Open-label withdrawal trial of budesonide in patients with immune mediated enteropathies

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INTRODUCTION

Study Title: Open-label withdrawal trial of budesonide in patients with immune mediated enteropathies

Synopsis:

Celiac disease is an immune-mediated enteropathy occurring in genetically susceptible patients in response to ingested gluten.[1] Other immune mediated enteropathies include autoimmune enteropathy, collagenous enteropathy, post-transplant lymphoproliferative disorder related enteropathy. These patients have been treated with off-label budesonide therapy. In clinical experience with refractory celiac disease, 92% showing improvement in symptoms and 89% had improvement of histological changes.[5] However, this therapy has never evaluated in a randomized, placebo-controlled trial. This is significant as there is no approved therapy in patients with RCD or other immune mediated enteropathies, and the sequelae of this illness include debilitating symptoms, malnutrition, osteoporosis and enteropathy associated T-cell lymphoma.[4] Furthermore, physicians and patients have concerns regarding the long-term use of budesonide therapy and an appropriate withdrawal strategy is not well defined.

This study aims to evaluate patients with immune mediate enteropathies for changes in symptoms and histology after budesonide withdrawal compared to continued therapy.

Objectives: To determine if withdrawal of budesonide therapy in patients with immune-mediated enteropathies doing well on therapy will result in worsening symptoms, histology, or micronutrient/nutritional status when compared to continued therapy.

Design and Outcomes

- **Design:** Open-label withdrawal of budesonide in patients with immune mediated enteropathies who have had histological and symptom improvement on oral budesonide.
- **Outcomes:**
    - **Primary:** Change in histology after withdrawal of budesonide compared to continued therapy
    - **Secondary:**
        - Change in symptoms after withdrawal of budesonide compared to continued therapy
        - Change from baseline micronutrient and nutritional status after blinded withdrawal of budesonide compared to continued therapy
        - Change in quality of life after blinded withdrawal of budesonide compared to continued therapy
        - Storage of serum and stool for future evaluation of possible non-invasive evaluation of bowel injury

Interventions and Duration

- **Intervention:** Withdrawal of budesonide therapy compared to continued therapy
- **Duration:** 12 weeks

Sample Size and Population

- **Sample Size:** 10 patients per arm (20 total)
- **Population:** Adult patients with immune-mediated enteropathies who have had histological small bowel improvement and symptom improvement on oral budesonide.

STUDY TEAM MEMBERS

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STUDY SPECIFICATIONS

1. **Study Objectives/Outcomes**
    i. **Primary:** Change in histology after withdrawal of budesonide compared to continuation of budesonide therapy
    II. **Secondary:**
        i. Change in symptoms after withdrawal of budesonide compared to continuation of budesonide therapy
        ii. Change from baseline micronutrient and nutritional status after withdrawal of budesonide compared to continuation of budesonide therapy
        iii. Change in quality of life after withdrawal of budesonide compared to continued budesonide therapy
        iv. Storage of serum and stool for future evaluation of possible non-invasive evaluation of bowel injury

2. **Background and Rationale for Study**
    I. **Background**
        i. Celiac disease is an immune-mediated enteropathy occurring in genetically susceptible patients in response to ingested gluten.[1] Other immune mediated enteropathies include autoimmune enteropathy, collagenous enteropathy, post-transplant lymphoproliferative disorder related enteropathy. Celiac disease prevalence is 0.7% of the United States population.[2] Less than two percent of patients with celiac disease do not respond to a gluten free diet and demonstrate recurrent/persistent symptoms and small bowel villous atrophy.[3,4] Refractory celiac disease (RCD) is defined as persistent symptoms and histological small bowel changes after at least six months on a gluten free diet.[4] These patients have been treated with off-label budesonide therapy with 92% showing improvement in symptoms and 89% showing histological changes.[5] However, this therapy has never evaluated in a randomized, placebo-controlled trial. This is significant as there is no approved therapy in patients with RCD or other immune mediated enteropathies, and the sequelae of this illness include debilitating symptoms, malnutrition, osteoporosis and enteropathy associated T-cell lymphoma.[4] Furthermore, physicians and patients have concerns regarding the long-term use of budesonide therapy and an appropriate withdrawal strategy is not well defined.

    II. **Rationale for Study**
        i. While the benefits of budesonide therapy in refractory, immune-mediated enteropathies has been suggested by clinical experience, no study has been conducted to determine when and if this therapy can be discontinued. This study aims to evaluate patients with immune mediated enteropathies who

have demonstrated symptomatic and histologic improvement on budesonide and randomize them to withdraw therapy versus continued budesonide.

This question is important as there are systemic effects of long term corticosteroid therapy, including budesonide. Studies have shown that adrenal suppression does occur in about 50% of patients on budesonide [6-8]. The medication is also costly.

3. Study Design

I. Patients with autoimmune mediated enteropathies (excluding refractory celiac disease type 2 and post-transplant lymphoproliferative disorder) on budesonide therapy with improvement in symptoms and histological small bowel changes will be recruited for a randomized, open-label trial of budesonide withdrawal. After recruitment and consent, subjects would record CDSD surveys daily for one week. For those individuals who are unable to travel to Rochester for that visit, CDSD will be activated and completed prior to consent under the assumption that the data can only be used if future written consent is obtained Then, on the day of randomization, the subjects undergo esophagogastroduodenoscopy (EGD) with biopsies taken from the duodenum, serum evaluation of micronutrient status, blood count, and creatinine will be assessed, and serum will be stored for future evaluation of non-invasive evaluation of bowel inflammation. At enrollment, stool test for gluten exposure, CDSD questionnaire and CD-QOL quality of life questionnaire will be administered. Subjects will record symptoms on CDSD daily during the study. Subject will be randomized to either withdrawal or continued budesonide therapy. Subjects in the withdrawal arm will be weaned off of budesonide over a period of two weeks. Those continued on therapy will continue at their current maintenance dose and dosing scheme. At 4 weeks, individuals will have laboratory studies drawn locally through a kit that will be mailed to them containing testing for blood count, creatinine, albumin, and CRP. Additionally, they will complete a phone interview with a study investigator to fill out the CD-QOL survey, to screen for adverse events, and to review study exclusion criteria. This would be repeated at 8 weeks. At 12 weeks, the subject will undergo repeat EGD with biopsies, serum assessment, QOL questionnaire, one week of CDSD symptom questionnaire, and stool gluten testing.

All subjects in the control arm will continue budesonide formulation and dosing scheme. Those noted on the budesonide open capsule regimen will continue this regimen as listed below.

If a subject has had a clinical EGD with biopsies within three months of randomization and the histology slides are available, this will serve as the baseline biopsy. In this case, no frozen biopsy for microbiology or biopsy in RNA later will be collected.

II. Open capsule budesonide regimen[5]: Oral budesonide 3 mg three times daily.

- First capsule is to be opened, emptied onto applesauce, stir, grind medication with teeth, and swallow with a glass of water.
- Second capsule is to be opened, emptied onto applesauce, stir, and swallow with glass of water.
- Third capsule is to be swallowed whole.
- Rationale: Deliver of the budesonide to the entire small bowel, given EC budesonide is pH dependent and intended to be released in the distal small bowel.
- This differs from the prescribing information from the enteric coated budesonide, but has been shown to be efficacious for refractory immune-mediated enteropathies[5].

4. Selection and Enrollment of Participants

I. Inclusion Criteria

i. Adult patients with immune mediated enteropathies who have had improvement in symptoms and histology on oral budesonide therapy.

II. Exclusion Criteria

i. Age <18 years
ii. Positive stool gluten testing in patients with refractory celiac disease
iii. Small bowel malignancy or history of small bowel malignancy
iv. Refractory celiac disease type 2
v. Post-transplant lymphoproliferative disorder associated enteropathy
vi. No prior improvement in symptoms and histology with budesonide therapy
vii. Discontinuation of budesonide therapy prior to the trial
viii. Other concurrent systemic corticosteroids
ix. Other immune mediating medications, for example but not limited to azathioprine, 6-mercaptopurine, cyclosporine, methotrexate, anti-TNF monoclonal antibodies, alpha-4 beta-7 integrin inhibiting monoclonal antibody, interleukin 12/23 inhibiting monoclonal antibody, JAK inhibitors.

5. Study Interventions

I. Interventions

i. Screening period:
- Review of inclusion/exclusion criteria
- Consent documentation and discussion

a. This may be conducted after the 7 day electronic run in questionnaire of symptoms have been completed. If written isn't obtained, questionnaire data will be deleted. This will be in those instances where subjects cannot travel to Rochester multiple times due to cost and availability because of the distance to Rochester.

b. For consents obtained in person, written or iPad consent through the PTRAX system will be used for electronic consent.

- Randomization to continued budesonide therapy or withdrawal
- Daily CDSD for seven days leading to start of study period

ii. Study Period

- Withdrawal Arm: Titration off budesonide as outlined
- Budesonide Arm: Continuation on current therapy and dosing scheme
- Esophagogastroduodenoscopy with biopsies at day 0 and day 84 (or withdrawal from the study).
    - **a.** If clinical EGD with biopsies within three months of randomization with histology slides available, this will serve as baseline biopsy.
- Blood draws as outlined at initiation of the trial, day 28, day 56 and day 84
    - **a.** The blood draws on day 28 and day 56 will be drawn at the patient's local lab in order to minimize travel requirements for subjects who live a distance from Rochester, Minnesota. Kits will be mailed to the subjects with the appropriate blood tests.
- Stool collection at day 0 and day 84 (or withdrawal from the study)
- Urine collection at day 84 (or withdrawal from the study).
- Daily CDSD survey collected weekly
- Monthly CD-QOL survey
- Meeting with study team for consent/enrollment and at days 0, and 84 (or withdrawal from the study)

II. Withdrawal Arm Titration for Patients Previously on Budesonide EC

i. Patients randomized to the withdrawal arm will be titrated off of budesonide over two weeks
ii. For days 1-7, they will receive 6 mg of budesonide, one opened, chewed capsule, one opened and granules mixed with applesauce.
iii. For days 8-14, they will receive 3 mg of budesonide, one opened, chewed capsule.
iv. For days 15-84, the will receive no budesonide

III. Withdrawal Arm Titration for Patients on Compounded Budesonide

i. For days 1-7, subject will receive 6 mg of budesonide
ii. For days 8-14, subject will receive 3 mg of budesonide
iii. For days 15-84, subject will receive no budesonide

6. Study Procedures

I. Schedule of Evaluation

i. Screening and Consent

- Patients will either meet in person with study member to discuss inclusion and exclusion criteria, study design, and consent, or this conversation will be held over the phone in those cases where patients live a distance from Rochester, Minnesota

- Age, sex, height, weight, date of diagnosis, medication reconciliation and physical exam. This information will be collected on day zero..
- Daily CDSD for 7 days leading to start of the trial. This may be done with patients who live a distance from Rochester, MN prior to written consent under the assumption that the data collected can only be used if consent is obtained on Day 0.

ii. Day Zero: EGD with duodenal biopsies, collection of serum and stool. CD-QOL and CDSD surveys. Randomization occurs.
- Age, sex, height, weight, date of diagnosis, medication reconciliation and physical exam if consent and screening was performed over the phone.
- Serum Studies: Complete blood count with differential, sodium, potassium, creatinine, albumin, tissue-transglutaminase IgA, total IgA, ferritin, serum iron, total iron binding capacity, zinc, copper, vitamin B12, 25-OH vitamin D, serum folate, c-reactive protein.
- Stool Studies: Gluten assessment in RCD1 patients, stool storage for future study and microbiology
- Urine Studies: Urine stored for future study
- Duodenal biopsies for histology and for microbiology

iii. Days 1-7:
- Withdrawal Arm: Budesonide 6 mg daily
- Budesonide Arm: Continued pre-study dose and frequency.
- All subjects daily CDSD.

iv. Days 8-14:
- Withdrawal Arm: Budesonide 3 mg daily
- Budesonide Arm: Continued pre-study dose and frequency.
- All subjects daily CDSD.

v. Days 15-84:
- Withdrawal Arm: No budesonide
- Budesonide Arm: Continued pre-study dose and frequency.
- All subjects daily CDSD.

vi. Day 28 +/- 3 days:
- Laboratory assessment including CBC with differential, sodium, potassium, creatinine, albumin, c-reactive protein performed locally via a kit that will be mailed to subjects.
- Phone visit to review CD-QOL, to gather information on weight measurement, to evaluate for adverse events, and to review exclusion criteria

vii. Day 56 +/- 3 days:
- Laboratory assessment including CBC with differential, sodium, potassium, creatinine, albumin, c-reactive protein performed locally via a kit that will be mailed to subjects.

- Phone visit to review CD-QOL, to gather information on weight measurement, to evaluate for adverse events, and to review exclusion criteria

viii. Day 84:
- Physical exam.
- EGD with duodenal biopsies, collection of serum, urine, and stool. CD-QOL and CDSD surveys.
- Serum Studies: Complete blood count with differential, sodium, potassium, creatinine, albumin, tissue-transglutaminase IgA, total IgA, ferritin, serum iron, total iron binding capacity, zinc, copper, vitamin B12, 25-OH vitamin D, serum folate, c-reactive protein.
- Stool Studies: Gluten assessment in RCD1 patients, stool storage for future study
- Urine Studies: Urine stored for future study
- Duodenal biopsies for histology and microbiology
- Subjects return to pre-study budesonide dosing schedule.

ix. Early Withdrawal-Safety or Elective
- If the subject requires early withdrawal due to safety concerns or elective withdrawal but agrees to final testing.
- EGD with duodenal biopsies, collection of serum, urine, and stool. CD-QOL and CDSD surveys.
- Serum Studies: Complete blood count with differential, sodium, potassium, creatinine, albumin, tissue-transglutaminase IgA, total IgA, ferritin, serum iron, total iron binding capacity, zinc, copper, vitamin B12, 25-OH vitamin D, serum folate, c-reactive protein.
- Stool Studies: Gluten assessment in RCD1 patients, stool storage for future study
- Urine Studies: Urine stored for future study
- Duodenal biopsies for histology and microbiology
- Subject prescribed budesonide 9 mg daily, open capsule scheme and recommend follow up with primary gastroenterologist.

7. Safety Assessments

I. Specifications of Safety Parameters

i. Serious Adverse Events
- Hospitalization for dehydration, malnutrition, or severe diarrhea
- These would result in withdrawal from the study. If possible, patients would undergo laboratory assessment, EGD with biopsies and questionnaires.

ii. Adverse Events-Meeting any of the following would result in withdrawal from the study with reassessment of serologies, EGD with biopsies, as outlined in the withdrawal portion of the protocol.
- Loss of greater than or equal to 5% of body weight

- Hemoglobin decrease by >2 grams without other clear etiology
- Albumin decrease by more than 1 g/dL as this was a predictor of greater mortality[9].
- CDSD Symptom of >6 bowel movements per day for 3 days in a week.

II. Methods and Timing for Assessing, and Recording Safety Parameters

i. Subjects would be able to contact our study office at any point during the trial to report adverse events.

ii. Formal assessment of laboratory parameters, weight parameters, and CDSD scores would occur at monthly visits.

III. Reporting of Adverse Events

i. Reporting of serious adverse events to the independent safety monitor would occur immediately.

ii. Reporting of adverse events not included as serious adverse events would be reported and reviewed quarterly by the independent safety monitor.

IV. Independent Safety Review

i. A gastroenterologist, independent of the study, will review serious adverse events and other adverse events as outlined above. She or he has the authority to abort the study at any point.

V. Follow up for adverse events

i. If the subject develops the predetermined adverse events requiring withdrawal from the trial, he or she will be started on 9 mg of budesonide open capsule formulation and scheduled for follow up with primary gastroenterologist.

8. Interventional Discontinuation

I. Completion of the Trial

i. At the completion of the trial, all subjects will resume budesonide dose and scheme they were prescribed prior to the trial.

ii. Subjects will be encouraged to follow up as scheduled with primary gastroenterologist.

II. Withdrawal from Trial

i. Safety/Adverse Events: If withdrawal from trial was due to safety or adverse events. The reassessment of disease with EGD and duodenal biopsies, serologies, urine and stool collection, and questionnaires will be completed if able.

- Subjects will be prescribed budesonide 9 mg daily utilizing open capsule formulation
- Follow up will be arranged with primary gastroenterologist

ii. Elective Withdrawal: If withdrawal is elective and not related to symptoms or adverse effects, the subjects will resume budesonide dose and frequency as to that before the trial.

- Subjects will be offered repeat EGD with duodenal biopsies, serologies, collection of urine and stool, and questionnaires.

- If there are concerns for worsening symptoms, the subject will be placed on budesonide 9 mg daily utilizing open capsule formulation with instructions to follow up with his/her primary gastroenterologist.

9. Statistical Considerations

I. General Design

i. Randomized, open-label withdrawal of budesonide therapy in patients with immune-mediated enteropathies who have had improvement in symptoms and small bowel histology with budesonide therapy.

II. Sample Size and Randomization

- **Sample Size:** Aim is 10 patients per arm (20 total)
- **Power Analysis:** Based on the fact that these are rare diseases, there is limited knowledge of what constitutes meaningful histologic change and recruitment may be limited. A decrease in villous height to crypt depth ratio from baseline of .8 (SD = .6) was used as the non-inferiority margin based on prior literature[11]. Assuming the expected change from baseline between the two groups is the same, 10 subjects are needed in each arm to achieve the target power of 0.80 using an alpha of 0.05 and a one-sided test.
- **Randomization:** Block randomization based on underlying immune-mediated enteropathy, either refractory celiac disease type 1 or other.
- **Treatment Assignment Procedures:** Block randomization will occur as above by computer generated randomization.
- **Statistical Analysis:** The primary aim in this study is to determine if subjects can safely be removed from budesonide therapy. The change of villous height to crypt depth ratio from baseline to 12 weeks (calculated as the difference of baseline and 12 weeks post treatment) between the randomized groups (withdraw versus continued therapy) will be assessed with a Wilcoxon rank-sum one-sided test. Analyses will be conducted in SAS statistical software (SAS Institute Cary, NC) and R statistical package (R Foundation for Statistical Computing, Vienna, Austria). An alpha level of .05 will be used to determine statistical significance.

III. Stopping Rules

i. Stopping rules: Section 7 defines serious adverse events and adverse events that would result in subjects being withdrawn from the trial for safety
   - The independent safety monitor will determine if the study must be stopped early due to concern for safety. Reporting to this monitor is outlined in section 7.

IV. Outcomes

i. **Primary Outcome**
   - **Histology Outcome:** Duodenal histology will be compared from initiation of the study to that at completion or withdrawal. Oberhuber-

Marsh Classification and villous-crypt height ratio and IEL's will be assessed by a masked pathologist.

ii. **Secondary Outcomes**

- **Symptom Outcome:** CDSD score will be monitored throughout the trial and evaluated as a continuous variable observing for changes in symptoms during treatment versus withdrawal
  - **Quality Outcome:** CD-QOL will be assessed monthly and at completion or withdrawal and changes will be evaluated for association with withdrawal versus continuation of budesonide.
- **Micronutrient/Nutritional Outcome:** Nutrient assessment will be completed at initiation and completion of the study assessing for micronutrient differences between those randomized to withdrawal of budesonide compared to continued therapy. Weight will be monitored monthly throughout the study and assessed for overall change.

10. Data Collection and Storage

I. Data Collection Forms

i. Forms for data collection are attached as Appendix IV.

ii. CDSD will be available via daily email link to those with internet and email access. Paper copies will be available to those without email or internet access.

II. Data Management

i. Data will be collected both on paper and electronically throughout the study. The data will be securely archived electronically.

ii. RedCap research database will be formulated to collect and manage data.

III. Protocol Deviations

i. All efforts will be made to ensure that the study does not deviate from the protocol.

ii. If changes need to be made for safety or logistics, they will be reviewed by the Institutional Review Board prior to any change.

IV. Monitoring

i. Safety will be monitored as stated above.

11. Participant Rights and Confidentiality

I. Institutional Review Board (IRB) Review

i. This study, any modifications, consent, and any documentation will be reviewed by the Mayo Clinic Institutional Review Board.

II. Informed Consent Forms

i. A study member will discuss the attached consent form with the participant prior to entry into the trial. This discussion may be performed over the phone. A copy of this will be provided to the participant, including contact information for the study team, Mayo Clinic IRB, research billing, and a research advocate.

III. Participant Confidentiality

i. Data will be collected and secured electronically. Any publication will not include any identifying information for study participants.

IV. Study Discontinuation

i. At the completion of each participant's time in the study, the protocol discussed medication recommendation and follow up. This includes completion of the trial and if the subject electively withdraws or the trial is stopped for subject safety.

ii. If the overall trial needs to be stopped due to safety concerns, all subjects will be contacted and returned to their prior dose and schedule of budesonide. They will receive recommendations to follow up with their primary gastroenterologist.

V. Participant Payment

i. $250 for each endoscopy completed

ii. Medication would be provided for the time enrolled in the trial

12. Ethical Considerations

I. The study will be conducted in accordance with the International Council on Harmonization guideline E6 Good Practice, the Declaration of Helsinki, and with local regulations for completion of clinical trials.

II. The study will be evaluated by the Mayo Clinic Institutional Review Board.

III. The study will be listed as a registered clinical trial with clinicaltrials.gov.

IV. It is possible that subjects randomized to budesonide withdrawal may lose future effect of budesonide therapy. This will be included as a risk in the consent documentation.

13. Committees

I. Independent Safety Review Committee as outlined above.

14. Publication of Research Findings

I. All findings will be submitted for publication after the completion of the study.

15. References

1. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. Gut 2013;62:43-52.
2. Choung RS, Unalp-Arida A, Ruhl CE, Brantner TL, Everhart JE, Murray JA. Less Hidden Celiac Disease But Increased Gluten Avoidance Without a Diagnosis in the United States: Findings From the National Health and Nutrition Examination Surveys From 2009 to 2014. Mayo Clin Proc 2016.
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5. Mukewar SS, Sharma A, Rubio-Tapia A, et al. Open-capsule budesonide for refractory celiac disease. Am J Gastroenterol 2017; 112:959-67.
6. Greenberg GR, Feagan BG, Martin F, et al. Oral budesonide for active Crohn's disease. Inflammatory Bowel Disease Study Group. *N Engl J Med* 1994;331:836-841.
7. Campieri M, Ferguson W, Doe T, et al. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. *Gut* 1997;41:209-214.
8. Tremaine WJ, Hanauer SB, Katz S, et al. Budesonide CIR capsules (once or twice daily dividided-dose) in active Crohn's disease: a randomized placebo-controlled study in the United States. *Am J Gastroenterol* 2002;97:1748-1754.
9. Rubio-Tapia A, Verbeek WHM, van Wanrooij RLJ, et al. Creation of a model to predict survival in patients with refractory coeliac disease using multinational registry. *Alimentary Pharmacology and Therapeutics* 2016;44:704-714.

16. Appendices

- **I. Study Timeline**
- **II. Informed Consent Form**
- **III. Esophagogastroduodenoscopy and Biopsy Guideline**

References:

1. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. Gut 2013;62:43-52.
2. Choung RS, Unalp-Arida A, Ruhl CE, Brantner TL, Everhart JE, Murray JA. Less Hidden Celiac Disease But Increased Gluten Avoidance Without a Diagnosis in the United States: Findings From the National Health and Nutrition Examination Surveys From 2009 to 2014. Mayo Clin Proc 2016.
3. Leffler DA, Dennis M, Hyett B, et al. Etiologies and predictors of diagnosis in nonresponsive celiac disease. Clin Gastroenterol Hepatol 2007;5:445e50.
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9. Rubio-Tapia A, Verbeek WHM, van Wanrooij RLJ, et al. Creation of a model to predict survival in patients with refractory coeliac disease using multinational registry. *Alimentary Pharmacology and Therapeutics* 2016;44:704-714.

Appendix I: Study Timeline

	Consent Visit**	Pre-Study	Day 0	Days 1-7	Days 8-14	Days 15-83	Day 28 +/- 3	Day 56 +/- 3	Day 84	Safety Withdrawal
Withdrawal Arm				Budesonide 3 mg BID	Budesonide 3 mg	0 mg			Home Dose	9 mg open capsule regimen
Drug Arm				Home Dose	Home Dose	Home Dose			Home Dose	9 mg open capsule regimen
Consent	X		X**							
Physical Exam	X		X**						X	X
Weight/Height	X		X				X	X	X	X
Vital Signs			X						X	X
Age	X		X							
Sex	X		X**							
Date of Diagnosis	X		X**							
EGD with biopsies for histology and microbiology			X*						X	X
CDSD		Daily x7 days	X	Daily	Daily	Daily			X	X
CD-QOL			X				X	X	X	X
Urine Pregnancy Test			X						X	
Sodium			X				X	X	X	X
Potassium			X				X	X	X	X
Creatinine			X				X	X	X	X
CBC with diff			X				X	X	X	X
TTG-IgA			X							
Total IgA			X							
Ferritin			X						X	X
Serum Iron			X						X	X
TIBC			X						X	X
25-OH vitamin D			X						X	X
Vitamin B12			X						X	X
Folate, serum			X						X	X
Zinc			X						X	X
Copper			X						X	X
Albumin			X				X	X	X	X
C Reactive Protein			X				X	X	X	X
Stored Serum			X						X	X
Urine Collection-Storage			X						X	X
Stool gluten (if celiac disease)			X						X	X
Urine Gluten (if celiac disease)			X						X	X
Stored stool for microbiology			X						X	X

(*) If clinical esophagogastroduodenoscopy has been completed within 3 months of randomization and slides are available, this will serve as initial biopsy. In this case, no biopsies will be stored for microbiology.

(**) For those patients who cannot travel easily to Rochester, n these cases, certain aspects of the screening visit will be obtained at the visit on Day 0, as indicated.

II. Informed Consent—Attached to IRB application.

III. Esophagogastroduodenoscopy and Biopsy Guideline

- Subjects will undergo endoscopy at the initiation of the trial and at completion (day 84) or after safety withdrawal.
- Initial EGD with biopsy may be omitted if clinical EGD with biopsies were completed within 3 months of initiation of the trial with histology slides available. Biopsy for microbiology will be omitted in this case.
- Moderate conscious sedation will be provided by a licensed Gastroenterologist and administered by a nurse.
- Biopsies will be obtained from the duodenum
    - 2 biopsies from the duodenal bulb for histology (2 biopsies per bottle)
    - 4 biopsies from the second portion of the duodenum for histology (2 biopsies per bottle)
    - 1 biopsy from the second portion of the duodenum for microbiology will be rapidly frozen (not fixed in formalin).
    - 1 biopsy from the second portion of the duodenum will be fixed in RNA later.
    - Tissue obtained for histology will be fixed in formalin and sent to the laboratory for sectioning, staining, and interpretation
    - Villous height to crypt depth ratio, Oberhuber-Marsh classification, and intraepithelial lymphocyte count will be assessed.
- Endoscopies will occur in the Clinical Research Unit.
- Subjects will be monitored by nursing staff after the procedure until awake and safe for dismissal.
- A licensed physician will be available if needed during the recovery period.

IV: Laboratory Collection, Handling, and Storage

Urine Studies:

A urine sample will be collected on days 0 and day 84 (or withdrawal from trial). This will be tested for 33mer gluten immunogenic peptides using the anti-gliadin G12 antibody and lateral flow device from GlutenTOX (Bioomedal, Sevilla, Spain). Once collected, 5 ml will be aliquoted and sent to BAP storage at -80 degrees C. This will be requested for gluten exposure testing and the remainder will be stored in BAP at -80 degrees C.

Stool Studies:

Stool will be collected on days 0 and 84 (or withdrawal from trial). This will be tested for 33mer gluten immunogenic peptides by ELISA. This will be collected in sterile container and 25 ml will be aliquoted and sent to BAP for storage at -80 degrees C. This will be requested for 33mer testing and the remainder will be stored at BAP at -80 degrees C.

Stored Serum:

All labs outlined in the protocol will be drawn and transported to the lab by the CRTU. Serum for storage will be collected. 2 serum gel tubes with silicone coat with clot activator (BD 367986), 5 ml each, will be collected, inverted 5 times, stored upright for 2 hours at room temperature. Then centrifuged at 2000 g for 20 minutes. Harvest and freeze within 180 minutes of collection. These can be sent to BAP. This will be available for future cytokine analysis.

A second tube, either serum gel tube or red top tube, 5 ml, will be collected, centrifuged, aliquoted and transported to BAP for storage.