** moderate straining **4** severe straining **5** very severe straining	**Did you feel like you completely emptied your bowels?** **1** no **2** yes
1 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
2 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
3 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
4 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐

(If more than 4…continue on reverse of this page)

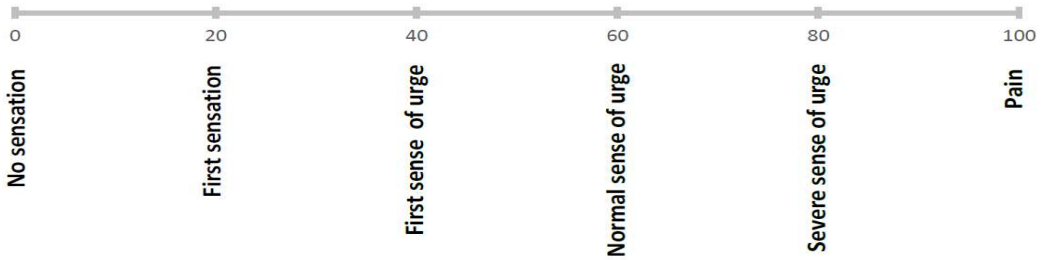
Appendix 4: Bristol Stool Chart

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 the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

Appendix 5: Assessment of rectal sensitivity using graded balloon distention

A standard non-latex rectal balloon (Mui Scientific, Mississauga, Ontario, Canada) will used for assessment of rectal sensitivity. After lubrication the balloon will be inserted into the rectum and will be advanced for 5 cm. The balloon will be inflated by 20 cc and pull back until sphincter resistance is appreciated. At this point the catheter will be advance 3cm and will be deflated. Following a 20 second hiatal, every minute the balloon will be inflated by 10 cc in 10 seconds. Patient will be asked about the sensation after 10 seconds. Patients will be blinded from the balloon volume or whether the balloon is inflated. The balloon will be deflated and inflated with 10cc incremental volumes until the first sensation, first sensation of urge, normal sensation of urge and severe sensation of urge is appreciated (see scale below). When these points are achieved, the balloon pressure will also be recorded (Posey 8199 Manometer, Arcadia, CA, USA). The maximum inflated volume will be 200 cc.



0- No sensation: No fullness is sensed in the rectum

20- First sensation: Feeling fullness in the rectum but no urge (would not go or plan to go to restroom)

40- First sense of urge to defecate: Sensation of fullness and mild urge to defecate (would not go to bathroom)

60- Normal urge to defecate: Usual sensation of urge to defecate (would plan to go restroom but would not rush)

80- Severe urge to defecate: Would stop any non-essential activity and rush to a bathroom.

100- Pain: Sensation of pain/discomfort different from urge.

Appendix 6: Weekly Questionnaire

BOWEL SYMPTOMS QUESTIONNAIRE
Week #: _____ Day #: _____

DATE: _____ CODE:

_____

AGE: _____

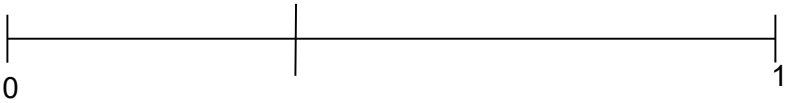
SEX: _____

HEIGHT: _____

WEIGHT: _____

INSTRUCTIONS: For each symptom indicated, please mark a vertical line on the scale that best represents the symptom severity that you experienced **during the past one week**.

EXAMPLE:



No Symptom Severe Symptom

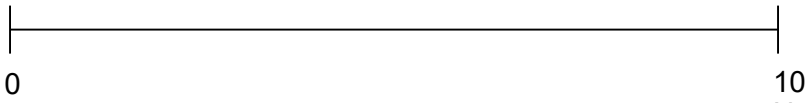
1. **Bloating**

2. **Excess Gas**

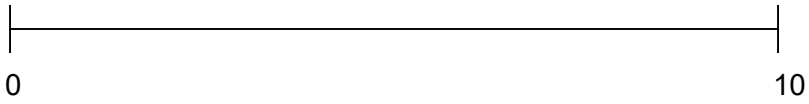
3. **Incomplete Evacuation** (feeling that all your stool has NOT come out)

4. **Abdominal Pain**

5. **Constipation**

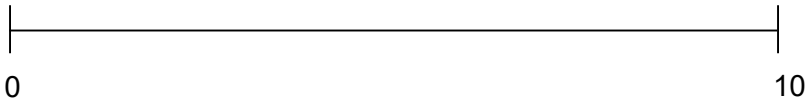


6. **Diarrhea**

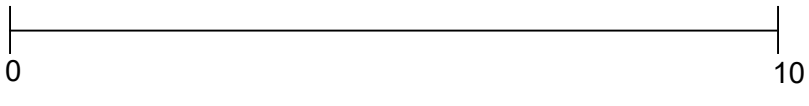


7. **Urgency**

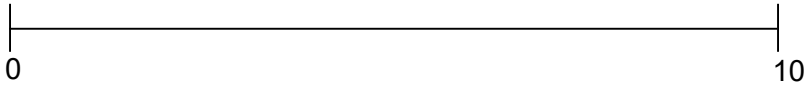
8. **Mucous from rectum**



9. **Straining during bowel movement**



10. **Fatigue**



11. **Overall improvement of your IBS symptoms**