GpCRC

Gastroparesis
Clinical Research Consortium

Nortriptyline for Idiopathic Gastroparesis: A Multicenter, Randomized, Double-Masked, Placebo-Controlled Trial (NORIG)

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Protocol

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NORIG Trial Protocol

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Design synopsis

Title

- **Nor**triptyline for **I**diopathic **G**astroparesis: A Multicenter, Randomized, Double-Masked Placebo-Controlled Trial (NORIG)

Sponsor

- NIDDK

Type of study

- Phase III randomized clinical trial
- Multicenter, double-masked, placebo-controlled trial of 2 parallel treatment groups

Objective

- To determine whether treatment with nortriptyline or placebo results in symptomatic improvement in patients with idiopathic gastroparesis.

Treatment groups

- Group 1: Nortriptyline; 10 mg, one capsule, po qhs (by mouth at bedtime each night) x 3 weeks,
  f03 visit, 25 mg, one capsule, po qhs x 3 weeks,
  f06 visit, 50 mg, two capsules, po qhs x 3 weeks,
  f09 visit, 75 mg, three capsules, po qhs x 6 weeks,
  f15 visit: taper study drug by one capsule a week, off study drug for the last week

- Group 2: Nortriptyline-placebo, 10 mg, one capsule, po qhs x 3 weeks,
  f03 visit, 25 mg, one capsule, po qhs x 3 weeks;
  f06 visit, 50 mg, two capsules, po qhs x 3 weeks;
  f09 visit, 75 mg, three capsules, po qhs x 6 weeks
  f15 visit: taper study drug by one capsule a week, off study drug for the last week

Population

- Patients aged 21 - 65 years old at registration with moderate to severe symptoms of idiopathic gastroparesis

Study duration – per patient

- Up to 16 weeks of screening prior to randomization, including a 6 week washout period for other tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOI).
- 15 weeks of treatment starting at randomization
- Tapering off study drug by one capsule a week from 15 to 17 weeks after randomization
- One week with no study drug from 17 to 18 weeks after randomization

Study duration – per calendar time

- Recruitment phase: 39 months
- Follow-up phase: 44 months

Sample size justification

- Total of 130 patients in 2 groups of equal size (65 per group)
- Primary comparison: nortriptyline vs. placebo
- Error protection: Type I = 0.05 and Type II = 0.10 (90% power)
- Minimum clinically important difference (MCID): 50% reduction in GCSI outcome (see below) during 15 weeks of treatment
  - Expected percent with improved GCSI in the placebo group: 30%
  - Expected percent with improved GCSI in the nortriptyline group: 60%
  - Source of estimates of MCID: Consensus of GpCRC clinicians
- Statistical test and sample size software
  - Chi-squared test for two proportions
  - Dupont and Plummer PS software

Number of clinical centers

- 7

Inclusion criteria

- Age 21 through 65 years old at registration
- Documentation of delayed gastric emptying on gastric emptying scintigraphy within 2 years of registration, defined as greater than 60% retention at 2 hours or greater than 10% retention at 4 hours
- Symptoms of gastroparesis for at least 6 months (does not have to be contiguous) prior to registration with Gastroparesis Cardinal Symptom Index (GCSI) score of ≥ 21
- Negative upper endoscopy or upper GI series within 2 years of registration

Exclusion criteria

- Normal gastric emptying confirmed with scintigraphy
- Diabetic gastroparesis or post-surgical gastroparesis including fundoplication
- Another active disorder which could explain symptoms in the opinion of the investigator
- History of significant cardiac arrhythmias and/or prolonged QTc
- History of seizures
- Use of narcotics more than 3 days per week
- Use of tricyclic antidepressants for refractory symptoms of gastroparesis within 6 weeks prior to randomization
- Use of strongly anticholinergic medications
- Use of calcium channel blockers
- Use of erythromycin
- Clear history of failed trial of nortriptyline use for gastroparetic symptoms
- Symptoms of primary depression or suicidal ideation
- Contraindications to nortriptyline:

a) hypersensitivity or allergy to any tricyclic antidepressant drug
b) concomitant therapy with a monoamine oxidase inhibitor (MAOI)
c) recent myocardial infarction
d) glaucoma

- Pregnancy or nursing
- Any other condition, which in the opinion of the investigator would impede compliance or hinder completion of the study
- Use of a G tube, J tube, or a central catheter for nutrition
- Use of a gastric electrical stimulator
- Failure to give informed consent

Outcome measures

- ***Primary:*** The primary outcome measure is defined as a decrease from the baseline GCSI score (sum of the 9 individual symptom scores) of at least 50% on any two consecutive follow-up visits during the 15 week treatment period with maximum tolerated study drug dose. A sensitivity analysis will compare cumulative GCSI symptom scores averaged across all follow-up visits to rule out the possibility that an effect present in the primary analysis was due to the GCSI score decreasing 50% on two consecutive visits with smaller improvement or worsening on other follow-up visits. All patients will be followed for the full 18 weeks after randomization regardless of response or course of treatment to permit an intention-to-treat primary analysis.

The GCSI total score ranges from 0 to 45 (highest severity) and is calculated as the sum of nine individual symptom scores:

GCSI = Nausea (0-5) +
Retching (0-5) +
Vomiting (0-5) +
Stomach fullness (0-5) +
Not able to finish a normal sized meal (0-5) +
Feeling excessively full after meals (0-5) +
Loss of appetite (0-5) +
Bloating (0-5) +
Stomach visibly larger (0-5)

As noted earlier, a GCSI score of 21 or greater is a requirement for enrollment into the trial. The primary outcome measure is a binary (0, 1) variable, which equals to 1, if a GCSI score reduction of 50% or greater, relative to the baseline score, is observed on at least two consecutive follow-up visits during the 15 weeks of treatment and follow-up.

- **Secondary outcome measures** will be defined to address the following areas:
  (1) Symptoms
  Subscores for the GCSI such as nausea/vomiting, postprandial fullness, bloating
  Individual symptom scores
  Global overall relief of symptom questionnaire
  Clinical global patient impression
  (2) Physiology
  Satiety test: Volume of Ensure® consumed during satiety testing
  Electrogastrography: Percent time in EGG dysrhythmias (outside 2.5-3.75 cycles per minute)
  Side effects to treatment requiring stopping medication

  Subgroup differences in response to nortriptyline will be addressed:
  (1) Differential response to nortriptyline based on pharmacogenetic analysis of patients
  (2) Differential response to nortriptyline based on blood levels of nortriptyline

Randomization

- Centrally administered randomization stratified by clinical center and blocked by calendar time

Visit schedule

- Screening: at least 1 visit separated by at least 1 calendar day from randomization; screening period can last no more than 16 weeks after registration
- Randomization: final pre-treatment interview, dispensing of study drug
- Follow-up visits:
  - every 3 weeks after randomization throughout the 18 week study

Statistical analysis

- All analyses will be on an "intention-to-treat" basis

Safety monitoring

- 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

NORIG Trial Protocol

1. Objectives

The principal objective of this multicenter, randomized, placebo-controlled trial is to evaluate whether treatment with nortriptyline will improve gastroparesis symptoms compared with placebo.

Other objectives include:

- To determine the effects of nortriptyline and placebo on satiety testing, and electrogastrography in patients with idiopathic gastroparesis.
- To determine the frequency of side effects to treatment with nortriptyline and placebo in patients with idiopathic gastroparesis.
- To determine if pharmacogenetic profiles of patients with idiopathic gastroparesis influence their treatment responses to nortriptyline.
- To determine if blood levels of nortriptyline correlate with treatment responses to nortriptyline in patients with idiopathic gastroparesis.

2. Background and significance

2.1 Introduction

Gastroparesis is a disorder of gastric neuromuscular sensory and motor function that affects patients in the prime of their life. Gastroparesis is a devastating disease affecting predominantly young women (females outnumber males by a ratio of 4:1, with an average 34 years of age)[1]. The symptomatic profile of gastroparesis includes nausea (90% of patients), vomiting (>80%), pain (~50%), early satiety (60%) and bloating (75%) and can vary in both the combination of symptoms and their severity[1]. Because of its chronic, and often intractable nature, the disorder has a tremendous impact on both patients and society at large. Gastroparesis remains difficult to treat, in large part because of the lack of knowledge of the underlying pathophysiology of this disease. Several factors, in particular, have impeded the progress in this field including the paucity of patients seen by any one center, the absence of uniform diagnostic criteria, the lack of generally available, reliable methods for physiological testing and the inaccessibility of tissue for histopathological correlation.

The Gastroparesis Clinical Research Consortium (GpCRC) is a cooperative network of seven clinical centers and one Data Coordinating Center (DCC) supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), through the mechanism of RFA-DK-05-004, established in 2006. Clinical centers are responsible for proposing protocols, participating in their overall development, recruiting patients, conducting the research, and disseminating research findings. The individual clinical centers participate in a cooperative and interactive manner with one another and with the DCC in all aspects of the GpCRC. The DCC supports protocol development; provides sample size calculations, statistical expertise, forms, and data analysis; supports manuscript preparation; and provides overall study coordination and quality assurance, including coordination of the activities of the Steering Committee and other standing committees.

2.2 Definition, prevalence, and natural history of gastroparesis

The traditional concept of gastroparesis is a disorder of delayed gastric emptying. This has dominated physician thinking for decades and has influenced the management approaches to these patients. Although there is a paucity of data on the true prevalence and incidence of gastroparesis in the community, it is clear that it imposes a huge burden of disease on its sufferers.

- The prevalence of gastroparesis is not known; however, it has been estimated that up to 4% of the population experiences symptomatic manifestations of this condition. The majority of gastroparetics, whether of the diabetic or idiopathic type, are women (up to 80% in some series). Patients are typically young to middle aged.

- The natural history of gastroparesis is poorly understood and, even in diabetics, symptoms may fluctuate considerably with many patients reporting relatively symptom-free intervals of varying durations. In others, a progressively downhill course is observed requiring interventional procedures to restore nutritional intake and provide palliation. A subset of the idiopathic variety may present with an abrupt onset of symptoms, sometimes in association with acute gastroenteritis or other non-specific illness, and it is presumed that this may represent a post-viral syndrome.

2.3 Pathogenesis of gastroparesis

The cause of gastroparesis is unknown. Three primary sub-groups of gastroparesis exist: diabetic, post-surgical, and idiopathic. In diabetic gastroparesis, vagal dysfunction is thought to be a main abnormality. In a significant subset of gastroparesis patients, no cause is found and the condition is deemed to be idiopathic in nature. Idiopathic gastroparesis is even less well understood than the diabetic variety. Clinical experience suggests that a subset of these patients may develop gastric dysfunction after an acute viral illness.

2.4 Current treatments of gastroparesis

Treatment of nausea, vomiting and abdominal pain in patients with gastroparesis can be difficult. Metoclopramide, a dopamine receptor antagonist, is the only medication currently approved for treatment for gastroparesis[2]. Metoclopramide, however, has side effects which often limit its use both for the short term and the long term. Although some studies suggest that domperidone, a peripherally acting dopamine receptor antagonist, may be of benefit in patients with gastroparesis and may have fewer side effects, it has not received FDA approval[3,4]. Erythromycin, an antibiotic which is also a motilin receptor agonist, improves gastric emptying; however, its use as a prokinetic is limited due to side effects and tachyphylaxis of its effects[5]. Tegaserod has been used for the treatment of gastroparesis; studies have shown an acceleration of gastric emptying with little effect on symptoms[6]. Thus, documented effective treatments for gastroparesis are few and rigorously controlled trials are largely lacking[7].

2.5 Tricyclic antidepressants in gastroparesis

Tricyclic antidepressants (TCA) may suppress symptoms in patients with gastroparesis and functional dyspepsia; studies suggest that they may decrease nausea and vomiting and abdominal pain[8]. It has been proposed that low doses of TCAs, such as amitriptyline, reduce sensory transmission and reduce visceral hypersensitivity. In one retrospective analysis of open label treatment, tricyclic antidepressants reduced symptoms in patients with functional vomiting[9]. The effective dose averaged 50 mg/day - lower than used for depression. In two studies in functional dyspepsia and one in diabetic gastropathy, low-dose tricyclic antidepressants decreased dyspeptic symptoms and abdominal pain[10,11]. In a retrospective evaluation of diabetic patients with nausea and vomiting, low dose TCAs provided better symptom reduction than prior trials of antiemetic and prokinetic drugs[12]. Nearly one third of patients exhibited delayed gastric emptying, suggesting that the presence of impaired motor function is not a contraindication for tricyclic antidepressants. The symptomatic response to TCAs does not appear to be due to an effect on gastric emptying.

Desipramine was helpful on a per protocol basis, but not on an intention to treat basis, in female patients with functional bowel disorders, primarily irritable bowel syndrome[13]. In this desipramine study, dose escalation occurred every week - initial dose was 50 mg po qhs, then 100 mg, then 150 mg/day. The mean treatment was for 85 days. There is also an ongoing NIH trial on TCAs for functional dyspepsia which is using amitriptyline at a dose of 50 mg compared to the selective serotonin reuptake inhibitor (SSRI), escitalopram 10 mg and placebo[14].

The classification of tricyclic antidepressants (TCAs) is based on their structure. Tertiary amines, including amitriptyline, imipramine, and doxepin have more anticholinergic activity and more side effects. Secondary amines including nortriptyline and desipramine have less anticholinergic activity and fewer side effects. Atypical TCAs include trazadone. In general, when treating patients with gastroparesis, physicians try to use TCAs with lower anti-cholinergic activity such as desipramine or nortriptyline.

Physicians' use of TCAs for GI symptoms is varied. There are different starting doses, different dose escalation time periods, and different final dosages to aim for. A reasonable starting dose for a tricyclic agent is 10-25 mg at bedtime. If benefit is not observed in several weeks, doses are increased by 10- to 25-mg increments up to 50-100 mg. Side effects may require a change in medication in some patients[8]. The secondary amines, nortriptyline and desipramine, may have fewer side effects.

2.6 Nortriptyline

This study will determine the clinical responses of patients with gastroparesis to treatment with nortriptyline, a symptom modulator/tricyclic antidepressant. Nortriptyline is FDA approved for treatment of depression. This study will evaluate whether patients' symptoms and underlying pathophysiologic abnormalities respond to nortriptyline directed towards visceral hypersensitivity/central processing. Although this therapeutic agent is employed in many clinical practices for gastroparesis, there is a lack of evidence that this treatment may be effective in symptomatic gastroparesis.

This study will employ a dose escalation strategy for nortriptyline, a practice that is conventionally used to treat patients with a tricyclic antidepressant and compare the symptom response to placebo. The purpose of this study protocol is not only to assess the efficacy of nortriptyline, but also to develop an understanding of the mechanism of action and to determine whether gastroparesis symptoms correlate with improvement in gastric physiology.

2.7 Pharmacogenetic profile influences treatment response

Drug metabolism is a critical component of a drug's pharmacokinetic profile and disposition; this determines in part the systemic concentrations which might affect therapeutic response as well as side effects. Pharmacogenetics focuses on genetic polymorphisms and the contribution of these polymorphic genes to variability in disease etiology and therapy. There may be genetic polymorphism in drug metabolism which affects the symptom response and side effects in individual patients. The need for pharmacogenetic studies in the field of gastroparesis and other GI disorders has been greatly emphasized by several investigators[15].

In this study, the hypothesis that pharmacogenetic patient profiles influence the treatment responses to nortriptyline for patients with idiopathic gastroparesis will be explored. Many therapeutic drugs are metabolized at least partly via cytochrome P450 enzymes (CYP) including tricyclic antidepressants and 5-HT4 receptor agonists. Genetic polymorphisms in human CYPs are very well documented, and are known to affect the clinical efficacy of numerous drugs.

The table below shows the most common polymorphisms for CYP2D6[16]. CYP2D6 polymorphisms have become classic examples of pharmocogenetics whereby people can be classified as "poor", "moderate", or "fast" metabolizers.

Major human polymorphic variant *CYP2D6* alleles and their population distribution

			Allele Frequency (%)			
Major variant allele*	**Mutation**	**Consequence**	**Caucasians**	**Asians**	**Black Africans**	**Ethiopians and Saudi Arabians**
CYP2D6*2xn	Gene duplication	Increased enzyme activity	1-5	0-2	2	10-16
CYP2D6*4	Defective splicing	Inactive enzyme	12-21	1	2	1-4
CYP2D6*5	Gene deletion	No enzyme	2-7	6	4	1-3
CYP2D6*10	P34S, S486T	Unstable enzyme	1-2	51	6	3-9
CYP2D6*17	T1071,R296C, S486T	Altered affinity for substrates	0	0	20-35	3-9

*All variant alleles are listed by the Human CYP Allele Nomenclature Committee at http://www.imm.ki.se/cypalleles/cyp2d6.htm

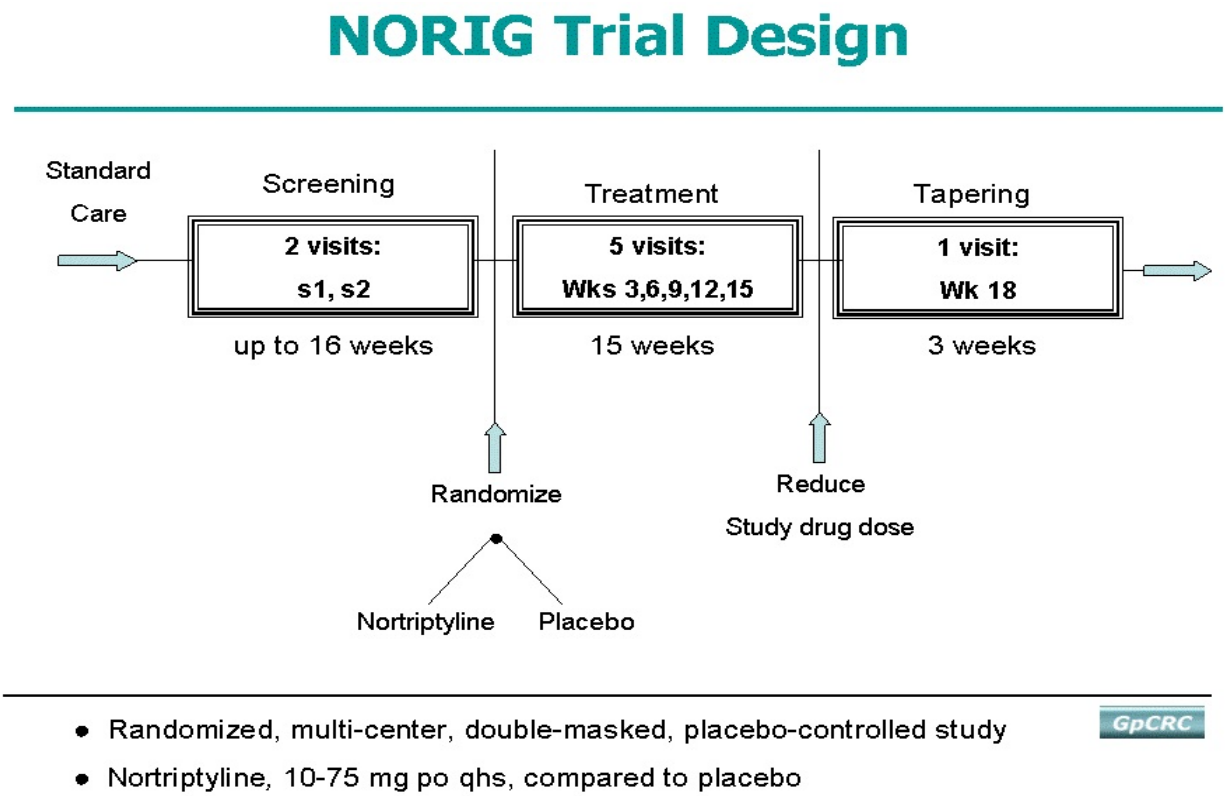
Individuals with multiple active gene copies metabolize drugs more rapidly, whereas individuals lacking functional CYP2D6 genes metabolize at a lower rate. Nortriptyline is metabolized by CYP2D6[17]. The activity of CYP2D6 can markedly affect nortriptyline levels and efficacy. These polymorphisms may require a change in the dose from 28-180% of the usual dose to achieve similar results. There is also some evidence that nortriptyline can also be metabolized to a small extent through CYP3A4 and 2C19[18].

Correlating the CYP2D6 status of an individual to their clinical response will provide important information on whether there is need to individualize nortriptyline dosages according to CYP2D6 status to achieve therapeutic benefit.

3. Study design

3.1 Design overview

NORIG is a multicenter, randomized, placebo-controlled, double-masked dose-escalation clinical trial of treatment with nortriptyline or placebo for patients with idiopathic gastroparesis. Screening for eligibility and collection of baseline data will span up to 16 weeks after obtaining informed consent and registration. Eligible patients will be randomized to receive either nortriptyline (starting dose 10 mg with dose escalation to 75 mg) or placebo po qhs for 15 weeks. At the end, there will be a tapering period with the dose decreased by 25 mg each week from 15 to 17 weeks to minimize potential symptoms attributed to the withdrawal of the study drug. At week 18, patients will return for a final visit to ensure patient safety following the end of treatment. After the trial has ended, patients will be given the option of participating in the Gastroparesis Registry, an IRB approved observational study funded by the NIDDK. A schematic of the trial design is presented below:



The primary comparisons will be made using an intention-to-treat analysis of the change in symptomatic improvement in patients with idiopathic gastroparesis as measured by the Gastrointestinal Cardinal Symptom Index (GCSI). Secondary analyses will include: the effect of treatment on individual symptom scores, the patients' assessment of global overall relief, physiological changes in satiety tests, and dysrhythmias detected by electrogastrography. The treatment response based on pharmacogenetic analysis of the patient and blood levels of nortriptyline will also be analyzed.

3.2 Treatment groups

Patients who have signed an informed consent statement and who meet the eligibility criteria will be randomly assigned to one of two groups for 15 weeks of treatment followed by a 3 week tapering period where the dose is decreased by 25 mg (one capsule) each week until week 17, then no study drug is taken for the last week of the trial:

Group 1: Nortriptyline; 10 mg, one capsule, po qhs (by mouth at bedtime each night) x 3 weeks,
f03 visit, 25 mg, one capsule, po qhs x 3 weeks,
f06 visit, 50 mg, two capsules, po qhs x 3 weeks,
f09 visit, 75 mg, three capsules, po qhs x 6 weeks,
f15 visit: taper study drug by one capsule a week, off study drug for the last week

Group 2: Nortriptyline-placebo; 10 mg, one capsule, po qhs x 3 weeks,
f03 visit, 25 mg, one capsule, po qhs x 3 weeks;
f06 visit, 50 mg, two capsules, po qhs x 3 weeks;
f09 visit, 75 mg, three capsules, po qhs x 6 weeks
f15 visit: taper study drug by one capsule a week, off study drug for the last week

The randomization scheme will assign patients in randomly permuted blocks of assignments stratified by clinical center; block size will be determined randomly. This scheme will ensure that the two groups will be balanced by calendar time of enrollment (to minimize secular effects) and by clinical center (to minimize clinic-specific effects of differences in patient populations and management).

The randomization plan will be prepared and administered centrally by the Data Coordinating Center (DCC) but will not require real time interaction with a DCC staff member. Requests for randomizations will be made by the clinical center using a web-based application. An assignment will be issued only if the database shows that the patient is eligible, has signed the consent statement, and has had all required baseline data keyed to the data system.

3.3 Study drug dosing schedule

Study drugs will be shipped to each clinical center's investigational drug pharmacy. The research pharmacy staff will then provide the investigator with masked study drug medication bottles based on the DCC randomization schedule. Patients will be dispensed one or more bottles labeled ***"nortriptyline or placebo"***.

Each evening, 30 minutes before bedtime, one or more capsules from the "nortriptyline or placebo" bottle will be taken with water. Study drug may be taken with food. The study drug will be either a dose of nortriptyline or matching placebo. Patients will be on a dose escalation regimen with an initial dose of one 10 mg capsule the first three weeks after randomization. At the week 3 visit, study drug dose will be increased to one 25 mg capsule for the next 3 weeks, if well tolerated. At the week 6 visit, study drug dose will be increased to 50 mg (two 25 mg capsules) for the next 3 weeks, if well tolerated. At the week 9 visit, a follow-up electrocardiogram (ECG) will be performed, the ECG findings will be reviewed and if well tolerated, the study drug dose will be increased to 75 mg (three 25 mg capsules) for the remaining 6 weeks until 15 weeks after randomization. At the week 12 visit, patients will have a second follow-up ECG and a blood draw for a complete blood count, metabolic and hepatic panel, and if well tolerated, the study drug dose will remain the same at 75 mg (three 25 mg capsules) for the remaining 3 weeks of treatment phase of NORIG trial. At the week 15 visit, patients will be instructed to taper the study drug, decreasing the dose to 50 mg (two 25 mg capsules) for one week, at week 16, decreasing to 25 mg (one 25 mg capsule) for one week, and starting with week 17, the study drug will be discontinued, i.e., no study drug will be taken for the final week.

At each follow-up visit, patients should return their medication bottles with any study drug not taken. The pharmacist or clinical coordinator should count and record the remaining capsules in study drug bottles on the NORIG data form.

3.4 Restarts and dose adjustments due to side effects

A standardized management plan for potential side effects and symptoms is detailed in section 5.7 Safety issues. If a common, non-serious side effect to the study drug develops which is noticeable but tolerable, investigators will follow a standardized management plan as outlined in section 5.7 of the protocol. These side effects include ones commonly seen with TCAs such as constipation, dry mouth, weight gain, bloating, dizziness, insomnia. The management plan for these common, non-serious side effects generally involves patient education about the side effect and adding over the counter therapies. The study drug is continued with dose escalation. If the side effect becomes bothersome and barely tolerable, then the study drug dosage is reduced to the last dose tolerated without stopping treatment. If the side effect is intolerable, then the study drug is discontinued for one week and then restarted at the lower dosage that was previously tolerated.

If side effects occur that may be more serious, such as heart palpitations, skin rash, anxiety, confusional states, panic, then the patient will be evaluated. For heart palpitations, an ECG will be

obtained. Investigators can initially attempt dose reduction to the previous well tolerated dose instead of treatment interruption. If patients developed serious or intolerable side effects requiring cessation of study drug, the drug will be stopped for one week. If the side effects disappear, a second attempt will be made to reintroduce the study drug after one week at the previous lower dose that the participant tolerated better. If the dose is well tolerated, the patient will be continued at this dose for the remainder of the study without further dose escalation. If the study medication is stopped, the patient will no longer receive the study drug, but will be followed in the study according to the protocol, in keeping with the "intention-to treat" paradigm.

3.5 Standard treatment recommendations

During the screening period, patients will receive a standardized set of recommendations to include dietary modification, weight loss if needed, and exercise. The patient's medications are reviewed to discontinue drugs that might exacerbate the underlying dysmotility disorder. Dietary modification and use of antiemetics or pain medications as appropriate are the primary management approaches. If symptoms require further treatment during the trial, patients will be instructed to take rescue medications that they would usually take such as ondansetron or promethazine for nausea and vomiting and propoxyphene or propoxyphene with acetaminophen for abdominal pain. These recommendations have been prepared by the GpCRC Steering Committee as standard of care in the management of patients with idiopathic gastroparesis (see Standard Operating Procedures IV: Standards of Care for Patients with Idiopathic Gastroparesis). This will help ensure that the patients in both treatment groups receive standard of care treatment for gastroparesis.

4. Patient selection

4.1 Recruitment

Approximately 130 patients will be recruited from the seven clinical centers of the GpCRC (averaging 22 patients per center) over a 39 month period:

- Stanford University, Palo Alto, CA (PI: P. Jay Pasricha, MD)
  - California Pacific Medical Center, San Francisco (PI: William Snape, MD)
- Temple University, Philadelphia, PA (PI: Henry Parkman, MD)
- Texas Tech University, El Paso, TX (PI: Richard McCallum, MD)
- University of Michigan, Ann Arbor, MI (PI: William Hasler, MD)
- University of Mississippi, Jackson, MS (PI: Thomas Abell, MD)
- Wake Forest University, Winston-Salem, NC (PI: Kenneth Koch, MD)

Patients with idiopathic gastroparesis will be identified and registered for screening at the participating clinical centers subject to the inclusion and exclusion criteria listed below. Eligible patients will be randomized to a treatment group after completion of all required study procedures, keying of all required data elements, and passing eligibility checks for the NORIG trial. Patients may be recruited directly to the NORIG trial or may be recruited from the Gastroparesis Registry (GpR).

Each clinical center will develop a recruitment plan. These plans will vary from clinic to clinic depending on the available pools of patients and local recruitment resources. Clinics will attempt to recruit sufficient overall numbers of minorities and males, so that trial results can be generalized to these population groups as well.

4.2 Inclusion criteria

Patients with moderate to severe symptoms of idiopathic gastroparesis will be studied. Patients should not have diabetic or post-surgical gastroparesis or dyspeptic symptoms with normal gastric emptying. In order to qualify for inclusion in the trial, patients must satisfy the following inclusion criteria:

1. Aged 21 – 65 years old at registration
2. Documentation of delayed gastric emptying on gastric emptying scintigraphy within 2 years of registration date, defined as greater than 60% retention at 2 hours or greater than 10% retention at 4 hours
3. Symptoms of gastroparesis for at least 6 months (does not have to be contiguous) prior to registration with Gastroparesis Cardinal Symptom Index (GCSI) score of ≥ 21
4. Negative upper endoscopy or upper GI series within 2 years of registration date

4.3 Exclusion criteria

Patients who satisfy any of the following exclusion criteria will be ineligible for randomization in the trial:

1. Normal gastric emptying confirmed with scintigraphy
2. Diabetic gastroparesis or post-surgical gastroparesis including fundoplication
3. Another active disorder which could explain symptoms in the opinion of the investigator
4. History of significant cardiac arrhythmias and/or prolonged QTc
5. History of seizures
6. Use of narcotics (including fentanyl patches) more than 3 days per week
7. Use of tricyclic antidepressants for refractory symptoms of gastroparesis within 6 weeks prior to randomization
8. Use of strongly anticholinergic medications
9. Use of calcium channel blockers
10. Use of erythromycin
11. Clear history of failed trial of nortriptyline use for gastroparetic symptoms
12. Symptoms of primary depression or suicidal ideation
13. Contraindications to nortriptyline:
    a) hypersensitivity or allergy to any tricyclic antidepressant
    b) concomitant therapy with a monoamine oxidase inhibitor (MAOI)
    c) recent myocardial infarction
    d) glaucoma
14. Pregnancy or nursing
15. Any other condition, which in the opinion of the investigator would impede compliance or hinder the completion of the study
16. Use of a G tube, J tube, or a central catheter for nutrition
17. Use of a gastric electrical stimulator
18. Failure to give informed consent

4.4 Run-in period

Patients must not have used any tricyclic antidepressants for refractory symptoms of gastroparesis within 6 weeks prior to randomization. Patients must not have used a monoamine oxidase inhibitor (MAOI) for the 6 weeks prior to randomization. Patients must not have used a narcotic analgesic for abdominal pain, strongly anticholinergic drugs, calcium channel blockers, or erythromycin on a daily basis for the 6 weeks prior to randomization. These agents are not to be used during screening nor for the duration of the trial. Patients will be interviewed in a detailed fashion at screening, randomization, and at every follow-up study visit to document the absence of such use.

Patients will be allowed to continue on prescription gastroparesis medications as well as any over-the counter medications or dietary supplements. If using a selective serotonin reuptake inhibitor (SSRI), the patient must have been on a stable dose in the 3 months prior to randomization.

5. Trial protocol

5.1 Visit schedule overview

The patient-related activities of the NORIG trial can be divided into 4 phases:

- Screening for eligibility (2 visits over a maximum of 16 weeks)
- Randomization to treatment (1 visit and it may be combined with the last screening visit)
- Treatment phase (5 visits over 15 weeks)
- Treatment tapering phase (from week 15 to 17 after randomization, last week without study medication, final visit at 18 weeks)

The visit and data collection schedule described below in detail is summarized in Appendix 9.2.

5.2 Screening and baseline data collection overview

Many of the NORIG participants will come from the Gastroparesis Registry (GpR) or from the patient rosters of the study physicians. Patients who appear to be eligible after chart review and completion of standard of care tests and procedures for gastroparesis will be invited to undergo screening for the NORIG trial. Patients considered by the clinical center investigator as likely to be eligible for participation in the NORIG trial may be consented, registered and screened at a visit that is part of the ongoing clinical care of the patient. Patients will be asked to consent for the collection, storage and use of DNA for genetic research, but may opt out of this component of the NORIG trial. Screening tests should be completed according to the standard of care as outlined in the Standard Operating Procedures IV: Standards of Care for Patients with Idiopathic Gastroparesis.

As part of the screening process for the NORIG trial, the gastroparesis patient must have a standardized 4 hour scintigraphic evaluation of gastric emptying using a low fat Egg Beaters meal that is available for review by the study physician as outlined in the Standard Operating Procedures, Part I, section 6.3. This may be repeated as part of standard of care for diagnosis or follow-up as determined by the clinical center investigator during screening. The standard of care gastric emptying scintigraphy may have been obtained at any time within 2 years prior to the registration date. Patients must also have a negative upper endoscopy within the last 2 years, to rule out other potential causes of symptoms such as mechanical obstruction, inflammatory or other structural lesions of the GI tract or non-gastrointestinal causes. Recording of screening data on trial forms may not start until the patient has signed the NORIG trial consent statement. Screening and baseline data collection procedures will include questionnaires, physical examination, various laboratory tests, clinical procedures on patients and review of the patient's medical chart. Data abstracted from a patient's chart may include laboratory, endoscopy, scintigraphy and radiology test results. Prior therapy for gastroparesis will be reviewed, and patients will be asked to stop specific treatments such as tricyclic antidepressants, monoamine oxidase inhibitors, strongly anticholinergic medications, calcium channel blockers, and erythromycin. Narcotic pain medication including fentanyl patches and other rescue medications such as propoxyphene or propoxyphene with acetaminophen may not be used more than 3 days per week.

All participants who sign the consent statement will be registered in the trial database. Each participant who starts screening will be accounted for at the end of screening, as either a screening success (randomization) or a screening failure. A screening failure is defined as a participant who signed the consent form and was registered in the NORIG trial data system, but is found to be ineligible prior to randomization; screening failures include patients who meet medical eligibility criteria but change their mind and do not consent to randomization into the trial. The reason for screening failure will be recorded on the randomization form and keyed in the trial database.

Screening and baseline data collection procedures will be conducted over two clinic visits completed on separate calendar days. The goal of the first screening visit is to obtain consent and start recording screening data regarding the trial's inclusion and exclusion criteria on NORIG data forms; the goal of the second screening visit is to complete collection of baseline data on patients who appear to be eligible. This separation of procedures between two visits is somewhat arbitrary and is provided as a guideline. Screening procedures and data collection can be organized as appropriate at each clinical center. The procedures completed during screening include:

• **Screening visit 1**: The patient should be in a fasting state (no food or drink after midnight the night before) for this visit. The patient will sign the consent at or prior to screening visit 1 and will undergo a history and physical examination to identify other illness and contraindications for participation such as use of narcotics for pain more than 3 days per week (including fentanyl patches), use of calcium channel blockers, use of erythromycin, use of medications that are strongly anticholinergic, hypersensitivity or allergy to any tricyclic antidepressant drug, concomitant therapy with a monoamine oxidase inhibitor (MAOI), recent myocardial infarction or glaucoma. The baseline medical history form will have a section to establish a baseline symptom profile for each participant and to document non-specific symptoms that may be attributed as side effects to study drug after randomization. The patient will be asked to respond to the clinical global patient impression (CGPI). Patients will complete the following questionnaires:

- Gastrointestinal Symptom Rating Scale (GSRS)
- Health-related quality of life questionnaire (SF-36)
- Beck Depression Inventory (BDI-II)
- Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM)
- State Trait Anxiety Inventory (STAI)
- Brief Pain Inventory (BPI)
- Patient Health Questionnaire (PHQ-15)

Anthropometric assessments (body weight [kg], body height [m], body mass index [BMI], waist circumference [cm], hip circumference [cm], vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature); and general physical findings will be collected and recorded. Patients will have an ECG performed at this visit. Laboratory test results that need to be recorded from chart review or obtained as part of screening visit 1 include: complete blood count (CBC): white blood cells, red blood cells, hemoglobin, platelets; a metabolic panel: sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogren (BUN), creatinine; a hepatic panel: albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin; and thyroid stimulating hormone (TSH).

Additional standard of care procedures required for screening:

Gastric emptying scintigraphy: Patients who have not had a standardized 4 hour gastric emptying scintigraphy within 2 years of the registration date or whose previous gastric emptying scintigraphy is of inadequate quality must have a standard of care gastric emptying scintigraphy prior to randomization. Instructions for the gastric emptying scintigraphy are found in the Standard Operating Procedures I: Clinical Center Operations, section 6.3.

Upper endoscopy: Patients who have not had an upper endoscopy within 2 years of the registration date must have a standard of care upper endoscopy prior to randomization.

• **Screening visit 2**: Patients will return to the clinical center in a fasting state (no food or drink after midnight the night before). They will have blood drawn for plasma and DNA banking; 20 mL of the blood drawn will be used for DNA banking for future pharmacogenomic analysis of CYP450 2D6 alleles; and 10 mL will be used for plasma banking for future measurement of the study drug blood levels. Patients will undergo a satiety test with electrogastrography (EGG).

Electrogastrography with satiety testing: On the morning of the electrogastrogram (EGG) and satiety test, the patient will arrive fasting, that is, nothing to eat or drink after midnight the night before the test. Subjects may take normal medications with a small amount of water up to two hours prior to the study, but should refrain from coffee, tea, or juice. Electrogastrography is the recording of the electrical activity of the smooth muscle in the stomach using electrodes similar to an electrocardiogram (ECG). EGG electrodes are placed on the abdominal skin. Skin preparation for these electrodes will consist of cleaning the skin with an electrode paste and then applying a conduction gel which is then wiped off. If needed, the abdominal surface where electrodes will be positioned is shaved. Patients will undergo a 15 minute baseline EGG recording.

Then, for the satiety test, subjects will drink Ensure® (1.1.kcal/ml) every 5 minutes until they feel completely full. This will be followed by another 30 minute EGG recording. The electrodes will then be removed. The satiety test will be analyzed by the amount of Ensure® consumed. The EGG will be analyzed for each of the fasting and post nutrient load 30 minute periods. The percentage distribution of the power in the normal frequency range (2.5-3.75 cycles per minute [cpm]), tachygastria (>3.75-10 cpm), bradygastria (<2.5 cpm) and duodenal-respiration (>10 cpm) will be calculated. A power ratio comparing mean signal amplitudes between postprandial and preprandial power will be calculated. The dominant frequency, and the percentage of time in the dominant frequency will be calculated and recorded. Data will be available in a digital format for further analysis. Detailed instructions for the electrogastrogram and satiety test are found in the SOP I, section 6.7.

The NORIG web based data system will include software to check patient eligibility based on keyed data forms. The eligibility check task may be run at any time, and there is no limit on the number of times it may be run before randomization. The output from the task will list the eligibility checks that the patient has failed and a summary finding that the patient is eligible or ineligible for

the trial. Clinical center staff can use this task to identify the items that still need to be completed, keyed, or verified after data from screening visits are keyed. The randomization visit should not take place until the eligibility check indicates that the patient is eligible except for the items that can be completed only at the randomization visit.

5.3 Randomization visit

Randomization is the act of generating the random study medication assignment from the web-based data management system and is the procedure which defines a patient's enrollment into the trial. Randomization can only occur after eligibility has been fully checked and all data collected at screening visits have been keyed to the trial database. The patient will re-affirm their consent and have their vital signs recorded. Women of child bearing potential must have a negative pregnancy test.

The final task at the randomization visit is the generation of the random treatment assignment. The generation process includes the same electronic check on eligibility that the staff may run prior to the randomization visit. The medication assignment will not be generated unless the check finds that the patient is eligible, and the clinic staff indicates that they want to randomize the patient.

The random treatment assignment will consist of a numbered medication bottle; this number will be unique as well as patient and visit specific. This will correspond to numbered bottles of medication which have been sent to the clinical center's research pharmacy (or clinical coordinator if not using a pharmacy) by the GpCRC Drug Distribution Center. The research pharmacy (or clinical coordinator) will issue the specific numbered bottle to the patient. Each patient's random treatment assignment will be generated for that specific patient and will not be transferable to another patient. Once the assignment has been generated, the patient should be issued the assigned study drug (in person) and instructed about when to take the study drug and monitoring for potential adverse effects. The study drug dispensed at the time of randomization will be either a 10 mg capsule of nortriptyline or a similar looking placebo capsule.

The date of randomization is the start (zero) time for reckoning all follow-up visits (i.e., all follow-up visits are scheduled at specific times measured from the date of randomization). The randomization computer program will generate a personalized appointment schedule for the patient; this schedule will indicate the target date for each follow-up visit, as well as the time window around the target date during which the follow-up visit may be done.

5.4 Follow-up visits

Patients will return for follow-up visits at 3, 6, 9, 12, 15, and 18 weeks after randomization. Patients will be given a new, higher dosage of the study drug at each follow-up visit until week 9 as long as in the opinion of the investigator, there are no significant side effects attributed to the study drug. If there have been side effects, investigators can either reduce the dose to the previous well-tolerated dose; or in the case of significant side effects, may stop therapy for one week to monitor symptoms as outlined in section 5.7 safety issues. The specific procedures to be completed at each of the follow-up visits are:

• **Week 3 visit**: Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question, and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II). Review study drug adherence and tolerance with the initial 10 mg dose of study drug with patient. Collect any remaining medication bottles with unused study drug. If 10 mg dose is well tolerated during the first 3 weeks after randomization, dispense study drug with instructions for a 25 mg dose.

• **Week 6 visit**: Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question; and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II). Review study drug adherence and tolerance with the 25 mg dose of study drug since the week 3 visit with patient. Collect any remaining medication bottles with unused study drug. If 25 mg dose is well tolerated during weeks 3-6 after randomization, dispense study drug with instructions for a 50 mg dose (two 25 mg capsules).

• **Week 9 visit**: Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question; physical exam (temperature, heart rate, respiratory rate, blood pressure); and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), a health-related quality of life questionnaire (SF-36), State Trait Anxiety Inventory (STAI), Brief Pain Inventory (BPI), Patient Health Questionnaire (PHQ-15), and Beck Depression Inventory (BDI-II). Once the questionnaires are completed, the patient will have an electrocardiogram (ECG). Review ECG findings, study drug adherence and tolerance with the 50 mg dose of study drug since the week 6 visit with patient. Collect any remaining medication bottles with unused study drug. If 50 mg dose is well tolerated during weeks 6-9 after randomization, dispense study drug with instructions for a 75 mg dose (three 25 mg capsules). Women of childbearing potential must have a negative pregnancy test.

• **Week 12 visit**: Patient should be in a fasting state (no food or drink after midnight the night before). Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question; physical exam (temperature, heart rate,

respiratory rate, blood pressure). They will have blood drawn for plasma banking and analysis; 10 mL of blood will be drawn for plasma banking; and 15 mL will be drawn for a complete blood count (white blood cells, red blood cells, hemoglobin, hematocrit, platelets), a metabolic panel (sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogen (BUN), creatinine, and a hepatic panel (albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin. The following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptom Rating Scale (GSRS), and Beck Depression Inventory (BDI-II). Once the questionnaires are completed, the patient will have an electrocardiogram (ECG) followed by the EGG and satiety test. For the EGG and satiety test, patients will have a 15 minute baseline EGG recording. Then the patient will drink Ensure® (1.1.kcal/ml) every 5 minutes until they feel completely full. This will be followed by a 30 minute EGG recording. The electrodes will then be removed. The satiety test will be analyzed by the amount of Ensure® consumed. The EGG will be analyzed for the fasting and post satiety test. Review ECG findings, study drug adherence and tolerance with the 75 mg dose of study drug since the week 9 visit with patient. Collect any remaining medication bottles with unused study drug. If 75 mg dose is well tolerated during weeks 9-12 after randomization, dispense study drug with instructions for a 75 mg dose (three 25 mg capsules). Women of childbearing potential must have a negative pregnancy test.

• **Week 15 visit**: Patient should be in a fasting state (no food or drink after midnight the night before). Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question, physical exam (temperature, heart rate, respiratory rate, blood pressure); 10 mL of blood will be drawn for plasma banking, and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptom Rating Scale (GSRS), a health-related quality of life questionnaire (SF-36), State Trait Anxiety Inventory (STAI), Brief Pain Inventory (BPI), Patient Health Questionnaire (PHQ-15), and Beck Depression Inventory (BDI-II). Review laboratory results, study drug adherence and tolerance with the 75 mg dose of study drug since the week 12 visit with patient. Collect any remaining medication bottles with unused study drug. Patients will be instructed to reduce their dosage to 50 mg (two 25 mg capsules) for one week and then to 25 mg (one capsule) the second week and end with one week of no study drug use and return for the final follow-up visit at week 18. Women of childbearing potential must have a negative pregnancy test.

• **Week 18 visit**: Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question, and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptom Rating Scale (GSRS), and Beck Depression Inventory (BDI-II). Collect any remaining medication bottles with unused study drug.

5.5 Standardized questionnaires

Several standardized questionnaires will be administered to patients enrolled in the NORIG trial. Questionnaires will be administered at baseline (prior to randomization) and during follow-up at specified intervals (see Appendix 9.2 for the data collection schedule). The purpose of the

questionnaires is to obtain important information regarding gastroparesis symptoms, side effects, and health-related quality of life.

Patient Assessment of Upper Gastrointestinal Disorders-Symptoms (PAGI-SYM). A validated 20 question questionnaire that quantifies symptoms of gastroparesis, dyspepsia, and gastroesophageal reflux disease on a 0 to 5 scale for each symptom[21]. The PAGI-SYM includes the 9 question Gastroparesis Cardinal Symptom Index (GCSI) - a validated symptom questionnaire that assesses the symptoms of gastroparesis[22, 23]. The GCSI is based on three subscales (postprandial fullness/early satiety, nausea/vomiting, and bloating). For this study, the total GCSI score, representing the sum of symptom scores of the 9 GCSI symptoms will be used.

Gastrointestinal Symptom Rating Scale (GSRS)[24]. A clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease.

Beck Depression Inventory, Second Edition (BDI - II)[25]. The BDI-II is a commonly used, reliable 21-item self-report measure designed to assess for depression.

State Trait Anxiety Inventory[26]. The STAI is a 40-item self-report measure designed to assess both situational and characterological anxiety. This measure provides two subscale scores (State and Trait) and has been shown to exhibit good reliability and internal consistency.

Patient Health Questionnaire (PHQ-15)[27]. The PHQ-15 is a brief, self-report measure of somatization. This test has good internal consistency and reliability.

Brief Pain Inventory. (BPI)[28]. Developed in 1989 by Dr. Charles Cleeland for rapid assessment of the severity and impact of pain in cancer patients. The BPI has since been translated into more than two dozen languages, and is widely used in both research and clinical settings.

SF-36 Health Survey (SF-36)[29]. The SF-36 is a 36-item, self-report measure designed to assess quality of life in patients. This measure also provides two summary scores (physical and mental health) and eight scale scores. It is reliable and internally consistent.

Gastroparesis symptoms/side effect profile: The baseline and follow-up medical histories will inquire about symptoms that may be attributed as side effects of nortriptyline. These symptoms include drowsiness, fatigue, dizziness, seizures, sleep disturbance, palpitations, blurred vision, dry mouth, skin rash, and urinary retention. The symptom profile will include 2 questions:

The global overall relief of symptom question which requests a yes/no answer, asks, "During the past 7 days, have you had adequate relief of your stomach symptoms?".

The clinical global patient impression (CGPI) question helps quantify overall relief of symptoms. This question asks, " Please consider how you felt this past week in regard to your stomach symptoms, in particular your overall well-being and stomach symptoms. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during the past week?

3	2	1	0	-1	-2	-3
Completely Better	Considerably Better	Somewhat Better	Unchanged	Somewhat Worse	Considerably Worse	Very Considerably Worse

5.6 Specimen repository

Biological specimens will be collected and stored for use as approved by the Steering Committee of the GpCRC (see Appendix 9.3 for whole blood draw schedule). Specimens to be stored include plasma and DNA. Blood will be collected at a screening visit and at follow-up visits (weeks 12 and 15) for plasma banking. The blood will be drawn in the morning during the study visit after the subject took the study medication the night before and is still fasting. The blood will be separated into plasma and will be divided into 0.5 mL aliquots. Plasma aliquots will be kept in a freezer at -70 degrees C and will be sent to the NIDDK Biosample Repository for banking. The plasma will be analyzed for nortriptyline levels at the end of the study. Nortriptyline levels will be determined using a Nortriptyline Immunoassay (Syra Co., Palo Alto, CA) similar to that performed in the functional bowel disorder study by Drossman[13].

For each NORIG participant that consents to DNA banking, blood will be collected at a screening visit and will be sent to the NIDDK Genetics Repository. DNA will be extracted and will be stored at -20 degrees C for analyses of CYP2D6 polymorphisms.

5.7 Safety issues

Safety issues can be divided into (a) safety concerns relating to nortriptyline, (b) safety concerns related to study procedures, and (c) concerns related to patient privacy. The following paragraphs discuss the important potential adverse events and the proposed safeguards to minimize the risks involved.

Safety concerns related to nortriptyline:

Study participants will receive nortriptyline or placebo. Nortriptyline is a tricyclic antidepressant (TCA). Tricyclic antidepressants act to inhibit the reuptake of the neurotransmitters norepinephrine and serotonin, leading to an increase in their effects. Contraindications to nortriptyline include: a) hypersensitivity or allergy to any tricyclic antidepressant drug, b) concomitant therapy with a monoamine oxidase inhibitor, c) recent myocardial infarction, and d) glaucoma. The dose (10-75 mg) of nortriptyline in this study is on the lower end of the conventional antidepressant dose (50-150 mg) approved to treat depression. Patients with cardiovascular disease should be given nortriptyline only under close supervision due to increased risk of myocardial infarction, arrhythmia and stroke. Arrhythmias may develop especially in patients with hyperthyroidemia or those receiving thyroid hormone replacement medication. Patients with a history of seizures will be excluded from the study because nortriptyline is known to lower the convulsive threshold. Concurrent administration of cimetidine with nortriptyline can produce

clinically significant increases in the plasma concentrations of nortriptyline.

Study participants will have an electrocardiogram (ECG) during screening and at follow-up visits 9 and 12 weeks after randomization to monitor for any signs of study-drug related toxicity. In addition, a complete blood count (CBC), a metabolic panel including sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogen (BUN), creatinine, and a hepatic panel including albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin will be performed at the week 12 visit. The following treatment interruption or termination rules will be followed:

- If hypokalemia (potassium <3.5mEq/L) or hypomagnesia (magnesium<1.5 mEq/L) is present at the week 12 visit, study participants will be given oral supplementation and electrolyte measures will be repeated within a week. If the electrolyte imbalance has not been remedied with oral supplementation as indicated by a serum potassium of <3.0 mEq/L and serum magnesium of less than 1.0 mEq/L, the study drug will be interrupted or terminated with tapering, as needed. The participant will continue with 15 week and 18 week follow-up visits as scheduled.

- If significant elevations (>2 times upper limit or normal) occur in alkaline phosphatase, alkaline aminotransferase (ALT), or aspartate aminotransferase (AST) at the week 12 visit, these enzymes will be repeated within a week. If any of these enzyme elevations persist above 3 times the upper limit of normal, the study drug will be interrupted or terminated with tapering, as needed. The participant will continue with 15 week and 18 week follow-up visits as scheduled.

- If thrombocytopenia (<100,000 cells per μL) is present at the week 12 visit, the study drug will be interrupted or terminated with tapering, as needed. The participant will continue with 15 week and 18 week follow-up visits as scheduled.

In general, side effects to nortriptyline are fewer than other TCAs since it does not have significant anticholinergic effects, however, side effects can still occur and can include: drowsiness, sedation, fatigue, dizziness, seizures, palpitations, blurred vision, dry mouth, constipation, and skin rash. A standardized management plan for the most common side effects as well as the more serious side effects are outlined below:

COMMON SIDE EFFECTS

Side effect severity	Investigator response
Noticeable but tolerable	Continue therapy and dose escalation
Bothersome and barely tolerable	Reduce dosage to the last dose tolerated without stopping treatment
Intolerable	Discontinue nortriptyline for one week and then restart it at the lower dosage that was previously tolerated

Endocrine metabolic:
Weight gain - Continue study medication with dose escalation as planned.

Gastrointestinal:
Constipation - Continue study medication with dose escalation as planned. Recommend patient to add fiber supplement and to increase fluid intake and drink eight ounce glasses of water daily.
Loss of appetite - Continue study medication with dose escalation as planned.
Nausea - Continue study medication with dose escalation as planned.
Bloating - Continue study medication with dose escalation as planned.
Dry Mouth - Continue study medication with dose escalation as planned. Patient can use sugarless hard candy, gum, or ice chips. Saliva substitutes may be needed.

Neurologic:
Asthenia - Continue study medication with dose escalation as planned.
Dizziness - Make sure patient is taking entire dose at bedtime. This symptom generally subsides after a few weeks. If continues, reduce dose to prior tolerable dose and maintain this dose for remainder of study. Usually dizziness is due to orthostatic hypotension and can be reduced by having the patient change positions slowly.
Headache - Continue study medication with dose escalation as planned.
Somnolence or drowsiness - Continue study medication with dose escalation as planned. Inform patient that this symptom generally subsides after a few weeks. Patient can move the time for medication from 30 min before bedtime to 60 minutes before bedtime. If continues, reduce dose to prior tolerable dose and maintain this dose for remainder of study.
Tremor - This symptom generally subsides after a few weeks. If continues and intolerable for the patient, reduce dose to prior tolerable dose and maintain this dose for remainder of study.
Confusion - Stop medicine for one week, and then restart at lower tolerable dose.

Cardiac: Palpitations/Tachycardia: Obtain ECG and check QTc interval. If normal, stop medication for one week and resume at lower tolerable dose. If ECG is abnormal, instruct patient to stop taking the study drug, monitor and refer as appropriate.

Ophthalmic: Blurred vision - Continue study medication with dose escalation as planned. This symptom generally subsides after a few weeks. If continues and intolerable, reduce dose to prior tolerable dose and maintain this dose for remainder of study.

Urinary: Urinary Retention - Continue study medication with dose escalation as planned. This symptom generally subsides after a few weeks. If continues and intolerable, reduce dose to prior tolerable dose and maintain this dose for remainder of study.

Dermatologic: Skin rash - Investigate if there are other potential causes for skin rash. If tolerable by patient, continue medication with dose escalation as planned. If skin rash worsens during the study, reduce dose to prior tolerable dose and maintain this dose for remainder of study. If skin rash continues to worsen, stop the study medication. Patient remains in study on no treatment.

Other: Fatigue - Continue study medication with dose escalation as planned. Inform patient that this symptom generally subsides after a few weeks. Patient can move the time for medication from 30 min before bedtime to 60 minutes before bedtime. If continues, reduce dose to prior tolerable dose and maintain this dose for remainder of study.

SERIOUS SIDE EFFECTS FOR WHICH STUDY MEDICATION WILL BE STOPPED AND THE PATIENT WILL BE FOLLOWED ON NO TREATMENT.

Patients will call in if they develop blurred vision, rapid heart beat, chest pain, orthostatic hypotension, dizziness upon standing or difficulty urinating.

Cardiovascular: Cardiac dysrhythmias, QTc prolongation (concern is for >440 – 450 msec in men or > 460 – 470 msec in women), concern for development of Torsades de Pointes or sudden death heartblock on ECG myocardial infarction (rare). Stop study medication. Ensure immediate follow-up with a cardiologist. Patient remains in study on no treatment. Repeat ECG after stopping study medication.

Hematologic: Agranulocytosis (rare), bone marrow depression (rare), drug-induced eosinophilia (rare), thrombocytopenia (rare). Stop study medication. Ensure immediate follow-up with a hematologist. Patient remains in study on no treatment.

Hepatic: Decreased liver function (rare), jaundice (rare). Stop study medication. Ensure immediate follow-up with a hepatologist. Patient remains in study on no treatment.

Dermatologic: Signs of an allergic reaction – unexplained hives, unexplained swelling, wheezing, swelling of face, lips, tongue, or throat. Stop medicine. Instruct patient to call 911 or go to emergency room for immediate care. Patient remains in study on no treatment.

Neurologic: Cerebrovascular accident (rare), seizure (rare). Stop study medication. Ensure immediate follow-up with a neurologist. Patient remains in study on no treatment.

Psychiatric: Depression, worsening, suicidal thoughts, suicide - Stop medicine. Refer to mental health professionals. Patient remains in study on no treatment. Symptoms of aggressiveness, akathisia (psychomotor restlessness), agitation, anxiety, insomnia, irritability, hostility, mania, impulsivity, and panic attacks may represent precursors to emerging suicidality.

Treatment with antidepressant agents have been reported to paradoxically be associated with suicide in patients with primary depression. Primary depression is an exclusion for participation in the NORIG trial. We will monitor patients for the most common severe serious side effects (cardiac and psychiatric) by using standardized questionnaires for side effects and the Beck Depression Inventory (BDI) score. The Suicidal Thoughts or Wishes item in statement 9 on the BDI-II will be used to determine if a patient is suicidal. A score of 1 on this item (I have thoughts of killing myself, but would not carry them out) should initiate a referral to a mental health professional for further investigation. A score of 2 (I would like to kill myself) or 3 (I would kill myself if I had the chance) should result in contacting the mental health consultant (pager/phone) for discussion about disposition, i.e., immediate meeting with the mental health consultant or getting the patient to the ER for possible inpatient treatment.

Also, severe depression is suggested by a patient response of 2 or 3 in the BDI-II statement 2 on Pessimism or a score of 28 or more total points on the BDI. With either a response of 2 or 3 on statement 2 or a total score of 28 or more, and in the absence of the suicide item trigger, this would result in a referral to the mental health consultant. Study staff will calculate the BDI total score and check statements 2 and 9 before the patient leaves. For each clinical center, a mental health professional (psychiatrist or psychologist) will be part of the study. Each consent form given to participants will have a self-referral list for psychological assistance if needed. In sum,

- If Severe Depression (BDI-II total > 28) with Statement 9 = 1; then refer for further mental health evaluation as soon as can be arranged (usually same day if patient is agreeable)

- If Suicidal Ideation without intent on Statement 9 = 1; then refer for further mental health evaluation as soon as can be arranged (usually same day if patient is agreeable)

- If Suicidal Ideation with possible intent on Statement 9 > 1; then contact mental health consultant immediately for further evaluation and disposition; handle as possible psychiatric emergency

Approximately half of the patients in NORIG will be assigned to the placebo group and will receive matching placebo instead of nortriptyline for the length of the study. The risks of receiving placebo are the same as not receiving any additional treatment for gastroparesis symptoms. All NORIG participants will be allowed to take the rescue medications for nausea, vomiting, and abdominal pain.

Safety concerns related to study procedures:

***EGG with satiety testing*:** EGG recording involves placement of EGG electrodes on the abdominal surface. There may be some soreness in removing the EGG electrodes. Otherwise, there are no immediate risks to EGG or the consumption of Ensure® during the satiety test.

***Other Risks*:** Blood draw may cause discomfort, such as swelling, temporary sensation of pain, or burning and/or a bruise that may develop and last for a few days. Less common risks include a blood clot at the site of puncture or swelling of the vein and surrounding tissues, and possible bleeding from the puncture site.

Safety issues related to patient privacy:

It is the investigator's responsibility to conduct the protocol under the current version of Declaration of Helsinki, Good Clinical Practice, and rules of local IRBs. The investigator must ensure that the patient's anonymity be maintained in their data submission to the Data Coordinating Center. Patients will be identified only by an identification code but not by their name, SSN, or hospital medical record number. Investigators will maintain a separate confidential enrollment log which matches identifying codes with the patients' names and addresses (i.e., available only to local clinic staff). All study material will be maintained in strict confidence.

5.8 Adherence and retention

Two important goals of this protocol are to optimize adherence to the pharmacological regimen and to maximize the retention of participants in the study. Assessment of adherence to the assigned study medication will provide clinic staff a means to identify participants having problems with adherence. Adherence will be assessed by:

- Counts of capsules in the patient's returned study medication bottles
- Conducting a brief, structured interview, in which the study coordinator will assist the patients to identify problems in taking the study medication and to estimate adherence to the prescribed medicine since their previous visit.

These assessments will guide the consideration of strategies to improve adherence.

5.9 Management of concomitant conditions

All other illnesses will be managed in conjunction with the patient's primary care physician according to the protocols described in the Standards of Care for Patients with Idiopathic Gastroparesis (SOP IV) document prepared by the GpCRC Steering Committee.

In the event of major dermatological reactions such as generalized urticaria, bullous rashes, exfoliative dermatitis, or Stevens-Johnson Syndrome, study medication will be discontinued immediately and not restarted. For local skin reactions, study medication may be discontinued if the skin reactions are potentially drug related. If the rashes clear, the study medication may be restarted. If local skin reactions recur with restarting the study medication, study medication should be discontinued. In cases where the study medication has been discontinued, the study medication will be unmasked after the completion of the trial and the participant, investigator, and the primary care provider will be notified in order to prevent future exposures.

5.10 Food and Drug Administration

The NORIG trial will be conducted under an Investigational New Drug (IND #102,404) held by the NIDDK. The investigators will complete a Statement of Investigator (FDA Form 1572) per the Code of Federal Regulations before the initiation of the NORIG trial. The safety data required to meet IND regulatory requirements will be collected through adverse event reporting by the clinic investigators and will be provided by the Data Coordinating Center to the NIDDK for transmission to the FDA.

5.11 Adverse event reporting

The NORIG trial will monitor and report adverse events to ensure patient 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", shared by 17 Departments and Agencies and (2) 21 CFR 312, 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." Since the definitions and reporting requirements for unanticipated events differ between the two sets of Federal regulations, the NORIG trial definitions and procedures for adverse events are designed to satisfy both sets of requirements.

Definitions

Adverse event. An adverse event is any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product or clinical procedure and which may or may not have a causal relationship with the treatment. Adverse events include any unanticipated problems involving risks to participants, or breaches of protocol which might entail risk to participants. The term "unanticipated problem" includes both new risks and increased rates of anticipated problems.

Serious adverse event. A serious adverse event (SAE) is an adverse event occurring at any time during the study that results in death, life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Other events may also be considered an SAE if, based on medical judgment, the event jeopardized the patient to the point of requiring medical or surgical intervention to prevent the occurrence of any of the conditions for an SAE listed above.

Unexpected adverse event. An unexpected adverse event is any adverse event with specificity or severity that is not consistent with the risk information in the study protocol, current investigator brochure, or current package insert.

Associated with the use of the drug means that there is a reasonable possibility that the adverse experience may have been caused by the drug.

Adverse events will be recorded on study data forms whether or not they are thought to be associated with the study or with one of the study drugs. Adverse events may be discovered during regularly scheduled visits or through unscheduled patient 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[30].

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.

Reporting serious adverse events

Serious adverse events (SAE) must be reported upon discovery at the clinical center per local IRB guidelines. This may involve completing an SAE form per local IRB guidelines, describing the severity and details of the event. If the serious adverse event is judged by the study physician to be associated with the study drug and unexpected per the package insert and above definitions, the SAE form, together with a memo summarizing the circumstances of the event and the current status of the patient, must be faxed to the Data Coordinating Center and to the NIDDK project officer within one working day of the discovery of the SAE and confirm receipt via email of telephone. The NIDDK project officer will work with the Data Coordinating Center to transmit the SAE form and memo to the DSMB Chairperson and Steering Committee members and all participating center investigators.

The DSMB Chair and NIDDK Project Officer will determine if all DSMB members should be made aware of the event at that time, or it is appropriate to wait until the next DSMB meeting. The DSMB wishes to remain masked, therefore, the SAE report should not unmask the readers.

As described above, if the serious adverse event is judged by the study physician as both unexpected AND associated with the study drug, then the NIDDK project officer will work with the DCC to notify the Steering Committee, all participating center investigators, the DSMB and the FDA no later than 15 days from the discovery of the SAE (no later than 7 days if the SAE is fatal or life threatening). The clinical center investigator may also complete an FDA MedWatch 3500 form.

The DSMB will review all SAE reports, at least quarterly. 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 expeditiously.

The clinical center must submit to the NIDDK project officer and to the Data Coordinating 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 NIDDK project officer will work with the Data Coordinating Center to distribute the follow-up memo to the Steering Committee, all participating center investigators and to the DSMB.

5.12 Procedures for unmasking treatment assignment

Treatment assignments are double masked throughout the study until all data collection for the NORIG trial has been completed (i.e., after completion of the 18 weeks of treatment and follow-up for all patients). Every effort will be made to maintain the masking throughout the study except in emergency situations. The code for masked study drug will not be broken without the knowledge of the clinical center's principal investigator. Even if the study drug is interrupted or terminated, as needed, the participant will continue with remaining NORIG follow-up visits as scheduled.

Unmasking of study medication will occur under the following conditions:

- **Severe allergic reaction (Stevens-Johnson Syndrome)**: Study medication is stopped indefinitely. The patient, 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 patient, PCP, and investigator will be notified of the assigned treatment and the associated risks of teratogenicity.

- **Development of significant arrhythmias**: Study medication is stopped indefinitely. The patient, primary care provider (PCP), and the investigator will be unmasked.

- **Development of persistent electrolyte imbalance**: As described in Section 5.7, if the electrolyte imbalance has not been remedied with oral supplementation as indicated by a serum potassium of <3.0 mEq/L and serum magnesium of less than 1.0 mEq/L, the study drug will be stopped. The patient, primary care provider (PCP), and the investigator will be unmasked.

- **Development of persistent enzyme elevation**: As described in Section 5.7, if alkaline phosphatase, alkaline aminotransferase (ALT), or aspartate aminotransferase (AST) enzyme elevations persist above 3 times the upper limit of normal, the study drug will be stopped. The patient, primary care provider (PCP), and the investigator will be unmasked.

- **Development of thrombocytopenia**: As described in Section 5.7, if thrombocytopenia <100,000 cells per μL develops, the study drug will be stopped. The patient, primary care provider (PCP), and the investigator will be unmasked.

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 occur.

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6. Statistical design and analysis

6.1 Hypotheses

Primary hypothesis:

- Treatment with nortriptyline, compared to treatment with placebo, will result in a sustained reduction in Gastroparesis Cardinal Symptom Index (GCSI) score of 50% or greater from baseline in patients with idiopathic gastroparesis.

Secondary hypotheses:

- Pharmacogenetic profiles of patients with idiopathic gastroparesis will identify subgroups of patients with differential response to nortriptyline, compared to placebo.
- Subgroups of patients with higher blood levels of nortriptyline during follow-up will experience a better response compared to placebo and compared to patients with lower blood levels of nortriptyline.
- Patients in the nortriptyline group will have improved satiety testing, but no change in electrogastrography compared to placebo.
- Treatment with nortriptyline will result in improved global overall relief of symptoms and Clinical Global Patient Impression (CGPI) compared to placebo.
- Patients in the nortriptyline group will have improvements in standardized quality of life scores, compared to placebo.
- A dose escalation strategy can be successfully used to optimize the dose of nortriptyline to maximize clinical benefit and reduce side effects.

6.2 Outcome measures

Primary outcome measure:

The primary outcome measure is defined as a decrease from the baseline GCSI score (sum of the 9 individual symptom scores) of at least 50% on any two consecutive follow-up visits during the 15 week treatment period with maximum tolerated study drug dose. A sensitivity analysis will compare cumulative GCSI symptom scores averaged across all follow-up visits to rule out the possibility that an effect present in the primary analysis was due to the GCSI score decreasing 50% on two consecutive visits with smaller improvement or worsening on other follow-up visits.

All patients will be followed for the full 18 weeks after randomization regardless of response or

course of treatment to permit an intention-to-treat primary analysis.

The GCSI total score ranges from 0 to 45 (highest severity) and is calculated as the sum of nine individual symptom scores:

GCSI = Nausea (0-5) +
Retching (0-5) +
Vomiting (0-5) +
Stomach fullness (0-5) +
Not able to finish a normal sized meal (0-5) +
Feeling excessively full after meals (0-5) +
Loss of appetite (0-5) +
Bloating (0-5) +
Stomach visibly larger (0-5)

As noted earlier, a GCSI score of 21 or greater is a requirement for enrollment into the trial. The primary outcome measure is a binary (0, 1) variable, which equals to 1, if a GCSI score reduction of 50% or greater, relative to the baseline score, is observed on at least two consecutive follow-up visits during the 15 weeks of treatment and follow-up.

Secondary outcome measures will be defined to address the following areas:
(1) Symptoms
- Subscores for the GCSI such as nausea/vomiting, postprandial fullness, bloating
- Individual symptom scores
- Global overall relief of symptom questionnaire
- Clinical global patient impression

(2) Physiology
- Satiety test: Volume of Ensure® consumed during satiety testing
- Electrogastrography: Percent time in EGG dysrhythmias (outside 2.5-3.75 cycles per minute)
- Side effects to treatment requiring stopping medication

Subgroup differences in response to nortriptyline will be addressed:
(1) Differential response to nortriptyline based on pharmacogenetic analysis of patients
(2) Differential response to nortriptyline based on blood levels of nortriptyline

6.3 Statistical analysis

The primary analysis will be made on "intention to treat" basis[31], which means that all randomized patients with GCSI scores at baseline and at any time during 15 weeks of treatment will be analyzed in the treatment group to which they were assigned. Any randomized patient who does not have the requisite GCSI scores will be treated as a non-responder and compared by assigned treatment group. Primary comparisons will be of the full nortriptyline group versus the full placebo group. Secondary, sensitivity analyses on a per-protocol basis will also be carried out, excluding patients from both groups who do not complete at least 60% (9 weeks) of the 15 weeks on assigned treatment.

Since the primary outcome measure is a binary indicator of improvement in GCSI score and since the randomization is stratified by clinic, P-values will be derived from the Mantel-Haenszel χ^2 test for stratified 2x2 tables[32], with stratification by clinic, comparing proportions improved in the group assigned to nortriptyline compared to the group assigned to placebo. The P-values so derived will be reported in the primary paper on the results of the trial. A P-value of 0.05 will be considered statistically significant.

Given the randomized design and adequate size planned for the NORIG trial, it is unlikely that confounding of the treatment groups by covariates related to the change in GCSI score will occur. However, if confounding should occur, sensitivity analyses using logistic regression models with GCSI score improvement as the binary response and treatment group indicator and any suspected confounders as covariates will be carried out to determine the sensitivity of the primary P-value to confounding; however, the Mantel-Haenszel derived P-value will be the primary P-value reported.

The first two secondary hypotheses listed above relate to differential effects of treatment in subgroups of patients defined by pharmacogenetic profiles and adherence levels (nortriptyline blood levels), respectively. The profiles and blood level cut offs will not be pre-defined, but will be made on the basis of the best available information at the time of analysis. To assess whether differential effects are present, a logistic regression model for the primary outcome with random effects for clinic and fixed effects for treatment group, subgroup indicator variables, and treatment group by subgroup interaction effects will be used. The evidence for differential subgroup effects will be considered statistically significant if the P-value for the interaction terms is <0.01.

Analyses related to the other secondary hypotheses (excluding the dose-escalation hypothesis, which will be addressed empirically) will be conducted in two ways. Improvement will be analyzed both as a binary outcome (improved vs. not improved) and also in terms of the numerical change in the outcome. Binary outcomes will be compared using the Mantel-Haenszel χ^2 test for stratified 2x2 tables[32.] Numerical changes will be analyzed by descriptively comparing the between-treatment group differences in mean and median changes; P-values will be derived from Wilcoxon rank sum tests for comparison of the distribution of changes in each group. If concerns about confounding arise, logistic regression models for improvement outcomes and linear regression models for numerical change outcomes will be used to correct for the confounding. No adjustments for multiple comparisons will be applied to the secondary hypotheses, which are pre-specified; however, any significant findings will be interpreted cautiously, taking into account the strength of the finding and its biologic plausibility.

6.4 Missing data

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 estimate that careful selection of patients during the screening phase and the consent process should result in no more than 10% missing data from patients who drop out before completing the full 15 week treatment period and the 3 week post-treatment follow-up. In the primary, intention-to-treat analysis, patients with a pattern of missing data that precludes determination of the primary outcome according to its definition will be counted as unimproved.

The proportions with missing data will be compared across treatment groups using χ^2 tests. If the amount of missing data exceeds 10%, then a variety of sensitivity analyses will be carried out to compare to the primary analysis using all available non-missing data and assuming that the missingness is either missing completely at random (MCAR) or missing at random (MAR): (1) compare pessimistic and optimistic imputations of the missing values, (2) correct for missing data using multiple imputation with 10 replicated samples, and (3) use mixed random effects logistic or linear regression models, depending on the type of outcome measure. It is possible that the missingness is not MCAR or MAR, but is missing not at random (MNAR). Few statistical methods are available when there are non-ignorable missing data patterns and these may be employed to assess sensitivity of the results to non-ignorable missing data if the level of missing data exceeds 10%; however, all such methods involve strong assumptions that cannot be verified from the available data.

6.5 Justification of sample size

The planned sample size for the NORIG trial is 130 patients with equal allocation to each of the two treatment groups (65 per group).

We based the sample size estimates on a two-group, binomial comparison of the proportions of patients satisfying the primary outcome, improvement in the GCSI score over the course of treatment. For sample size purposes, the expected proportions improved (0.6 in the nortriptyiline group compared to 0.3 in the placebo group), were derived from the expert opinions of clinicians on the GpCRC Steering Committee, based on their experience with the GCSI in patients with idiopathic gastroparesis similar to those meeting the eligibility criteria for the trial. The size of the smallest clinically meaningful effect (0.60 vs 0.30 response rates) was also based on the expert opinion of Steering Committee, taking into account the expected missing data rate of 10% and its consequent reduction in improvement rates.

The sample calculations were performed using the nQuery Advisor 5.0[33] software, which uses the formula:

$$n = \frac{\left[z_{1-\alpha/2}\sqrt{2\bar{\pi}(1-\bar{\pi})} + z_{1-\beta}\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}\right]^2}{(\pi_1-\pi_2)^2}$$

where,

n = sample size per group

π_1 = expected proportion with 50% improved GCSI in placebo group (assumed=0.30)

π_2 = expected proportion with 50% improved GCSI in nortriptyline group (0.60)

$\bar{\pi}$ = average of π_1 and π_2

α = Two-sided type I error (0.05)

β = Type II error (0.10; i.e., 90% power)

The number per group, using the above formula is 56 for a total of 112. To allow for possible mis-specification in the estimated response rates used in the calculation, we propose a sample size of 65 patients per group, or a total of 130 for the trial.

6.6 Interim analysis

An independent Data and Safety Monitoring Board (DSMB), appointed by the NIDDK, is responsible for approving the protocol for the NORIG trial and for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy. The DSMB is a multi-disciplinary group with a written charge provided by the NIDDK. The DSMB reports to the NIDDK, which will, in turn, communicate DSMB recommendations to the investigators, as appropriate.

The DSMB meets to approve the protocol. After the trial commences, the DSMB meets twice a year to review data or other issues. 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.

Interim data on safety measures requested by the DSMB are reviewed at each of the scheduled semi-annual full meetings. Two additional written safety reports will be reviewed by the DSMB between scheduled full meetings. Serious adverse events will be reviewed by the DSMB as they occur with the option of a teleconference discussion if any DSMB member so requests.

The DSMB reviews one planned interim analysis of the primary outcome measure. O'Brien-Fleming statistical stopping guidelines for efficacy apply. This interim efficacy analysis will occur when approximately 50% of the data are complete or when approximately 65 of the 130 patients have completed the 18 week trial. The interim monitoring bounds were adjusted for one interim look as follows: We propose guidelines (boundaries) with O'Brien-Fleming[34] Type 1 error spending functions for the primary outcome.

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.

7. Human subjects issues

Overview and IRB approval

The study protocol and consent form will be submitted to each clinical center's IRB. Additionally, each clinical center will submit to their IRB any recruitment materials to be used at their site. A clinical center may not initiate any patient contact about the NORIG Trial until the center has IRB approval and the DCC has certified the center for initiation of patient activities. Consent forms must have IRB approval. Centers must provide the DCC with copies of the initial IRB approval notice and subsequent renewals, as well as copies of the IRB approved consent statement. All study personnel will have completed training in the Protection of Human Subjects per NIH guidelines.

The proposed study anticipates recruiting a significant proportion of women and racial/ethnic minorities (African American, Hispanics or Latino, Asian, American Indian/Alaska Native, Native Hawaiian or other Pacific Islander) as well as non-Hispanic white subjects. We anticipate that the patients will be recruited from diverse sources, largely from tertiary referral populations and will represent the entire spectrum of idiopathic gastroparesis.

All subjects enrolled in the NORIG Trial will receive the standard of care for idiopathic gastroparesis and identified associated medical problems as defined by the GpCRC Steering Committee (see Standards of Care for Patients with Gastroparesis). This will include provision of health care counseling and educational materials at enrollment and during follow-up.

Informed Consents

A prototype consent will be prepared for the study. Individual centers may add material but may not delete material thought to be necessary for informed consent. Centers may reformat and reword information to conform to their local IRB requirements. A signed consent form will be obtained from the subject. 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 subject and this fact will be documented in the subject's record.

Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that are part of the study data collection and entry materials will be identified by coded number only to maintain subject confidentiality. All records will be kept in locked file cabinets with access limited to GpCRC investigators. All computer entry and networking programs will identify patients by patient identification number. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB or DSMB. Clinical information may be reviewed during site visits, but use of personal identifiers will be avoided. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with individual center IRB and NIH requirements for compliance with The Health Insurance Portability and Accountability Act (HIPAA).

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9. Appendices

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9.1 Participating centers

Clinical Centers

- Stanford University
  - California Pacific Medical Center
- Temple University
- Texas Tech University Health Science Center
- University of Michigan
- University of Mississippi Medical Center
- Wake Forest University Medical Sciences

Data Coordinating Center:

- Johns Hopkins University

National Institutes of Health:

- National Institute of Diabetes and Digestive and Kidney Diseases

9.2 Data collection schedule

	Screening Visits			Follow-up visits Weeks from randomization					
Assessment/Procedure	**s1**	**s2**	**rz**	**3**	**6**	**9**	**12**	**15**	**18**
Consent	X	.	.	.	.	.	.	.	.
Gastric emptying scintigraphy review	X	.	.	.	.	.	.	.	.
Upper endoscopy review	X	.	.	.	.	.	.	.	.
Baseline medical history	X	.	.	.	.	.	.	.	.
PAGI-SYM questionnaire	X	.	.	X	X	X	X	X	X
GSRS questionnaire	X	.	.	X	X	X	X	X	X
SF-36 QOL questionnaire	X	.	.	.	.	X	.	X	.
Beck Depression Inventory-II	X	.	.	X	X	X	X	X	X
State Trait Anxiety Inventory	X	.	.	.	.	X	.	X	.
Brief Pain Inventory	X	.	.	.	.	X	.	X	.
PHQ-15 questionnaire	X	.	.	.	.	X	.	X	.
Electrocardiogram (ECG)	X	.	.	.	.	X	X	.	.
Physical exam	X	.	X	.	.	X	X	X	.
Satiety test with electrogastrography (EGG)	.	X	.	.	.	.	X	.	.
Study drug dispensed	.	.	X	X	X	X	X	.	.
Review of study drug adherence	.	.	.	X	X	X	X	X	X
Follow-up medical history including review of adverse events	.	.	.	X	X	X	X	X	X
Labs	.	.	.	.	.	.	.	.	.
CBC, metabolic and hepatic panel	X	.	.	.	.	.	X	.	.
TSH	X	.	.	.	.	.	.	.	.
Plasma banking	.	X	.	.	.	.	X	X	.
DNA banking	.	X	.	.	.	.	.	.	.
Pregnancy test	X		X	.	.	X	X	X	.

Physical exam: includes measurement of weight, height, waist and hip circumferences, vital signs (temperature, heart rate, blood pressure) general physical findings

CBC: Complete blood count: white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count

Metabolic panel: sodium, potassium, chloride, carbon dioxide, glucose, calcium, magnesium, blood urea nitrogen (BUN), creatinine.

Hepatic Panel: albumin, total protein, bilirubin, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST)

TSH: Thyroid Stimulating Hormone

9.3 Whole blood draw schedule

	Study visit (wk)								
Procedure	s1	s2	3	6	9	12	15	18	**Total**
Complete blood count	5	.	.	.	.	5	.	.	**10**
Metabolic panel	5	.	.	.	.	5	.	.	**10**
Hepatic panel	5	.	.	.	.	5	.	.	**10**
Thyroid stimulating hormone	5	.	.	.	.	.	.	.	**5**
Blood for DNA banking - including pharmacogenomic analysis	.	20	.	.	.	.	.	.	**20**
Blood for plasma banking - including study drug level measurement	.	10	.	.	.	10	10	.	**30**
Total (in mL)	**20**	**30**	**0**	**0**	**0**	**25**	**10**	**0**	**85**

Complete blood count: white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count

Metabolic panel: sodium, potassium, chloride, carbon dioxide, glucose, calcium, magnesium, blood urea nitrogen (BUN), creatinine

Hepatic panel: albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin

9.4 Glossary

ALP	-	alkaline phosphatase
ALT	-	alanine aminotransferase
AST	-	aspartate aminotransferase
BMI	-	body mass index (kg/m^2)
BUN	-	blood urea nitrogen
CBC	-	complete blood count
CGPI	-	Clinical Global Patient Impression question
C-kit	-	CD117; a tyrosine kinase receptor type III
CMP	-	complete metabolic panel
CPM	-	cycles per minute
CTCAE	-	Common Terminology Criteria for Adverse Events
CYP	-	cytochrome P450 enzyme
CYP2D6	-	enzyme that metabolizes nortriptyline; can affect drug levels and efficacy
DCC	-	Data Coordinating Center
DSMB	-	Data and Safety Monitoring Board
EGG	-	electrogastrography
FD	-	functional dyspepsia
FDA	-	Food and Drug Administration
GE	-	gastric emptying
GCSI	-	Gastroparesis Cardinal Symptom Index
GpCRC	-	Gastroparesis Clinical Research Consortium
GpR	-	Gastroparesis Registry
GSRS	-	Gastrointestinal Symptom - Rating Scale
HbA1c	-	glycosylated hemoglobin A1c
HIPAA	-	Health Insurance Portability and Accountability Act
ICC	-	interstitial cells of Cajal
IND	-	Investigational New Drug application
IRB	-	Institutional Review Board
MAOI	-	monoamine oxidase inhibitor
MAR	-	missing at random
NIDDK	-	National Institute of Diabetes and Digestive and Kidney Diseases
NORIG	-	Nortriptyline for Idiopathic Gastroparesis
PAGI-SYM	-	Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index
po	-	by mouth, orally
PHQ-15	-	Patient Health Questionnaire on somatization
qhs	-	at bedtime
QTc	-	QT interval corrected for heart rate; time between start of the Q wave and end of the T wave in the heart's electrical cycle
SAE	-	serious adverse event
SOP	-	standard operating procedures
SSRI	-	selective serotonin reuptake inhibitor
TCA	-	tricyclic antidepressant
TSH	-	thyroid stimulating hormone
WBC	-	white blood cell count

9.5 Document History

Nortriptyline for Idiopathic Gastroparesis (NORIG) Protocol (02 May 08)

Nortriptyline for Idiopathic Gastroparesis (NORIG) Protocol (31 July 08)

Numerous editorial and wording changes were made to the following sections:

§ IND #102, 404 added to the cover page

§ Design synopsis:

Changed **Study duration – per calendar time**

- Recruitment phase: September 2008 - March 2010
- Follow-up phase: September 2008 - August 2010
- Added to sample size justification
- Total of 140 patients in 2 groups of equal size (70 per group)
- Primary comparison: nortriptyline vs. placebo
- Error protection: Type I = 0.05 and Type II = 0.10 (90% power)
- Minimum clinically important difference (MCID): 50% reduction in GCSI outcome (see below) during 15 weeks of treatment
  - Expected percent with improved GCSI in the placebo group: 30%
  - Expected percent with improved GCSI in the nortriptyline group: 60%
  - Source of estimates of MCID: Consensus of GpCRC clinicians
- Statistical test and sample size software
  - Chi-squared test for two proportions
  - Dupont and Plummer PS software
- Exclusion criteria
  - Changed "Gastroparesis from diabetic on post-surgical etiologies" to "Diabetic gastroparesis or post-surgical gastroparesis including fundoplication"
  - Added: Use of erythromycin
  - Added: Use of a G tube, J tube, central catheter, or gastric electrical stimulator

§3.3 Study drug dosing schedule

- The 2nd paragraph, 5th sentence: Changed "At week 3, dose will be increased to one 25 mg capsule for the next 3 weeks; at week 6, dose will be increased to 50 mg (two 25 mg capsules) for the next 3 weeks; at week 9, dose will be increased to 75 mg (three 25 mg capsules) for the remaining 6 weeks until 15 weeks after randomization." to "At the week 3 visit, study drug dose will be increased to one 25 mg capsule for the next 3 weeks, if well tolerated. At the week 6 visit, study drug dose will be increased to 50 mg (two 25 mg capsules) for the next 3 weeks, if well tolerated. At the week 9 visit, a follow-up electrocardiogram (ECG) will be performed, the ECG findings will be reviewed and if well tolerated, the study drug dose will be increased to 75 mg (three 25 mg capsules) for the remaining 6 weeks until 15 weeks after randomization.

At the week 12 visit, patients will have a second follow-up ECG and a blood draw for a complete blood count, metabolic and hepatic panel, and if well tolerated, the study drug dose will remain the same at 75 mg (three 25 mg capsules) for the remaining 3 weeks of treatment phase of NORIG trial.

§3.5 Standard treatment recommendations

- The 4th sentence: Changed "If symptoms require further treatment during the trial, patients will be instructed to take rescue medications that they would usually take such as ondansetron or prochlorperazine for nausea and vomiting and tramadol for abdominal pain." to "If symptoms require further treatment during the trial, patients will be instructed to take rescue medications that they would usually take such as ondansetron or promethazine for nausea and vomiting and propoxyphene or propoxyphene with acetaminophen for abdominal pain.

§4.1 Recruitment

- Changed recruitment phase from 2 years to 18 months
- Added: California Pacific Medical Center, San Francisco, CA (PI: William Snape, MD) as a satellite center under Stanford University

§4.3 Exclusion criteria

- Changed item 2 from "Gastroparesis from diabetic or post-surgical etiologies" to "Diabetic gastroparesis or post-surgical gastroparesis including fundoplication"
- Added item: Use of erythromycin
- Added item: Use of a G tube, J tube, central catheter, or gastric electrical stimulator

§4.4 Run in period

- Changed to 3rd sentence "Patients must not have used a narcotic analgesic for abdominal pain, anticholinergic drugs or calcium channel blockers on a daily basis for the 6 weeks prior to randomization." to "Patients must not have used a narcotic analgesic for abdominal pain, strongly anticholinergic drugs, calcium channel blockers, or erythromycin on a daily basis for the 6 weeks prior to randomization."

§5.2 Screening and baseline data collection overview

- Changed last 2 sentences "Prior therapy for gastroparesis will be reviewed, and patients will be asked to stop specific treatments such as tricyclic antidepressants, monoamine oxidase inhibitors, strongly anticholinergic medications, calcium channel blockers and narcotic pain medication including fentanyl patches more than 3 days per week. " to "Prior therapy for gastroparesis will be reviewed, and patients will be asked to stop specific treatments such as tricyclic antidepressants, monoamine oxidase inhibitors, strongly anticholinergic medications, calcium channel blockers, and erythromycin. Narcotic pain medication including fentanyl patches and other rescue medications such as propoxyphene or propoxyphene with acetaminophen may not be used more than 3 days per week."

§5.2 Screening visit 1

- Added use of erythromycin as an exclusion
- Changed "Laboratory test results that need to be recorded from chart review or obtained as part of screening visit 1 include: complete blood count (CBC): white blood cell count, red blood cell count, white blood cell differential, hemoglobin, hematocrit, platelet count), metabolic panel: (sodium, potassium, chloride, bicarbonate, calcium, phosphate, blood urea nitrogen (BUN), creatinine, uric acid, albumin, total protein), and thyroid stimulating hormone (TSH) levels." to "Laboratory test results that need to be recorded from chart review or obtained as part of screening visit 1 include: complete blood count (CBC): white blood cells, red blood cells, white blood cell differential, hemoglobin, platelets; a metabolic panel: sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogren (BUN), creatinine; a hepatic panel: albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and thyroid stimulating hormone (TSH).
- Changed ABDiagnostics to Advanced Breath Diagnostics in this section and throughout

§5.2 Week 9 visit

- Changed 3rd sentence to "Once the questionnaires are completed, the patient will have an electrocardiogram (ECG) followed by the EGG and satiety test. Review ECG findings, study drug adherence and tolerance with the 50 mg dose of study drug since the week 6 visit with patient."

§5.2 Week 12 visit

- Changed 3rd sentence from: "Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question as assessed at baseline; physical exam (temperature, heart rate, respiratory rate, blood pressure); 10 mL of blood will be drawn for plasma banking, and the following questionnaires should be completed:" to "They will have 25 mL of blood drawn for banking and analysis; 10 mL of blood will be drawn for plasma banking; and 15 mL will be drawn for a complete blood count (white blood cells, red blood cells, white blood cell differential, hemoglobin, hematocrit, platelets), a metabolic panel (sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogen (BUN), creatinine), and a hepatic panel (albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin)."
- Changed 4th sentence: "Review study drug adherence and tolerance with the 75 mg dose of study drug since the week 9 visit with patient." to " Review ECG findings, study drug adherence and tolerance with the 75 mg dose of study drug since the week 9 visit with patient."

§5.2 Week 15 visit

- Changed 3rd sentence: "Review study drug adherence and tolerance with the 75 mg dose of study drug since the week 12 visit with patient." to "Review laboratory results, study drug adherence and tolerance with the 75 mg dose of study drug since the week 12 visit with patient. "

§5.2 Safety concerns related to nortriptyline

- Added new 2nd paragraph:
  Study participants will have an electrocardiogram (ECG) during screening and at follow-up visits 9 and 12 weeks after randomization to monitor for any signs of study drug-related toxicity. In addition, a complete blood count (CBC), a metabolic panel including sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogen (BUN), creatinine, and a hepatic panel including albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin will be performed at the week 12 visit. The following treatment interruption or termination rules will be followed:
- If hypokalemia (potassium <3.5mEq/L) or hypomagnesia (magnesium<1.5 mEq/L) is present at the week 12 visit, study participants will be given oral supplementation and electrolyte measures will be repeated within a week. If the electrolyte imbalance has not been remedied with oral supplementation as indicated by a serum potassium of <3.0 mEq/L and serum magnesium of less than 1.0 mEq/L, the study drug will be interrupted or terminated with tapering, as needed. The participant will continue with 15 week and 18 week follow-up visits as scheduled.
- If significant elevations (>2 times upper limit of normal) occur in alkaline phosphatase, alkaline aminotransferase (ALT), or aspartate aminotransferase (AST) at the week 12 visit, these enzymes will be repeated within a week. If any of these enzyme elevations persist above 3 times the upper limit of normal, the study drug will be interrupted or terminated with tapering, as needed. The participant will continue with 15 week and 18 week follow-up visits as scheduled.
- If thrombocytopenia (<100,000 cells per μL) is present at the week 12 visit, the study drug will be interrupted or terminated with tapering, as needed. The participant will continue with 15 week and 18 week follow-up visits as scheduled

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§5.10 Food and Drug Administration

- IND # 102, 404 replaced #TBD in the 1st sentence.

§5.12 Procedures for unmasking treatment assignment

- Added the following to the end of the1st paragraph: “Even if the study drug is interrupted or terminated, as needed, the participant will continue with remaining NORIG follow-up visits as scheduled.”
- Added to: Unmasking of study medication will occur under the following conditions:

- **Development of persistent electrolyte imbalance**: As described in Section 5.7, if the electrolyte imbalance has not been remedied with oral supplementation as indicated by a serum potassium of <3.0 mEq/L and serum magnesium of less than 1.0 mEq/L, the study drug will be stopped. The patient, primary care provider (PCP), and the investigator will be unmasked.

- **Development of persistent enzyme elevation**: As described in Section 5.7, if alkaline phosphatase, alkaline aminotransferase (ALT), or aspartate aminotransferase (AST) enzyme elevations persist above 3 times the upper limit of normal, the study drug will be stopped. The patient, primary care provider (PCP), and the investigator will be unmasked.
- **Development of thrombocytopenia**: As described in Section 5.7, if thrombocytopenia <100,000 cells per μL develops, the study drug will be stopped. The patient, primary care provider (PCP), and the investigator will be unmasked.

§9.1 Participating centers
- Added: California Pacific Medical Center, San Francisco, CA (PI: William Snape, MD) as a satellite center under Stanford University

§9.2 Data collection schedule
- Data collection schedule was revised

§9.3 Whole blood draw schedule
- Whole blood draw schedule was revised

§9.4 Glossary
- Added entries for ALP, ALT and AST

§9.5 Document History
- Added document history

Nortriptyline for Idiopathic Gastroparesis (NORIG) Protocol (12 August 2009)

Editorial and wording changes were made to the following sections:

§ Design synopsis:
- Population: Changed age from 25 to 21
- Study Duration-per calendar time: Changed recruitment phase to January 2009- June 2010
  Changed follow-up phase to January 2009-November 2010
- Number of clinical centers: changed from 5 to 7
- Inclusion criteria: "Changed Age 25 through 65 years old at registration to" "Age 21 through 65 years old at registration"
- Exclusion criteria: Changed "Use of a G tube, J tube, central catheter or gastric electrical stimulator" to "Use of a G tube, J tube, or a central catheter for nutrition"
  Added "Use of a gastric electrical stimulator"

§3.2 Treatment groups
- Under Group 2 removed extra "po qhs x 15 wks" after f09 visit

§4.1 Recruitment

- Changed "Approximately 140 patients will be recruited from the five clinical centers of the GpCRC (averaging 28 patients per center) over an 18 month period" to "Approximately 140 patients will be recruited from the seven clinical centers of the GpCRC (averaging 23 patients per center over an 18 month period"
- Added Texas Tech University Health Science Center

§4.2 Inclusion criteria

- Changed "Age 25 through 65 years old at registration" to "Age 21 through 65 years old at registration"

§4.3 Exclusion criteria

- Changed "Use of a G tube, J tube, central catheter or gastric electrical stimulator"' to "Use of a G tube, J tube, or a central catheter for nutrition"
- Added "Use of a gastric electrical stimulator"

§5.2 Screening visit 1- Baseline gastric emptying breath test

- Changed 4th sentence from **"**The patient is then administered the standardized 230 kCal meal consisting of a standardized ^{13}C-labeled egg component and 6 saltine crackers. " to "The patient is then administered a standardized 230 kCal meal consisting of ^{13}C-labeled egg component and 6 saltine crackers."

§5.2 Screening visit 2

- Changed 2nd sentence from "They will have 30 mL of blood drawn for plasma and DNA banking; 20 mL of the blood drawn will be used for DNA banking for future pharmacogenomic analysis of CYP450 2D6 alleles; and 10 mL will be used for plasma banking for future measurement of the study drug blood levels." to "They will have blood drawn for plasma and DNA banking; 20 mL of the blood drawn will be used for DNA banking for future pharmacogenomic analysis of CYP450 2D6 alleles; and 10 mL will be used for plasma banking for future measurement of the study drug blood levels."
- Changed 2nd to last sentence of the section from "Clinical center staff can use this task to identify the items that still need to be completed, keyed, or verified after data from screening visits 1 are keyed, and again after data from screening visit 2 are keyed." to "Clinical center staff can use this task to identify the items that still need to be completed, keyed, or verified after data from screening visits are keyed."

§5.2 Screening visit 2- Electrogastrography with satiety testing

- Changed 7th sentence from "Patients will undergo a 30 minute baseline EGG recording." to "Patients will undergo a 15 minute baseline EGG recording."

§5.3 Randomization visit

- Changed 2nd sentence from **"**Randomization can only occur after eligibility has been fully checked and all data collected at screening visits 1 and 2 have been keyed to the trial database." to **"**Randomization can only occur after eligibility has been fully checked and all data collected at screening visits have been keyed to the trial database."

§5.4 Follow-up visits

- Changed 1st sentence from "Patients will return in a fasting state (no food or drink after midnight the night before) for follow-up visits at 3, 6, 9, 12, 15, and 18 weeks after randomization." to "Patients will return for follow-up visits at 3, 6, 9, 12, 15, and 18 weeks after randomization."

§5.4 Follow-up visits

Week 3 follow-up visit

- Removed 1st sentence: "Patient should be in a fasting state (no food or drink after midnight the night before)."
- Changed 2nd sentence from "Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question; physical exam (temperature, heart rate, respiratory rate, blood pressure); 10 mL of blood will be drawn for plasma banking, and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II)." to "Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question; and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II)."
- Removed 3rd sentence: "Once the questionnaires are completed, the patient will have the EGG and satiety test."
- Removed last sentence: "Women of childbearing potential must have a negative pregnancy test."

§5.4 Follow-up visits

Week 6 follow-up visit

- Removed 1st sentence: "Patient should be in a fasting state (no food or drink after midnight the night before)."
- Changed 2nd sentence from "Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question; physical exam (temperature, heart rate, respiratory rate, blood pressure); 10 mL of blood will be drawn for plasma banking, and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II)." to "Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question; and the following

questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II)."

- Removed 3rd sentence: "Once the questionnaires are completed, the patient will have the EGG and satiety test."
- Removed last sentence: "Women of childbearing potential must have a negative pregnancy test."

§5.4 Follow-up visits
Week 9 follow-up visit

- Removed 1st sentence: "Patient should be in a fasting state (no food or drink after midnight the night before)."
- Changed 2nd sentence from "Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question; physical exam (temperature, heart rate, respiratory rate, blood pressure); 10 mL of blood will be drawn for plasma banking, and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II)." to "Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question; physical exam (temperature, heart rate, respiratory rate, blood pressure); and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II)."
- Changed 3rd sentence from "Once the questionnaires are completed, the patient will have an electrocardiogram (ECG) followed by the EGG and satiety test." to "Once the questionnaires are completed, the patient will have an electrocardiogram (ECG)."

§5.4 Follow-up visits
Week 12 follow-up visit

- Changed 3rd sentence from "They will have 25mL of blood drawn for banking and analysis; 10 mL of blood will be drawn for plasma banking; and 15 mL will be drawn for a complete blood count (white blood cells, red blood cells, white blood cell differential, hemoglobin, hematocrit, platelets), a metabolic panel (sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogen (BUN), creatinine, and a hepatic panel (albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin" to "They will have blood drawn for plasma banking and analysis; 10 mL of blood will be drawn for plasma banking; and 15 mL will be drawn for a complete blood count (white blood cells, red blood cells, white blood cell differential, hemoglobin, hematocrit, platelets), a metabolic panel (sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogen (BUN), creatinine, and a hepatic panel (albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin."

- Added new sentences 5-10: "For the EGG and satiety test, patients will have a 15 minute baseline EGG recording. Then the patient will drink Ensure® (1.1.kcal/ml) every 5 minutes until they feel completely full. This will be followed by a 30 minute EGG recording. The electrodes will then be removed. The satiety test will be analyzed by the amount of Ensure® consumed. The EGG will be analyzed for the fasting and post satiety test periods.""

§5.4 Follow-up visits
Week 15 follow-up visit

- Changed header from **"Week 15 (2 weeks of tapering off study medication) visit**:" to "**Week 15 visit**:"
- Changed 2nd sentence from " Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question, physical exam (temperature, heart rate, respiratory rate, blood pressure); gastric emptying breath test (GEBT); 10 mL of blood will be drawn for plasma banking, and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptom Rating Scale (GSRS), a health-related quality of life questionnaire (SF-36), State Trait Anxiety Inventory (STAI), Brief Pain Inventory (BPI), Patient Health Questionnaire (PHQ-15), and Beck Depression Inventory (BDI-II)." to "). Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question, physical exam (temperature, heart rate, respiratory rate, blood pressure); 10 mL of blood will be drawn for plasma banking, and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptom Rating Scale (GSRS), a health-related quality of life questionnaire (SF-36), State Trait Anxiety Inventory (STAI), Brief Pain Inventory (BPI), Patient Health Questionnaire (PHQ-15), and Beck Depression Inventory (BDI-II)."
- Added new sentences 5-9: "Upon completion of the questionnaires, the patient will undergo the gastric emptying breath test. The patient is administered a standardized 230 kCal meal consisting of a ^{13}C-labeled egg component and 6 saltine crackers. Four ounces of water accompanies the meal. The patient is asked to consume the meal within 10 minutes. A timer is set upon completion of the GEBT meal. Breath samples are then collected at the 45 minutes, 90 minutes, 120 minutes, 150 minutes, and 180 minutes post-meal time points. Breath samples will be sent to a reference laboratory for analysis by stable isotope ratio mass spectrometry."

§5.4 Follow-up visits
Week 18 follow-up visit

- Removed 1st sentence: "Patient should be in a fasting state (no food or drink after midnight the night before)."

- Changed 2nd sentence from"Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question; physical exam (temperature, heart rate, respiratory rate, blood pressure); 10 mL of blood will be drawn for plasma banking, and the following questionnaires should be completed: Patient

Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II)." to "Medical history including side effect or symptom profile, global overall relief of symptoms question and clinical global patient impression question; and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II)."

- Removed 3rd sentence: "Once the questionnaires are completed, the patient will have the EGG and satiety test."

§5.6 Biospecimen Repository

- Changed 3rd sentence from "Blood will be collected at screening visit 2 (s2) and at each of the follow-up visits (weeks 3, 6, 9, 12, 15 and 18) for plasma separation and banking." to "Blood will be collected at a screening visit and at follow-up visits (weeks 12 and 15) for plasma banking."

§9.1 Participating centers

- Added: Texas Tech University Health Science Center, El Paso, TX (PI: Richard McCallum, MD)

§9.2 Data collection schedule

- Data collection schedule was revised to remove the electrogastrogram from weeks 3, 6, 9, 12, and 18. Plasma banking was removed from weeks 3, 6, 9, and 18. The physical exam was removed from weeks 3, 6, and 18.

§9.3 Whole blood draw schedule

- Whole blood draw schedule was revised to remove plasma banking from weeks 3, 6, 9, and 18.

Nortriptyline for Idiopathic Gastroparesis (NORIG) Protocol (12 April 2010)
Editorial and wording changes were made to the following sections:

§ Design synopsis:

- Study Duration-per calendar time:
  Changed recruitment phase to January 2009 - December 2010
  Changed follow-up phase to January 2009 - March 2011

§4.1 Recruitment

- Changed "Approximately 140 patients will be recruited from the seven clinical centers of the GpCRC (averaging 23 patients per center) over an 18 month period" to "Approximately 140 patients will be recruited from the seven clinical centers of the GpCRC (averaging 23 patients per center over a 22 month period"

§5.2 Screening visit 1:

- Second paragraph, changed "Anthropomorphic assessments (body weight [kg], body height [m], body mass index [BMI], waist circumference [cm], hip circumference [cm], vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature); and general physical findings will be collected and recorded." to "Anthropometric assessments (body weight [kg], body height [m], body mass index [BMI], waist circumference [cm], hip circumference [cm], vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature); and general physical findings will be collected and recorded."

Nortriptyline for Idiopathic Gastroparesis (NORIG) Protocol (9 July 2010)
Editorial and wording changes were made to the following sections:

§ Design synopsis:

- Study Duration-per calendar time:
  Changed recruitment phase to January 2009 - March 2011
  Changed follow-up phase to January 2009 -August 2011
- Sample size justification:
  Changed "Total of 140 patients in 2 groups of equal size (70 per group)" to "Total of 130 patients in 2 groups of equal size (65 per group)"

§4.1 Recruitment

- Changed "Approximately 140 patients will be recruited from the seven clinical centers of the GpCRC (averaging 23 patients per center over a 22 month period." to "Approximately 130 patients will be recruited from the seven clinical centers of the GpCRC (averaging 22 patients per center over a 27 month period."

§5.2 Screening visit 1

- Second paragraph, changed 3rd sentence from "Laboratory test results that need to be recorded from chart review or obtained as part of screening visit 1 include: complete blood count (CBC): white blood cells, red blood cells, white blood cell differential, hemoglobin, platelets; a metabolic panel: sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogren (BUN), creatinine; a hepatic panel: albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin; and thyroid stimulating hormone (TSH)." to "Laboratory test results that need to be recorded from chart review or obtained as part of screening visit 1 include: complete blood count (CBC): white blood cells, red blood cells, hemoglobin, platelets; a metabolic panel: sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogren (BUN), creatinine; a hepatic panel: albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin; and thyroid stimulating hormone (TSH).

§5.2 Screening visit 1- Baseline gastric emptying breath test

- Changed 5th sentence from "Four ounces of water accompanies the meal." to "Six ounces of water accompanies the meal."

§5.4 Follow-up visits

Week 12 follow-up visit

- Changed 3rd sentence from "They will have blood drawn for plasma banking and analysis; 10 mL of blood will be drawn for plasma banking; and 15 mL will be drawn for a complete blood count (white blood cells, red blood cells, white blood cell differential, hemoglobin, hematocrit, platelets), a metabolic panel (sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogen (BUN), creatinine, and a hepatic panel (albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin." to "They will have blood drawn for plasma banking and analysis; 10 mL of blood will be drawn for plasma banking; and 15 mL will be drawn for a complete blood count (white blood cells, red blood cells, hemoglobin, hematocrit, platelets), a metabolic panel (sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogen (BUN), creatinine, and a hepatic panel (albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin."

Week 15 follow-up visit

- Changed 5th sentence from "Four ounces of water accompanies the meal." to "Six ounces of water accompanies the meal."

§6.4 Missing Data

- Changed 2nd sentence from "We estimate that careful selection of patients during the screening phase and the consent process should result in no more than 10% missing data from patients who drop out before completing the 15 week treatment period and the 3 week post-treatment follow-up." to "We estimate that careful selection of patients during the screening phase and the consent process should result in no more than 10% missing data from patients who drop out before completing the full 15 week treatment period and the 3 week post-treatment follow-up."
- Changed 3rd sentence from "In the primary, intention-to-treat analysis, patients with missing data will be counted and considered unimproved on the primary outcome measure." to "In the primary, intention-to-treat analysis, patients with a pattern of missing data that precludes determination of the primary outcome according to its definition will be counted as unimproved."
- Second paragraph, removed 2nd and 3rd sentences: "Nonsignificant P-values indicate that the data are missing at random (MAR). If this is the case, analyses of the non-missing data are not threatened.
- Changed 4th sentence from "If the amount of missing data exceeds 10% and the data are MAR, then a variety of sensitivity analyses will be carried out to compare to the primary analysis using all available non-missing data: (1) compare pessimistic and optimistic imputations of the missing values, (2) correct for missing data using multiple imputation with 10 replicated

samples, and (3) use mixed random effects logistic or linear regression models, depending on the type of outcome measure." to "If the amount of missing data exceeds 10%, then a variety of sensitivity analyses will be carried out to compare to the primary analysis using all available non-missing data and assuming that the missingness is either missing completely at random (MCAR) or missing at random (MAR): (1) compare pessimistic and optimistic imputations of the missing values, (2) correct for missing data using multiple imputation with 10 replicated samples, and (3) use mixed random effects logistic or linear regression models, depending on the type of outcome measure.

- Changed 5th sentence from "Although unlikely in a large trial, it is possible that the missing data are not MAR and the missing data are non-ignorable." to "It is possible that the missingness is not MCAR or MAR, but is missing not at random (MNAR)."
- Changed 6th sentence from "Few statistical methods are available when there are non-ignorable missing data and these may be employed to assess sensitivity of the results to non-ignorably missing data; however, all such methods involve strong assumptions that cannot be verified from the available data." to "Few statistical methods are available when there are non-ignorable missing data patterns and these may be employed to assess sensitivity of the results to non-ignorable missing data if the level of missing data exceeds 10%; however, all such methods involve strong assumptions that cannot be verified from the available data.

§6.4 Justification of sample size

- Changed 1st sentence from "The planned sample size for the NORIG trial is 140 patients with equal allocation to each of the two treatment groups (70 per group)." to "The planned sample size for the NORIG trial is 130 patients with equal allocation to each of the two treatment groups (65 per group).
- Changed 4th paragraph from "The number per group, using the above formula is 56 for a total of 112. To allow for possible mis-specification in the estimated response rates used in the calculation, we propose a sample size of 70 patients per group, or a total of 140 for the trial." to "The number per group, using the above formula is 56 for a total of 112. To allow for possible mis-specification in the estimated response rates used in the calculation, we propose a sample size of 65 patients per group, or a total of 130 for the trial.

§6.6 Interim analysis

- Changed 4th paragraph, 2nd sentence from "This interim efficacy analysis will occur when approximately 50% of the data are complete or when approximately 70 of the 140 patients have completed the 18 week trial." to "This interim efficacy analysis will occur when approximately 50% of the data are complete or when approximately 65 of the 130 patients have completed the 18 week trial.

§9.2 Data collection schedule

- Data collection schedule was revised to remove white blood cell differential from the complete blood count

§9.3 Whole blood draw schedule

- Whole blood draw schedule was revised to remove white blood cell differential from the complete blood count

Nortriptyline for Idiopathic Gastroparesis (NORIG) Protocol (9 December 2010)

Editorial and wording changes removing the gastric emptying breath test were made to the following sections:

§ Design synopsis:

- Exclusion criteria
  Deleted "Contraindications to gastric emptying breath test such as a known allergy to egg, wheat, or algae"
- Secondary outcome measures
  Deleted (2) "Gastric emptying breath test measures at 45 min, 90 min, 120 min, 150 min, and 180 min."

§ 1. Objectives

- Removed "gastric emptying breath testing," to "To determine the effects of nortriptyline and placebo on satiety testing and electrogastrography in patients with idiopathic gastroparesis."

§2.1 Introduction

- Changed second paragraph, 1st sentence" to "The Gastroparesis Clinical Research Consortium (GpCRC) is a cooperative network of **seven** clinical centers and one Data Coordinating Center (DCC) supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), through the mechanism of RFA DK 05 004, established in 2006."
- Removed "the Data and Safety Monitoring Board" from second paragraph, last sentence: "The DCC supports protocol development; provides sample size calculations, statistical expertise, forms, and data analysis; supports manuscript preparation; and provides overall study coordination and quality assurance, including coordination of the activities of the Steering Committee and other standing committees."

§3.1 Design overview

- Removed "gastric emptying rates measured by gastric emptying breath test (GEBT) in 2nd sentence" to "Secondary analyses will include: the effect of treatment on individual symptom scores, the patients' assessment of global overall relief, physiological changes in satiety tests, and dysrhythmias detected by electrogastrography."

§3.4 Restarts and dose adjustments due to side effects

- Deleted 7th sentence in 2nd paragraph: "If the symptoms reappear, the study physician will discuss termination of the study drug with the members of the Steering Committee."

§4.3 Exclusion criteria

- Deleted "14. Contraindications to gastric emptying breath test such as a known allergy to egg, wheat, or algae"; renumbered items 15-19.

§5.2 Screening visit 1

- Removed "allergy to egg, wheat or algae."in 2nd sentence: "The patient will sign the consent at or prior to screening visit 1 and will undergo a history and physical examination to identify other illness and contraindications for participation such as use of narcotics for pain more than 3 days per week (including fentanyl patches), use of calcium channel blockers, use of erythromycin, use of medications that are strongly anticholinergic, hypersensitivity or allergy to any tricyclic antidepressant drug, concomitant therapy with a monoamine oxidase inhibitor (MAOI), recent myocardial infarction, or glaucoma ."

- Removed "also undergo a gastric emptying breath test (GEBT) and" in the last sentence to "Patients will complete the following questionnaires"

§5.2 Screening visit 1

- Deleted **"Baseline gastric emptying breath test:** Gastric emptying will be performed using Advanced Breath Diagnostics ^{13}C-*Spirulina* Gastric Emptying Breath Test (^{13}C-*Sp*GEBT) for clinical research[19,20]. The patient must fast overnight. Upon arrival at the clinical center, the patient provides a baseline (pre-meal) breath sample. The patient is then administered a standardized 230 kCal meal consisting of a ^{13}C-labeled egg component and 6 saltine crackers. Six ounces of water accompanies the meal. The patient is asked to consume the meal within 10 minutes. A timer is set upon completion of the GEBT meal.
  Breath samples are then collected at the 45 minutes, 90 minutes, 120 minutes, 150 minutes, and 180 minutes post-meal time points. Breath samples will be sent to a reference laboratory for analysis by stable isotope ratio mass spectrometry. Detailed instructions for the GEBT are found in the Standard Operating Procedures I: Clinical Center Operations (SOP I) section 6.5.
  Advanced Breath Diagnostics provides the standardized meal as an oral pharmaceutical product in compliance with the FDA's Good Manufacturing Practices. Final kit assembly is performed in compliance with the FDA's quality system regulations for medical devices and in vitro diagnostics."

§5.4 Follow-up visits

Week 15 follow-up visit

- Deleted 3rd-9th sentences: " Upon completion of the questionnaires, the patient will undergo the gastric emptying breath test. The patient is administered a standardized 230 kCal meal consisting of a ^{13}C-labeled egg component and 6 saltine crackers. Six ounces of water accompanies the meal. The patient is asked to consume the meal within 10 minutes. A timer is set upon completion of the GEBT meal. Breath samples are then collected at the 45 minutes, 90 minutes, 120 minutes, 150 minutes, and 180 minutes post-meal time points.

Breath samples will be sent to a reference laboratory for analysis by stable isotope ratio mass spectrometry."

§5.7 Safety Issues
Safety concerns related to study procedures:

- Deleted paragraph: ***Gastric Emptying Breath Test*:** Each subject will undergo two ^{13}C-*Spirulina* Gastric Emptying Breath Test (^{13}C-*Sp*GEBT) in this study - during screening and at end of the study. The gastric emptying breath test is simple and easily administered. The test should not be administered to subjects with a known egg, algae or wheat allergy. Clinical studies were performed validating the ^{13}C-*Sp*GEBT against gastric emptying scintigraphy at the Mayo Clinic, Rochester[19, 20]. Furthermore, these studies were conducted to satisfy the FDA's requirement to collect the appropriate efficacy data required for a Pre-Market Approval (PMA) application for commercial distribution. There were no reported adverse events during the development phase of this test.

§5.10 Food and Drug Administration

- Changed 1st sentence to "The NORIG trial will be conducted under an Investigational New Drug (IND #102,404) held by the NIDDK ."

§5.11 Adverse event reporting
Definitions
Serious adverse event:

- Corrected spelling of judgment in the last sentence.

Reporting serious adverse events

- Deleted 4th paragraph and replaced with new 4th paragraph "The DSMB will review all SAE reports, at least quarterly. 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 expeditiously.

§6.1 Secondary hypotheses:

- Deleted 3rd bullet: "Patients in the nortriptyline group will have improved satiety testing, but no change in gastric emptying compared to placebo in patients with idiopathic gastroparesis."

§6.2 Outcome measures:
Secondary outcome measures
(2) Physiology

- Deleted first item "Gastric emptying breath test measures at 45 min, 90 min, 120 min, 150 min and 180 min"

§6.6 Interim analysis

- Changed 2nd paragraph, 2nd sentence to "After the trial commences, the DSMB meets twice a year to review data or other issues."

• Deleted 2nd paragraph, last sentence "For example, all serious adverse events are reported to the DSMB for their consideration and recommendations as they occur."

§9.2 Data collection schedule

• Data collection schedule was revised to remove gastric emptying breath test

§9.4 Glossary

• Removed GEBT: gastric emptying breath test

Nortriptyline for Idiopathic Gastroparesis (NORIG) Protocol (14 Mar 2011)
Editorial and wording changes were made to the following sections:

§ Design synopsis:
Changed calendar months to:
Study duration – per calendar time

- Recruitment phase: 39 months
- Follow-up phase: 44 months

§ 4.1 Recruitment

Changed recruitment phase from 27 months to 39 months: "Approximately 130 patients will be recruited from the seven clinical centers of the GpCRC (averaging 22 patients per center) over a 39-month period"