Buspirone for Early Satiety and Symptoms of Gastroparesis: A Multicenter, Randomized, Placebo-Controlled, Double-Masked Trial (BESST)

Protocol Number: 10

National Clinical Trial (NCT) Identified Number: NCT03587142

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IND Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

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Version Number: 1.3

13 January 2022

Summary of Changes from Previous Versions, v1.2 (11 Sep 2020):

Affected Section(s)	Summary of Revisions Made	Rationale
1.1 Synopsis	Changed Total Study Duration to 137 weeks (31.5 months) Changed Recruitment to 131 weeks (30 months) Changed: Expected enrollment rate to .6 participants per month per clinical center (18 participants each at 6 centers)	Recruitment has been slower than expected. This will extend through February 28, 2022.
5.5.1 Recruitment	Changed recruitment time to 30 months	Recruitment has been slower than expected. This will extend through February 28, 2022.
10.1.5	Added new Medical Monitor William Hasler, MD Mayo Clinic Arizona 13400 E. Shea Blvd., Scottsdale, AZ 85259 480-347-3538 hasler.william@mayo.edu	Added new Medical Monitor

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP), the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies, and the terms and conditions of the award from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The Principal Investigators will assure that no deviation from or changes to the protocol take place without prior agreement from the Investigational New Drug (IND) sponsor, prior agreement from the funding agency, and documented approval from the Institutional Review Board (IRB) serving as the IRB for the trial, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and participant materials will be submitted to the IRB for review and approval prior to use. Any amendment to the protocol will first require review and approval by the NIDDK, then by the IRB before the changes are implemented. All changes to the consent form will be approved prior to implementation; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent using a previously approved consent form. Any protocol amendments will be sent to the FDA.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: **Buspirone for Early Satiety and Symptoms of Gastroparesis: A Multicenter, Randomized, Placebo-Controlled, Double-masked Trial (BESST).**

Study Description:

This is a multi-center, randomized, double-masked, placebo-controlled, parallel treatment groups phase 2 trial to determine whether buspirone, a 5-HT 1a receptor agonist, can improve early satiety and postprandial fullness in participants with symptoms of gastroparesis and with at least moderately severe symptoms of early satiety and/or postprandial fullness. After enrollment, participants aged 18-85 years will be treated with buspirone (10 mg three times per day) or a matching placebo for 4 weeks, followed by a 2-week post-treatment washout period. The primary outcome for the study is the 4-week change (week 4 minus baseline) in the 4-item postprandial fullness/early satiety subscore (higher scores indicate worse symptoms) from the Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) questionnaire. We hypothesize that 10 mg t.i.d. buspirone treatment will reduce mean postprandial fullness/early satiety symptom severity subscores over 4-weeks compared to treatment with placebo.

Objectives: **Primary Objective:** To determine whether 4 weeks of treatment with buspirone, a 5-HT 1a receptor agonist, compared to treatment with placebo improves symptoms of postprandial fullness and early satiety as indicated by the change in the PAGI-SYM questionnaire's postprandial fullness/early satiety subscore (score at 4-weeks minus score at baseline).

Secondary Objectives: To determine whether 4 weeks of treatment with buspirone compared to treatment with placebo improves overall and other gastroparesis symptoms, and other participant clinical characteristics (gastric retention, anxiety, depression, quality of life) and to determine the safety and tolerability of buspirone in adult participants with gastroparesis symptoms and at least moderate symptoms of postprandial fullness and early satiety.

Outcomes:

Primary Outcome: The primary outcome is the change in the postprandial fullness/early satiety subscore from baseline to 4 weeks; this subscore is calculated by averaging the scores for 4 PAGI-SYM questionnaire items: stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, and loss of appetite.

Secondary Outcomes: Changes over 4-weeks (week 4 minus baseline) in:

1. Gastroparesis Cardinal Symptom Index (GCSI) total score; GCSI is comprised of the first 9-items of the PAGI-SYM questionnaire.
2. Four PAGI-SYM questionnaire subscores: nausea/vomiting (3 items: nausea, retching, vomiting), bloating (2 items: bloating, stomach visibly larger), upper abdominal pain (2 items: upper abdominal pain, upper abdominal discomfort), GERD (7 items: heartburn during the day, heartburn when lying down, feeling of discomfort inside chest during the day, feeling of discomfort inside chest during sleep, regurgitation or reflux during the day, regurgitation when lying down, bitter, acid or sour taste in mouth)
3. Eight single-item PAGI-SYM questionnaire symptom severity scores: nausea, vomiting, stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, loss of appetite, bloating, upper abdominal pain
4. Gastrointestinal Symptom Rating Scale (GSRS) total score
5. Clinical Patient Grading Assessment Scale (CPGAS) score
6. Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL) questionnaire total score
7. Hospital Anxiety and Depression Scale (HADS) questionnaire anxiety score and depression score
8. Patient Health Questionnaire 15 Somatic Symptom Severity Scale (PHQ-15) questionnaire total somatization score
9. SF-36v2 Quality of Life questionnaire Physical Component Score and Mental Component Score
10. Percent gastric emptying retention at 2 and 4-hours.
11. Anthropometric measurements (Body Mass Index (BMI)/ weight, waist circumference) (safety)
12. ECG measures (safety)
13. Laboratory measures (ALT, creatinine, glucose) (safety)
14. Frequency of side effects and adverse events, as well as severity of adverse events. (safety and tolerability)

Exploratory/Ancillary Outcomes: These outcomes either use novel techniques (items 1, 2, and 3) or are outcomes that have lower statistical power yet might provide insight into paths for future research (items 4,5). The outcome measures are changes over 4 weeks (week 4 minus baseline) in:

1. Intragastric meal distribution (IMD) as a measure of Fundic Accommodation (FA) using digital analyses of the GES test images
2. Gastric dysrhythmia and volume of water consumed until full measured with electrogastrogram (EGG) with water load satiety test
3. GCSI-DD total score and single-item scores on the ANMS GCSI-DD questionnaire: nausea, postprandial fullness, early satiety, upper abdominal pain, episodes of vomiting, episodes of retching, overall symptom severity; this instrument is completed daily and the score for an item at a time point is the average score for the item over the past 7 days, and change in the score from baseline is the average for the last 7 days minus the average for the 7-days of baseline completion
4. 12 symptom severity items measured on the PAGI-SYM questionnaire and not included in secondary outcomes item 3, including retching, lower abdominal pain, lower abdominal discomfort, constipation, and diarrhea
5. 5 subscores of the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire

Study Population: The study population will be 108 adult men and women aged 18-85 years, located in the United States, who have at least moderately severe postprandial fullness and/or early satiety and other symptoms of gastroparesis.

Phase: Phase 2

Description of Sites/Facilities Enrolling Participants: Participants will be recruited from the six clinical sites of the GpCRC located throughout the United States. (see *12.1* for sites)

Description of Study Intervention:

- Group 1: Buspirone 10 mg capsule three times daily, 30 minutes before each meal, for 4 weeks
- Group 2: Matching oral placebo capsule three times daily, 30 minutes before each meal, for 4 weeks

Total Study Duration: 137 weeks (31.5 months)

- Recruitment: 131 weeks (30 months)
- Participant follow-up: 6 weeks
- Expected enrollment rate: ~1 (.6) participant per month per clinical center (18 participants each at 6 centers)

Participant Duration:

Up to 14 weeks

- Up to 8 weeks of screening prior to randomization
- 4 weeks of treatment starting at randomization
- 2 weeks' post-treatment period

Inclusion Criteria:

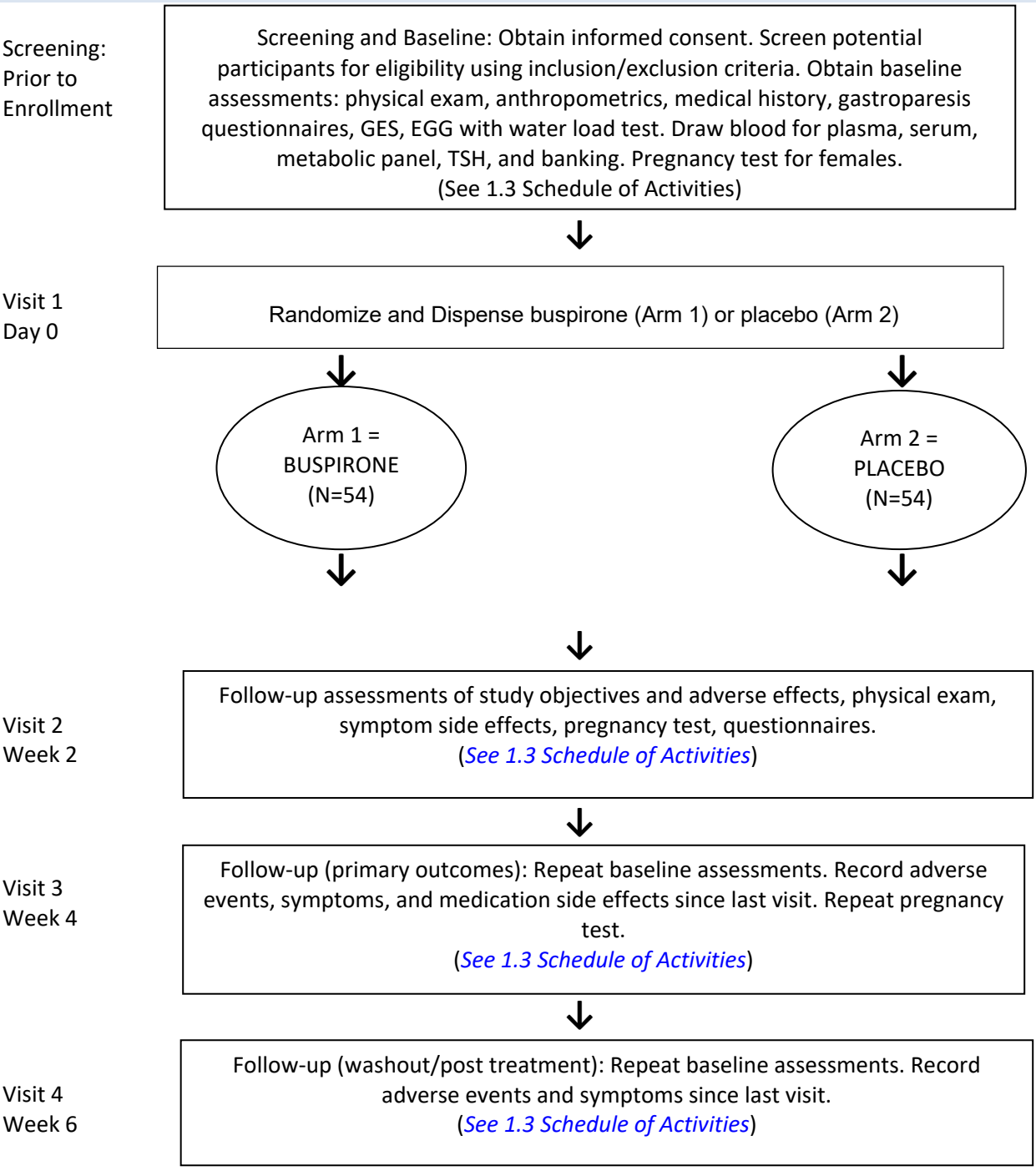
- Age 18 to 85 years of age at the initial screening interview
- Symptoms compatible with gastroparesis or other functional gastric disorder for at least 3 months (does not have to be contiguous) prior to the initial screening interview
- Diagnosis of either diabetic or idiopathic gastroparesis
- Delayed or normal gastric emptying retention on screening 4-hour Gastric Emptying Scintigraphy test
- Symptoms of gastroparesis measured by the 9-item PAGI-SYM Gastroparesis Cardinal Symptom Index (GCSI) total score > 2.0 at enrollment
- Symptomatic with postprandial fullness/early satiety severity at enrollment using the PAGI-SYM questionnaire postprandial fullness/early satiety subscore ≥ 3
- Upper endoscopy or upper GI series without ulcers or mass lesions in the 2 years prior to enrollment

Exclusion Criteria:

- Post-surgical gastroparesis, including prior pyloromyotomy, pyloric resection, vagotomy, bariatric surgery, or post-Nissen fundoplication
- Another active disorder that could explain symptoms in the opinion of the investigator
- Concurrent use of opiate narcotic analgesics more than 3 days per week
- Significant hepatic injury as defined by alanine aminotransferase (ALT) elevation of greater than 2xULN or a Child-Pugh score of 10 or greater
- History of significant cardiac disorders (prior heart attack, prior stroke, unstable angina) or significant cardiac arrhythmias or ECG abnormalities defined as history of, or current, arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsade des Pointes and/or prolonged QTc on ECG (>450 msec for men and >470 for women)
- History of chronic kidney disease or on hemodialysis or peritoneal dialysis
- Impaired renal function as defined by estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73^2 using the *Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculator*
- Uncontrolled diabetes defined as HbA1c (%) of 10% or more within 60 days of enrollment
- Allergy to buspirone
- Concurrent or prior use (within 30 days) of monoamine oxidase (MAO) inhibitors
- Concurrent or prior use (within 30 days) of benzodiazepines

- Concurrent or prior use (within 30 days) of buspirone, warfarin, haloperidol, and drugs to treat seizures (e.g., phenytoin and carbamazepine)
- For women of child-bearing potential, either pregnancy, planned pregnancy, unwillingness to use effective birth control during the trial or, breast feeding
- Any other condition, which in the opinion of the investigator would impede compliance or hinder completion of the study
- Failure to give informed consent

1.2 SCHEMA


Screening: Prior to Enrollment
Screening and Baseline: Obtain informed consent. Screen potential participants for eligibility using inclusion/exclusion criteria. Obtain baseline assessments: physical exam, anthropometrics, medical history, gastroparesis questionnaires, GES, EGG with water load test. Draw blood for plasma, serum, metabolic panel, TSH, and banking. Pregnancy test for females.
(See 1.3 Schedule of Activities)
Visit 1 Day 0
Randomize and Dispense buspirone (Arm 1) or placebo (Arm 2)
Arm 1 = BUSPIRONE (N=54)
Arm 2 = PLACEBO (N=54)
Visit 2 Week 2
Follow-up assessments of study objectives and adverse effects, physical exam, symptom side effects, pregnancy test, questionnaires.
(See 1.3 Schedule of Activities)
Visit 3 Week 4
Follow-up (primary outcomes): Repeat baseline assessments. Record adverse events, symptoms, and medication side effects since last visit. Repeat pregnancy test.
(See 1.3 Schedule of Activities)
Visit 4 Week 6
Follow-up (washout/post treatment): Repeat baseline assessments. Record adverse events and symptoms since last visit.
(See 1.3 Schedule of Activities)

1.3 SCHEDULE OF ACTIVITIES (SOA)

	Screening visits		**Follow-up visits- Weeks from Randomization**		
Assessment/Procedure		**RZ**	**F02**	**F04***	**F06**
Consent, HIPAA authorization, demographics	X	.	.	.	.
Baseline medical history	X	.	.	.	.
Follow-up medical history	.	.	X	X	X
Side effects survey	X	.	X	X	X
Review for adverse effects	.	.	X	X	X
Review for concomitant medications	X	X	X	X	X
Hospital anxiety and depression (HADS)	X	.	X	X	X
SF-36v2 Quality of life	X	.	.	X	.
PAGI-SYM questionnaire (includes the GCSI)	X	.	X	X	X
Gastrointestinal Symptom Rating Scale (GSRS)	X	.	.	X	X
PAGI-QOL questionnaire	X	.	.	X	X
Patient Health Questionnaire (PHQ-15)	X	.	.	X	.
Clinical Patient Grading Assessment Scale (CPGAS)		.	X	X	X
Detailed (D) or focused (F) physical exam	D	F	F	D	D
Gastric emptying Scintigraphy (GES) test	X	.	.	X	.
Electrogastrogram (EGG) with water load test*	X	.	.	X	.
Provide supplies of GCSI-DD	X	X	X	X	.
Collection of participant's completed GCSI-DD	.	X	X	X	X
Standard of care materials provided	.	X	.	.	.
Eligibility confirmation	X	X	.	.	.
Study drug dispensing	.	X	.	.	.
Review of study drug adherence	.	.	X	X	.
Labs: Complete blood count (CBC)	X	.	.	X	X
Comprehensive metabolic panel (CMP)	X	.	.	X	X
Thyroid stimulating hormone (TSH)	X	.	.	.	.
Fasting HbA1c	X	.	.	.	.
Pregnancy test	X	X	X	X	.
Banking: Fasting serum and plasma	X	.	.	X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X
Closeout form					X

Detailed physical exam (D): anthropometric assessments (body weight [kg], body height [m], waist circumference [cm], and hip circumference [cm]); vital signs (temperature, heart rate, respiratory rate, blood pressure), organ systems chest, lungs, heart, abdomen, liver and spleen, nervous), resting electrocardiogram (ECG)
Focused physical exam (F): anthropometric assessments (body weight [kg], body height [m], waist circumference [cm], and hip circumference [cm]); vital signs (temperature, heart rate, respiratory rate, blood pressure)
Complete blood count (CBC): concentration of white blood cells (WBC), red blood cells, hemoglobin, hematocrit, platelet count
Comprehensive metabolic panel (CMP): glucose, calcium, sodium, potassium, CO2 (carbon dioxide/bicarbonate), chloride, blood urea nitrogen (BUN), creatinine, total protein, albumin, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT)
Thyroid Stimulating Hormone test (TSH)
*The EGG with water load test is scheduled for a separate day than the GES testing at Screening and F04 week visits.

2 INTRODUCTION

2.1 STUDY RATIONALE

Gastroparesis is a chronic symptomatic disorder associated with delayed gastric emptying [1]. Gastroparesis predominantly affects young women (females outnumber males by a ratio of 4:1, the average age is 34). The symptomatic profile of gastroparesis includes nausea (90% of patients), vomiting (>80%), bloating (75%), early satiety (60%), and abdominal pain (approximately 50%) [2]. Symptoms in individual patients can vary in both their combination and their severity. Because of its chronic and often intractable nature, the disorder has a tremendous impact on both patients and society.

Gastroparesis remains difficult to treat, in large part because of the lack of knowledge of the underlying pathophysiology. Several factors in particular have impeded progress in this field, including the paucity of patients seen by any one center, the absence of uniform diagnostic criteria, and the lack of generally available and reliable methods for physiological testing. Given the complexity of the disorder and its profound degree of morbidity, an important need exists to appropriately study new treatments for patients.

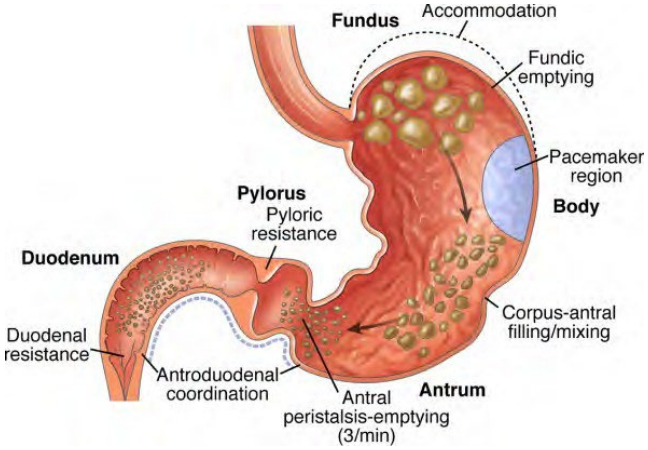
A variety of agents have been used for the treatment of gastroparesis [1,3]. These include classic agents such as prokinetic metoclopramide, cisapride (restricted use) and domperidone (not available in the U.S.). The track record of these drugs is mixed at best, a problem compounded by the paucity of high quality trials. A meta-analysis has suggested that in double-blind, controlled studies, cisapride produced a mean improvement in symptom score of only 8%, whereas metoclopramide produced a mean improvement of 36%. Also, improvement in symptoms generally does not correlate well with changes in gastric emptying. This is important as it reinforces the concept that symptoms are not necessarily being driven by the gastric emptying abnormalities and redirects attention to other aspects of gastric dysmotility and to central mechanisms for symptoms. There is, therefore, a need for new and innovative approaches to evaluation and treatment of symptoms of gastroparesis.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established the Gastroparesis Clinical Research Consortium (GpCRC) in 2006 to help address unmet research needs in this condition. The mission of the GpCRC is to improve understanding of the pathogenesis and natural history of gastroparesis of all etiologies and to advance the diagnosis and therapies of patients affected. The overall objectives of the GpCRC are to conduct multicenter observational studies and randomized, controlled treatment trials on well-characterized patients with gastroparesis. The GpCRC is a cooperative network of six clinical sites and one Scientific Data Research Center (SDRC). The individual clinical centers participate in a cooperative and interactive manner with one another and with the SDRC in all aspects of the GpCRC.

In a substantial number of patients who present with symptoms suggestive of gastroparesis (e.g., chronic nausea, vomiting, early satiety, postprandial fullness), gastric emptying tests are normal. Although the pathogenesis of symptoms in these patients is not known, it is presumed that most have some form of gastric dysfunction. Further, they appear to have a demographic and clinical profile that is nearly indistinguishable from classical gastroparesis and their treatment remains just as challenging. The GpCRC uses the term Chronic Unexplained Nausea and Vomiting (CUNV) to describe this group of patients. Both groups of patients will be eligible for the GpCRC BESST.

2.2 BACKGROUND

Normally with food ingestion, the proximal stomach relaxes, with an increase in volume, allowing the proximal stomach to accommodate the ingested meal [4,5]. This is followed by progressively tonic contraction to deliver food into the distal stomach. Within the antrum, regular peristaltic contractions grind down solid food to smaller particles that can be passed through the pyloric sphincter into the small intestine for absorption. This is illustrated in the figure on the right [6].



Patients with gastroparesis have symptoms of early satiety, postprandial fullness, nausea, vomiting, and/or abdominal pain. It is now better appreciated that symptoms of gastroparesis are not well correlated with current standardized gastric emptying results which assess only total gastric emptying [7]. As noted above, some patients have symptoms similar to gastroparesis but normal gastric emptying, an entity that the GpCRC has called CUNV (defined above) [8]. For this reason, the successful GpCRC APRON trial of aprepitant vs. placebo enrolled patients with nausea and vomiting, whether with delayed or normal emptying [9].

Impaired gastric accommodation to a meal may also cause postprandial symptoms [10]. With impaired accommodation, there is increased pressure in the upper stomach which compromises the ability of the upper stomach to act as a reservoir for ingested food, resulting in rapid transit of food into the distal stomach. Impaired accommodation has been shown to be associated with early satiety and weight loss in both functional dyspepsia [11] and idiopathic gastroparesis [12]. Accommodation can be assessed with barostat, gastric mucosal labeling with single photon emission computed tomography (SPECT) imaging, and magnetic resonance imaging. Although much has been learned with these technologies, they are costly and time consuming and not used routinely in clinical evaluation of patients. Gastric emptying scintigraphy (GES) measures overall gastric retention of the ingested meal over time; it can also assess, in the same study, intragastric meal distribution (IMD) [13]. With normal fundic accommodation (FA), the food initially resides in the proximal portion of the stomach, whereas with impaired accommodation, the food is quickly transferred to the antrum [12]. Including assessment of intragastric meal distribution as part of a standard GES study will permit improvement in the assessment of the relationship between symptoms of gastroparesis with abnormal gastric motility. This additional information may lead to therapy directed to improve gastric accommodation.

Use of GES to assess proximal gastric accommodation was originally suggested in observational studies by Troncon, et al [12]. Using scintigraphy in patients with functional dyspepsia Piessevaux, Tack et al quantitated the ratio of the proximal gastric counts to the distal gastric counts [14]. Forty-five percent of patients had distal redistribution of the solid phase of the meal. Early satiety was associated with early distal redistribution, suggesting impaired fundic accommodation.

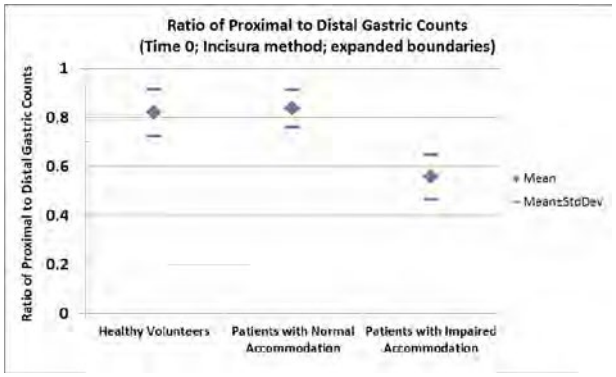
In the GpCRC BESST, images from GES will be analyzed for intragastric meal distribution (IMD) as an assessment of transit through the stomach and fundic accommodation. We have previously described proximal retention in GERD, distal retention in functional dyspepsia, and global retention in gastroparesis [15]. A recent preliminary study performed by us [16] showed that impaired gastric accommodation can be evaluated visually using current standardized solid-meal GES images. A simple visual assessment of normal gastric accommodation defined as

visualization of the majority of gastric activity (e.g. >50%) being present in the upper portion of the stomach in the first set of post-meal ingestion (t=0 minutes) images was used. The upper stomach was defined as the portion of the stomach that extends from the fundus to the incisura. Overall, impaired gastric accommodation was significantly associated with the severity of early satiety and stomach fullness. Impaired gastric accommodation in patients with normal GES was associated with early satiety, whereas impaired gastric accommodation in patients with delayed gastric emptying was associated with stomach fullness and postprandial fullness. Thus, this study showed that routine visual assessment of gastric accommodation as a part of a GES study may allow for better correlation of symptoms to abnormalities of gastric motility.

GpCRC investigators have been assessing regional gastric transit in the GES studies of the patients in the Gastroparesis Registry 2. We developed a semi-automated analysis of regional intragastric meal distribution during GES. The scintigraphic images were read using a GPCRC-developed application written for MATLAB software, which has a freely available runtime environment. We designed the application to construct the longitudinal axis of the stomach and subdivide the stomach into two (proximal, distal) regions of interest, allowing assessment of the meal distribution during the test. The amount in the proximal region of interest provides a measure of fundic accommodation (FA). From our preliminary data, 8 patients with visually impaired gastric accommodation had less percent radioactivity in the proximal stomach at time 0 (55.7±9.1%) than the 16 patients with normal accommodation (83.7±7.7%) and 20 normal subjects (82.6±9.6%). Examples and figure below:

Normal intragastric meal gastric distribution at time 0. (normal accommodation)

Rapid proximal transit (impaired accommodation)



We have thus achieved the first really semi-automated computer approach to analyzing GES images. This unique analysis offers additional promise to more fully automate analysis of GES. Our studies have shown that fundic accommodation can be assessed visually during routine GES with moderate pairwise agreement and high panel consistency among nuclear medicine physicians using the semi-automated software quantified IMD with an optimum cutoff of IMD<0.568 to define abnormal IMD/impaired FA [17]. Abnormal IMD was significantly associated with early satiety, loss of weight, and low BMI and was seen predominantly in nondiabetic patients. Assessment of fundic accommodation during GES is associated with several important patient clinical findings and symptoms. This approach will be used in this GpCRC BESST trial to help understand the mechanism of action of buspirone.

In addition, as a prelude to BESST, we assessed our patients in Gastroparesis Registry 2 (GpR 2), for the relationship of early satiety to patient characteristics [18]. We specifically wanted to assess relationships of early satiety with etiology of gastroparesis, quality of life, body weight, gastric emptying, and water load testing. 165 patients with gastroparesis (111 IG, 54 DG) were assessed. Early satiety was severe or very severe in 83 of 165 (50%) patients. Severity scores for early satiety were similar between idiopathic and diabetic gastroparesis. Increasing severity of early satiety was associated with increasing gastroparesis severity (p=0.0008), decreasing BMI (p=0.006), decreased quality of life from PAGI-QOL (p=0.06) and SF-36v2 physical health summary score (p=0.05). Increasing severity of early satiety was associated with increasing gastric retention of a solid meal at 4 hours (p=0.03) and decrease in

volume consumed during the water load test (p=0.02). Thus, early satiety is a common symptom in both diabetic and idiopathic gastroparesis. Early satiety severity is associated with measures of gastroparesis severity, body weight, quality of life, gastric emptying, and water load testing. These relationships make early satiety an important symptom characterizing gastroparesis.

In BESST, we will investigate an agent that improves fundic accommodation and determine its impact on improving symptoms, specifically early satiety and postprandial fullness. Buspirone is a 5-HT 1 receptor agonist that is approved for the treatment of anxiety. It is an anxiolytic psychotropic drug of the azapirone chemical class, used primarily to treat generalized anxiety disorder. Unlike most drugs predominantly used to treat anxiety, buspirone's pharmacology is not related to benzodiazepines or barbiturates, and so it does not carry the risk of physical dependence and withdrawal symptoms for which those drug classes are known.

The proximal gastric fundus tone is mediated by a balance of excitatory cholinergic and inhibitory non-adrenergic, none-cholinergic (NANC) neural input. Recently, 5-HT 1a receptor expression has been reported in the myenteric plexus of the GI tract including the stomach [19]. Buspirone was effective in relaxing the gastric fundus via the 5-HT 1 receptor pathway in both in vitro and in vivo experimental models using guinea pigs. Buspirone's effect on improving gastric accommodation has also been shown in studies in normal subjects [20]. In these normal subjects, buspirone slowed solid and liquid gastric emptying at the 20 mg dose, but not at lower doses including 10 mg, which is the dose to be used in BESST. In studies of patients with functional dyspepsia, buspirone 10 mg three times daily in a 4-week study improved gastric accommodation and symptoms of early satiety, postprandial fullness, and bloating [21]. In this study of patients with functional dyspepsia, buspirone did not alter the rate of gastric emptying of solids or sensitivity to gastric distension, but slightly delayed gastric emptying of liquids. Interestingly, acute anxiety and anxiety disorders have been reported to impair gastric accommodation (22).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks of buspirone: Common buspirone side effects may include: headache; dizziness, tiredness, drowsiness, and lightheaded feeling; sleep problems (insomnia); nausea, upset stomach; blurred vision; nervousness or excitement, nonspecific chest pain; sore throat, nasal congestion, tinnitus; and rarely, tardive dyskinesia. Common drug interactions of buspirone include monoamine oxidase (MAO) inhibitors. Thus far, there is no direct evidence that buspirone causes physical dependence or drug-seeking behavior.

Interference with cognitive and motor performance: Studies indicate that buspirone hydrochloride tablets are less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its central nervous system effects in any individual participant may not be predictable. Therefore, participants should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely. In general, because the effects of concomitant administration of buspirone with most psychotropic (CNS-active) drugs have either not been studied or validated, the concomitant use of psychotropic drugs and buspirone should be approached with caution.

While formal studies of the interaction of buspirone hydrochloride with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for Withdrawal Reactions in Sedative/Hypnotic/anxiolytic drug-dependent participants:
Because buspirone hydrochloride tablets do not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with buspirone hydrochloride tablets, it is advisable to withdraw participants gradually from their prior treatment, especially participants who have been using a CNS depressant drug chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending on the type of drug and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even seizures.

General risks: The condition of the participant may or may not get better or may become worse while in this study. During the study, participants will continue to receive clinical care by their primary care physician.

Stopping medications for gastroparesis: Participants may remain on their current treatments for gastroparesis, including use of a Gastric Electric Stimulator, if the participant is on a stable drug dose for at least 3-months prior to enrollment, and is willing to remain on this stable dose throughout the study (including screening, treatment, and post-treatment washout). The participant will not need to stop these drugs for the testing days for either the GES or the EGG with water load procedures. An exception is that the participant may not take narcotics the 3 days prior to a GES test. If participants are obtaining symptom relief due to any of the exclusionary medications (MAOIs, benzodiazepines, narcotics more than 3 times per week, warfarin, haloperidol, or drugs to treat seizures), other choices can be arranged with their Primary Care Provider (PCP) or the potential participant will not be able to participate in the trial. This possible medication regimen change may be inconvenient to the participant but is judged to not cause any undue hardship on the participant who wants to participate in the trial.

Questionnaires: The questionnaires cover demographics, medical history (comorbidities and medications), symptoms of gastroparesis, quality of life, and feelings of anxiety and depression. They will take about 1 hour to complete. A subject with significant scores on the Hospital Anxiety and Depression Scale (HADS) questionnaire will be referred to a clinical psychologist for follow-up (see section *8.2*).

Blood drawing: Blood draw may cause mild discomfort, such as swelling, temporary sensation of pain, burning, or a bruise that may develop and last for a few days. Less common risks include a blood clot at the site of puncture, swelling of the vein and surrounding tissues, and possible bleeding from the puncture site. Very rarely, fainting, blood clots or an infection at the site can occur. During the entire study period (up to 14 weeks), subjects will have approximately 6 tablespoons of blood drawn (88 mL) (see section *12.2*).

Electrogastrogram (EGG) with water load satiety test: EGG testing involves placement of EGG electrodes on the abdominal skin. An EGG will be performed twice: during screening and at 4 weeks. There may be some soreness in removing the EGG electrodes. During the water load test, the participant drinks water until they are full. Diabetics will have their glucose checked at the beginning and the end of the tests, with appropriate measures being taken if hypoglycemia or hyperglycemia is detected. In addition, each of these two EGG tests will be performed on different days than each of the Gastric Emptying Scintigraphy tests, which may cause inconvenience to the participant.

Gastric emptying scintigraphy (GES) test: A GES test will be performed twice: during screening and at 4 weeks. The total radiation dose for the administration of 0.5-1 microcuries (mCi) 99m-Tc sulfur colloid for one GES test is an Effective Dose Equivalent of 37-53 millirem (adult male and adult female, respectively). The internal organ or tissue receiving the highest radiation dose is the upper large intestine, which will receive 215 millirad. The total

radiation dose for the 0.5-1 mCi administration of 99m-Tc sulfur colloid for the two GES tests included in BESST is an Effective Dose Equivalent of 74-106 millirem. The annual average background value that an individual receives in the United States is 300 millirem. The internal organ or tissue receiving the highest radiation dose is the upper large intestine, which will receive 430 millirad total during BESST. A urine pregnancy test is obtained at study screening and at each visit during study treatment to ensure female participants of child-bearing potential are not pregnant when exposed to radiation or while taking study drug.

Treatment of side effects: During BESST, if a participant develops non-life threatening side effects that may be attributed to the study drug, the study drug will be stopped only if the participant so desires. If the participant chooses to no longer receive the study drug, the participant will continue to be followed in the trial, in keeping with the intention-to-treat paradigm. In the event of major dermatological reactions such as generalized urticaria, bullous rashes, exfoliative dermatitis, or Stevens-Johnson Syndrome, study drug will be discontinued immediately. Such skin reactions are expected to be infrequent adverse events.

Study visits: This study requires approximately 8 visits to the study center (up to 3 screening visits, randomization visit, and 4 post randomization visits) which may cause some inconvenience to some individuals.

Pregnancy: Since there may be unknown risks to pregnant women and their unborn children, potential participants who are breast feeding, pregnant, or planning to become pregnant will not be allowed to participate in BESST. Participants need to confirm to the best of their knowledge that they are not pregnant and if they become pregnant during the course of the study, they must notify the study investigator immediately and the study drug will be stopped. A urine pregnancy test is obtained at study enrollment and at each visit during study treatment for any females of child-bearing potential to help assure that the participant is not pregnant.

Safety issues related to participant privacy: For this study, data is being recorded about each participant's medical condition via medical records and case report forms. All data will be kept confidential. Case report forms on which a participant's data or results from specified procedures have been recorded will be stored in locked drawers of file cabinets. Study data are keyed to the GpCRC BESST web-based study database with encrypted (https:) transmission of data and via a secure network using an encrypted, password-protected computer accessible only by the study coordinator, the site Principal Investigator (PI), and study-certified study personnel. It is the investigator's responsibility to conduct the protocol under the current version of Declaration of Helsinki, Good Clinical Practice, and the rules of local IRBs. Each investigator must ensure that the participant's anonymity is maintained in their data submissions to the SDRC. Participants will be identified by an arbitrary unique identification code and not by their name, social security number, address, or hospital medical record number. Under no circumstances will any identifiable data be transmitted and stored in the BESST study database or be sent in email, scans, or paper-based transmissions to the SDRC. Investigators will locally maintain a separate confidential enrollment log, which links identification codes with the participants' names and addresses (i.e., available only to local clinic staff). All study material will be maintained in strict confidence.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants may experience short-term relief of the symptoms of anxiety, with low potential of buspirone becoming habit-forming.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Justification of the risks*:* All participants will receive standard of care as part of the trial and will potentially benefit if they are in the buspirone treatment arm and buspirone improves symptoms relative to placebo. All of

the participants in the study have gastroparesis or gastroparesis-like symptoms and are in need of treatment beyond lifestyle changes. By conducting the trial and furthering the understanding of buspirone for the treatment of gastroparesis, all of the participants in the study stand to benefit in the future if buspirone is proven to be effective.

3 OBJECTIVES AND OUTCOMES

OBJECTIVES	OUTCOMES	JUSTIFICATION FOR OUTCOMES
Primary		
To determine whether 4-weeks of treatment with buspirone, a 5-HT 1a receptor agonist, improves symptoms of early satiety and postprandial fullness in participants with symptoms of gastroparesis compared to placebo.	*The primary outcome is the change in the PAGI-SYM postprandial fullness/early satiety subscore from baseline to 4 weeks; this subscore is calculated by averaging the scores for 4 PAGI-SYM questionnaire items: stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, and loss of appetite.*	*Buspirone has been shown to be effective in relaxing the gastric fundus via the 5-HT 1 receptor pathway in both in vitro and in vivo experimental models using guinea pigs, as well as improving gastric accommodation in normal subjects and symptoms of early satiety and postprandial fullness in participants with functional dyspepsia. (66,67,69).*
Secondary		
***The secondary objectives** have been selected to provide further information on whether 4-weeks of treatment with buspirone compared to treatment with placebo improves overall and other gastroparesis symptoms, and other participant clinical characteristics (gastric retention, anxiety, depression, quality of life) and to determine the safety and tolerability of buspirone in adult participants with gastroparesis symptoms and with at least moderate symptoms of postprandial fullness and early satiety.*	**Changes at 4 weeks from baseline in the following measures: (calculated as score at 4-weeks minus score at baseline in:** 1. *GCSI total score* 2. *Four other PAGI-SYM questionnaire subscores: <u>nausea/vomiting</u> (3 items: nausea, retching, vomiting), <u>bloating</u> (2 items: bloating, stomach visibly larger), <u>upper abdominal pain</u> (2 items: upper abdominal pain, upper abdominal discomfort), <u>GERD</u> (7 items: heartburn during the day, heartburn when lying down, feeling of discomfort inside chest during the day, feeling of discomfort inside chest during sleep, regurgitation or reflux during the day, regurgitation when lying down, bitter, acid or sour taste in mouth)* 3. *Eight single-item PAGI-SYM symptom severity scores: Nausea, vomiting, stomach fullness, inability to finish a normal-sized meal,*	*These outcomes were selected because they measure important gastroparesis symptoms or co-morbidities of gastroparesis and are useful for determining if buspirone improves other symptoms commonly associated with gastroparesis and that buspirone is safe to use in adult gastroparesis patients.*

OBJECTIVES	OUTCOMES	JUSTIFICATION FOR OUTCOMES
	feeling excessively full after meals, loss of appetite, bloating, upper abdominal pain 4. *Gastrointestinal Symptom Rating Scale (GSRS) total score* 5. *Clinical Patient Grading Assessment Scale (CPGAS) score* 6. *Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL) total score* 7. *Hospital Anxiety and Depression Scale (HADS) anxiety score and depression score* 8. *Patient Health Questionnaire 15 Somatic Symptom Severity Scale (PHQ-15) total somatization score* 9. *SF-36v2 Quality of Life questionnaire, Physical Component Score and Mental Component Score* 10. *Percent gastric emptying retention at 2 and 4-hours* 11. *Anthropometric measurements (Body Mass Index (BMI)/weight, waist circumference) (safety)* 12. *ECG measures (safety)* 13. *Laboratory measures (ALT, creatinine, glucose) (safety)* 14. *Frequency of side effects and adverse events, as well as severity of adverse events. (safety and tolerability)*	
Tertiary/Exploratory	**Changes from screening to 4 weeks:**	
Tertiary: exploratory/ancillary *objectives were selected as a basis for explaining or supporting findings of the primary analysis and key secondary outcomes in sensitivity analyses and for suggesting further hypotheses for future research.*	**Changes at 4-weeks from baseline (calculated as score at 4 weeks minus score at baseline) in:** 1. *Intragastric meal distribution as an assessment of Fundic Accommodation (FA) using digital analyses of the GES test images* 2. *Gastric rhythm and water ingestion when full measured with EGG with water load test.* 3. *ANMS GCSI-DD 7 item scores: nausea, postprandial fullness, early satiety, upper abdominal pain,*	*Fundic accommodation (FA) is the primary target of the 5-HT 1 receptor pathway and will provide information on the hypothesis of action of buspirone on the stomach (item 1).* *Gastric dysrhythmia outcomes from the EGG water load test will help to provide insight into the action of buspirone on the stomach (item 2).*

OBJECTIVES	OUTCOMES	JUSTIFICATION FOR OUTCOMES
	episodes of vomiting, episodes of retching, overall symptom severity; each single item score is the average of the daily score from the last 7 days 4. *Each of the 15 symptom severity items measured on the PAGI-SYM questionnaire not included in secondary outcomes item 3, including retching, lower abdominal pain, lower abdominal discomfort, constipation, and diarrhea* 5. *Each of the 5 subscores of the Gastrointestinal Symptom Rating Scale (GSRS).*	*The ANMS GCSI-DD uses a Patient-Reported Outcome (PRO) daily-diary to capture symptoms of gastroparesis; however, this instrument is still being validated (item 3).* *Improvements in other gastroparesis symptoms will be explored to study possible other effects of buspirone (items 4, 5).*

4 STUDY DESIGN

4.1 OVERALL DESIGN

- The primary hypothesis of the trial is that buspirone treatment improves early satiety and postprandial fullness as measured by the PAGI-SYM questionnaire postprandial fullness/early satiety subscore; we will test this hypothesis by comparing the mean change from baseline in this subscore over the 4 weeks of treatment in the group treated with buspirone to the mean change from baseline in this subscore in the group treated with placebo (ANCOVA test for mean between-group differences in differences using baseline value as the covariate)
- Phase 2
- A multi-center, randomized, double-masked, placebo-controlled, parallel treatment groups phase 2 trial with primary outcome defined as symptomatic improvement in early satiety and postprandial fullness. The primary outcome is the change in the postprandial fullness/early satiety subscore from baseline to 4 weeks; this subscore is calculated by averaging the scores for 4 PAGI-SYM questionnaire items: stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, and loss of appetite.
- Methods to decrease bias will include placebo control, double masking and randomization.
- Two study arms
- Multisite
- Study intervention is buspirone 10 mg capsule three times daily, 30 minutes before each meal, for 4 weeks or matching placebo.
- The randomization design will be stratified by clinical center with participants' assignments into one of two groups (buspirone or placebo) in permuted blocks of random length within each clinic.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study design is a multi-center, randomized, double-masked, placebo-controlled, parallel treatment groups phase 2 trial.

Rationale for a Placebo Group: Currently, there are few effective treatments for symptoms in participants with gastroparesis and related syndromes. Studies of various agents have shown placebo effects ranging from 10% and

higher. In the NIDDK GpCRC Aprepitant for the Relief of Nausea (APRON) trial, 40% of the participants treated with placebo improved on the primary outcome [9]. In the NIDDK GpCRC 48-week Outcomes paper, approximately 28% of the participants showed substantial symptomatic improvement at 48 weeks with Standard of Care (SOC) [23]. Therefore, it is important to have a placebo group to be able to discriminate a treatment effect over and above SOC and the lifestyle advice provided to all of these participants.

In addition, in order to assess the efficacy of an agent in gastroparesis, a placebo group is needed to determine the relative efficacy in improving symptoms and physical functions. In order to have the highest quality of evidence to test our hypothesis, the BESST trial uses a randomized, double-masked, placebo-controlled study design.

The trial is double-masked to prevent bias by investigators and participants. The trial is 4 weeks since the Minimum Clinically Important Difference (MCID) in gastroparesis symptoms has been shown in the literature to be detected in that timeframe. The trial is powered at 90% to detect a MCID in the PAGI-SYM questionnaire postprandial fullness/early satiety subscore primary outcome measure; it is powered at 80% to detect a MCID in the GCSI total score, the key secondary outcome.

4.3 JUSTIFICATION FOR DOSE

Buspirone is a 5-HT 1 receptor agonist that is approved for the treatment of anxiety. It is an anxiolytic psychotropic drug of the azapirone chemical class, used primarily to treat generalized anxiety disorder. Unlike most drugs predominantly used to treat anxiety, buspirone's pharmacology is not related to benzodiazepines or barbiturates, and so does not carry the risk of physical dependence and withdrawal symptoms for which those drug classes are known. The proximal gastric fundus tone is mediated by a balance of excitatory cholinergic and inhibitory non-adrenergic, none-cholinergic (NANC) neural input. Recently, 5-HT 1a receptor expression has been reported in the myenteric plexus of the GI tract including the stomach [19].

Buspirone was effective in relaxing the gastric fundus via 5-HT 1 receptor pathway in both in vitro and in vivo experimental models using guinea pigs. Buspirone's effect on improving gastric accommodation has also been shown in studies in normal subjects [20]. In these normal subjects, buspirone slowed solid and liquid gastric emptying at the 20 mg dose, but not at lower doses, including 10 mg, which is the dose to be used in BESST.

In studies of participants with functional dyspepsia, buspirone 10 mg three times daily in a 4-week study improved gastric accommodation and symptoms of early satiety, postprandial fullness, and bloating [21]. In this study of participants with functional dyspepsia, buspirone did not alter the rate of gastric emptying of solids or sensitivity to gastric distension but slightly delayed gastric emptying of liquids. Interestingly, acute anxiety and anxiety disorders have been reported to impair gastric accommodation [19]. Based on this preliminary data, we will use the same dose as used in the functional dyspepsia study.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure (or at the close of the final study visit window) shown in the Schedule of Activities (SoA), *Section 1.3.*

The end of the study globally is defined as completion of the last study visit (or closure of the final study window) shown in the SoA for the last randomized participant.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

- Aged 18 to 85 years at initial screening interview
- Symptoms compatible with gastroparesis or other functional gastric disorder for at least 3 months (does not have to be contiguous) prior to initial screening interview
- Diagnosis of diabetic or idiopathic gastroparesis
- Delayed or normal gastric retention on screening 4-hour Gastric Emptying Scintigraphy test
- Symptoms of gastroparesis measured by the 9-item Gastroparesis Cardinal Symptom Index (GCSI) total score > 2.0 at enrollment
- Symptomatic with postprandial fullness/early satiety severity (PAGI-SYM questionnaire subscale $\geq$ 3) at enrollment
- Upper endoscopy or upper GI series without findings of ulcers or mass lesions in the 2 years prior to enrollment

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Post-surgical gastroparesis, including prior pyloromyotomy, pyloric resection, vagotomy, bariatric surgery or post-Nissen fundoplication
- Another active disorder which could explain symptoms in the opinion of the investigator
- Concurrent use of opiate narcotic analgesics more than 3 days per week
- Significant hepatic injury as defined by alanine aminotransferase (ALT) elevation of greater than 2xULN or a Child-Pugh score of 10 or greater
- History of significant cardiac disorders (prior heart attack, prior stroke, unstable angina) or significant cardiac arrhythmias or ECG abnormalities defined as history of, or current, arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsade des Pointes and/or prolonged QTc on ECG (>450 msec for men and >470 for women)
- History of chronic kidney disease or on hemodialysis or peritoneal dialysis
- Impaired renal function as defined by estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73^2 using the *Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculator*
- Uncontrolled diabetes defined as HbA1c (%) of 10% or more within 60 days of enrollment
- Allergy to buspirone
- Concurrent or prior use (within 30 days) of monoamine oxidase (MAO) inhibitors
- Concurrent or prior use (within 30 days) of benzodiazopines
- Concurrent or prior use (within 30 days) of buspirone, warfarin, haloperidol, and drugs to treat seizures (e.g., phenytoin and carbamazepine)
- For women of child-bearing potential, either pregnancy, planned pregnancy, unwillingness to use effective birth control during the trial or breast feeding
- Any other condition, which in the opinion of the investigator would impede compliance or hinder completion of the study
- Failure to give informed consent

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 STANDARD TREATMENT RECOMMENDATIONS

Standard of care (SOC) recommendations prepared by the GpCRC Steering Committee for the management of patients with gastroparesis or related disorders cover these broad categories as follows:

- Standardized set of recommendations on following a Gastroparesis diet.
- Recommendations on the use of pain medications and to eliminate drugs that might exacerbate the underlying dysmotility disorder or prevent the beneficial actions of a prokinetic.

These recommendations will be included in the BESST Standard of Care Standard Operating Procedures (SOP) and will be provided to each participant.

Also, during the BESST study, participants are asked to:

- Refrain from consumption of alcohol, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, and fruit juices until after the final dose.

These guidelines are given in the investigator's brochure for buspirone and are included due to possible alteration of p450 degradation pathways.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to a study treatment group. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demographics, reason for screen failure, and any serious adverse event (SAE). Screening failures also include participants who meet medical eligibility criteria but change their mind and do not consent to randomization into the trial. We collect all of the above information on each screen failure using a case-report form keyed into the BESST database.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a contraindicated medication or who is unable to complete all tests within the allotted screening window may be rescreened one time. A rescreened participant is assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

5.5.1 RECRUITMENT

Approximately 108 participants will be recruited from the six clinical centers of the GpCRC (averaging 18 participants per center) over a 30-month period. Participants will be recruited from outpatient clinics and inpatient hospital settings.

Potentially eligible participants will be identified and registered for screening at the participating clinical centers subject to the inclusion and exclusion criteria listed above. Eligible and consenting participants will be randomized to a treatment group after completion of all required screening procedures, keying of all required data elements into the data system, and passing eligibility checks for the BESST trial.

Each clinical center will develop a specific recruitment plan. These plans will vary from clinic to clinic depending on the available pools of participants and local recruitment resources. Clinics will attempt to recruit sufficient overall

numbers of minorities and males since gastroparesis is reported to be rare in African-Americans and infrequent in men, so that the study results can be generalized to these sub-groups of the U.S. population.

Participants may be reimbursed for travel expenses for each visit completed depending on each clinic's resources.

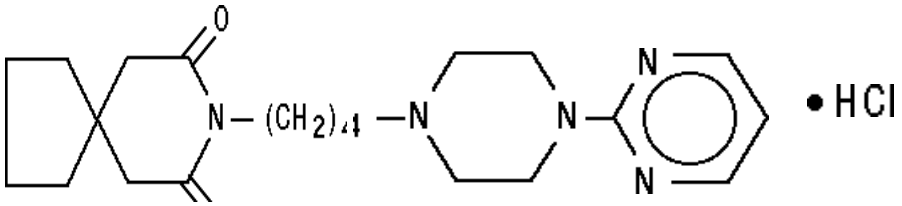
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION FROM FDA PACKAGE INSERT

Buspirone hydrochloride tablets, USP is an antianxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative/anxiolytic drugs. Buspirone hydrochloride is a white crystalline, water soluble compound with a molecular weight of 422.0.

Chemically, buspirone hydrochloride is 8-[4-[4-(2-pyrimidinyl)-1piperazinyl]butyl]-8-azaspiro[4.5]decane- 7,9-dione monohydrochloride. The empirical formula C21H31N5O2 • HCl is represented by the following structural formula:



The mechanism of action of buspirone is unknown. Buspirone differs from typical benzodiazepine anxiolytics in that it does not exert anticonvulsant or muscle relaxant effects. It also lacks the prominent sedative effect that is associated with more typical anxiolytics. In vitro preclinical studies have shown that buspirone has a high affinity for serotonin (5-HT 1a) receptors. Buspirone has no significant affinity for benzodiazepine receptors and does not affect γ-aminobutyric acid (GABA) binding in vitro or in vivo when tested in preclinical models.

Buspirone has moderate affinity for brain D2-dopamine receptors. Some studies do suggest that buspirone may have indirect effects on other neurotransmitter systems. Buspirone is rapidly absorbed in humans and undergoes extensive first-pass metabolism. In a radiolabeled study, unchanged buspirone in the plasma accounted for only about 1% of the radioactivity in the plasma. Following oral administration, plasma concentrations of unchanged buspirone are very low and variable between subjects. Peak plasma levels of 1 ng/mL to 6 ng/mL have been observed 40 to 90 minutes after single oral doses of 20 mg. The single-dose bioavailability of unchanged buspirone when taken as a tablet is on the average about 90% of an equivalent dose of solution, but there is large variability.

The effects of food upon the bioavailability of buspirone have been studied in eight subjects. They were given a 20 mg dose with and without food; the area under the plasma concentration-time curve and peak plasma concentration (Cmax) of unchanged buspirone increased by 84% and 116%, respectively, but the total amount of buspirone immunoreactive material did not change. This suggests that food may decrease the extent of presystemic clearance of buspirone.

Buspirone is a 5-HT 1 receptor agonist that is FDA approved for the treatment of anxiety. It is an anxiolytic psychotropic drug of the azapirone chemical class, used primarily to treat generalized anxiety disorder. Unlike most drugs predominantly used to treat anxiety, buspirone's pharmacology is not related to benzodiazepines or

barbiturates, and so does not carry the risk of physical dependence and withdrawal symptoms for which those drug classes are known. The proximal gastric fundus tone is mediated by a balance of excitatory cholinergic and inhibitory non-adrenergic, none-cholinergic neural input. Recently, 5-HT 1a receptor expression has been reported in the myenteric plexus of the GI tract including the stomach (66). Buspirone was effective in relaxing the gastric fundus via 5-HT 1 receptor pathway in both in vitro and in vivo experimental models using guinea pigs.

6.1.2 DOSING AND ADMINISTRATION

In this trial, a 10 mg buspirone tablet will be over encapsulated in a size 0 gelatin capsule (approximately 2.2 cm) with partial filler, the inactive ingredients being: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The matching placebo capsule will contain only filler. Each bottle contains 120 capsules.

The random treatment assignment will consist of a numbered study drug bottle; each bottle number will be unique and each participant will be assigned a specific bottle number. The bottle number issued by the randomization program will correspond to numbered bottles of study drugs which have been sent to the clinical center's research pharmacy by the SDRC's GMP Research Pharmacy. Upon learning the bottle number to be issued to the specific participant, the research pharmacy will issue that bottle to the participant. Each participant's random treatment assignment will be generated for that specific participant and will not be transferable to another participant. Once the assignment has been generated, the participant will be issued the study drug and instructed about taking the study dug orally 30 minutes before meals every day and monitoring for potential adverse effects. The study drug dispensed at the time of randomization will be a bottle containing either over-encapsulated 10 mg tablets of buspirone or identical looking placebo capsules.

Participants will receive an **Information for Patients** document with their study medication. This document will instruct the participant as follows:

1. Do not take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
2. Do not take an MAOI within 2 weeks of stopping buspirone unless directed to do so by your physician.
3. Do not start buspirone if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.
4. Inform your Primary Care Physician that you are participating in a randomized, controlled trial comparing buspirone hydrochloride (10 mg 3 times per day) and placebo.
5. Inform your physician and the study investigator about any prescription or non-prescription medications, prescription or non-prescription supplements, alcohol, or drugs that you are now taking or plan to take during your participation in BESST.
6. Inform your physician if you are pregnant or breastfeeding, or if you are planning to become pregnant, or if you become pregnant while you are taking buspirone hydrochloride tablets.
7. Until you experience how this BESST study medication affects you, do not drive a car or operate potentially dangerous machinery.
8. During your treatment with BESST study medication, avoid consumption of grapefruit juice or eating grapefruit, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices until after the final dose.
9. If you miss a dose of this medicine, take it as soon as possible unless it is almost time for your next dose, in which case, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

An investigator may not administer an investigational new drug to human subjects until the IND goes into effect (30 days after IND receipt by FDA) or sooner if notified. After review by the FDA, the use of buspirone in the BESST trial was given an IND exempt status. All masked drug and placebo bottles will be distributed to the individual GpCRC Clinical Centers' Investigational Pharmacies or responsible entities by the SDRC's contracted GMP Drug Distribution Center according to the directions of the SDRC. The GMP Drug Distribution Center will purchase the study drug (buspirone) and the materials needed for manufacturing the placebo capsules, over-encapsulating the buspirone capsule, manufacturing the microcrystalline powder contained in the matching placebo capsule, encapsulating the placebo capsule, bottling the active and placebo capsules individually, labeling bottles according to the SDRC directions, and shipping the drugs to the clinics. Expired and returned study drug will be disposed of by each clinical center after authorization from the SDRC.

The local Investigational Pharmacy will provide the clinic investigator or coordinator with a masked BESST study drug bottle upon request after the participant's randomization. The SDRC provides the bottle number to be requested from the local pharmacy after the randomization request by the clinic. Participants will be dispensed a bar-coded medication bottle as labeled by the GMP Research pharmacy: "Buspirone 10 mg or placebo. Take one capsule orally 3 times per day, 30 minutes prior to meals."

Participants are instructed to take a single capsule of 10 mg buspirone or placebo three times a day, approximately 30 minutes prior to meals.

Drug accountability information is maintained by the GMP Research Pharmacy, the local clinic investigational pharmacy, and in the study database for adjudication coordinated by the SDRC at the end of the trial or at any time during the trial, as needed.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Buspirone hydrochloride is supplied by several pharmaceutical manufacturers and will be purchased by the SDRC's GMP Research Pharmacy, and then over-encapsulated in a gelatin capsule for oral administration. Half the capsules will contain 10 mg buspirone hydrochloride, USP (equivalent to 9.1 mg of buspirone free base, respectively). The buspirone tablets contain the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The other half of the gelatin capsules (placebo) will contain only the filler.

6.2.3 PRODUCT STORAGE AND STABILITY

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

6.2.4 PREPARATION

No preparation is required because capsules will be provided to sites in participant ready packaging.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization: The randomization scheme will assign participants in randomly permuted blocks of assignments stratified by clinical center. This scheme will ensure that the two groups will be of nearly equal size and will be balanced by calendar time of enrollment to ensure equal numbers of participants by time of enrollment (to minimize secular effects) and by clinic (to minimize clinic effects).

The randomization plan will be prepared and administered centrally, using a secure web application, by the SDRC. An assignment will be issued only if the trial database shows that the participant is eligible, has signed the consent statement, and has had all required baseline data keyed to the data system.

Treatment assignments are double-masked throughout the study until all data collection for the BESST trial has been completed, i.e., after completion of the 2-week post-trial follow-up visit for all participants. Every effort will be made to maintain the masking throughout the study except in emergency situations. The randomization code masking the bottle contents will not be provided by the SDRC without the knowledge of the clinical center's principal investigator.

Unmasking of study medication will occur under the following conditions:

- **Severe allergic reaction (Stevens-Johnson Syndrome)**: Study medication is stopped indefinitely. The participant, primary care provider (PCP), and the investigator will be unmasked.

- **Pregnancy during the study**: Study medication will be stopped indefinitely, and the coded medication will be unmasked. The participant, PCP, and investigator will be notified of the assigned treatment and the associated risks of teratogenicity.

In unforeseen situations where the clinical center principal investigator considers unmasking is in the best interest of the participant's health and well-being, unmasking may be done after notifying the Executive Committee. The Data and Safety Monitoring Board will review all instances of unmasking that have occurred.

6.4 STUDY INTERVENTION COMPLIANCE

Assessment of adherence to the assigned study drug will provide clinic staff a means to identify participants having problems with adherence. Adherence will be assessed by:

- Counts of capsules in the participant's returned medication bottle at the end of the trial
- Conducting a brief, structured interview, in which the study coordinator will assist the participants to identify problems in taking the study drug and to estimate adherence to the prescribed medicine since their previous visit during the trial.

These assessments will guide the consideration of strategies to improve adherence and to assess adherence at the end of the trial.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Forms (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

Medication histories are collected at enrollment and at each follow-up visit. The participant is requested to bring all medication and supplement bottles (prescription and non-prescription) or a photo of each bottle to the clinic visit.

The drug interaction/contraindication list from the buspirone manufacturer's drug label (package insert) will be the definitive source of identifying which concomitant pharmaceuticals and herbal supplements should be considered in determining eligibility for this study and which medications can be safely taken with buspirone during the trial.

Medications known to interact with buspirone hydrochloride (buspirone) are excluded from use during the trial. These include:

- MAO inhibitors, such as phenelzine, linezolid, isocarboxazid, methylene blue, moclobemide, phenelzine, procarbazine, rasagiline, safinamide, selegiline, and tranylcypromine
- The blood thinner warfarin (Coumadin)
- Haloperidol
- Benzodiazepines
- Drugs used to treat seizures, such as phenytoin (Dilantin) and carbamazepine (Tegretol)

In addition, using buspirone with any of the following medicines may cause an increased risk of certain side effects. These medications are selective serotonin reuptake inhibitors (SSRIs)(e.g., fluoxetine, nefazodone and trazodone (Oleptro)), and tricyclic antidepressants (TCA; e.g., amitriptyline/nortriptyline, trazodone). Some drugs interact with buspirone to affect the clearance rate of buspirone, including azole antifungals (e.g., itraconazole, ketoconazole), some antibiotics (including erythromycin, rifampin), nefazodone, cimetidine, ritonavir, diltiazem, verapamil, and certain anticonvulsants (e.g., phenytoin, phenobarbital).

Drugs with the possibility of a serious adverse event or disruption of the clearance rate have been listed as exclusions to the study. The treating physician will assess each participant's medication profile both for study eligibility at screening and for ongoing safety during the trial, and participants will be excluded from randomization or have trial treatment discontinued on a case-by-case basis per local clinical judgment.

Participants will be questioned regarding any new medications at each visit and counseled by the study physician not to use drugs on the list of exclusions above, unless they are medically necessary. The study physician will decide whether suspension of the study medication is indicated.

6.5.1 RESCUE MEDICINE

If symptoms are severe and require further treatment during the trial, participants will be instructed to take rescue medications that they would usually take, such as prochlorperazine or ondansetron for nausea and vomiting, and acetaminophen, ibuprofen, hyoscamine or tramadol for abdominal pain.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants may withdraw voluntarily from the study or the PI may, for cause, discontinue a participant from the study. In addition, participants who discontinue the study medication will be encouraged to remain in the study for follow-up purposes, especially for safety and efficacy study outcomes. Study medication discontinuations and participant discontinuations/withdrawals from the study will be documented on case report forms, which capture the dates and the specific underlying reasons for discontinuations of study medications or participant discontinuations/withdrawals.

7.1 DISCONTINUATION OF STUDY INTERVENTION

If the participant develops a treatment-related CTCAE v5.0-defined adverse event (grade 3 or above) on the 10 mg dose, the study medication will be stopped after assessment by the site study investigator, who is a licensed physician. If in the view of the study investigator, the participant is intolerant of the medication, the participant will be withdrawn from the study medication, but will continue to be followed to the end of the trial.

Discontinuation from buspirone or placebo does not mean discontinuation from the study -- all remaining study data should be completed as indicated by the study protocol. If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. If indicated, adverse event (AE) case report forms will be completed and entered into the study database.

The data to be collected at the time of study intervention discontinuation will include the following:

- Labs and anthropometrics at the prior visit or at the AE occurrence
- Study medication bottle numbers and documentation of capsule counts

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon written request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant is unable to receive buspirone for 7 days.
- The sponsor or investigator terminates the study.

If, during the trial, a participant develops non-life threatening side-effects, the study medication will be suspended if the participant insists, after consultation with a study physician. If the participant decides to stop the study medication, the participant will still be followed in the trial according to the protocol, in keeping with the

intention-to-treat paradigm. In the event of major dermatological reactions such as generalized urticaria, bullous rashes, exfoliative dermatitis, or Stevens-Johnson Syndrome, study drug will be discontinued immediately.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for one scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 7 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or private study file, but will not be documented in the study database.
- If the participant cannot be reached, the participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up. All study data collected prior to the lost to follow-up will be used.

The occurrence of missing data in this trial is expected to be low and, when present, is expected to be equally distributed across the 2 treatment groups. We believe, from past experience, that careful selection and education of participants during the screening phase before the consent will result in no more than 10% lost to follow-up before completing the full 4-week treatment period and the 2- week post-treatment follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 VISIT SCHEDULE OVERVIEW

The participant-related activities of the BESST trial can be divided into 4 phases:

- Screening for eligibility for enrollment (up to 3 visits over 8 weeks)
- Randomization to treatment (1 visit)
- Treatment phase (3 visits over 4 weeks: 1 visit at 2 weeks and 2 visits at 4-weeks)
- Post-treatment washout phase (1 visit at 6 weeks)

8.1.2 SCREENING AND BASELINE DATA COLLECTION

Patients that are likely to meet eligibility requirements after clinic visit or chart review of standard of care tests and procedures will be invited to undergo screening. The study will be explained to the potential participant, and if interested, the patient will sign the IRB-approved consent form.
To minimize in-person contact time between the participant and staff during the Covid-19 pandemic and as permitted by the site-specific IRBs or sIRB, participants will be offered a telephone or virtual review of the consent in place of the in-person review of the consent. Signature of the consent will take place in person at the study

visit and after confirmation that all of the participant's questions about the study have been answered. Recording of screening data on GpCRC BESST forms may not start until the participant has signed the consent statement. Screening and baseline data collection procedures will include questionnaires (*see 8.1.5*) (baseline medical history, HADS, SF-36v2, GSRS, PAGI-QOL, PHQ-15, PAGI-SYM, symptoms side effects), physical examination and ECG, measurement of fasting complete blood count (CBC), comprehensive metabolic panel (CMP), thyroid stimulating hormone (TSH) and HbA1c, a Gastric Emptying Scintigraphy (GES) test, an Electrogastrogram (EGG) with water load test (on a separate day), a pregnancy test (if female of child-bearing potential) and fasting blood collection for serum and plasma banking. Prior therapy for gastroparesis and concomitant medications will be reviewed as outlined in the inclusion and exclusion criteria. Patient charts will be reviewed for historical medical information and procedures. A diagnostic upper endoscopy or an upper GI radiographic series will be scheduled if the potential participant has not had this test within the past two years.

Once a potential participant has agreed and consented to participate in BESST, a Gastric Emptying Scintigraphy (GES) test will be scheduled. In addition, the preference is to schedule the Electrogastrogram (EGG) with water load test within a week of the GES test. Immediately prior to the GES test, females of childbearing potential must have a negative pregnancy test. For the GES test, the participant will arrive at the clinic after an 8-hour fast, that is nothing by mouth after midnight except for small sips of water and narcotic free the 3-days prior to the test. The PAGI-SYM questionnaire (*see section 8.1.5a*) will be completed and then the participant will undergo the GES test as described in *section 8.1.6*. Symptoms will be monitored at the beginning and during the GES test.

The potential participant will be given a set of the daily symptom diary (ANMS GCSI-DD) forms to complete each night at home. These are returned to the clinic at their second clinic screening visit after 7-days have been completed.

For the second screening visit, the participant will arrive at the clinic after an 8-hour fast, that is nothing by mouth after midnight, and have the EGG with water load test as described in *section 8.1.6*.

The GpCRC BESST web-based database management system has an application to check patient eligibility based on data forms keyed and verified into the study database. The eligibility check application is used during screening a patient to show failed inclusion/exclusion eligibility checks, to show missing required data. Clinic staff can use this task to identify the items that still need to be completed, keyed, or verified after data from the screening visits are keyed. To avoid inconvenience to potential participants, the randomization application should not be attempted until the eligibility check application indicates that the patient is eligible except for the items that can only be completed at the randomization visit.

8.1.3 RANDOMIZATION VISIT

The randomization visit is the visit at which randomization takes place and the participant is issued the study medication which is randomly assigned to the participant. Randomization is the act of generating the random study medication assignment and is the procedure which defines a participant's enrollment into the trial. Randomization can occur after eligibility has been fully checked and all data collected at the screening visits have been keyed to the trial database. Since these processes take time, randomization cannot be done at a screening visit, and since study medication needs to be issued to the participant, the randomization visit must be completed in person with the participant. Therefore, a visit separate from the screening visits is necessary. Since this will be a visit on a different calendar day and medication will be started at this visit, good clinical practice requires that a few basic checks of the participant's well-being be completed at the randomization visit.

The procedures completed at the randomization visit are: pregnancy test for females of child bearing potential, verification that the participant is feeling well, affirmation of consent, review of concomitant drugs and vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature). All participants will be given information on a healthy life style and gastroparesis diet, and instructions on when to take their drug, and information to be aware of while taking buspirone (see section *6.1.2*). A set of daily-dairy forms will be distributed to the participant to complete each day and return to the clinic at their week 2 study visit.

8.1.4 FOLLOW-UP VISITS

Participants will return to the clinical center for follow-up visits at 2 and 4 weeks. A post-treatment washout phase visit will occur at week 6. Each visit will have an interval of time surrounding the ideal date for the visit during which the visit may be done and the data included in the trial database. The ideal date for the week 2 visit is the randomization date plus 2 weeks (14 days); the ideal date for the week 4 visit is the randomization date plus 4 weeks (28 days). Visit windows will be constructed to be contiguous, so that at any point in time, some visit window is open, subject to a check on the minimum separation of at least one week between consecutive visits. The specific assessments and procedures required at each of the follow-up visits are:

- **Week 2**: pregnancy test for females of child bearing potential, follow-up medical history with review of adverse events, concomitant medications and study adherence, assessment of vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature), and the following surveys: Hospital anxiety and depression (HADS), PAGI-SYM, and the Clinical Patient Grading Assessment Scale (CPGAS)(*see section 8.1.5*) and a symptoms side-effect questionnaire (see *section 8.2* for details). In addition, the participant will return their Daily-Diary forms and receive another set to complete for return at the Week 4 visit.

- **Week 4:** the week 4 visit will require two fasting visits scheduled as close together as possible, preferably 1 day apart.
  - The participant will refrain from taking their buspirone the morning of the GES test, and take it 30 minutes prior to the GES test. Information to be collected at this visit includes: pregnancy test for females of child-bearing potential, a GES test, follow-up medical history with review of adverse events and concomitant medications, physical exam and ECG, fasting blood draw for CMP and CBC, review of adherence and the following surveys: HADS, SF-36v2 Quality of Life, PAGI-SYM, GSRS, PAGI-QOL, PHQ-15, symptom side-effects, and the CPGAS. Fasting blood will be drawn for serum and plasma banking. In addition, the participant will return their daily-diary forms and receive one more set of daily-diary forms to complete each night to return at their 6-week visit.
  - The EGG test with water load test will be undergone the morning of the following day or as soon as can be possibly scheduled within the visit window. The participant will wait and take their buspirone dose 15 minutes prior to the EGG baseline recording. The participant will return all bottles of the study drug dispensed to the clinic staff. The participant will be instructed to not take any more drug after this visit.

- **Week 6:** At this visit, the participant will return their final set of daily-diary forms. Information to be collected includes: the follow-up medical history form with review of adverse events and concomitant medications, physical exam and fasting blood draw for CMP, CBC, and for banking plasma and serum with the NIDDK Biorepository, and the following questionnaires: HADS, PAGI-SYM, GSRS, PAGI-QOL, symptom side-effects, CPGAS. A BESST study close-out form will document the participant's end of participation in BESST.

8.1.5 STANDARDIZED QUESTIONNAIRES

Standardized questionnaires to assess efficacy:

Several standardized questionnaires will be administered to participants enrolled in the BESST trial. Questionnaires will be administered at baseline (prior to randomization) and during follow-up at specified intervals (see *1.3* for the Schedule of Activities). The purpose of the questionnaires is to obtain information regarding gastroparesis symptoms, side effects, and health-related quality of life.

a. **The Patient Assessment of Upper GI Symptoms (PAGI-SYM)** assesses the severity of symptoms of gastroparesis, functional dyspepsia, and gastroesophageal reflux disease [24]. The scale assesses symptoms over the prior two weeks, graded by the participant from none (0) to very severe (5). It includes the nine symptoms of the Gastroparesis Cardinal Symptom Index (GCSI), a validated patient-reported outcome (PRO) for gastroparesis using a two-week recall period. The nine symptom GCSI (nausea, vomiting, retching, stomach fullness, unable to finish a meal, feeling excessively full after meals, loss of appetite, bloating, belly visibly larger) is based on three subscales (postprandial fullness/early satiety, nausea/vomiting, and bloating) [25]. The PAGI-SYM also includes upper abdominal pain, which will be used for this study. The PAGI-SYM is in the public domain for use by investigators and physicians.

b. **ANMS GCSI-DD** is a daily dairy developed by the American Neurogastroenterology and Motility Society (ANMS) for gastroparesis [26]. The ANMS GCSI-DD is undergoing qualification by the FDA for use as a patient-reported outcome (PRO) outcome for clinical trials evaluating new treatments for either diabetic or idiopathic gastroparesis [27]. The ANMS GCSI-DD consists of five core symptoms (nausea, vomiting, early satiety, postprandial fullness, upper abdominal pain). Each night, participants grade the severity of symptoms over the prior 24 hours. The ANMS GCSI-DD core symptom composite score (an average of the five core symptoms) is designed to detect clinical improvement in symptoms of gastroparesis and to be used as a PRO outcome for clinical trials.

c. **Clinical Patient Grading Assessment Scale (CPGAS)** will be used to help assess the therapeutic response of the participants. Participants will be asked if their rating of relief of symptoms during the past week compared to the way the participant usually feels has improved, stayed the same, or worsened with study treatment. The clinical response of their gastroparesis symptoms to study treatment with one point gradations from (+7) = completely better; (0) = no change, and (-7) = very considerably worse. Responders are defined as those with score of > 0 and non-responders with score of $\leq$ 0 by CPGAS [28].

d. **Health Survey (SF-36v2)** is a 36-item, self-report measure designed to assess quality of life in participants [29]. This measure also provides two summary scores (physical and mental health) and eight scale scores. It is reliable and internally consistent. A higher summary score indicates better quality of life.

e**. Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL)** is a self-completed disease-specific quality of life questionnaire; the respondent scores each of 30 factors from 0 (none of the time) to 5 (all of the time) [30]. Items cover how often gastrointestinal problems have affected different aspects of their quality of life and well-being in the past two weeks. There are five domains: Daily Activities, Clothing, Diet and Food Habits, Relationship, and Psychological Well-Being and Distress. Overall PAGI-QOL scores are calculated by taking means of all subscores after reversing item scores; thus a mean PAGI-QOL score of 0 represents poor quality of life while 5 reflects the best life quality.

h. The **Hospital Anxiety and Depression Scale (HADS)** [31] was developed by Zigmond and Snaith (1983) and is commonly used to determine the levels of anxiety and depression that a patient is experiencing. The HADS is a fourteen-item scale that generates ordinal data. The HADS is comprised of 2 subscores, each scored from 0-21 points: HADS-A is the anxiety subscore and HADS-D is the depression subscore. Each subscore includes 7 questions which are each scored from 0 (not at all) to 3 (most of the time). The items for each subscore are summed and the average results in the subscore.

g. The **Gastrointestinal Symptoms Rating Scale (GSRS)** is a clinical rating scale for gastrointestinal symptoms in participants with irritable bowel syndrome and peptic ulcer disease [32]. There are 15 items on the instrument, which are scored on a 7-point Likert scale from 0=no discomfort to 7=very severe. Using the scoring manual, total score and 5 scales can be computed (Abdominal pain, Reflux syndrome, Diarrhea syndrome, Indigestion syndrome, Constipation syndrome).

h. The **Patient Health Questionnaire 15 Somatic Symptom Severity Scale (PHQ-15)** [33] is a brief, self-administered questionnaire that may be useful in screening for somatization and in monitoring somatic symptom severity in clinical practice and research. The total PHQ-15 score ranges from 0 to 30 comprising the sum of 15 somatic symptoms in the past 4 weeks rated in severity from 0 (not bothered at all) to 2 (bothered a lot).

8.1.6 STUDY PROCEDURES

Tests to assess efficacy:

Gastric Emptying Scintigraphy (GES)
Gastric emptying scintigraphy will be performed using a low-fat, egg white Eggbeaters® meal with imaging at 0, 1, 2, 4 hours after meal ingestion, as endorsed by the Society of Nuclear Medicine and American Neurogastroenterology and Motility Society (ANMS) (34,35). This protocol ensures standardized information about gastric emptying across multiple sites. Participants are instructed to come to the Nuclear Medicine Section in the morning after an 8-hour overnight fast, that is nothing by mouth after midnight and narcotic free for the 3-days prior to the scheduled test. The morning of the week-4 GES test, the participant will wait to take their buspirone until thirty minutes *prior to the start of the GES test*. If the participant normally takes insulin, then they should take one-half of their normal long-acting insulin dose prior to the visit. All diabetics will have their glucose checked prior to starting the GES test, with appropriate treatment measures being taken if low blood sugar (hypoglycemia or glucose < 60 mg/dL) or high blood sugar (hyperglycemia or glucose >270 mg/dl) is detected. GES is performed using a standard low-fat, egg-white Eggbeaters® meal to measure solid emptying. The meal consists of the equivalent of two large eggs radiolabeled with 0.5-1 mCi Tc-99m sulfur colloid served with two pieces of white bread and jelly. Participants are given 120 ml water. Following ingestion of the meal, imaging is performed at 0, 1, 2 and 4 hrs with the participant upright for measuring gastric emptying of Tc-labeled solids. In between imaging, participants generally sit in the nuclear medicine waiting area. Symptoms (nausea, fullness, pain severity, and episodes of vomiting) will be monitored and recorded during the GES test. Gastric emptying is analyzed as percent of radioactivity retained in the stomach over time using the geometric center of the decay-corrected anterior and posterior counts for each time point. Gastric retention of Tc-99m >60 % at 2-hours and/or >10% at 4-hours is considered delayed gastric emptying of solids. Delayed gastric emptying is graded according to the gastric retention at 4-hours: mild (≤20% gastric retention at 4 hours), moderate (>20 to 35%), and severe (>35%) [35].

Intragastric meal distribution (IMD), as an assessment of fundic accommodation (FA), during GES.
Analysis of regional intragastric meal distribution will be performed of the digital archived gastric emptying images, both at baseline and at the 4-week visit. We will use a modification of the method reported by Piessevaux, Tack, et al to assess intragastric meal distribution [14]. We will use our semi-automated analysis of regional intragastric meal distribution during GES. The analysis begins by aligning the images, then drawing regions of interest around the stomach using thresholding. The longitudinal axis of the stomach is then constructed. The stomach is then divided into two (proximal, distal) regions of interest by finding the midpoint of the longitudinal axis. The amount of radioactivity in each gastric region will be expressed as a percent of the total amount of radioactivity in the stomach at time 0. This will be assessed over time. The ratio of proximal over distal counts will be computed for each time period (0, 1, 2, 4 hours). The amount in the proximal region of interest at time 0

provides a measure of fundic accommodation. Impaired fundic accommodation using IMD is <0.568 ratio of the proximal gastric counts to the total gastric counts.

Electrogastrogram (EGG) with water load satiety test [36]**:**
For each EGG and water load test, the clinical center needs to have a one-liter opaque cup for water, 3 EGG leads, a dedicated quiet area for the EGG recording, a reclining chair, a blanket and the 3CPM EGG equipment and software. In addition, if the participant normally takes insulin, then they should take one-half of their normal long-acting insulin dose prior to the visit. The morning of the week-4 EGG, the participant will wait to take their buspirone dose *until 15 minutes before the baseline EGG*.

On the morning of the EGG and water load satiety test, the participant will arrive at the center after an 8-hour fast, that is nothing by mouth after midnight. Participants may take their usual medications with a small amount of water (up to 4 ounces) up to two hours prior to the study, but should refrain from coffee, tea, or juice. After arriving at the clinic, diabetic participants' blood glucose level will be checked to ensure it is less than 270 mg/dL. If the participant's blood glucose level is greater than 270 mg/dL, it is either treated and rechecked before proceeding or the EGG and water load satiety test will be rescheduled for another day under better glucose control. The participant will take their buspirone dose fifteen minutes prior to the 4-week baseline EGG recording. Baseline symptoms prior to EGG recording will be obtained using visual analog scales for stomach fullness, hunger, nausea, bloating, and abdominal discomfort. The subject will mark each symptom scale with a vertical line to indicate how they currently feel in terms of that symptom's severity on a score from 0 (no symptoms) to 100 (the most severe symptoms). Once the EGG and respiratory signals are stable, the baseline EGG recording period can begin. Participants will undergo a 15-minute baseline EGG in a reclining chair with the subject positioned at a 30-45 degree tilt. Participants will then begin the water load satiety test. For this, participants will sit upright. During the test, participants will drink cool water from the 1-liter cup. They will drink for a 5-minute period until they feel "**completely full**." It is important that the research associate at each site gives every participant the same instructions as follows:

> "I want you to drink water from this container until you feel **completely full.** You have **up to five minutes** to reach the feeling of **being** completely full. You may stop at any time, up to the five-minute time limit, when you feel completely full. This is not at test to see how much you can drink, but to drink until you **feel you are completely full** in the five-minute period. Do you have any questions about this?"

The total volume of water consumed in mL will be recorded.

A continuous 30-minute EGG recording is then obtained. The participant's symptoms are recorded using a visual analog scale at 10, 20, and 30 minutes after ingestion of the water (at the end of the 0-10 minute, 11-20 minute, and the 21-30 minute periods after the water load ingestion (post-satiety periods)). The test is completed after the 30-minute recording period and the electrodes are removed.

Specimen repositories

Specimens will be collected and stored in the NIDDK Biosample Repository for use as approved by the Steering Committee of the GpCRC and the NIDDK Central Repository after a specified period of time. Specimens include serum and plasma. The blood collected during screening, and at the 4 and 6-week follow-up visits will be separated into plasma and serum, and divided into 0.5 mL aliquots. Aliquots will be kept in a storage facility at -70 to -80 degrees Centigrade until they are shipped on dry ice to the NIDDK Biosample Repository at Precision Medicine.

8.2 SAFETY AND OTHER ASSESSMENTS

Assessments for Safety

- **Physical examination** (e.g., height, weight, waist measurements, vital signs (temperature, heart rate, respiratory rate, blood pressure, ECG).
- **Laboratory results –** All labs including creatinine, ALT, and glucose will be monitored at sites and in the central database and all abnormal values will be managed by the site investigator. If the ALT, creatinine, or glucose levels are elevated, that measure will be repeated within 5 days. If necessary, the participant will be given management advice and information will be provided to the participant's PCP.

- **Standardized Questionnaires:**
    a. **Symptom side effects**: Participants will be asked if they experienced any side effects from the BESST drug treatment and to describe any side effects. The baseline and follow-up medical histories will inquire about symptoms that may be attributed as side effects of buspirone using a standard set of questions. These symptoms include: headache, dizziness, tiredness, drowsiness, sleep problems (insomnia), nausea, upset stomach, blurred vision, nervousness or excitement.
    b. **Adverse Event Report form**: This form will document occurrence of an adverse event that threatens the integrity of the BESST trial or the well-being of a study participant during the trial.
    c. **Serious Adverse Event/IND Safety Report**: This form will document occurrence of any event reported on the Adverse Event Report form that satisfies the FDA expedited IND Safety Report requirement.

- **Biological specimen collection and laboratory evaluations are included in the Schedule of Activities and section in *12.2*.** Instructions for the preparation, handling, storage, and shipment of specimens are detailed in the BESST Standard Operating Procedures manual.

If a participant has scores on the psychological questionnaire indicating significant anxiety or depression (HADS-A ≥ 15 and/or HADS-D ≥ 15 indicating severe symptoms) or by the clinician's assessment, the clinical center investigator or staff will suggest that they see a clinical psychologist or psychiatrist and information on these referrals will be given to the participant [37]. If the clinician is concerned that a participant is actively suicidal or at risk of self-harm, the clinical center investigator will help make arrangements for them to be seen that day for further assessment.

For assessment of study intervention adherence see Study Intervention Compliance, *section 6.4*.

Management of Comorbid Conditions

Any participant's comorbid conditions, including diabetes, will be managed according to the best clinical practice or evidence-based practices by the site principal investigator with input from the participant's primary care physician (PCP), and with consideration for medications contraindicated for use with buspirone (listed in *section 6.5*). Most of the comorbid conditions will be treated by continuing the treatments already instituted by the participant's regular physicians; worsening of the condition will be treated by the PI according to best clinical practice along with the participant's regular physicians. If the physician determines that the participant's safety is at risk, the participant's study drug will be discontinued. For follow-up care, the physician will refer the participant to their PCP or a specialist, if needed, and also continue to follow the participant at the site.

A uniform set of practices to be applied by the GpCRC investigators in the care of these participants will be provided in the trial SOP (Standard of Care document), prepared by the GpCRC Steering Committee, including the

Study Medical Safety Officer, and in conjunction with the BESST PI. This document is based on accepted best clinical practice and guidelines from the American Gastroenterological Association, the American Neurogastroenterology and Motility Society, and the American College of Gastroenterology.

If a participant develops diabetes during the participant's participation in the trial and the physician determines the need for antidiabetic medication (e.g., because of lack of response to life style changes), the use of medications not contraindicated with buspirone will be recommended for the specialist to consider. Likewise, for other classes of drugs (anti-hypertensives or anti-depressants) that may be prescribed for a worsening comorbid condition, careful consideration must be given to whether there is a non-contraindicated treatment with buspirone that can be prescribed to the participant, with the ultimate decision being the participant's safety.

Pregnancy will be managed according to the guidelines and study drug will be discontinued immediately upon discovery. For safety, a pregnancy test is done for female participants of child-bearing potential at each follow-up visit and before each GES procedure. In the event of major dermatological reactions such as generalized urticaria, bullous rashes, and exfoliative dermatitis, study drug will be discontinued immediately and not restarted. For local skin reactions, study drug may be discontinued if the skin reactions are potentially drug related. If the rashes clear, the study drug may be restarted.

Monitoring for comorbid conditions is done at each study visit through a follow-up medical history, follow-up physical exam, follow-up adverse event reports, and laboratory measures of glucose or other labs, as well as assessments of vital signs.

In addition to the medications listed in *section 6.5*, which are exclusionary for the BESST trial, the Buspirone Investigator's Brochure does not recommend use of the drug in patients with impaired hepatic or renal function. Prospective participants with these conditions will be excluded from the trial. Most adverse events reported while taking buspirone are infrequent to rare, and are unexpected in the 4-weeks of treatment in the BESST trial.

Follow-up of Ongoing Adverse Events

Provisions for follow-up of adverse events (AE) include phone calls by the coordinators to assess symptoms, in-person follow up exams when needed to assess vital signs and physical findings and referral to local ongoing care by the PCP or hospital when needed.

The participant is queried about the adverse event until there has been a resolution of the AE. All information is recorded on the Adverse Event Report form and reviewed by the DSMB twice a year or at more frequent intervals if the DSMB determines the need. In addition, any AE with a severity grade greater than 2 is reviewed by the BESST Medical Safety Officer as soon as the event is keyed to the data system.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used to classify Adverse Events when possible.

8.3.3.1 SEVERITY OF EVENT

All Adverse Events (AEs) will be assessed by the study clinician and classified and graded for severity using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 when possible. The GpCRC Medical Safety Officer was involved in deciding which grading system to use for the GpCRC.

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment.

The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenological definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other

drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The Study Physician will be responsible for determining whether an AE is expected or unexpected. An AE is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed; "unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while in the study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE unless the AE results from a study procedure performed during screening. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Study Physician and Clinical Coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

The GpCRC BESST Trial will monitor and report adverse events to ensure participant safety. There are two separate sets of government regulations that apply to unanticipated or adverse events in research studies: (1) 45 CFR Part 46, Subpart A: the Common Rule,42 shared by 17 Departments and Agencies and (2) 21 CFR 312,41: the FDA regulation for adverse events. The Common Rule requires written procedures and policies for ensuring reporting of unanticipated problems involving risks to participants to IRBs, appropriate institutional officials, and the Department or Agency Head. The FDA regulation requires notification of the FDA and participating investigators of any adverse event associated with the use of a test article that is both serious and unexpected. Investigators should refer to the 2009 FDA guidance Improving Human Subjects Protection,43 for adverse events reportable to their institutional IRB. Since the definitions and reporting requirements for unanticipated events differ between the two sets of Federal regulations, the GpCRC BESST Trial definitions and procedures for adverse events are designed to satisfy both sets of requirements.

Adverse events will be recorded on the Adverse Event data forms whether or not they are thought to be associated with the study or with the study drug. Adverse events may be discovered during regularly scheduled visits or through unscheduled participant contacts between visits. Summary data on adverse events will be monitored by the DSMB quarterly and at its semi-annual meetings or more frequently, as needed. These summaries will include analyses comparing rates of adverse events by treatment group, by clinic, or in other subgroups requested by the DSMB. Where applicable, signs and symptoms associated with the adverse event will be graded as to severity by the clinical site staff as mild, moderate, or severe using the Common Terminology Criteria for Adverse Events version CTCAE v5.0.

After each meeting, the DSMB will issue a written summary of its review of the study data, including adverse events, for transmission to the IRBs at each of the study centers. Analyses or listings of adverse events will not be provided to the IRBs; however, adverse events involving unanticipated problems involving risks to participants, or breaches of protocol which might entail risk to participants must be reported to local IRBs as soon as possible after they are discovered. Each participating center is responsible for ensuring that all local IRB requirements for reporting adverse events are met. A summary of adverse events will be reported to the FDA as part of the IND annual report.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Serious adverse events (SAE) must be reported upon discovery at the clinical center per local IRB guidelines. This will involve completing an Adverse Event (AE) data form describing the severity and details of the serious adverse event. This must be submitted to the SDRC within one business day for review by the Medical Safety Officer. **If the serious adverse event is** judged by the study physician to be **unexpected with a reasonable possibility of being caused by the buspirone study drug**, then the investigator must also submit to the SDRC a SAE/IND Safety Report (SR) form, along with a narrative summarizing the circumstances of the event, the current status of the participant, and a copy of the IRB report within two working days. The SDRC will submit a preliminary report to the NIDDK for review within three calendar days of receiving the SAE/IND Safety Report (SR) form. The pharmaceutical manufacturer will be notified within one working day but no longer than three calendar days of all fatal/life threatening serious adverse events, regardless of association to study drug,

If NIDDK determines that the SAE requires an expedited IND Safety Report, the NIDDK Program Official or the NIDDK Regulatory Affairs Specialist will notify the FDA no more than 15 calendar days from the initial receipt of the SAE by the SDRC (no later than 7 calendar days if the SAE is fatal or life threatening). The clinical center investigator may also be responsible for completing an FDA MedWatch 3500 form and additional information for a follow-up SAE report as information becomes available. If the FDA determines that a change to the Investigators Brochure, IND or protocol is needed, the SDRC will send a copy of the IND Safety Report to all clinical centers, with

instructions to forward the report to their IRB. NIDDK will determine if the DSMB members should be made aware of the event at that time, or it is appropriate to wait until the next DSMB meeting.

The SDRC will maintain a list of all SAEs for reporting and review at Steering Committee meetings and DSMB meetings. The DSMB will review all SAE reports, at least twice a year. On a case-by-case basis, the NIDDK program staff, in conjunction with the DSMB chairperson, will determine whether the DSMB should review SAE reports more efficaciously. The DSMB will review each SAE report and provide comments to the NIDDK Program Official. If requested by any member of the DSMB, a teleconference will be scheduled to discuss the SAE and recommend any actions to the NIDDK. The clinical center must submit to the NIDDK and to the Scientific Data Research Center a follow-up memo within one month of the SAE (and periodic updates if needed) to report the details of the disposition of the SAE.

The SDRC will provide to the pharmaceutical manufacturer copies of all SAEs regardless of association to buspirone study drug which involve disability, congenital anomaly/birth defects/fetal losses, hospitalizations, and important medical events, such as cancers with no prior history within five calendar days of receipt. In addition, the SDRC will report any pregnancy occurring in association with the use of study drug to the pharmaceutical manufacturer within three calendar days. The SDRC will report overdoses of the buspirone study drug to the pharmaceutical manufacturer every six months. An overdose that results in an SAE or is associated with an SAE, will follow the normal SAE reporting process and timeframe.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

Female participants must confirm that they are not pregnant or breastfeeding and if they become pregnant during the course of the study, participants must notify the study investigator immediately. A pregnancy test is obtained at study enrollment and at each visit to help assure that the participant is not pregnant. If a participant is found to be pregnant, study medication will be stopped indefinitely, and the coded medication will be unmasked. The participant, PCP, and investigator will be notified of the assigned treatment and the associated risks.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the SDRC/principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) must be reported to the IRB and to the SDRC/study sponsor within one working day from the date the investigator was aware of the event.
- All other UP will be reported to the IRB and to the DCC/study sponsor within 10 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections within 10 days of the IRB's receipt of the report of the problem from the investigator.
- Reports should be sent to: *IRPT.OS@hhs.gov*
- All timelines related to SAE reporting with details are provided in protocol section 8.3.6.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

These would be reported to participants if they are unexpected, related or possibly related, and suggest a greater risk of harm to participants.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Hypothesis: Buspirone at 10 mg three times daily for 4 weeks is better than placebo in improving early satiety and postprandial fullness in adults with symptoms of gastroparesis measured as change in the PAGI-SYM postprandial fullness/early satiety subscore.

- Secondary Efficacy Hypotheses: Buspirone at 10 mg three times daily for 4 weeks is better than placebo in improving the following outcomes:
    1. Changes in GCSI total score
    2. Changes in PAGI-SYM subscores: nausea/vomiting, bloating, upper abdominal pain, GERD
    3. Changes in PAGI-SYM severity scores: Nausea, stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, loss of appetite, bloating, upper abdominal pain
    4. Changes in Gastrointestinal Symptom Rating Scale (GSRS) total score
    5. Changes in Clinical Patient Grading Assessment Scale (CPGAS) score
    6. Changes in PAGI-QOL total score
    7. Changes in the Hospital Anxiety and Depression Scale (HADS) total scores for anxiety and depression

8. Changes in Patient Health Questionnaire (PHQ-15) total somatization score
9. Changes in the SF-36v2 Quality of Life questionnaire physical and mental components scores
10. Changes in percent of gastric emptying retention

9.2 SAMPLE SIZE DETERMINATION

Summary of sample size and computation of primary outcome:

The primary outcome variable is change in the PAGI-SYM postprandial fullness/early satiety subscore from baseline to 4 weeks. This subscore is calculated by averaging the scores for 4 PAGI-SYM items: stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, and loss of appetite. Each item score ranges from 0 (none) to 5 (very severe) on an ordinal scale. The 4-item average is treated as continuous in the primary ANCOVA analysis of change and for sample size purposes.

The planned 108 participants sample size for this trial was derived using the following assumptions and methods:

- 2 equal size groups
- Power=90%
- Type 1 error (2-sided) = 0.05
- Two-sided tests
- Sample size increased by 10% to allow for 10% loss in primary outcome measure
- Placebo group assumptions: Based on the APRON RCT placebo data [9], we assumed that:
    - Mean (SD) change in postprandial fullness/early satiety subscore at 4-weeks = 3.7 (0.8)
    - Change from baseline at 4-weeks of fullness/early satiety subscore = -0.7 (1.0)
    - Correlation of postprandial fullness/early satiety subscore at baseline and 4-weeks = 0.55
- Method of analysis = ANCOVA of the change in the primary outcome score controlling for baseline value of the primary outcome score
- Intention-to-Treat Analysis using all randomized participants, corrected for missing outcome data:
    - Multiple imputation of the ANCOVA model using the chained equations method with 50 imputations using the Stata Software Command: *mi*
- Minimal Clinical Important Difference (MCID) = 0.62 SD (0.5 subscore points)
- Sample size software: Stata Software Command: *power repeated*
- **Sample size = 108 total (54 per group)**

Sample size for the primary outcome varying the MCID

MCID in SD units	**0.3 SD**	**0.50 SD**	**0.62 SD***	**1 SD**
MCID subscore units	0.24	0.4	0.5	0.8
Total sample size	**460**	**168**	**108**	**42**
Number per group	230	84	54	21

* MCID between investigator-related severity and fullness/early satiety subscore range=0.62-0.70 SD [25]

For the key secondary outcome, symptom improvement by 1-point or more in the PAGI-SYM GSCI total score from baseline to week 4, we determined that the total sample size of 108 participants (54 per group) gives 80% power to detect an MCID for a relative improvement ratio=1.8 (60% buspirone vs. 32% (placebo based on APRON

placebo data)). We used a nominal Type 1 error of 5%, with no corrections of the Type 1 error for the multiplicity of secondary outcomes.

The investigators conducting this trial have previously recruited for two trials for the GpCRC and along with their experiences in their clinic research were confident that the estimated number of 18 participants per site at a rate of one participant per month per site was a recruitment target that could be met.

9.3 POPULATIONS FOR ANALYSES

Analysis datasets will include:

a. Intention-to-Treat – all randomized participants
b. Safety Analysis Dataset – participants who took at least one dose of treatment
c. Other Datasets for Sensitivity analyses on a per-protocol basis (as needed: by etiology, sex, race, narcotic use, etc.)
    i. Complete-Case Analysis Dataset – subset of participants with 4-week outcome data
    ii. Adherence Analysis Dataset – subset of participants who took at least 80% of treatment

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The primary analysis is an intention-to-treat analysis of the change in the PAGI-SYM questionnaire postprandial fullness/early satiety subscore over 4-weeks of treatment. This subscore is calculated as the average of four items on the PAGI-SYM questionnaire: stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, and loss of appetite. The subscore average and each item score ranges from 0 (none) to 5 (very severe) on an ordinal scale and is treated as a continuous measure. The statistical model for change in postprandial fullness/early satiety at 4-weeks will be an ANCOVA model with an indicator variable for treatment group adjusted for the baseline value of the postprandial fullness/early satiety subscore. If a participant has missing 4-week outcome data, then multiple imputation modeling for missing data will be used.

Secondary, sensitivity analyses on a per-protocol basis will also be carried out, excluding participants from both groups who do not have the 4-week outcome data, but conclusions about the primary objective will be based on the intention-to-treat analysis. In addition, sensitivity analysis may be done using the subset of participants with adherence (defined as taking their treatment at least 80% of the time).

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY OUTCOME(S)

- Intention-to-Treat (ITT) Analysis Dataset

The primary outcome will be change in the PAGI-SYM questionnaire postprandial fullness/early satiety subscore from baseline to 4 weeks; this subscore is calculated by averaging the scores for 4 PAGI-SYM items: stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, and loss of appetite. The subscore average and each item score ranges from 0 (none) to 5 (very severe) on an ordinal scale and is treated as a continuous measure. The treatment effect will be estimated using an intention-to-treat (ITT) analysis of covariance (ANCOVA) model, regressing the change from baseline in postprandial fullness/early satiety subscore at 4-weeks on an indicator variable for treatment group and the baseline value of the outcome. The treatment group difference in adjusted mean change will be presented, along with a two-sided 95% confidence interval, and a P-value.

The confidence limits and P-value will come from the Intention-to-Treat multiple imputation ANCOVA model using all randomized participants, corrected for missing data, as described in *Section 9.2* above.

Descriptive analyses will address the assumption of normality of the outcomes using distributional tests (Shapiro-Wilks) and plots (lowess smoothed histograms, boxplots). Tests of normality of the residuals post-ANCOVA regression will be done. If the normality assumptions are not met, then sensitivity analyses using bootstrapped ANCOVA regression will be used to assess validity of the confidence limits and P-values.

Secondary, sensitivity analyses of the primary outcome will use the ITT Dataset and include:

- Complete case ANCOVA, excluding participants with missing data
- The same analysis as above comparing subsets of participants with high vs. not high adherence
- Repeat the Intention-to-Treat analysis adjusting for potential confounders not balanced by the randomization, such as use of narcotics, gastroparesis etiology, percent gastric retention, sex, and age.
- Other secondary, sensitivity analysis conducted will be to model each of the four individual symptom scores of the PAGI-SYM questionnaire postprandial fullness/early satiety subscore using the same methods as above.
- Graphs plotting the time course of mean change scores of the outcome and two-sided 95% confidence intervals by treatment group across visit (screening, 2, 4, 6 weeks) will be done. The significance of the overall treatment effect of change over time will be computed from generalized estimating equations (GEE) linear regression, modeling change as a function of treatment group, visit code indicator, baseline value of the outcome, and a treatment group by visit code interaction term.
- Using the PRO GCSI-DD, the two items, “not able to finish a normal-sized meal” and “feeling excessively full after meals” will be averaged to measure postprandial fullness/early satiety. The same method as above will be used; however, the baseline value is the average of the 7-day screening period daily-diary responses, and the 4-week measure is the average of the last 7-days of treatment. The change in each outcome is computed as the baseline average value subtracted from the 4-week average measure. A sensitivity analysis using a repeated measures method to account for within participant correlation will also be used.

9.4.3 ANALYSIS OF THE SECONDARY OUTCOME(S)

- Analysis of secondary outcomes are not dependent on findings of the primary endpoint
- Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)
- Complete-Case Dataset

The analyses of secondary and exploratory outcomes are not dependent on findings of the primary outcome. The ITT Analysis Dataset will be used for any binary efficacy outcomes, and for continuous efficacy outcomes with 10% or more of the participants having missing data for the 4-week outcome. In that case, the ITT Analysis Dataset using multiple imputation with chained equations method modeling missing data on treatment group and baseline value of the outcome using 50 datasets will be done. Otherwise, the Complete-Case dataset may be used to analyze the continuous secondary efficacy outcomes and all safety outcomes. Except for improvement in GCSI total score defined as being 1 or more points less at 4-weeks than at baseline, and some safety measures (adverse event counts), the other secondary outcomes are continuous changes from baseline at 4-weeks.

Secondary outcomes are listed in *section 9.1*. Assumptions will be checked and models checked post-estimation of the regressions as stated in *section 9.4.3*.

The "main" secondary outcome is the change in the total GCSI score. This will be analyzed as both a continuous change variable, and also as the binary improvement variable using a logistic regression model regressing improvement on treatment group and the baseline value of the total GCSI. Relative Odds, two-sided 95% confidence intervals and a significance level computed using a likelihood ratio test will be reported.

The analysis of secondary outcomes will use complete-case analysis of covariance (ANCOVA) models for continuous outcomes, regressing the change from baseline in outcome at 4-weeks on an indicator variable for treatment group and the baseline value of the outcome. The treatment group difference in adjusted mean change will be presented, along with a two-sided 95% confidence interval, and P-value for each secondary outcome from the ANCOVA model for the between-groups difference in the means. P-values will be nominal, and not be adjusted for the multiplicity of secondary outcomes.

9.4.4 SAFETY ANALYSES

Safety data will be presented by treatment group to the Data and Safety Monitoring Board during the course of the trial. Each adverse event will be displayed showing AE name per the CTCAE v5.0 when applicable, class, severity grade, random patient ID, clinic, treatment group, time since randomization, resolution status and physician's assessment of relatedness to treatment. Participant-specific summary tables including any adverse event (yes vs no), frequency of multiple adverse events (i.e., 0, 1, 2, 3+) and highest severity grade of adverse event (none, mild, moderate, severe, life-threatening) will be displayed by treatment group along with p-values from Fisher's exact tests.

In addition, rates of adverse events and hospitalizations will be reported between treatment groups, both by number of events and by participant. Count data will be analyzed using a negative binomial model accounting for over-dispersion of the count data.

Other safety data to be monitored include baseline levels and changes in laboratory measures, weight, and ECG results. These will be compared between treatment groups using ANCOVA models for change in measures or Fisher's Exact Tests for categorical outcomes.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline data will be presented by treatment group and total. Data include demographics, complete metabolic panel, complete blood count, HbA1c, TSH, concomitant medications, comorbidities, physical exam measures and baseline values of the outcome measures including the GCSI total score, PAGI-SYM questionnaire subscores and individual severity item scores, GSRS total score, other questionnaires, percent gastric retention at 4-hours, and EGG and satiety results. Means and standard deviations (continuous), medians and inter-quartile range (skewed continuous) or number and percent (binary, categorical) will be reported. P-values will be presented in the footnotes as descriptive statistics only if reaching ≤ 0.05 level and noting that any treatment group differences are due to chance.

Binary and categorical variables will be analyzed using chi-square tests, and continuous variables using t- tests. If a continuous variable is highly skewed, then a nonparametric test (Wilcoxon rank sum tests for comparison of the distribution of changes in each group) will be used to determine significance.

9.4.6 PLANNED INTERIM ANALYSES

There are no planned interim analyses for efficacy or safety. This is a trial with a very short duration of treatment of 4-weeks, that is using a drug that has a history of safety and is non-habit forming. Safety will be monitored by the DSMB throughout the trial.

9.4.7 SUB-GROUP ANALYSES

Post-hoc subgroup analysis of the primary outcome will be done by possible confounders including clinic, etiology (diabetic or idiopathic), gastric retention (delay or not delayed), sex, age (< 50, ≥50 yrs), adherence (80% or more of dose vs <80%), narcotic use at baseline and during trial (vs no use), symptoms at baseline (severe/very severe vs none to moderate), BMI group (normal/underweight vs overweight/obese). If available at the time of the primary paper analyses, then fundic accommodation at baseline (impaired vs normal) will also be included in the subgroup analyses.

Subgroup analyses will use the same models as used for the Intention-To-Treat ANCOVA models for the complete data, as described above. Difference in effects between subgroups will be assessed using the same ANCOVA models augmented with an interaction term for the difference in treatment effects between the subgroups; a P-value less than 0.01 for the interaction term from the augmented ANCOVA will be required for statistical significance of the subgroup difference. If subgroup differences are found, these will be reported and used to provide additional information about the effectiveness of the drug in subgroups of this participant population; however, the primary result of the trial will stand regardless of any subgroup differences that may be found.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

For monitoring of adverse effects, individual data may be presented to the Data and Safety Monitoring Board. In that case, study participants will be identified only by study IDs. Names and other unique individual identifiers such as Social Security Number are not collected by the study and therefore will not be presented to the DSMB. Individual data including ID will not be presented in a manuscript.

9.4.9 EXPLORATORY ANALYSES

Outcomes for exploratory or ancillary analysis, depending on the timeframe of additional work required to interpret and quality control data from the gastric emptying scintigraphy tests and the electrogastrogram test digital scans at the GpCRC central resource centers, are listed below:

The first and second outcomes are ancillary:

1. Changes at 4-weeks in Fundic Accommodation (FA) using digital analyses of the GES test images
2. Changes and mean changes, respectively, at 4-weeks in EGG test gastric rhythm measures and water satiety: a) clinical EGG diagnosis (normal, tachygastria, bradygastria, mixed gastric dysrhythmias; b) percentage time and distribution of power in normal 3 cpm EGG activity before and after the water load satiety test and c) total volume of water ingested.

This following outcome is exploratory since it is using the PRO daily-diary version of the ANMS GCSI questionnaire that is not currently validated; however, these outcomes may provide sensitivity analyses on several secondary outcomes.

3. Mean changes at 4-weeks in each of the 7 items on the ANMS GCSI-DD questionnaire: nausea, postprandial fullness, early satiety, upper abdominal pain, episodes of vomiting, episodes of retching, overall symptom severity, as well as the total core symptom composite score. The average severity scores from the last 7-days of treatment are subtracted from the 7-day average baseline severity scores for each of the items.

These two outcomes listed below are ancillary since they are not necessarily powered to detect a change between treatment groups; however, they may provide information on buspirone to develop further hypotheses in the future.

4. Changes at 4-weeks in each of the 15 symptom severity items measured on the PAGI-SYM instrument not included in secondary outcomes item 3, including retching, lower abdominal pain, lower abdominal discomfort, constipation, and diarrhea
5. Changes at 4-weeks in each of the 5 subscores of the Gastrointestinal Symptom Rating Scale (GSRS).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Template consents will be prepared for the GpCRC BESST Trial by the SDRC. Individual clinical centers may add material, but may not delete material thought to be necessary for informed consent. Clinical centers may reformat and reword information to conform to their local IRB requirements. A consent form must be signed by each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant and this fact will be documented in the subject's study files.

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention and administration of the study intervention and procedures. The following consent materials, BESST Combined Consent – HIPPA Adult, are submitted to IRBs with this BESST protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will first explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants.

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the BESST study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed

consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source documents (including the date) for the participant, and the form signed before the participant undergoes any study-specific procedures. The rights and welfare of the potential participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.
To minimize in-person contact time between the participant and staff during the Covid-19 pandemic and as permitted by the site-specific IRB and/or the sIRB, participants will be offered a telephone or virtual review of the consent in place of the in-person review of the consent. Signature of the consent will take place in person at the study visit and after confirmation that all of the participant's questions about the study have been answered.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funding agency, the Investigational New Drug (IND) sponsor (N/A) and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the DSMB, sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All laboratory specimens, study forms, reports, and other records that are part of the study data collection materials will be identified by coded number to maintain participant confidentiality. All records will be kept in locked file cabinets. All electronic records of study data will be identified by the coded number. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB. Consent procedures and forms, and the communication, transmission and storage of participant data will comply with individual site IRB and NIH requirements for compliance with The Health Insurance Portability and Accountability Act (HIPAA).

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying the study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the GpCRC SDRC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique identification number and letter code. The study data entry and study management systems used by clinical sites and by GpCRC SDRC research staff will be secured, password-protected and are encrypted. At the end of the study, all study databases will be de-identified and archived at the NIDDK Data Repository.

Consent procedures and forms, and the communication, transmission and storage of participant data will comply with individual site IRB and NIH requirements for compliance with The Health Insurance Portability and Accountability Act (HIPAA).

Per NIH Notice NOT-OD-17-109 (Notice of Changes to NIH Policy for Issuing Certificates of Confidentiality https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html), this research is deemed to be issued a Certificate through this Policy and is therefore required to protect the privacy of individuals who are subjects of such research in accordance with subsection 301(d) of the Public Health Service Act.

This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Biological specimens will be collected and stored for use as approved by the Steering Committee of the GpCRC (see *Appendix 12.2* for blood collection schedule). Specimens to be stored include plasma and serum. Twenty mL of blood will be collected at the screening visit and at the week 4 and 6 follow-up visits. The blood will be drawn in the morning during the study visit while the participant is still fasting. The blood will be separated into plasma and serum and then divided into 0.5 mL aliquots. Plasma and serum aliquots will be kept in a freezer at -70 or -80 degrees Centigrade and will be sent to the NIDDK Biosample Repository for banking.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

BESST Principal Investigator	**BESST Principal Investigator**	**Medical Monitor**
Henry P. Parkman, MD	*Pankaj Jay Pasricha, MD*	*William Hasler, MD*
Temple University Hospital	*Johns Hopkins University School of Medicine*	*Mayo Clinic Arizona*
3401 North Broad St., 8th Floor Philadelphia, PA 19140	*720 Rutland Ave., Room 958 Baltimore, MD 21287*	*13400 E. Shea Blvd., Scottsdale, AZ 85259*
215-707-7579	*410-955-8612*	*480-347-3538*
henry.parkman@temple.edu	*ppasric1@jhmi.edu*	hasler.william@mayo.edu

GpCRC Executive Committee (EC) - Consists of GpCRC co-chairpersons, SC representatives, principal investigator of the SDRC, NIDDK program official, and NIDDK project scientist. The GpCRC EC discusses directions and strategic issues related to the scientific aims of the GpCRC; organizes and sets agenda for Steering Committee meetings and provides oversight of study.

GpCRC Steering Committee (SC) – Consists of the principal investigators of each of the clinical centers, the principal investigator of the SDRC, and the NIDDK project scientist, each of whom has one vote in any decision requiring a formal vote. The GpCRC SC is the major decision-making body for GpCRC, which provides oversight in the planning and conduct of studies. The SC votes on all important decisions and approves the final database and protocol and any amendments or modifications of the protocol.

10.1.6 SAFETY OVERSIGHT: DATA AND SAFETY MONITORING BOARD

- Each participating clinical center is responsible for ensuring that local IRB requirements for reporting adverse events are met.
- The SDRC staff at the Johns Hopkins Bloomberg School of Public Health follows the JHSPH IRB guidelines and reports the unanticipated problems or adverse events to the NIDDK and the DSMB.
- The NIDDK appointed DSMB will monitor the data for safety and efficacy for outcomes such as toxicity and any other outcomes or events identified as safety-related.

Safety oversight will be under the direction of an independent Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including gastroenterology, internal medicine, and statistics. Members of the DSMB are independent from the study conduct and free of conflict of interest.

The DSMB is appointed by the NIDDK and will review the protocol for the BESST trial and monitor the safety data as the trial progresses to ensure participant safety. The DSMB is a multidisciplinary group with a written charge provided by the NIDDK. The DSMB reports to the NIDDK, which will communicate DSMB recommendations to the investigators, as appropriate. The DSMB will hold a meeting to approve the protocol. The DSMB will review performance and safety data. The DSMB may request more frequent meetings if necessary to fulfill its charge. It may also request additional safety reports on a more frequent basis. All serious adverse events are reported to the DSMB for their consideration and recommendations as they occur.

The DSMB also reviews the overall progress of the trial in terms of recruitment and data quality and makes a formal recommendation to the NIDDK at the end of each scheduled meeting as to whether the trial should continue unmodified, continue with protocol modifications, or be stopped.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial complies with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the SDRC of the GpCRC.
- To ensure data quality and reduce data entry error, double-data entry of all data collection forms is required. The SDRC will incorporate into the data entry programs a series of edit checks, including range checks, logic checks (e.g., skip patterns), and consistency checks, both within a data form and across forms. These integral checks are designed to detect deficiencies in the data before they are entered into the study database, so that the deficiencies may be easily and accurately corrected. In addition, the SDRC will perform frequent computerized edit checks on entered data. The SDRC will also perform ongoing comparisons of copies of entered data forms with the databases to ensure that data entered into the data system reflect those recorded on the forms. Such audits will help to pinpoint problems that cannot be detected by computer editing and may be used to guide increased scrutiny when needed. Any data queries identified will be flagged for action by the clinical site until resolved.
- The data system will maintain a clear and complete audit trail of all changes to the study databases. All changes to data forms will be documented appropriately on the paper form and entered into GpCRC BESST data system. All forms entered and/or edited in the data system will be identified by the unique Personal Identification Number (PIN) of the operator, the network address (the “IP” address) of the computer being used, and the date and time of the operation. Records will not be deleted but rather marked as having been superseded. The SDRC will implement various procedures to ensure the quality of its internal operations. These will include the development and maintenance of documentation regarding procedures for receiving, processing, and analyzing data, and duplicated programming for selected procedures to check for errors in software database and analysis systems.
- Performance monitoring: The web-based data system will allow for real-time reporting of most recruitment and data management activities. However, additional performance reports will be generated and circulated monthly and typically reviewed at each Steering Committee (SC) meeting. These reports include several key indicators of study performance, including counts of participants screened and randomized, of completed visits and of missing key data, of missed visits, and statistics summarizing performance with respect to timeliness of data entry and response to data queries.
- The SC and the DSMB will conduct a formal review of the study by conference call or in-person meeting twice a year and will address quality assurance as part of their agenda. These Committees will have responsibility for recommending corrective actions based on the performance data. It is anticipated that the primary responsibility for formulating and implementing these actions will reside in the SC. Potential actions might include specific recommendations for training, redistribution of study resources, or possibly termination of support for a center.
- Independent audits outside the SDRC will not be conducted.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that are run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the GpCRC monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the GpCRC, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hard copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data and clinical laboratory data) will be entered into the GpCRC database, a 21 CFR Part 11-compliant data capture system provided by the SDRC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents (case report forms).

10.1.9.2 STUDY RECORDS RETENTION

The NIDDK records retention policy is to maintain clinical trial records for 3 years after the granting period ends or the trial ends, whichever is later.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Standard Operating Procedures (SOP) requirements. The noncompliance may be on the part of either the participant, the investigator, or the study site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to NIDDK Program Official and the SDRC. Protocol deviations must be sent to the reviewing IRB per local site policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the SOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results and information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer- reviewed journals.

Data from this study may be requested from the NIDDK Central Repository (*https://www.niddkrepository.org/search/study/*) two years after the completion of the primary outcome.

This study will not be collecting DNA specimens from participants, so there will be no genomic data or genomic sequencing data from DNA to deposit in in the NIH Genomic Repository.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The GpCRC study leadership in conjunction with the NIDDK has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

None

10.3 ABBREVIATIONS

5-HT	5-hydroxytryptamine
AE	Adverse Event
ALT	Alanine Aminotransferase
ANMS	American Neurogastroenterology and Motility Society
APRON	Aprepitant for the Relief of Nausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin Trial
AST	Aspartate Aminotransferase
BMI	Body Mass Index (kg/m^2)
BUN	Blood Urea Nitrogen
CO2	Carbon Dioxide/bicarbonate
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CMP	Complete Metabolic Panel
CNS	Central Nervous System
CPGAS	Clinical Patient Grading Assessment Scale
CPM	Cycles Per Minute
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CUNV	Chronic Unexplained Nausea and Vomiting
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EGG	Electrogastrogram
FA	Fundic Accommodation
FDA	Food and Drug Administration
GES	Gastric Emptying Scintigraphy
GCSI	Gastroparesis Cardinal Symptom Index
GCSI-DD	Gastroparesis Cardinal Symptom Index – Daily Diary
GERD	Gastroesophageal reflux disease
GpCRC	Gastroparesis Clinical Research Consortium
GpR	Gastroparesis Registry (study)
GSRS	Gastrointestinal Symptoms Rating Scale
HADS	Hospital Anxiety Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
IMD	Intragastric Meal Distribution
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intention-to-Treat
MAOI	Monoamine oxidase inhibitor
MCID	Minimal Clinical Important Difference
N/A	Not applicable
NIDDK	National Institute of Diabetes and Digestive Kidney Diseases
OHRP	Office of Human Research Protections
PAGI-QOL	Patient Assessment of Upper Gastrointestinal Disorders-AGI Life
PAGI-SYM	Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index
PCP	Primary Care Provider
PHQ-15	Patient Health Questionnaire 15 Somatic Symptom Severity Scale

PI	Principal Investigator
PIN	Personal Identification Number
PRO	Patient-Reported Outcome
RCT	Randomized Control Trial
SAE	Serious Adverse Event
SDRC	Scientific Data and Research Center
SoA	Schedule of Activities
SOP	Standard Operating Procedures
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UP	Unanticipated Problems

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version 1.2; 11 Sep 2020	**Description of Change**	**Brief Rationale**
	1.1 Synopsis Changed age range from 18-75 to 18-85 Changed Total Study Duration to 96 weeks (24 months) Changed Recruitment to 90 weeks (22.5 months) Changed: Expected enrollment rate to .8 participant per month per clinical center (18 participants each at 6 centers)	Compliance with Inclusion across the Lifespan policy. Recruitment has been slower than expected. This will extend through May 31, 2021.
	1.3 Schedule of Activities Removed x at screening for Clinical Patient Grading Assessment Scale (CPGAS)	This is only done during follow-up
	5.1 Inclusion Criteria Changed Aged 18 to 75 years at initial screening interview to Aged 18 to 85 years at initial screening interview	Compliance with Inclusion across the Lifespan policy.
	5.5.1 Recruitment Changed recruitment time to 22.5 months	Recruitment has been slower than expected. This will extend through May 31, 2021.
	8.1.6 Study Procedures Deleted: This analysis reads the scintigraphic images in an application written for MATLAB software [17].	Remove reference to software used as this may change.
	8.1.2, 10.1.1.2 Added: To minimize in-person contact time between the participant and staff during the Covid-19 pandemic and as permitted by the site-specific IRB and or sIRB, participants will be offered a telephone or virtual review of the consent in place of the in-person review of the consent. Signature of the consent will take place in person at the study visit and after confirmation that all of the participant's questions about the study have been answered.	COVID19
	7.2 Participant Discontinuation/Withdrawal from the Study Added: The sponsor or investigator terminates the study.	COVID19
	10.3 Abbreviations Bicarbonate; accommodation	Corrected spelling
	11. References Added PMID to References	NIH format

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12 APPENDIX

12.1 PARTICIPATING CENTERS

Clinical Centers

Johns Hopkins Hospital, Baltimore, MD

Massachusetts General Hospital, Boston, MA

Temple University, Philadelphia, PA

Texas Tech University Health Science Center, El Paso, TX

University of Louisville, Louisville, KY

Wake Forest University Health Sciences, Winston-Salem, NC

Scientific Data Research Center

Johns Hopkins University, Baltimore, MD

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

EGG Reading Center

Wake Forest University Health Sciences, Winston-Salem, NC

GES Reading Center for Fundic Accommodation

Temple University, Philadelphia, PA

NIDDK Central Repository

12.2 BLOOD COLLECTION SCHEDULE (amounts in mL)

	Screening visits		**Follow-up visits** Weeks from Randomization			**mL**
Labs		**RZ**	**f2**	**f4**	**f6**	**Total mL**
Complete blood count (CBC)	5		.	5	5	15
Comprehensive metabolic panel (CMP)	2	.	.	2	2	6
Thyroid Stimulating Hormone (TSH)	2	.	.	.	.	2
Fasting HbA1c	5	.	.	.	.	5
Banking:						
Fasting plasma	10	.	.	10	10	30
Fasting serum	10	.	.	10	10	30
Total	**34**	**0**	**0**	**27**	**27**	**88**

All BESST study visits with blood collection are fasting visits and need to be scheduled for early morning. Fasting is defined as nothing by mouth after midnight, except for a small amount of water to take medications.