Pancreatic Enzyme Supplementation for Celiac Disease

NCT: 02475369

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PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	Pilot Study of the efficacy of pancreatic enzyme supplementation for symptom control in celiac disease not responding to the gluten free diet
Principal Investigator	Ciaran P Kelly, MD

B1. PURPOSE OF PROTOCOL

The purpose of this protocol is to conduct a pilot study to investigate whether pancreatic enzyme supplementation will improve symptoms in individuals with celiac disease who suffer persistent symptoms despite a gluten free diet. This protocol specifically aims to:

(1) Evaluate the efficacy of pancreatic enzyme supplementation for reduction of gastrointestinal symptoms in patients with celiac disease on a gluten free diet.

(2) Assess the ability of fecal elastase levels to predict response to pancreatic enzyme supplementation in patients with celiac disease on a gluten free diet.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Celiac disease is a systemic immunological disorder in which the sentinel lesion is an enteropathy triggered by ingestion of prolamine-rich, cereal protein-derived, polypeptides collectively called "gluten" including proteins from wheat (gliadin), rye (secalin) and barley (hordein).1,2 Ingestion of the offending proteins leads to intestinal inflammation and mucosal damage, which frequently results in a spectrum of gastrointestinal symptoms, increased intestinal permeability, maldigestion and malabsorption, occult gastrointestinal bleeding, diarrhea and systemic manifestations including malignancy, osteoporosis, fertility abnormalities and autoimmune disease.1-3

Celiac disease is unique among chronic, auto-immune inflammatory disorders as both instigating antigen and end-organ pathology are well defined.4,5 The elucidation of the gluten proteins as the offending agent in celiac disease6 has allowed for highly efficient in vitro and in vivo investigations that have identified what are currently accepted to be the three pivotal steps in celiac disease activation. First, intact gluten peptides are delivered to the small intestinal mucosa.7 Second, gluten peptides are selectively deamidated in the extracellular matrix of the intestinal submucosa.8 Finally, deamidated gluten peptides bind to HLA DQ2 or HLA DQ8 on antigen presenting cells activating both cell mediated and humoral immunity.9,10

Understanding of this pathway has markedly advanced clinical practice, most clearly though allowing development of a simple and accurate serologic test in the form of antibody to tissue transglutaminase (tTG).11 Using serological assays, the prevalence of celiac disease in the United States and Europe ranges between 1:250 and 1:67.12 A growing body of literature supports the conclusion that celiac disease is a common entity in diverse populations across the globe.

While we have an excellent understanding of celiac disease pathophysiology,13,14 diagnosis,11 clinical manifestations,1,2 response to gluten withdrawal15-19, and gluten challenge20,21, treatment of celiac disease is not significantly different now than 50 years ago. Unfortunately, while the gluten free diet is safe, it is not as effective as patients or clinicians would like. Studies currently suggest that up to 30% of celiac patients return to their doctor for persistent or recurrent symptoms and that a much larger proportion have symptoms that do not trigger medical evaluation.19,22-24

There are multiple reasons for persistent symptoms, but one of the etiologies that has been observed across multiple studies is pancreatic exocrine insufficiency.[19,22,25,26] The role of pancreatic endocrine dysfunction as a cause of persisting or recurrent symptoms in patients with celiac disease already adhering to a gluten free diet is well known and repeatedly described in the clinic literature on celiac disease.[19,27,28] A recent summary can be obtained from the 2013 ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease.[29] The abstract/summary of the guidelines states: "Persistent or recurring symptoms should lead to… evaluation for disorders associated with celiac disease that could cause persistent symptoms, such as microscopic colitis, pancreatic exocrine dysfunction, and complications of celiac disease, such as enteropathy-associated lymphoma or refractory celiac disease, should be entertained." The importance of considering pancreatic insufficiency in nonresponsive celiac disease is discussed further in the text of the Guidelines but the discussion is based on review articles and case series. No treatment trials are referenced reflecting the lack of prospective studies on this topic.

Despite awareness in the celiac community of the potential for pancreatic exocrine insufficiency as a complication of celiac disease, there have been few prospective studies of pancreatic enzyme replacement in celiac disease and no studies to date that have taken place in the United States. As the population with celiac disease has expanded rapidly in recent years,[30] the potential for adjunctive therapies for celiac disease has become more apparent. In this study, we propose to conduct a rigorous prospective study of the utility of pancreatic enzyme replacement in celiac disease and assess the ability of fecal elastase levels to predict response to therapy.

Our goal is to provide adequate supplementation over the 10 day treatment period so as to maximize the opportunity for an evident therapeutic effect if indeed pancreatic enzyme insufficiency is contributing to the subjects' symptoms.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Overview

This is a single-center investigator initiated phase IV trial to examine the efficacy of pancreatic enzyme supplementation in individuals with celiac disease who suffer persistent symptoms despite a gluten free diet.

Hypothesis

Pancreatic enzyme supplementation will improve symptoms in individuals with celiac disease who suffer persistent symptoms despite a gluten free diet.

Specific Aims:

Specific Aim 1: Evaluate the efficacy of pancreatic enzyme supplementation for reduction of gastrointestinal symptoms in patients with celiac disease on a gluten free diet.

Specific Aim 2: Assess the ability of fecal elastase levels to predict response to pancreatic enzyme supplementation in patients with celiac disease on a gluten free diet.

Primary Objective(s)/End Point(s):

The primary endpoint for Specific Aim 1 will be the average per individual subject on-treatment score in the Celiac Disease Gastrointestinal Symptom Rating Scale (CeD GSRS) domains of Diarrhea, Indigestion, and Abdominal pain comparing active treatment to placebo (i.e. a paired comparison of CeD GSRRS on treatment versus on placebo for each subject).[31,32] The outcome measures used in the study and in particular the CeD GSRS have been employed previously by the investigators in their published studies.[31-33]

As a primary endpoint for Specific Aim 2, baseline fecal elastase measurement will be correlated to the average difference in on-treatment score in the CeD GSRS [active versus placebo].

Secondary Objective(s)/End Point(s):

(1) Assessment of response to pancreatic enzyme supplementation in patients with celiac disease and either normal or low baseline fecal elastase levels.
(2) Improvement in Celiac Symptom Index (CSI) with active treatment vs. placebo.
(3) Reduction in number of total stools and loose stools (defined as a Bristol Score of 6-7) per week with active treatment vs. placebo.

Experimental Design & Number and Description of Each Treatment Arm/Group:

We propose a randomized, double blind, placebo-controlled, crossover trial of 40 participants overall. Participants would have a 7 day placebo run in period for documentation of symptoms at baseline (study phase 1), followed by a 10 day treatment/placebo period (study phase 2), after which there would be another 7 day wash out period (study phase 3) and a final 10 day cross over (study phase 4) resulting in a total study duration of 34 days.

Participants will be recruited from the Celiac Center at Beth Israel Deaconess Medical Center which currently has over 1900 registered patients with biopsy proven celiac disease. Patients will be enrolled in the out-patient clinic and though targeted mailings and advertisements. Males and Females over the age of 18 with biopsy-proven celiac disease and persisting symptoms despite adherence to a strict gluten free diet will be targeted[19].

Study visits would occur at screening (Visit 1), beginning of the third study phase (day 17-21, Visit 2) and study conclusion (day 35-40, Visit 3). Participants will regularly complete symptom surveys (Celiac Dietary Adherence Test [CDAT], to be administered at baseline; the CSI, to be administered daily; CeD-GSRS & a modified CSI, which are to be administered at the end of each study phase), a daily stool log (frequency and consistency), and a daily medication log. Participants will be contacted every 3 (±1) days after enrollment for safety and compliance assessments (e.g. medication, symptoms surveys, and stool log review).

Active drug would be taken at a dose of 3 (three) 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase tablets with meals and 2 (two) 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase tablets with snacks. Dosing will occur with meals and snacks (approximately 3 meals and 3 snacks per day). Our goal is to provide adequate supplementation over the 10 day treatment period so as to maximize the opportunity for an evident therapeutic effect if indeed pancreatic enzyme insufficiency is contributing to the subjects' symptoms. Omeprazole (20mg orally once per day) will be co-prescribed all 34 days of study drug administration to facilitate duodenal digestion of the study drug.

Duration of study Treatment (Per Subject):

34 Days

Doses per Subject per Treatment

Pancreatic enzyme supplement dosage will be scaled according to the weight of the patient in OMR or by patient report.

With meals patient will take the active pancreatic enzyme supplement as follows:

- 59 kg and greater
  - 3 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase tablets with meals and 2 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase tablets with snacks.
    - Total daily use = 3 x 3 and 2 x 3 = 15 units

- Total per subject use = 150 (15 x 10 days)

- Between 53 and 58 kg
  - 2.5 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase tablets with meals and 2 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase tablets with snacks.
    - Total daily use = 2.5 x 3 and 2 x 3 = 13.5 units
    - Total per subject use = 135 (13.5 x 10 days)

- Between 47 and 53 kg
  - 2.5 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase tablets with meals and 1.5 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase tablets with snacks.
    - Total daily use = 2.5 x 3 and 1.5 x 3 = 12 units
    - Total per subject use = 120 (12 x 10 days)

- Between 40 and 46 kg
  - 2 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase tablets with meals and 1.5 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase tablets with snacks.
    - Total daily use = 2 x 3 and 1.5 x 3 = 10.5 units
    - Total per subject use = 105 (10.5 x 10 days)

Placebo: gelatin-based capsules filled with microcrystalline cellulose will match the above dosing schedule.

The Viokace and placebo will be encapsulated to match. However, due to their size the Viokace tablets must be crushed and split between two capsules. Consequently, in order to consume the units of Viokace per day during the active treatment phase, each subject will need to take twice as many capsules as units listed above. To maintain the blind, subjects will also need to consume a matching number of placebo capsules each day during the 7-day run-in, 7-day wash-out, and 10-day crossover phases.

Because Viokace is not enteric-coated it must be co-prescribed with a proton-pump inhibitor to facilitate digestion in the duodenum. Study subjects will be prescribed 20mg Omeprazole to be taken orally once a day before breakfast for the entire 34 days of study medication administration. Subjects who are already taking omeprazole or another PPI at enrollment will be allowed to continue taking it as prescribed with no need to discontinue or switch over the course of the study.

While study subjects will be provided with the study medication and omeprazole (collectively referred to as “study treatment”) necessary to complete study phases 1 and 2 at visit #1, they will be asked to refrain from initiating study treatment until they have been notified by study staff that they can do so. This delay is intended to accommodate the lag in time between visit #1 and the receipt of screening lab results (CBC, BMP, and celiac serologies). Once these results have been received and reviewed by a study physician, study subjects will be called by study personnel notifying them of whether they can initiate study treatment. Subjects who are eligible to continue in the study will be instructed to begin to take the study treatment the following day. The day on which the subject begins the study treatment will be considered Day 1, and the timing of all subsequent study visits and assessments will follow accordingly as described within this protocol.

Study treatment administration will be explained to subjects in detail by the study coordinator at Visit #1 and via a study medication instructions sheet.

Number and Timing of Visits/Evaluations:

Study visits will occur at screening (Visit 1), beginning of the second study phase (day 14-21, Visit 2) and study conclusion (day 35-40, Visit 3). Each of these visits will include medical history review by study personnel, a physical exam performed by a licensed study physician, and the collection of vital signs. Visit 1 will include a dietetic assessment to be completed with a Celiac Center dietician. This dietetic assessment will occur either in-person at Visit 1 following the consent or following Visit 1 over the phone prior to the start of the study medication. The purpose of this dietetic assessment is to (1) evaluate for recent gluten exposure and obvious other food intolerances (e.g. moderate lactose intolerance, FODMAP intolerance), and (2) educate the subject regarding the diet they should follow while on the study.

At Visit 1 participants will be asked to complete the CeD-GSRS, CSI, and CDAT questionnaires. Following Visit 1, participants will be asked to complete the CSI once each day for the duration of the study period. Participants will additionally complete the CeD-GSRS and a specialized CSI that includes a question regarding potential gluten exposure at the end of each study phase, i.e at days 7, 17, 24, and 34 (please see the protocol schema on page 14 below for a depiction of the study phases).

If participants do not attend Visit 2 until after study day 17 they will be instructed to stop taking study medication, including omeprazole if prescribed for the study, until they attend Visit 2 and can receive the placebo washout.

Participants will additionally complete a daily medication log to record when they take the study medication and a daily paper stool log to record bowel movement frequency and consistency.

Participants will be contacted every 3 (±1) days after enrollment for safety and compliance assessments (e.g. medication, symptoms survey, and stool log review).

Laboratory Assessments:

Safety outcomes will be assessed at visit 1 (screening) and 3 (study conclusion) and will include:

- Celiac serologies (IgA tTG and IgA/IgG DGP)
- Complete blood count (CBC)
- Basic metabolic panel (BMP)

Fecal elastase will additionally be assessed at Visit 1. Stool sampling for fecal elastase testing will occur at Visit 1 when possible or a stool sample will be returned at Visit 2.

Female subjects will be asked to provide a urine sample at Visit 1 for β-HcG pregnancy testing.

Safety Evaluations:

Safety evaluations will occur at all study visits and contacts through interview with study personnel, and/or physical examination, and/or symptom monitoring via the weekly surveys. Safety outcomes will include celiac serologies (IgA tTG and IgA/IgG DGP), CBC, and BMP on screening and study conclusion.

Adverse events (AEs) will be assessed at study visits and contacts. Serious adverse events (SAEs) will be defined as those that: result in death; are an immediate threat to life; require inpatient hospitalization, or prolongation of existing hospitalization; result in persistent or significant disability/incapacity; and/or are a congenital anomaly or birth defect.

For all AEs we will provide an assessment of causal relationship to the IP. Causal relationship will be assessed by answering the following question: Is there a reasonable possibility the IP caused the event? The answer to this question is “yes” if there is evidence to suggest a casual relationship between the drug and the adverse event (i.e. there is a reasonable temporal relationship, and/or the events are unlikely to be attributable to underlying disease, other drugs, or

other factors). Dechallenge and/or rechallenge (if available) is positive. The answer to this question is "no" if the relationship is unlikely or nonexistent (i.e. there is no reasonable temporal relationship and/or the events are likely to be manifestations of underlying diseases, or commonly occur in the study population independent of drug exposure or other drugs/factors provide plausible explanations for the events), or the patient did not take the investigational product.

The Principal Investigator will inform Forest Global Drug Safety of all SAEs. Forest Global Drug Safety will be notified immediately regarding any SAE that occurs after informed consent is obtained.

The Principal Investigator will report the event within 24 hours of first knowledge of any AE that meets one of the criteria for an SAE, to Forest Global Drug Safety on an SAE report form. If, during follow-up, any nonserious AE worsens and eventually meets the criteria for an SAE, that AE will be recorded as a new SAE.

The study center will transmit the SAE report form to the SAE fax number **(631) 858-7906** within 24 hours of first awareness of the event at the study center.

Supplemental information shall be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

Regarding the reporting of pregnancy: Study center personnel will report every pregnancy on a pregnancy report form as soon as possible (within 24 hours of first awareness of the pregnancy to the pregnancy fax number, **(631) 858-7906**), even if no AE has occurred, and follow it to term. If, however, the pregnancy is associated with an SAE (e.g. if the mother is hospitalized for dehydration), in addition to the pregnancy report form, a separate SAE report form will be filed.

All relevant SAE or pregnancy information will be faxed to the Forest Global Drug Safety Department at **(631) 858-7906**.

B. Statistical Considerations

Sample Size Justification:

As this is a pilot study and the response of celiac symptoms to pancreatic enzyme supplementation has never been assessed, sample size is not possible to definitively calculate. However, based on the literature, a standard deviation of σ=0·55 is estimated and a >0.4 point change in CeD-GSRS can be considered clinically significant. Allowing for a type-1 error rate of α=0·05, and assuming a 10% drop-out rate, 32 total participants would provide 80% power to detect a 0·4-point difference in CeD-GSRS score between pancreatic enzyme treatment and placebo using a two treatment cross over design. Allowing for drop out and treatment non-compliance we plan to recruit until 30 participants have completed the treatment phases, up to a maximum of 40 eligible individuals. While this may appear somewhat overpowered, this sample size is feasible and allows for what is a very high degree of uncertainty regarding both the possible treatment effect and the influence of fecal elastase levels on efficacy, as described below.

Data Analysis:

Efficacy analyses will include all patients receiving ≥1 dose of study drug during double-blind treatment and with ≥1 post-baseline assessment (Modified Intent-to-Treat [MITT] population). Baseline score will be considered the last non-missing observation before the first dose of pancreatic enzyme or placebo. The primary endpoint is the difference in mean CeD-GSRS score on treatment vs. placebo. Mean score for each participant will be generated by averaging the daily patient reported outcome (CeD-GSRS and CSI) scores across the study periods, such that there will be a single mean score per participant for the run-in phase and each treatment phase. The mean intra-subject score will then be averaged across the entire cohort for the relevant study phase.

We will use standard two-treatment cross over study analysis in which participant scores during drug treatment ($GSRS_{rx)}$ for the primary outcome are compared to participant scores on placebo ($GSRS_{pcb)}$. Assuming the data are normally distributed, if pancreatic enzyme supplementation is effective we would expect $GSRS_{rx} < GSRS_{pcb.}$ The study as describe above is powered so that we will reach statistical significance if $GSRS_{pcb} - GSRS_{rx} > 0.4$ using Student's paired t-test $p<0.05$.

Sensitivity analyses will be conducted using Mixed Model for Repeated Measures (MMRM). MMRM analyses will include treatment and study week as main effects, gender, baseline CeD-GSRS score as covariates, and weekly CeD-GSRS scores as repeated measures. Should data be non-normal, we will transform results into categorical data by calculating the proportion of patients with a >30% reduction in CeD-GSRS score on treatment and on placebo compared to their individual scores at baseline. If treatment is effective, we would expect a significantly greater proportion of patients to have a minimally clinically significant difference in GSRS score on treatment compared to placebo which can be evaluated using the Fishers Exact Test.

A primary secondary outcome will be an assessment of treatment response by fecal elastase status. We will assess the ability of fecal elastase levels to predict response to therapy in two separate analyses. In the first, we will assess the proportion of treatment responders among individuals with low fecal elastase defined as levels less than 100, compared to those with fecal elastase levels greater than 100. This proportion will be compared using Fisher's exact test. Separately, as we cannot reliably predict the spectrum of fecal elastase levels or the degree of improvement with therapy we will evaluate any correlation between fecal elastase levels and change in CeD-GSRS scores both in univariate analysis and after controlling for demographics and relevant clinical variables including time on the gluten free diet.

Further secondary outcomes will include mean CSI scores on treatment vs. placebo, as well as difference between mean run-in CeD-GSRS and CSI scores and mean scores on treatment vs. placebo, and the proportion of patients achieving a 50% reduction in mean abdominal pain score from baseline with drug vs. placebo. Secondary endpoints will be analyzed similarly to the primary endpoint using Student's T test for normally distributed continuous variables and fishers exact test for non-normal or categorical variables.

All descriptive data, including participant demographics, will be presented as the mean and 95% confidence interval.

All statistical tests will be analyzed with SPSS software (version 19; SPSS Software, Microsoft Corp., Redmond, WA, USA). A *P* value of .05 or less will be considered statistically significant.

Safety assessments will performed for all patients who received ≥1 dose of pancreatic enzyme or placebo.

C. Subject Selection

Inclusion Criteria:

1. Biopsy proven celiac disease.
2. Age 18-80.
3. Ongoing symptoms defined as a CeD-GSRS score in the highest domain of 3 or greater at Visit 1.
4. Subject must be following a gluten free diet.
5. tTG < 40 units at screening.

Exclusion Criteria:

1. Taking prescription or over the counter enzyme supplements for 1 month prior to enrollment.
2. Pregnant, breastfeeding or planning pregnancy. Woman using acceptable methods of contraception will be included. Acceptable methods of contraception include oral hormonal contraceptives, implanted hormonal contraceptives, diaphragm with spermicide, condoms, intra-uterine device, abstinence, and male partner vasectomy.
3. Patients with a pork allergy or who are unwilling to consume pork products.
4. English proficiency unsuitable for completion of surveys.
5. Known severe pancreatic disease.
6. Known history of prior cancer (except squamous or basal cell skin cancer).
7. Patients with lactose intolerance who are unable to tolerate a minimum of 1oz (2 tablespoons) of whole milk per day.
8. Clinically significant abnormality in safety lab values (i.e. CBC and BMP) at screening that may impact subject safety or the scientific integrity of the study.
9. Other known active GI condition including but not limited to inflammatory bowel disease, small intestine bacterial overgrowth, and obvious FODMAP intolerance.
10. History of all major gastrointestinal surgery other than appendectomy or cholecystectomy.
11. Comorbid condition that in the opinion of the investigator would interfere with the subject's participation in the study or would confound the results of the study.

B4. POSSIBLE BENEFITS

If effective, pancreatic enzyme supplementation may improve symptoms in individuals with celiac disease who suffer persistent symptoms despite a gluten free diet.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Possible risks include those associated with the study drug and blood draw.

Viokace

Common Adverse Effects:

- Gastrointestinal: Diarrhea (up to 10%), Indigestion (10%)
- Respiratory: Cough (6% to 10%)

Serious/Rare Side Effects:

- Gastrointestinal: Distal intestinal obstruction syndrome, Fibrosing colonopathy (Rare), Stricture of colon (Rare)
- Immunologic: Anaphylaxis, Hypersensitivity reaction

- Other: Recurrent tumor, Carcinoma

There is additional theoretical risk of transmission of viral disease from Viokace to the study participant as Viokace is sourced from porcine pancreatic tissue. This risk has been reduced by testing for and inactivating certain viruses during manufacturing. No cases of transmission of an infectious illness associated with use of porcine pancreatic products have been reported to-date.

Omeprazole
Common Adverse Effects

- Gastrointestinal: Abdominal pain (5.2%), Diarrhea (3.7%), Flatulence (2.7%), Nausea (4%), Vomiting (3.2%)
- Neurologic: Headache (6.9%)

Serious/Rare Side Effects:

- Dermatologic: Erythema multiforme (rare), Stevens-Johnson syndrome (rare), Toxic epidermal necrolysis (rare)
- Endocrine metabolic: Hypomagnesemia (rare)
- Gastrointestinal: Clostridium difficile diarrhea, Pancreatitis (rare)
- Hematologic: Agranulocytosis (rare), Hemolytic anemia (rare)
- Hepatic: Hepatic encephalopathy (rare), Hepatic necrosis (rare), Liver failure (rare)
- Immunologic: Anaphylaxis (rare)
- Musculoskeletal: Fracture of bone (rare), Hip fracture (rare), Rhabdomyolysis (rare)
- Renal: Interstitial nephritis (rare), acute (rare)

Blood Sampling
When blood is drawn from the vein, there may be some temporary discomfort and a slight risk of local pain, bruising, swelling, or blockage of the vein. Rarely, fainting or nerve damage may occur.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment
Potential subjects will be identified in several ways. Some may be found through OMR review of patients seen at the Celiac Center. Patients may be approached by a co-investigator in clinic. Our CCI approved research databases (2007-P-000283 and 2010-P-000006) will be examined for likely candidates. These will be sent a recruitment letter or email or contacted by phone. This study may also be advertised through local celiac support groups such as the Healthy Villi. It is expected that the only subjects for the established celiac disease group will be contacted by mail, email or through ads. And advertisement will also be placed in the Metro.

Participants from prior Celiac-focused studies (2013-P-000035 and 2011-P-000335) will be contacted by phone sent or an email and/or a letter. This email and letter will be identical to the email and letter sent to other prospective participants.

Before contacting patients identified from the medical records or who participated in prior studies, the patient's primary gastroenterologist will be contacted for prior approval.

Consent
Whenever possible, prospective subjects will be sent a copy of the ICF to review in advance of the screening visit. They will have the opportunity to read the ICF and ask any questions they have before they decide to schedule the screening visit. At the screening visit, before any research activities take place, an investigator will review the entire ICF with the subject. The subject will be completely informed verbally of the study procedures, risks and requirements. The subject will be

given the opportunity to read the ICF. A physician will be available to answer any questions that the subject has. If the subject chooses to enter the study, an MD co-investigator will obtain written informed consent from the subject as well as sign the consent form at that time.

Subject Protection
None of the subjects in this study should be vulnerable to coercion or undue influence.

B7. STUDY LOCATION

Privacy
Patient privacy will be maintained throughout the study. It is expected that most recruitment will be done over the phone or email. Potential subjects will have the option of choosing a location that is comfortable for them before talking with the study staff on the phone. All study visits will be in the CRC. Additional recruitment may occur in the GI clinic.

Physical Setting
All study visits will be take place in the CRC. Phone calls to subjects and potential subjects will be made from offices in the Dana, Rabb, and Stoneman buildings.

B8. DATA SECURITY

Electronic data will be stored in a secure folder on password protected computers in locked offices. Paper data will be kept in locked offices on an access card restricted floor of the hospital.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☒ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☒ No

B10 Dissemination of Research Results

Subjects will be thanked for their participation at the end of the study. Subjects may contact the investigators to ask about the research findings either during a future medical appointment or by contacting the PI or study coordinator.

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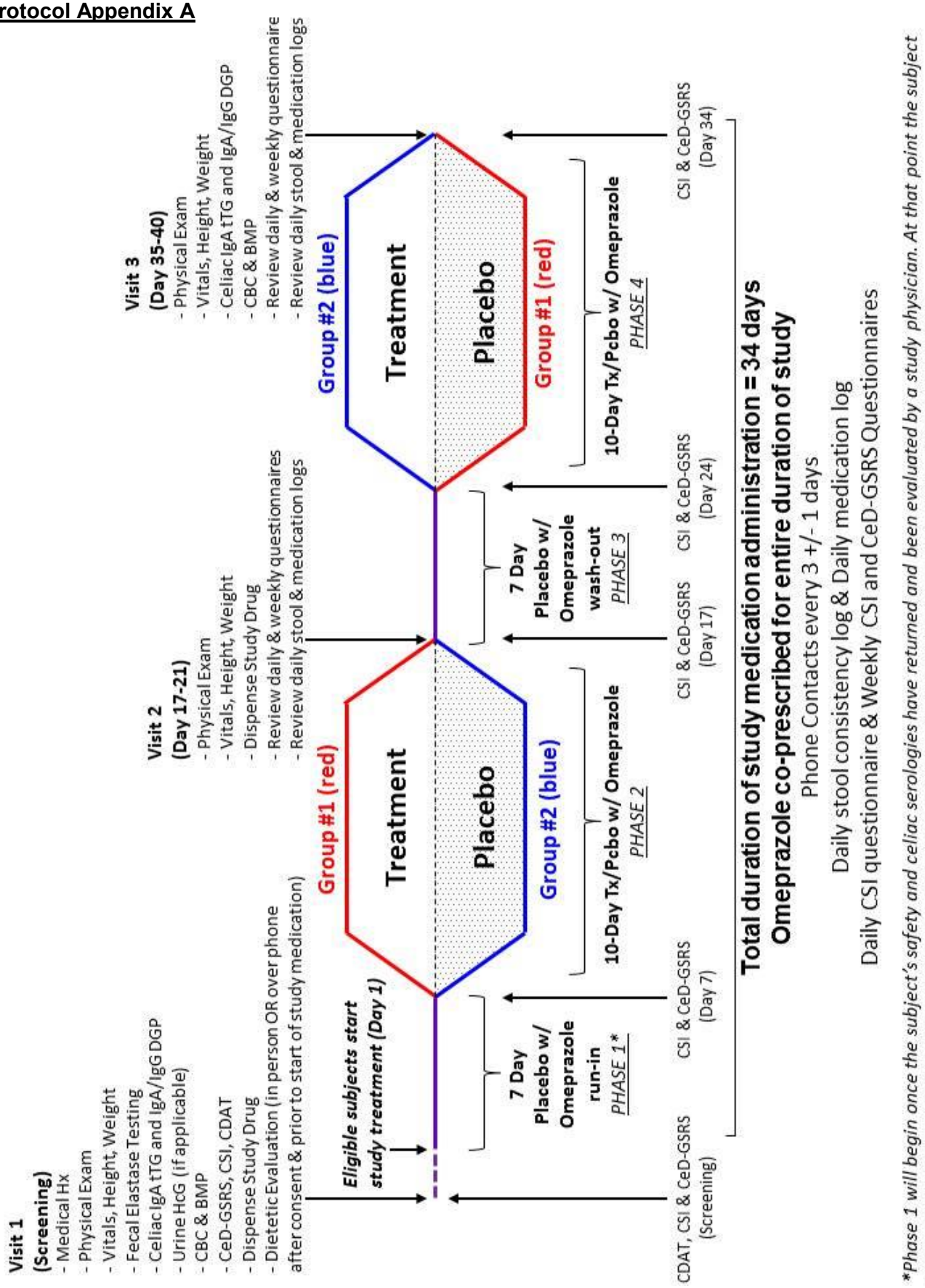
Protocol Appendix A



**Phase 1 will begin once the subject's safety and celiac serologies have returned and been evaluated by a study physician. At that point the subject will be instructed to begin taking the study medication and to begin completing the daily and weekly questionnaires.*