# The Effect of Long-Acting Mesalamine on Post-Infective Irritable Bowel Syndrome- A Double-Blind Placebo Controlled Pilot Study

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**Protocol Summary**
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# The Effect of Long-Acting Mesalamine on Post-Infective Irritable Bowel Syndrome: A Double-Blind Placebo Controlled Pilot Study

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**BACKGROUND AND INTRODUCTION:** Up to one-third of patients with irritable bowel syndrome (IBS) describe the onset of their symptoms following an episode of acute gastroenteritis. This is called post-infective IBS (PIIBS). [1] It is associated with an increase in inflammatory mediators such as prostaglandins, cytokines, and nerve growth factors. [2] Routine colon histology is usually normal; however, there is often an increase in the number of mast cells and T-cells on microscopic examination.[3] It is thought that the initial inflammatory response triggers a cascade of events (mediated by incorporation of Toll-like receptors and NF-KB) leading to proliferation of mast cells and activation of enterochromaffin (EC) cells. Intestinal mucosal mast cells attract inflammatory cells and initiate the innate and adaptive immune system manifested by invasion of T-lymphocytes, and also enhance visceral hypersensitivity and abdominal pain.[4] Enterochromaffin cells secrete serotonin which regulates intestinal motility and secretion. It remains unclear whether the inflammation is the response to injury or initiates the disease. Nor is it known why the disease becomes self-perpetuating.

NF-κB (nuclear factor kappa-light chain-enhancer of activated B cells) is a transcription factor that plays a central role in inflammation and immune regulation. [5] Mesalamine (5-ASA) is a PPAR γ (peroxisome proliferator-activated receptor γ) agonist which among other things inhibits NF- κB. [6] There is anecdotal evidence that it is effective in the treatment of microscopic colitis which has many pathophysiologic similarities to PI-IBS[7-9]. We hypothesize that patients with PI-IBS are also likely to respond to mesalamine.

A recent study in IBS patients demonstrated a reduction in colonic mast cells after mesalamine but no improvement in symptoms.[10] A double-blind placebo controlled study of mesalamine by our group also failed to show improvement in symptoms but did demonstrate a trend toward improvement in quality-of-life (QOL) suggesting that other mechanisms may be involved- perhaps suppression of the immune response which is partly responsible for the extraintestinal symptoms of fatigue, etc. Compliance was a problem in this study as patients were not receptive to taking 4 tablets of mesalamine twice per day. We propose that compliance and therapeutic response could be improved by using long acting mesalamine. Salt Lake City is an ideal area to conduct this study in that there is a large population of Mormon missionaries and who return from abroad with altered bowel function. We have previously demonstrated that most of these patients have PI-IBS.[11, 12]

The purpose of this study is to evaluate the effects of long acting mesalamine (Lialda ®) in patients with PI-IBS. We will evaluate gastrointestinal symptoms, IBS specific quality of life (IBS-QOL) before and after treatment with Lialda ®.

**Significance of this study:**
This study will test long acting mesalamine in the management of PI-IBS. It has the potential to improve QOL and perhaps gastrointestinal symptoms, in patients with PI-IBS. The results of this study, if positive, will provide preliminary data for a large scale clinical trial.

**Aim**:
To determine if mesalamine will relieve symptoms, improve QOL and reduce inflammation in patients with PI-IBS.

IBS
IBS is characterized by abdominal pain or discomfort associated with altered bowel function (diarrhea and/or constipation) in the absence of any structural abnormality.[13] It is a poorly understood disorder that is probably a heterogeneous group of conditions producing similar symptoms. IBS is associated with reduced QOL and significant economic burden.[14] It is the most frequent GI disorder seen by physicians, comprising 50% of referrals to gastroenterologists and as many as 3.5 million visits to physicians each

year in the United States. [15] The direct cost of IBS in the US is estimated at $1.5 to 10 billion and the indirect cost, $20 billion. The cause of IBS is not known. The speculated mechanisms of IBS include altered GI motility, visceral hypersensitivity, aberrant brain-gut interaction, and psychological factors, perhaps with a genetic predisposition. [16] A proposed triggering mechanism in patients with PI-IBS is mucosal injury with subsequent inflammatory/ immune response which becomes self-perpetuating.[2]

PI-IBS

IBS occurs in 7% to 30% of subjects after an episode of gastroenteritis.[1] Several factors have been shown to predispose to PI-IBS: severity of the initial illness, bacterial toxigenicity, hypochondriasis, depression and adverse life events in the previous 3 months. [17] PI-IBS is characterized by predominance of diarrheal symptoms, less psychiatric illness, and increased serotonin-containing enterochromaffin cells compared to those with non-PI-IBS.[17]

There are several factors which suggest that inflammation plays a part in the pathogenesis of PI-IBS. For example, an infection activates mast cells in the GI tract. When activated, mast cells release humoral mediators which induce the adaptive and subsequently the innate immune response leading to attraction of both cytotoxic and helper T- lymphocytes. Mast cell derived cytokines TNF-α and IL-Iβ also play an important role in generation of visceral hypersensitivity and abdominal pain. Activated enterochromaffin cells secrete serotonin which regulates intestinal motility and secretion. [18] Anxiety and depression which are more common in IBS are also related to serotonin and can cause bowel symptoms compatible with IBS.

Recent studies have demonstrated that acute gastroenteritis triggers a self-perpetuating immune and chemical response which is responsible for maintaining symptoms after the acute injury has resolved. [19-22] In PI-IBS, the colon is grossly normal but biopsy reveals an increased number of EC and mast cells as well as sub-epithelial inflammatory cells, specifically T-lymphocytes.[23] Chadwick et al demonstrated an increased number of activated T lymphocytes in all 77 symptomatic patients with IBS. Patients with PI-IBS show an increased level of expression of the pro-inflammatory cytokine IL-1β in the rectal mucosa. Other studies have shown high levels of the proinflammatory cytokines IL-1β, IL-6 and TNF-α in peripheral blood mononuclear cells. It has also been speculated that IBS patients may be more susceptible to infection and are thus genetically predisposed to produce lower amounts of the anti-inflammatory cytokine, IL-10. A recent study has shown abnormalities in the IL-10/1L-12 ratio in patients with IBS favoring inflammation. Mast cell degranulation and increased pro-inflammatory cytokines may contribute to symptom perception as they have been shown to generate visceral hypersensitivity via direct activation of sensory nerves. [4, 24]

Enterochromaffin cells contain 85 percent of the total body serotonin which is involved in visceral hypersensitivity, the peristaltic reflex and intestinal secretions. [25] However, inflammation alone is not sufficient to cause IBS as most of the patients with gastroenteritis recover completely. Psychologic stress is also known to affect gut function. It has been shown to release mast cell and enterochromaffin cell mediators in the colon and thus may play a role in the perpetuation of IBS. [26, 27]

Mesalamine

5-aminosalicylic acid (5-ASA) is a topically acting anti-inflammatory agent that is used in the treatment of inflammatory bowel disease. 5-ASA activates the peroxisome proliferator-activated receptor γ (PPAR-γ). [6] PPAR-γ is a transcription factor which is highly expressed in the colonic epithelium. It modulates cytokine production and, specifically, decreases activity of NF-κβ, which is a central factor in inflammation.[5] It also reduces synthesis of prostaglandins and leukotrines which are also mediators of the inflammatory response.

Mesalamine and PI-IBS

There is strong evidence that PI-IBS is triggered by inflammation and persists because of self perpetuating immune response: 1) it starts after gastroenteritis, 2) presence of mast cells which induce the innate and adaptive immune systems 3) the increase in pro-inflammatory and decrease in anti-inflammatory cytokines in blood, 4) PI-IBS shares many of the features of lymphocytic colitis (chronic diarrhea, grossly normal endoscopic findings, mucosal inflammation and a benign course). [7-9]

It is logical that an anti-inflammatory agent will be effective in PI-IBS. Experimental data show that inflammation, even if mild, can lead to persistent changes in gastrointestinal nerve and smooth muscle function, resulting in dysmotility, rectal hypersensitivity and gastrointestinal dysfunction.[28, 29] Research has also shown that functional changes in mice intestine after infection may be reversed using non-selective or selective anti-inflammatory agents administered after recovery from infection [30, 31] Dunlop et al studied the role of oral steroids in reducing inflammation and enterochromaffin cells numbers. Their study demonstrated a significant decrease in the T-lymphocyte number in the lamina propria but was not associated with an improvement in symptoms. A recent study evaluated mesalamine in non-selective patients with IBS. There was improvement in colon histology but no improvement in symptoms.[10] We have shown that there is trend to improvement in QOL with mesalamine.

The purpose of this study is to evaluate the effects of long acting mesalamine (Lialda®) in patients with PI-IBS. We will evaluate gastrointestinal symptoms and IBS specific quality of life (IBS-QOL) before and after treatment with Lialda®

## OBJECTIVES:

***Objective #1:*** Determine the efficacy of mesalamine in patients with PI-IBS.
Hypothesis: Treatment with mesalamine compared to placebo will improve QOL, and global as well as individual symptoms of IBS

## PARTICIPANT SELECTION CRITERIA:

Patient Population

Ambulatory patients, 18 years of age or older with PI-IBS symptoms for at least 6 months, will be enrolled in the study. The study population will consist of previously healthy patients who developed IBS after an episode of gastroenteritis. Patients will be identified by the Bowel Disease Questionnaire which is sensitive to Rome Criteria.[32] Rome III criteria will be used to define IBS. PI-IBS patients are usually diarrhea-predominant and patients whose predominant symptom is constipation will not be enrolled in this study. Patients will be recruited from the Internal Medicine and Gastroenterology clinics at the University Hospital and the VA Medical Center.

*Inclusion Criteria*

1. Men and women age 18-75 years
2. Rome III criteria for IBS
3. Symptom onset after apparent acute gastroenteritis
4. Symptoms of 6 months or greater duration
5. Normal gross appearance of the colonic mucosa other than erythema and polyps
6. Negative markers for celiac disease (tissue transglutaminase antibody or endomysial antibody).
7. No clinically significant abnormality in thyroid function (Thyroid Stimulating Hormone) and serum calcium
8. Stable medication regimens for more than 1month.

9. Sexuallly active female patient of child bearing potential have negative urine pregnancy test or practices accepted method of birth control during the study.
10.

*Exclusion Criteria*

1. Age <18 or > 75 years
2. Constipation-predominant IBS.
3. Clinically significant chronic cardiac, pulmonary, hepatic, renal dysfunction or HIV
4. Presence of active malignancy Current evidence of any gastrointestinal disorder such as celiac disease, inflammatory bowel disease, chronic pancreatitis, scleroderma, HIV, small bowel or colonic resection, paraplegia or quadriplegia
5. Current evidence of drug or alcohol abuse as judged by the investigator
6. Allergy to mesalamine or aspirin
7. Investigator perception of patient's inability to comply with the study protocol
8. Unstable psychiatric disease
9. Recent change in gastrointestinal medications

**DESIGN:** Randomized double-blind placebo-controlled.

**Study End-points**

Primary: Improvement in self reported overall Bowel Symptom Scores (BSS) after 8 weeks of treatment will be used as the primary endpoint.

Secondary:

1) Change in specific bowel symptoms: bowel frequency, bowel consistency, abdominal pain, urgency, and bloating after 8 weeks treatment.

2) IBS-QOL at end of treatment

*Definition of a Responder*: Patient who report at least 50% of the weeks of treatment with satisfactory relief (30% or more reduction in symptom) will be designated as responders.

**Methods**

*Rome III criteria for IBS*[13]

Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two or more of the following:

1. Improvement with defecation
2. Onset associated with change in frequency of stool
3. Onset associated with change in form (appearance) of stool.

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Diarrhea-predominant IBS is defined by the presence of loose (mushy) or watery stools at least 25% of times and hard or lumpy stool <25% of times (in the absence of anti-diarrheal or laxative use).

Constipation-predominant IBS: hard or lumpy stools ≥25% and loose (mushy) or watery stools <25% of bowel movements.

Mixed IBS: hard or lumpy stools ≥25% and loose (mushy) or watery stools ≥25% of bowel movements.

Unsubtyped IBS: insufficient abnormality of stool consistency to meet criteria for IBS-C, D, or M.

The validated Bristol Stool Form scale will be used to determine the participants usual stool consistency.[33]

*Criteria for PI-IBS*

Acute onset of symptoms of IBS subsequent to two or more of the following: 1) fever, 2) vomiting, 3) diarrhea.

**STUDY PROCEDURES:**

This study will be conducted at the University of Utah and the VA Medical Center. Information collected at the VA will be stored at the VA. For purposes of statistical analysis the information from the VA will be de-identified and sent to the University of Utah.

All patients will have a complete blood count, comprehensive biochemical profile (including serum calcium), thyroid-stimulating hormone (TSH), tissue transglutaminase antibody (TTG), C- reactive protein, and stool examination for electrolytes (optional), ova and parasite, C.difficile toxin (not required if stool is formed), Calprotectin or lactoferrin, and Giardia antigen. These tests will not be repeated if they were collected in the last 6 months. Blood and stool samples will be collected for storage if the patient consents. Flexible sigmoidoscopy and biopsy of the colonic mucosa will be performed in all patients at the beginning of treatment. Patients with red flag symptoms (onset in older than >50 years, progressive or non-fluctuating symptoms, unexplained weight loss, rectal bleeding or anemia, family history of colon cancer, fever, abnormal examination or laboratory tests) will have colonoscopy and biopsy. Patients with structural, biochemical, or infective disorders will be excluded from the study. A flexible sigmoidoscopy or colonoscopy will not be done if an acceptable biopsy was completed within 5 years. If the procedures are done a biopsy will be collected for storage.

*Questionnaires*

*Bowel Disease Questionnaire*

The Bowel Disease Questionnaire (BDQ) will be used to identify patients with IBS.[32] The BDQ has been modified to include Rome III criteria for functional bowel disorders. We have used the BDQ and the modified version in our previous studies.[11, 34]

*Bowel Symptom Scale (BSS)*

BSS is a validated IBS outcome measure which consists of 100-mm visual analog scales related to each symptom of IBS (pain/ discomfort, bloating, constipation, diarrhea) and an overall severity scale.[35] All questions contribute equally to the total score, which ranges from 0-400. Similarly reflux disease questionnaire (RDQ) measures change in upper gastrointestinal symptoms before and after treatment.

*Psychological Symptom Questionnaire*

The BSI-18 questionnaire (Brief Symptom Inventory, a short form of symptom check list-90-revised, SCL-90-R) will be used.[36] The BSI-18 has 18 items, six each on the somatization, depression, and anxiety dimensions. The global severity index represents the global or total score, which summarizes the respondent's overall level of distress. Each item response is scored 0-4. This questionnaire can be completed in 4 minutes. The psychological symptoms and composite scores from BSI-18 test correlate highly (i.e.>0.90) with SCL-90-R.

*IBS-QOL Questionnaire*

The disease-specific IBS-QOL will be used for evaluation of subjects QOL.[37] The IBS-QOL is a validated disease specific quality of life questionnaire for use in patients with IBS. It has 34 items and measures 8 domains found to be relevant to patients with IBS: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, and relationships. The IBS-QOL has high internal consistency and high reproducibility. IBS-QOL has been shown to be sensitive to treatment response in patients with IBS. [38]

*Nepean Dyspepsia Index*

The Nepean Dyspepsia Index (NDI) will be used to evaluate how a patient's life and daily activities are affected by their stomach problems.

*Treatment Schedule*
This study will compare mesalamine two (Lialda®) 1.2 gm tablets orally daily to placebo in 68 patients with diarrhea predominant PI-IBS. The patients will be consented and enter into the screening which can last up to 8 weeks. This will be followed by an 8 week treatment period.

Patients will be re-consented to the newest version of the consent form if changes have been made while they are enrolled on the study. The patient may not be rescreened if there is no change in patient's symptoms if they are outside the screening window.
All patients will fill out the following questionnaires:

1) The Bowel Symptom Scale (BSS) at the beginning, at 4 weeks and at the end of the study period to assess any change based simply on admission to the trial.
2) The BSI-18 at the beginning of the screening period.
3) The IBS-QOL at the beginning, at 4 weeks and end of treatment.
4) The Nepean Dyspepsia Index at the beginning, 4 weeks and end of treatment as well as during the mail-in/phone call visits.BDQ (Bowel Disease Questionnaire) at screening.

Drug, Dose and Duration Rationale
Mesalamine with MMX (Multi Matrix System) technology (Lialda®) will be used for this study. This is a novel oral, high strength (1.2 gm/tablet) formulation of 5-ASA designed for once or twice daily administration. Lialda has been shown to be well tolerated for the treatment of mild to moderate ulcerative colitis.[40] Previous studies have shown that clinical and endoscopic remission with 2.4 and 4.8 gm/ day was similar.[40] Therefore the 2.4gm once daily dose will be used for this study. A placebo capsule will be provided by the makers of Lialda, Shire Pharmaceuticals, Inc. All study medication will be stored and dispensed at the University of Utah and VA pharmacies.

Assessment of Compliance
Every subject will be evaluated so that they are at least 80% compliant for continuous dosing of medication by pill count. Adverse reactions will be assessed. Patients will be called by the study coordinator every two weeks during the 8 week treatment period to check for medication compliance.

Concomitant Medications
All concomitant medications will be recorded. Drugs which affect the gastrointestinal motility will not be allowed during the study unless the patient has been on a stable dose for >1 month and symptoms are still persisting. - The following medications will be prohibited: oral anti-cholinergics (dicyclomine, hyocyamine, and propatheline), narcotics, tramadol, colchicine, misoprostol, antacids, antidiarrheal agents, bismuth compounds and laxatives.

Time Line
*Location of Study*
This study will be performed at the University of Utah Hospital and Clinics and the VA Medical Center.

*Time Table of study*: Approximately 1 Years from the start of patient recruitment

Subject recruitment will start immediately upon IRB approval and continue throughout the duration of the study. We estimate that 50% of recruited patients will qualify for enrollment. Sixty-eight patients with diarrhea-predominant or mixed IBS (with diarrhea as predominant symptom) will be enrolled at the rate of 1-2 per week. The estimated dropout rate is 10%, leaving 64 patients to study. This population will include but not be limited to returned missionaries. We have previously worked with missionaries who have high prevalence of PI-IBS.

*Study visits* (Table 1. Figure 1.)
First visit:
Orientation to the study and informed Consent
Inclusion/Exclusion check
History and physical examination,
Questionnaires: BDQ, IBS-QOL, BSI-18, BSS, Nepean Dyspepsia Index (NDI)
Blood and stool tests (not repeated if done in past 6 months unless there has been an alteration in the symptoms)
Collection of stool sample for storage (if consent is given)
Urine pregnancy Test for women of child bearing potential
Instructions to complete 2 week stool diary during 8-week run in period

Second visit:
Flexible sigmoidoscopy/ colonoscopy with biopsy, if indicated (not repeated if performed during last 5 years, results within normal limits and no change in symptoms)

Third visit
Subjects will be randomly assigned to either two Lialda 1.2gm tablets daily or two placebo tablets daily according to a block randomization schedule generated by the statistician. Medicines will be provided by and dispensed at the Pharmacy. Medication may be mailed at patients' convenience and they will be informed on dosing and storage of medication by telephone.

Mail-in/ telephone visit
Patients will be asked to fill BSS IBS-QOL and NDI at week 4 of the 8 week treatment either by mail or on telephone.

Fourth visit
End of treatment- Questionnaires-BSS, IBS-QOL, andNDI and physical examination
Study drug count
Return all unused study drug and the study drug bottle(s)

**Standard of Care vs. Research-Related Procedures:** all procedures for this study are research-related.
**Data Safety and Monitoring:**
Patient Safety: Adverse Events (AE) and Serious Adverse Events (SAE):
Any untoward medical occurrence in a patient temporarily associated with the use of Lialda whether or not considered related will be recorded. SAE is defined as life threatening event or death. Safety data will be assessed by the age and race. The study side effects will be reviewed by the PI, and unexpected side effects will be reported to the IRB. All adverse events will be recorded and reported to Shire Developmental Inc.

The Data Safety Monitoring Plan consists of setting up a Data Safety Monitoring Board (DSMB). The DSMB will consist of a physician (Dr. Harry Rosado-Santos, M.D., Division of Infectious Disease), a pharmacist (Anthony Dalpiaz, Pharm.D) and a biostatistician (Tom Greene, PhD). The board will meet every 4 months to review the study's progress and endpoints, monitoring of safety data (adverse events or serious adverse events), and recommendations whether to continue, modify or stop the study.

**STATISTICAL METHODS, DATA ANALYSIS AND INTERPRETATION:**

Sample Size

The sample size for this trial is based on primary end-point of overall improvement in BSS. A previous IBS treatment trial reported baseline BSS of 183±65. [35] To detect 25% change in BSS, 32 patients in each group will provide 80% power using two-sided alpha 0.05 comparisons. Assuming 5% drop out rate, we would require a total of 68 patients (n=34 in each group). Assuming proportional estimates for the individual symptoms of IBS, a similar power will be achieved with this sample size.

The Lialda treated group will be compared to the placebo group on improvement in the BBS global symptoms of IBS (continuous scale, range 0 to 400) and BBS individual symptoms of IBS (continuous scales, range 0 to 100). Given the repeated measurements on continuous outcomes, the data will be analyzed with mixed effects linear regression.

Primary analysis will be based on intention to treat. Exploratory analyses assessing "compliers" will also be reported. We will compare the results of placebo and Lialda treated group. The key comparisons between treatment arms will assess changes from baseline to end of treatment using parametric approaches such as the t- test and, when data is highly skewed, nonparametric approaches such as the Wilcoxon test. We note that it is feasible to construct confidence intervals as well as significance tests in the setting of nonparametric comparisons. For some of the secondary efficacy approaches, such as those with binary/ categorical outcomes, follow-up status will be compared between treatment arms using the chi-squared test of the Mantel-Haenszel chi-square for ordered categorical outcomes. Exact versions of these tests will be performed when cell sizes are excessively small.

In addition to the unadjusted primary analyses we will perform exploratory analyses which will use the logistic regression model for binary outcomes, and the linear regression model for continuous outcomes (transformations or categorization may be necessary for the cell count variables). We expect that psychological factors may affect the response to treatment and therefore will do pre-study psychological analysis and will control for them while evaluating response to treatment.

We note that IBS-QOL will be collected at 4-week intervals. Therefore, approaches incorporating repeated measures, notably the linear mixed model, will be implemented to assess and quantify trends (e.g., a linear divergence between treatment arms) over time. These approaches also allow the inclusion of available data from patients who drop out in the middle of the study in the analysis. We are aware, however, that the dropout pattern in this study may not be the "Missing at Random" pattern required for such available-data models to yield valid inference. We will examine and report characteristics of study completers versus dropouts, to obtain some empirical evidence for or against this missingness assumption.

We are familiar with imputation approaches, and will implement these when appropriate. Simplistic approaches such as substituting each subject's "worst" value, or the "worst" value observed for any subject, for missing values may shed light on the robustness of any significant findings to missing data. However, such substitution approaches are not useful for formal statistical inference.

**ADMINISTRATIVE RESPONSIBILITIES:**

**Study Resources:**

Study procedures will be conducted at the University of Utah Hospital and the VA Medical Center. The data gathered for the study at the University of Utah will be stored in the Division of Gastroenterology at The University of Utah Hospital. Data collected at the VA Medical Center will be stored in the Gastroenterology Division of the VA Medical Center. The data analysis for all patients will be conducted at the University of Utah. All information will be de-identified and securely transferred to the University of Utah for analysis. Confidentiality and privacy of patient's research data (patient's demographics) will be maintained by saving the documents in locked cabinets and keeping them in secure files in the GI research offices. The computerized data will be saved on password-protected computers, also in secured research offices. The principal investigator, co-investigator, study coordinator, and research staff, will have access to this data. The patients' names will not be recorded in this database. Patients will be identified by an assigned number and patient's initials only. The database will be password-protected to ensure security.

The data and results of the study may be published or presented. In this case, patients' will be identified by number only in order to maintain confidentiality. The data will be stored indefinitely.

For data verification purposes, authorized representatives, a regulatory authority, or IRB may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history. The principal investigator, co-investigators study coordinator and research staff as well as the Federal Drug Administration, a regulatory agency, will also have access to patient's information and collected data.

Subjects will be given the opportunity to read the consent form and ask questions to the study staff until subjects express that they fully understand the consent form and their responsibilities for participation in the study. Subjects will sign and date the consent form and will be given a copy of the consent form to keep. No study procedures will be performed until the consent form is signed. The data and results of the study may be published or presented. In this case, patients will be identified by number only in order to maintain confidentiality.

The Gastroenterology Division at the University of Utah Hospital and Clinics has 12 examination rooms and the GI Laboratory has four endoscopy rooms. More than 25 procedures are performed in the laboratory each day. More than 150 patients are seen in the Gastroenterology clinics each week. The University of Utah draws patients from throughout intermountain region. There is deep freezer available to the PI for specimen storage at the University of Utah and VA Medical Center.

The PI has two full time study coordinators and facilities for questionnaire optical scanning, printing, and copying. Ashok Tuteja, M.D., M.P.H., is the principal investigator of this project. John Fang, M.D. (Division of Gastroenterology, University of Utah) and Rahul Anand, M.D. (Division of Infectious Diseases, University of Utah) are co-investigators. They will help the PI in patient recruitment and conducting study related procedures. The study coordinators will help the study team in arranging patients' study visits, recruitment, and other study related procedures. Nicholas J. Talley, M.D. PhD. (Pro-Vice-Chancellor, University of Newcastle, Australia) and Keith G. Tolman, M.D. (University of Utah) are consultant to this grant. Dr. Talley is an internationally known expert in IBS and Dr. Tolman, Professor of Medicine and Pharmacology has expertise in conducting pharmaceutical trials.

**Future studies**

We will store blood, stool, and colon biopsy specimens obtained before and after treatment (as indicated above) for future studies looking at genetic and histo-chemical biomarkers which may predict response to mesalamine.

The informed consent form will ask every study patient if their blood, colon biopsy specimen, and stool sample(s) can be stored at the end of this research project for use in future research. A separate question will ask if their name and identifying information be stored along with the samples for future research.

**Recruitment:**
Patients will be recruited from the gastroenterology, infectious diseases and internal medicine clinic at the University of Utah Hospitals and clinics and VA Medical Center. Patients will also be recruited from community Physicians referral letters, flyers, and newspaper advertisements. A report will also be created of all previous patients seen in GI clinic with the diagnosis of IBS within the past year. The report will assist in recruiting potential patients within the department of Gastroenterology. After reviewing the records from the report if it appears patients qualify we would contact the provider. The provider then contacts the patient to see if they are interested in the study and if it would be ok for the study staff to contact them. If they are, then the provider lets the study staff know and we contact the patient. Patients will be contacted via phone, in person while in clinic or via mail using the recruitment letter. We will also post our study site contact information on the University of Utah, School of Medicine, Department of Internal Medicine, Division of Gastroenterology website, http://medicine.utah.edu/internalmedicine/gastroenterology/. Many patients and practitioners use this site to gather information on PI-IBS and other functional GI disorders, so a web posting may serve as additional advertising for our site. We also have a database of patients with IBS who have agreed to be participating/ to be contacted in case of any research study.

Mass emails may also be used as recruitment methods. The mass emails will be sent to all the university staff and students as well as other organizations like Westminster College, Salt Lake Community College etc. The groups will be identified by cognizant Vice President or other authorized personnel. However we may decide on sending the mass email to one organization at a time. The university procedure for sending mass emails will be followed and approval for the text of the email will be obtained from the IRB prior to sending of the emails. Permission from the cognizant VP of the college or organization will be obtained before sending the mass e-mails and the form for sending the mass email will be filled with the Information Technology Services at the university. Similar procedure may be followed at other organizations.

We will also use the Division of Infectious /International Travel Clinic at the University of Utah. The travel clinic evaluates a large number of returned missionaries and other travelers who have PI-IBS.

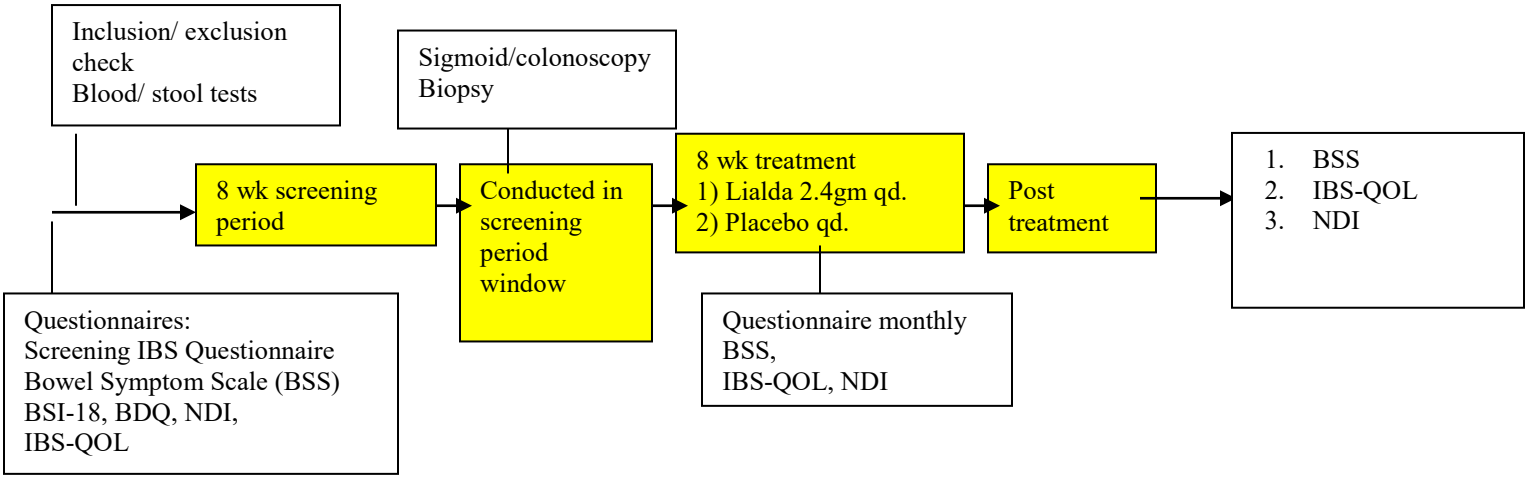
Table: Study Procedures (Total number of patients N=66-68)

| | Visit 1 | Visit 2 | Visit 3 | Mail/Telephone Visit | Visit 4 |
|---|---|---|---|---|---|
| Trial Duration | Screen 8 week | Procedure. Completed during screening period | Treatment started | 4 wk. | 8wk (end of treatment |
| Visit Type | In- | In-person | In- | Mail/ telephone | In-person |

| | person | | person/mail | | |
|---|---|---|---|---|---|
| Informed consent | X | | | | |
| History & Physical examination | X | | | | |
| Inclusion/Exclusion check | X | | | | |
| Blood tests (CBC, CRP, CMP, TSH, TTG) | X | | | | |
| Blood sample (serum and buffy coat) for storage | X | | | | X |
| Stool Test (O&P, Giardia antigen/ C. difficile toxin, calprotectin) | X | | | | |
| Stool sample for storage | X | | | | X |
| Stool Diary | X | | | | |
| *Sigmoidoscopy/Colonoscopy Biopsy | | X | | | |
| BDQ and BSI-18 Psychological Questionnaire | X | | | | |
| BSS questionnaire | X | | | X | X |
| IBS QOL Questionnaire | X | | | X | X |
| The Nepean Dyspepsia Index (NDI) | X | | | X | X |
| Study Medication Compliance | | | X | X | X |

*Colonoscopy if needed

Figure 1. Flow Chart.



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