A Randomized, Double-Blind, Placebo-Controlled Trial of Budesonide For The Treatment Of Active Lymphocytic Colitis

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A Randomized, Double-Blind, Placebo-Controlled Trial of Budesonide For The Treatment Of Active Lymphocytic Colitis

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I. Abstract:

Microscopic colitis is an increasingly diagnosed cause of chronic diarrhea, with two main subtypes: collagenous and lymphocytic colitis. Uncontrolled reports have suggested that various drugs can be beneficial in treating microscopic colitis, but few treatments have been evaluated in randomized controlled trials. Thus, treatment is guided mostly by anecdotal reports, case series, and physicians' experience. In our uncontrolled experience, corticosteroids are one of the most effective therapies for microscopic colitis, but are not typically used as a first line therapy because of toxicity. Budesonide has been reported to be of clinical benefit in small, uncontrolled series of patients with microscopic colitis, and recent controlled trials showed that it is superior to placebo in collagenous colitis. We propose a study of budesonide in patients with the lymphocytic type of microscopic colitis.

II. Background and Significance:

Microscopic colitis is a relatively common cause of chronic watery diarrhea. The two main types of microscopic colitis are lymphocytic and collagenous colitis. Numerous therapies have been described for these conditions (1), but only bismuth subsalicylate (2) and budesonide (3, 3a, 3b) have been studied in randomized controlled trials. In the largest uncontrolled series of patients with lymphocytic colitis (4) and collagenous colitis (5), corticosteroids are among the most effective therapies with response rates of 70-80%. However, traditional corticosteroids have significant short- and long-term side effects, causing some clinicians to avoid their use. Budesonide is a synthetic corticosteroid with high potency but limited systemic bioavailability due to high first-pass hepatic metabolism (6). The controlled ileal release (CIR) formulation of budesonide available in the US (Entocort

EC) is designed to deliver drug maximally to the distal ileum and proximal colon, compared to the Budenofalk formulation used in the Baert study (3), that is designed to deliver drug to the colon (6). Thus, Entocort EC is theoretically less ideal for a pancolonic process like microscopic colitis. However, only 52-79% of budesonide is absorbed in the ileocecal region, leaving 21-48% of the drug for delivery to the colon (6). Furthermore, several case reports have shown efficacy of the CIR formulation in collagenous and lymphocytic colitis (5, 7-9), including prednisone-refractory cases (8), and two randomized trials have shown the CIR formulation to be superior to placebo in patients with collagenous colitis (3a, 3b). Therefore, CIR budesonide may also prove to be an effective treatment for lymphocytic colitis.

The concept of "satisfactory control" of diarrhea is similar to the "adequate relief" end point developed to provide a meaningful, patient-evaluated measure of improvement in subjects with diarrhea-predominant IBS (12). In addition, the daily number of stools will be used as a quantitative measure of efficacy. In IBS, "adequate relief" correlates with various "objective" measures such as pain severity scores and frequency and consistency of stools (12). This concept is being adapted for the present study to add a subjective component to the patient's evaluation, since diarrhea as a symptom is subjective and simply showing a change in the number of stools per day may not reflect the patient's experience.

Although microscopic colitis may be considered uncommon by some, it accounts for approximately 10% of chronic diarrhea. In European studies, its incidence is approximately 5.7/100,000 (1), approaching that of Crohn's disease (10) and ulcerative colitis (11). The

significance of the proposed study lies in the fact that there are few controlled trials to guide therapeutic choices in patients with lymphocytic colitis.

Fecal Lactoferrin Analysis: A variety of stool markers have been assessed as diagnostic tests to distinguish patients with diarrhea due to inflammatory conditions from those with noninflammatory causes. Lactoferrin is a glycoprotein contained in neutrophilic secondary granules that is released in response to neutrophil activation. Of several proteins released by activated neutrophils, lactoferrin was shown to be the most stable in feces, and its release was found to be most efficient (Sugi, et al. Am J Gastro 1996;91:921). Fecal lactoferrin is increased in patients with bacterial causes of diarrhea which result in inflammation compared to patients with diarrhea due to noninflammatory bacteria, viruses, or those in which no organism was identified (Greenberg, et al. J Infect Dis 2002;185:944, McIver, et al. Pathology 2001;33:353, Choi. J Clin Microbiol 1996;34:2337). In fact, some authors consider it as the screening test of choice for patients with acute diarrhea to determine who should have stool cultures performed (Huicho Pediat Infect Dis J 1997;16:644). Fecal lactoferrin has been shown to be as useful as fecal occult blood testing in detecting various colorectal diseases (Saitoh Intern Med 2000;39:778).

Fecal lactoferrin has been studied fairly extensively in inflammatory bowel disease and has been shown to be a sensitive and specific marker of active IBD compared to irritable bowel syndrome and healthy controls (Kane, et al. Gastroenterology 2001;120:A276, Buderus, et al. Gastroenterology 2002;122:A219 #1, Fine. Am J Gastro 1998;93:1300).

In patients with IBD, the levels of fecal lactoferrin correlate with disease activity (Boone, et al. Gastroenterology 2000;118:A1118, Buderus, et al. Gastroenterology 2002;122:A219 #1), and in individual patients, the level of lactoferrin decreases when remission is induced (Buderus, et al. Gastroenterology 2002;122:A219 #2).

There is only one report in the literature where fecal lactoferrin levels were studied in microscopic colitis (Fine et al. Am J Gastro 1998;93:1300). In this small study, 8% of patients with microscopic colitis had elevated fecal lactoferrin levels.

HLA Associations: One study of HLA haplotypes showed an increase in A1 and DRW53 in lymphocytic colitis and a decrease in DQ2 in collagenous colitis (13). However, this same group later reported increased A1 and decreased in A3 in lymphocytic colitis and no HLA associations in collagenous colitis (14). Fine and colleagues showed an increase in DQ2 and DQ1,3 in lymphocytic colitis and collagenous colitis, similar to the pattern seen in celiac sprue (15). Others have found no HLA associations (16). Abnormal HLA DR expression on colonic epithelial cells has been described, suggesting that MHC-restricted immune activation could be involved in the pathogenesis of microscopic colitis (17,18). Given the discrepant findings, however, it is difficult to draw conclusions about HLA associations in microscopic colitis.

III. Hypotheses:

1) Budesonide will be safe and effective compared with placebo for the treatment of diarrhea in lymphocytic colitis.

2) Fecal lactoferrin levels will correlate with symptoms and histologic disease activity in patients with lymphocytic colitis.

IV. Specific Aims:

1) To compare efficacy of budesonide and placebo in lymphocytic colitis in providing relief of diarrhea (primary endpoint) as well as in improving frequency, consistency, and urgency of diarrhea and degree of inflammation on colon biopsies (secondary endpoints).

2) To compare the safety and tolerability of budesonide compared to placebo in patients with lymphocytic colitis (secondary endpoint).

3) To assess the correlation between fecal lactoferrin concentrations and symptoms and degree of inflammation on mucosal biopsies in patients with lymphocytic colitis.

3) To characterize HLA typing in patients with lymphocytic colitis.

V. Preliminary studies: The therapeutic potential of budesonide for the treatment of lymphocytic colitis is discussed above. From 1997-1999, inclusive, approximately 200 patients with lymphocytic colitis and 200 with collagenous colitis were evaluated at Mayo, or 133 patients per year with either condition. We have previously reported our experience with therapy in patients with lymphocytic colitis (4). In addition, our group has extensive experience with clinical trials in patients with inflammatory bowel disease.

VI. Research Design and Methods:

A. Study design: We propose a prospective, randomized, double blind, placebo-controlled trial of budesonide for the treatment of lymphocytic colitis.

B. Recruitment: Potentially eligible subjects will be identified at Mayo Rochester in several ways. First, recently diagnosed cases will be identified by daily review of the diagnoses made in the Department of Pathology. Second, the GI appointment office at the Mayo Clinic will identify subjects referred with a diagnosis of lymphocytic colitis. Third, patients who have been diagnosed within the last three years at Mayo will be contacted by letter (Appendix 1) and informed of the study. As noted above, approximately 133 patients with microscopic colitis are seen each year at Mayo, and approximately 400 were seen in the last three years, giving a pool of over 500 subjects with microscopic colitis. Approximately half of these will have lymphocytic colitis, leaving ~250 potential subjects for enrollment. We will recruit subjects until we enroll 30 with lymphocytic colitis.

C. Inclusion Criteria:

1. Age $\geq$ 18 years of age.

2. Diarrhea, defined as a minimum of 3 bowel movements per day and greater than "mild" (see below), currently on no treatment or active despite treatment.

3. Lymphocytic colitis confirmed histologically by the study pathologist (TCS) on left sided colon biopsies. If biopsies are not available within one year of study entry, repeat flexible sigmoidoscopy with left sided biopsies (2 sigmoid, 2 descending) will be performed.

D. Exclusion Criteria:

1. Previous unsuccessful treatment with corticosteroids or immunosuppressive drugs.

2. History of severe corticosteroid side effects.

3. Corticosteroid, ticlopidine, or flutamide use within the previous 4 weeks.

4. Antibiotic, mesalamine or bismuth subsalicylate use within two weeks.

5. Current use of anticholinergics, cholestyramine, narcotics, ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, or grapefruit juice.

6. Known active medical conditions, including cancer, infection, uncontrolled hypertension or diabetes, osteoporosis, peptic ulcer disease, glaucoma, cataracts, liver cirrhosis or history of tuberculosis.

7. Other diarrheal conditions (sprue, infection, hyperthyroidism, lactose intolerance).

8. Pregnant or nursing females.

9. Patients without a telephone or unable to communicate in English over the telephone, or unable or unwilling to give consent.

10. Known hypersensitivity to or intolerance of budesonide.

E. Methods: Patients with biopsy-proven lymphocytic colitis will complete a symptom questionnaire (Appendix 2). There will be a one-week period of observation prior to study entry to insure sufficiently significant diarrhea. All drugs used to treat colitis will be discontinued for the appropriate time period (see exclusion criteria above) prior to the start of this observation period. Loperamide will be stopped at least two days prior to the observation period.

During the one-week observation period, subjects will make a daily record of the number of bowel movements and subjectively score their diarrhea as "none" (0), "mild" (1), "moderate" (2), or "severe" (3). To qualify for the study, the mean number of daily bowel movements must be > 4, and the mean diarrhea score must be >1.

After ensuring sufficiently severe diarrhea for participation, a stool sample will be collected for measurement of the fecal lactoferrin level (see below). Once during the study blood will be drawn for HLA typing (see below). Women of childbearing potential will have a serum pregnancy test performed. Thirty subjects with lymphocytic colitis will be randomized equally (1:1) by the use of random-ordered, sealed, opaque envelopes to budesonide 9 mg/d or a placebo. The study drug will be taken daily for 8 weeks.

The study assistant will monitor subjects by telephone weekly for compliance, efficacy, and side effects. Loperamide will be allowed as "rescue" therapy for $\geq$7 bowel movements per day, and the number of tablets taken will be recorded and used as a secondary outcome measure.

Fecal lactoferrin analysis: We will use the IBD-SCAN quantitative lactoferrin ELISA test provided by TechLab, Blacksburg, Virginia. A standard curve is generated using purified human lactoferrin. Patient fecal specimens are diluted serially 1:10, and the dilution giving an optical density on the linear part of the curve is used to determine lactoferrin concentration.

F. Safety Monitoring: In prior studies, budesonide treatment for 8 weeks has been extremely safe, with an adverse event profile similar to placebo. Thus, we are proposing to do this study without a Drug Safety Monitoring Board. In addition, we do not plan on having stopping rules in place for toxicity. We will monitor for any adverse events in study patients, and we will monitor for lack of efficacy. As mentioned above, loperamide will be allowed for those patients who have $\geq$ 7 bowel movements per day. If the diarrhea does not respond to this

symptomatic treatment, the patient will be withdrawn from the study, counted as a treatment failure, and provided open-label treatment at the direction of one of the study physicians or their regular physician.

G. Follow-up and Endpoint Ascertainment: Each patient will record the consistency and frequency of stools, urgency, abdominal discomfort, and any other symptoms daily (Appendix 3). At each weekly telephone follow-up, the primary endpoint of "satisfactory control of diarrhea" will be assessed. After 8 weeks of treatment, the study drug will be stopped and a return office visit will occur. Repeat flexible sigmoidoscopy with left sided colon biopsies (2 sigmoid, 2 descending) will be obtained within 7 days. A blinded pathologist (TCS) will compare these biopsies to pretreatment biopsies according to the parameters listed in Appendix 4. Responders will be followed weekly for another four weeks for recurrence, defined as >4 stools per day or a stool consistency score of 4 or 5 (Appendix 3).

H. Anticipated Results: We anticipate that budesonide will be superior to placebo without increased side effects.

I. Data Analysis: The primary analysis will compare the proportion of patients in each treatment group with satisfactory control of diarrhea during at least three of the last four weeks of the study (primary endpoint). A two-sample z-score test for proportions will be used to test whether the "relief rates" are different between the groups. Secondary analyses will compare the two treatment groups on: 1) response, defined as 50% decrease in number of stools per day (mean pre-treatment week vs. mean during week 8 of treatment); 2) the proportion (per patient) of total study days without diarrhea; 3) the proportions of patients experiencing "improvement"

in stool consistency, urgency and abdominal pain by at least one point (on the scale used in Appendix 3). These results will be compared using a two-sample test for proportions. Finally, histologic improvement compared to baseline biopsies will be assessed (Appendix 4) as well as side effects and time (in days) to recurrence of diarrhea after discontinuation of study drug.

Alternative analyses for the primary and secondary endpoints will be based on generalized regression models incorporating potentially important covariates (e.g. age, gender, subtype of colitis) along with treatment group as predictors of response. For example, a logistic regression analysis of satisfactory control of diarrhea (Yes,No) as the binary dependent variable will be examined, and the odds ratio (95% CI) for relief (treated:not treated) estimated using the regression coefficient from the model. Additional summaries of patient characteristics, histology, and side effects will be generated for each treatment group.

Fecal lactoferrin levels will be compared with the degree of diarrhea and histology (Appendix 4) at baseline and at week 8. HLA type distribution will be described.

Data will be analyzed using an "intention-to-treat" methodology, and drop-outs will be counted as failures.

J. Sample Size Assessment:

Based on uncontrolled data, the response to steroids in microscopic colitis is approximately 70-80% (4, 5). The average response to budesonide in the randomized trials in collagenous colitis was 77%, while the best response to placebo was 21%. At an alpha of 0.05 and using a two-

sided test, 15 patients will be needed in the treatment group and 15 in the placebo group to have 80% power to detect a similar difference in our study of patients with lymphocytic colitis. Thus, the total sample size will be 30 subjects.

Timetable:

If the number of subjects seen at Mayo remains stable, we would expect to see 65 patients each year with lymphocytic colitis. We have no data on how many would satisfy the inclusion and exclusion criteria. We will attempt to increase enrollment by contacting patients seen in the last three years at Mayo, informing them by mail of the study and inviting their participation (Appendix 1). We anticipate enrolling 3-5 subjects per month, or 30 subjects in 6-9 months, and completing the study within 12 months.

VII. Human Subjects:

1. Population: Adults ≥ 18 years old with active lymphocytic colitis.
2. Research materials: Study data will include demographics, symptoms, colon biopsies, stool for lactoferrin analysis and blood for HLA typing.
3. Recruitment: Patients will be identified at Mayo through the Department of Pathology and the Division of Gastroenterology and Hepatology. In addition, patients seen within the past three years at Mayo will be contacted by mail (Appendix 1).
4. Potential risk/protection: Budesonide has a very favorable safety profile, with side effects comparable to placebo (package insert). It is FDA approved for use in Crohn's disease. Flexible sigmoidoscopy with mucosal biopsy is a very safe procedure, with <1% risk of serious adverse events. The main risks will be discomfort related to the use of enemas and

of the procedure itself. Although budesonide was superior to placebo in prior studies in collagenous colitis (3, 3a, 3b), it has not been studied in lymphocytic colitis. In addition, a significant rate of spontaneous remission has been reported in microscopic colitis (1). Furthermore, we will allow the use of loperamide for breakthrough diarrhea. Thus, a placebo control arm is justified and ethical.

5. Benefits: The average benefit of budesonide in collagenous colitis was 77% in controlled studies (3, 3a, 3b). Similar benefit is expected in those with lymphocytic colitis. No benefit is expected for those subjects randomized to placebo. Remuneration will not be offered. Costs related solely to the study (study medication, follow up sigmoidoscopy and biopsy) will be paid for by the study budget.

VI. Gender/ Minority Mix:

In most reports, collagenous colitis occurs mainly in females whereas lymphocytic colitis has a more even gender distribution. There are no data on racial distribution, but most reported cases are Caucasians. We will enroll subjects of either gender and any race.

Appendix 1. Recruitment Letter

Dear ,

My colleagues and I are performing a research study of a new medication for the treatment of lymphocytic colitis. According to our records, you have been diagnosed with this condition in the past. If your diarrhea is still significant, you might qualify to enroll in this study. If you are interested or have any questions, please contact (study assistant) at [redacted].

Your decision to take part in this study is entirely voluntary. Current or future medical care at the Mayo Clinic will not be affected by your decision.

Sincerely,

Darrell S. Pardi, MD

Appendix 2. Initial symptom questionnaire.

Name _____ MCN _____

1) How would you rate your diarrhea?

0	1	2	3
None	Mild	Moderate	Severe

2) What is the consistency of your stools usually?

1	2	3	4	5
Very hard	Hard	Formed	Loose	Watery

3) How severe is your abdominal pain usually?

0	1	2	3
None	Mild	Moderate	Severe

4) In the last year, have you had abdominal pain for at least 12 weeks? Yes / No

5) Is the pain relieved by a bowel movement? Yes / No

6) Is the pain associated with your diarrhea? Yes / No

7) Is the pain associated with a change in stool form (appearance)? Yes / No

8) Are your bowel movements usually associated with urgency? Yes / No

9) How many bowel movements do you have on a usual day? _____

10) Is your diarrhea constant or intermittent?

11) Have you lost any weight? Yes / No If yes, how much? _____ pounds

12) Do you use aspirin or other arthritis/pain medications at least three days per week?

13) If yes, which drug and what dose? _____

14) Do you smoke? Yes / No If Yes, how much per day? _____

15) If no, did you smoke in the past? Yes/No If Yes, how much per day? _____

Appendix 3.

Daily Symptom Questionnaire Today's Date _____

1) How would you rate your diarrhea in the last 24 hours?

0	1	2	3
None	Mild	Moderate	Severe

2) What was the consistency of your stools in the last 24 hours?

1	2	3	4	5
Very hard	Hard	Formed	Loose	Watery

3) How severe was your abdominal pain in the last 24 hours?

0	1	2	3	4
None	Mild	Moderate	Intense	Severe

4) Were your bowel movements yesterday associated with urgency? Yes / No

5) How many bowel movements did you have yesterday? _____

6) How many loperamide/Imodium did you use yesterday? _____

Weekly Study coordinator interview questionnaire:

"In the past seven days, have you had satisfactory control of your diarrhea?"

"In the past seven days, have you had satisfactory control of your abdominal pain?"

"Have you had any side effects from the study medication?"

"Have you had any new symptoms?"

"Do you have any questions?"

Appendix 4. Histopathology Scoring System

ITEM/SCORE	0	1	2	3
Epithelial changes	None	Mild	Moderate	Severe
Lamina propria cellularity	Normal	Mildly increased	Moderately increased	Densely increased
Intraepithelial lymphocytes	Normal	Mildly increased	Moderately increased	Severely increased

Maximum score = 9, minimum = 0

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INVESTIGATOR: Dr. D. Pardi and Colleagues

APPROVED BY INSTITUTIONAL REVIEW BOARD:

This is an important form. Please read it carefully. It tells you what you need to know about this study. If you agree to take part in this research study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

Why is this study being done?

This study is being done to find out what effects (good and bad) budesonide has on you and on the diarrhea and other symptoms you have from your lymphocytic colitis (also known as microscopic colitis). Budesonide is a medication that decreases inflammation and has been effective in treating other causes of diarrhea. It has been approved by the FDA, but has not been approved for use in lymphocytic colitis.

How many people will take part in the study?

The plan is to have 30 people take part in this study. All will be enrolled at Mayo.

What will happen in the study?

Within two weeks prior to starting the study medication, you will undergo a physical examination, a review of your medical history, and screening blood and stool tests if necessary as part of a regular clinical evaluation. In addition, colonoscopy or sigmoidoscopy (scope into the colon) with biopsies may be taken if necessary. If these tests indicate that lymphocytic colitis is the only cause for your diarrhea, you will be asked to fill out a simple, one page form describing your diarrhea and other symptoms. You will also be asked to stop your diarrhea medications and follow your diarrhea and other symptoms for one week. At that point, it will be decided if you qualify for the study.

If you qualify for the study, you will submit a stool sample and have a small amount of blood drawn. If you are a female able to have children, some of the blood will be used to be sure you are not pregnant. In addition, if you have not had biopsies from your colon in more than one year as part of your regular medical care, you will have a repeat sigmoidoscopy and biopsies as part of the study.

Then, if you are not pregnant, you will be put in one of two groups by chance (as in the flip of a coin). One group will receive **budesonide** in the form of 3 milligram tablets. The other group will receive a **placebo (sugar)** tablet. Subjects in each group will take three tablets per day for eight weeks. The 9 milligram dose of budesonide will be used in this study as it has been found to be effective in treating other types of diarrhea.

For the eight week duration of the study, you will be asked to keep a simple daily record of your diarrhea and other symptoms. The study assistant will call you on the telephone once per week to see how you are doing. At the end of eight weeks, the study medication will be stopped. You will submit a second stool sample. A repeat sigmoidoscopy (scope into the lower colon) with biopsies will be performed at Mayo within seven days. This procedure is part of the study and therefore will not be billed to you or your insurance company. If your symptoms have improved on treatment, we will follow you over the next four weeks to see if your symptoms return after the medication is stopped.

During the study, you should not use any other medications for diarrhea except those you have discussed with your doctor, including over-the-counter (non-prescription) medications. You will be able to use Imodium (loperamide) to control your diarrhea if you are having more than six bowel movements per day, but you should not use any other diarrhea medications without contacting the doctor or study assistant.

How long will I be in the study?

You will be in the study for eight weeks, with four additional weeks of follow up if you respond to the medication.

Are there reasons I might leave this research study early?

Taking part in this research study is your decision. You may decide to stop at any time. You should tell the researcher if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the researchers or Mayo may stop you from taking part in this study at any time if it is in your best interest, if you do not follow the study rules, or if the study is stopped.

Will any biological sample(s) be stored and used for research in the future?

No. Your samples will be used as described for this study, then they will be destroyed.

What are the risks of the study?

As with any medication, allergic reactions to budesonide are a possibility. Other adverse events associated with budesonide may include headache, respiratory infection, nausea or vomiting, back pain, stomach pain, dizziness, gas, and fatigue. While you are taking part in this study, you are at risk for these side effects. You should talk to your study doctor and/or your medical doctor about these side effects. There also may be other side effects that are not known. Other drugs may be given to make side effects less serious and less uncomfortable. Many side effects go away shortly after the budesonide is stopped, but in some cases side effects can be serious or long lasting.

The risks of drawing blood include pain, bruising, or rarely, infection at the site of the blood draw.

A flexible sigmoidoscopy may cause abdominal discomfort and cramping. The risk of serious side effects such as heavy bleeding and perforation (producing a hole in the colon) from the procedure is rare (less than one percent).

There is not enough medical information to know what the risks might be to a breast-fed infant or to an unborn child carried by a woman who takes part in this study. Therefore, ***pregnant women*** and ***nursing mothers*** may not participate in this study. Furthermore all women who can become pregnant and are sexually active, or their sexual partners, must use birth control measures while in this study. The following birth control measures are acceptable: birth control pills, condoms, a diaphragm, or an intrauterine device. Breast-feeding mothers must stop breast-feeding to take part in this study. Women who can become pregnant must have a pregnancy test before taking part in this study. For the pregnancy test, blood will be taken from a vein in your arm with a needle 1-2 days before the study. You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to take part in the study. If you become pregnant during the study, you must immediately discontinue the study drug and inform the investigators.

Are there benefits to taking part in this study?

This study may not make your health better. However, in previous studies of budesonide in collagenous colitis, 50-100% of participants responded to the medication with improvement in their diarrhea. Therefore, there is reason to expect that budesonide may help your diarrhea. However, there is a chance that you could receive the placebo medication, and therefore no definite benefit can be expected from participation in this study.

What other choices do I have if I don't take part in this study?

You do not have to be in this study to receive treatment for your condition. If you decide not to participate in this study, another anti-diarrhea or anti-inflammatory

medication, including budesonide, may be tried. You should talk to the researcher and your regular doctor about each of your choices before you decide if you will take part in this study.

Will I need to pay for the tests and procedures?

You will not need to pay for any tests and procedures that are done just for this research study. These tests and procedures are the flexible sigmoidoscopy and colon biopsies, the blood work, and the stool studies. However, you and/or your health plan will need to pay for all other tests and procedures that you would normally have as part of your regular medical care. These tests and procedures are the office visit, blood and stool tests and the sigmoidoscopy done before you are enrolled into the study.

The study medication will be provided free of charge.

What happens if I am injured because I took part in this study?

If you have side effects from the study treatment, you need to report them to the researcher and your regular doctor, and you will be treated as needed. Mayo will bill you or your insurer for these services at the usual charge. Mayo will not offer free medical care or payment for any bad side effects from taking part in this study. Medical services necessary for a research related illness or injury will be covered by Astra-Zeneca, the study sponsor, to the extent they are not covered by your health insurance.

What are my rights if I take part in this research study?

Taking part in this research study does not take away any other rights or benefits you might have if you did not take part in the study. Taking part in this study does not give you any special privileges. You will not be penalized in any way if you decide not to take part or if you stop after you start the study. Specifically, you do not have to be in this study to receive or continue to receive medical care from Mayo Clinic. If you stop the study you would still receive medical care for your condition.

You will be told of important new findings or any changes in the study or procedures that may affect you or your willingness to continue in the study.

Who can answer my questions?

You may talk to Dr. Pardi at any time about any question you have on this study. You may contact Dr. Pardi (or an associate) by calling the Mayo operator at [redacted].

You can get further information about Mayo policies, the conduct of this study, or the rights of research subjects from [redacted], Administrator of the Mayo Foundation Office for Human Research Protection, telephone [redacted].

Authorization To Use And Disclose Protected Health Information

By signing this form, you authorize Mayo Clinic Rochester and the investigators to use and disclose any information created or collected in the course of your participation in this research protocol.

This information may be given to other researchers in this study, representatives of the company sponsoring the study, or private, state or federal government parties responsible for overseeing this research. These may include the Food and Drug Administration, the Office for Human Research Protections or other offices within the Department of Health and Human Services, and the Mayo Foundation Office for Human Research Protections or other Mayo groups involved in protecting research subjects.

This information will be given out for the proper monitoring of the study, checking the accuracy of study data, analyzing the study data, and other purposes necessary for the proper conduct and reporting of this study.

This authorization lasts until the end of the study.

You may stop this authorization at any time except if Mayo Clinic Rochester needs information already collected to ensure complete and accurate study results. This might mean that Mayo may continue to use your information collected as part of this study even after you have told us to stop. If this is a research study that also involves treatment, you may no longer be eligible to receive study treatment if you tell Mayo to stop using this information. The only way you can tell Mayo to stop using the information is in writing addressed as follows:

Mayo Foundation
Office for Human Research Protections
ATTN: Notice of Revocation of Authorization
200 First St. SW
Rochester, MN 55905

If this information is given out to someone else, the information may no longer be protected by federal privacy regulations and may be given out by the person or entity that receives the information.

A copy of this form will be placed in your medical record.

I have had an opportunity to have my questions answered. I have been given a copy of this form. I agree to take part in this research study.

(Date)	(Printed Name of Participant)	(Clinic Number)

(Signature of Participant)

(Date)	(Printed Name of Individual Obtaining Consent)

(Signature of Individual Obtaining Consent)