GpCRC

Gastroparesis
Clinical Research Consortium

Aprepitant for the Relief of Nausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin: A Multicenter, Randomized, Double-Masked, Placebo-Controlled Trial (APRON)

IND # 108,939

Protocol

Confidential

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Contents

Design synopsis

Title

- **Ap**repitant for the **R**elief **o**f **N**ausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin: A Multicenter, Randomized, Double-Masked, Placebo-Controlled Trial (APRON)

Sponsor

- National Institute of Diabetes and Digestive and Kidney Diseases

Type of study

- Phase 3 randomized clinical trial
- Multicenter, double-masked, placebo-controlled trial of 2 parallel treatment groups

Objective

- To determine whether treatment with aprepitant or placebo results in symptomatic improvement of nausea in patients with chronic nausea and vomiting of presumed gastric origin.

Treatment groups

- Group 1: Aprepitant (125 mg q.d.)
- Group 2: Aprepitant-placebo (q.d.)

Population

- Age 18 years or older at registration with nausea, vomiting, and other symptoms suggestive of patients with chronic nausea and vomiting of presumed gastric origin, with or without delayed gastric emptying

Study duration

- Up to 4 weeks of screening prior to randomization
- 4 weeks of treatment starting at randomization
- 2 weeks of washout period
- Length of recruitment: 16 months

Sample size justification

- Total of 120 patients in 2 groups of equal size (60 per group)
- Primary comparison: aprepitant vs. placebo
- Error protection: Type I = 0.05 two-sided and Type II = 0.10 (90% power)

Number of clinical sites

- 8

Inclusion criteria

- Age 18 years or older at registration
- Gastric emptying scintigraphy within 2 years of registration
- Normal upper endoscopy or upper GI series within 2 years of registration
- Symptoms of chronic nausea or vomiting compatible with gastroparesis or other functional gastric disorder for at least 6 months (does not have to be contiguous) prior to registration with Gastroparesis Cardinal Symptom Index (GCSI) score of ≥ 21
- Significant nausea defined with a visual analog scale (VAS) score of ≥ 25 mm on a 0 to 100 mm

scale

Exclusion criteria

- Another active disorder which could explain symptoms in the opinion of the investigator
- Use of narcotics more than 3 days per week
- Significant hepatic injury as defined by significant alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations of greater than 2xULN or a Child-Pugh score of 10 or greater
- Contraindications to aprepitant such as hypersensitivity or allergy
- Concurrent use of warfarin, pimozide, terfenadine, astemizole, or cisapride
- Pregnancy or nursing
- Any other condition, which in the opinion of the investigator would impede compliance or hinder completion of the study
- Failure to give informed consent

Outcome measures

- ***Primary:*** The primary outcome measure is a binary (0,1) variable indicating improvement in nausea or not in the mean of available VAS scores over the 28 day treatment period compared to the mean of VAS scores during the 7 day baseline period. The criteria for improvement are either a 25 mm or more reduction in mean VAS or attaining a mean VAS during the treatment period of < 25 mm.
- **Secondary outcome measures** will be defined to address the following areas:
  (1) Gastrointestinal symptoms
    - Subscores for the GCSI: nausea/vomiting, postprandial fullness, bloating
    - Subscores for the GCSI Daily Diary
    - Individual symptom scores for nausea, retching or vomiting
    - 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

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 4 weeks after registration
- Randomization: final pre-treatment interview, dispensing of study drug
- Follow-up visits: every 2 weeks after randomization throughout the 6 week study

Statistical analysis

- All analyses will be on an "intention-to-treat" basis. Patients who do not have any of the VAS nausea scores recorded during the period of treatment will be counted as not improved (i.e., 0) for the primary outcome
- Secondary, sensitivity analyses on a per-protocol basis will also be carried out, excluding patients from both groups who do not complete at least 50% (2 weeks) of the 4 weeks on assigned

treatment, but conclusions about the primary objective will be based on the intention-to-treat analysis.

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

1. Objectives

The principal objective of this multicenter, randomized, placebo-controlled trial is to evaluate whether 4 weeks of treatment with aprepitant will improve nausea as compared with placebo in patients with symptoms of chronic nausea and vomiting of presumed gastric origin.

Other objectives include:

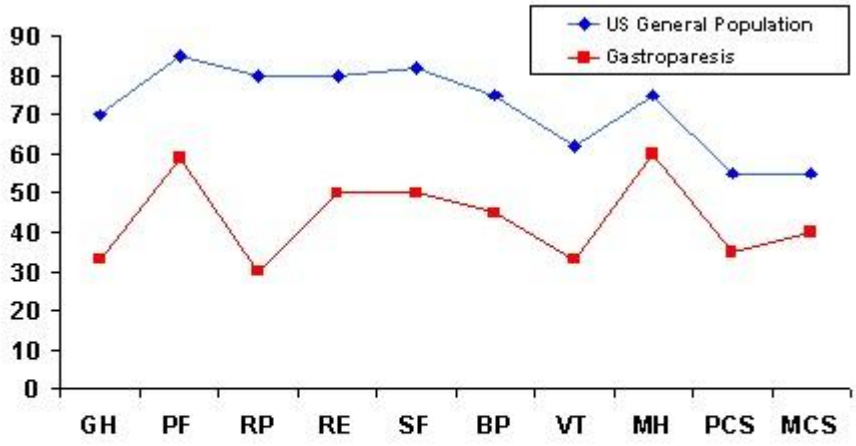
- To determine the effects of aprepitant and placebo on other symptoms such as stomach fullness, hunger, bloating and abdominal discomfort as measured during satiety testing
- To determine the effects of aprepitant and placebo on overall symptoms of chronic nausea and vomiting of presumed gastric origin as measured by the Gastrointestinal Cardinal Symptom Index Daily Diary
- To determine the effects of aprepitant on gastric physiological function as measured by electrogastrography
- To determine the effects of aprepitant on other symptoms associated with chronic nausea and vomiting of presumed gastric origin such as pain and depression
- To determine the nature and incidence of adverse effects from a four week course of aprepitant in patients with chronic nausea and vomiting of presumed gastric origin

2. Background and significance

2.1. Introduction

Gastroparesis is a devastating disease affecting predominantly young women (females outnumber males by a ratio of 4:1, with an average age of around 34).[1] The symptomatic profile of gastroparesis includes nausea (90%), 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.[2,3] This is reflected in quality of life surveys such as that shown in Figure 1.

Figure 1. SF-36 quality of life scores of patients with gastroparesis.[3]



PF = physical function; BP = bodily pain; RP = role-physical; GH = general health; SF = social function; VT = vitality; RE =role-emotional; MH = mental health; PCS = physical component summary; MCS = mental component summary

In order to address the unmet research needs in this condition, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), through the mechanism of RFA-DK-05-004, established the Gastroparesis Clinical Research Consortium in 2006 and determined its continuation for another 5 years addresses unmet needs in gastroenterology. The Gastroparesis Clinical Research Consortium (GpCRC) is a cooperative network of eight clinical sites and one Data Coordinating Center (DCC). 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. Disorders that may be related to gastroparesis

In a substantial number of patients who present with symptoms suggestive of gastroparesis (e.g. chronic nausea, vomiting, post-prandial fullness, bloating, etc.), gastric emptying tests are normal. Although the pathogenesis of symptoms in these patients is not known, it is presumed that most have some form of gastric dysfunction. Further, they appear to have a demographic and clinical profile that is virtually indistinguishable from classical gastroparesis and their treatment remains just as challenging. The GpCRC charter calls for enrolling these patients in the Gastroparesis Registry 2 along with patients with established gastroparesis, in a ratio of approximately 1:4. Both these groups of patients will be entered into the APRON trial.

2.3. Current Therapies for Gastroparesis and related disorders

A variety of agents have been used for the treatment of gastroparesis.[4-8] These include classic agents such as prokinetic metoclopramide, cisapride (restricted use) and domperidone (not available in the U.S.). The track record of these drugs is mixed, at best,[9] a problem compounded by the paucity of high quality trials. A meta-analysis has suggested that in double-blind, controlled studies, cisapride produced a mean improvement in symptom score of only 8%, whereas metoclopramide produced a mean improvement in this score of 36%.[10] Also, improvement in symptoms generally does not correlate well with changes in gastric emptying.[9] This is important as it reinforces the concept that symptoms are not necessarily being driven by the motor abnormalities and redirects attention to central mechanisms of nausea. However, this approach needs further investigation, since very little effective relief is available for the nausea of gastroparesis, despite the wide choice of antinauseant drugs. Thus, many of these patients with refractory nausea are candidates for more invasive therapies such as gastric electrical stimulation, whose efficacy, while promising, has yet to be established unequivocally.[11] There is, therefore, a need for new and innovative approaches to nausea, the most distressing of gastroparetic symptoms.

2.4. Rationale for targeting the neurokinin receptor, NK1, in gastroparesis and related disorders

Gastroparesis is a complex disorder characterized by a combination of deranged physiology (delayed gastric emptying) and physical symptoms (nausea, pain) leading to anxiety and depression. As reviewed further, the novel NK1 receptor antagonist, aprepitant, has been shown to be useful for nausea, anxiety, and depression in non-gastroparetic populations. There is suggestive experimental evidence that aprepitant may alleviate (neurogenic) inflammation and pain, and may improve gastric emptying particularly in abnormal or sensitized states. Aprepitant may be beneficial in gastroparesis and represents an innovative mechanistic approach to this intractable condition.

Centrally acting neurokinin receptor (NK1) antagonists have broad spectrum anti-emetic effects against both central (e.g. motion and opioids) and peripheral (vagal) afferent emetogenic pathways (e.g. cytotoxic drugs, radiation and gastric irritants). One of the most important sites of NK1 activity is believed to be in the nucleus tractus solitarius, upstream from the afferent vagal terminal. Other sites include neurons in the dorsal motor vagal nucleus which supplies efferents to the visceral organs. The widespread distribution of these receptors accounts for the experimental observation that NK1 receptor antagonism is an effective anti-emetic strategy regardless of the nature of the inciting stimulus. This has led to the concept of the NK1 receptor being regarded as the emesis “gate” for stimuli arising from different sources such as blood-borne via the chemoreceptor trigger zone, visceral via the vagus and nucleus tractus solitarius.[12]

2.5. Clinical experience with aprepitant

Aprepitant (Emend®, Merck; formerly MK-869 and L-754030) is the first FDA approved NK1 receptor antagonist and is indicated for delayed nausea due to chemotherapy induced emesis such as with cis-platinum and typically occurring 2-5 days after chemotherapy and not very responsive to 5-HT3 antagonists, as compared with nausea that occurs within 24 hours of chemotherapy.[13] The tested indications include chemotherapy-induced nausea, vomiting and postoperative nausea, vomiting.[14]

Initially, aprepitant has been found to be effective in depression in a multicenter, randomized, double-blind, placebo-controlled, multicenter phase 2 trial.[15] In this landmark study comparing 300 mg/day of aprepitant (MK-869) to paroxetine (20 mg/day) or placebo in patients with major depressive disorder and moderately high anxiety, both active drugs produced comparable improvement in depression (about 50% change from baseline as compared with 28% in the placebo group). However, this effect in depression was not confirmed in successive larger, multicenter, randomized double-blind placebo-controlled phase 3 trials.[16]

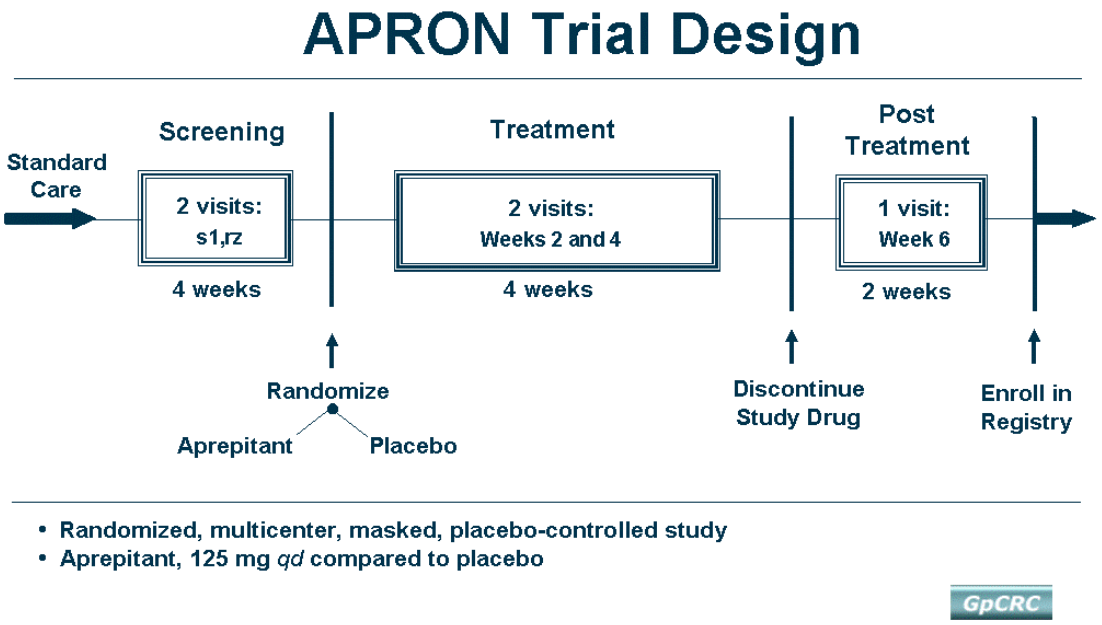
In addition, aprepitant has been tested in clinical trials with over 2000 patients in doses that ranged from 40 to 240 mg per day and for durations up to 10 months for a variety of indications including chemotherapy-induced nausea and vomiting,[17-19] postoperative nausea and vomiting,[20] and urge urinary incontinence[21] of postmenopausal women with overactive bladder. In these trials, aprepitant appears to have been well tolerated, with generally mild adverse experiences. Recently, the effect of aprepitant on gastrointestinal propulsion was tested in healthy humans[22] and the results suggest that aprepitant does not change gastric retention, gastric half emptying time, gastric mean transit time, small intestinal mean transit time or colonic geometric center after 24, 48 and 72 hours.

Currently, aprepitant (Emend®) is indicated for (1) the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy and (2) the prevention of postoperative nausea and vomiting.[14] In a patient with severe diabetic gastroparesis, intractable vomiting and ketoacidosis refractory to standard treatments; aprepitant was reported to stop vomiting successfully.[23] Aprepitant was continued for 4 months with a substantial improvement in this patient's quality of life and overall glycemic control. Although not formally tested, anecdotal and personal experience with a small number of gastroparetic patients suggests that aprepitant seems to work reasonably well for nausea in these patients. However, aprepitant as labeled today is only approved for a 3-day regimen in doses of 125 mg a day at most, a dose and duration which may be inadequate to determine its true utility in gastroparesis. In addition, aprepitant has the potential for several additional beneficial effects including pain and inflammation,[24] and these may benefit patients with gastroparesis and related disorders. Therefore, we are conducting a randomized, controlled trial of aprepitant, which is directed against NK1, in the relief of symptoms in patients with gastroparesis and related disorders.

3. Study design

3.1. Design overview

APRON is a multicenter, randomized, double-masked, placebo controlled trial of 4 weeks of treatment with aprepitant or placebo for patients with symptoms of gastroparesis and related disorders. Screening for eligibility and collection of baseline data will span up to 4 weeks after obtaining informed consent and registration. Eligible patients will consist of patients with symptoms of gastroparesis and will be randomized to either aprepitant (125 mg per day) or placebo for 4 weeks. The symptoms will be measured with the Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD)[25,26] for one week at baseline and for four weeks after randomization. In addition, the nausea symptom will be measured daily on a 0 to 100 mm visual analog scale (VAS)[14, 27-29] for one week at baseline and daily for four weeks after randomization. There will be a 2 week washout period at the end of the treatment to ensure patient safety following the end of treatment. A schematic of the trial design is presented below:



The primary comparisons will be made using an intention-to-treat analysis of improvement in nausea symptoms measured by VAS, from baseline to 4 weeks of treatment after randomization. Secondary analyses will include changes in the Gastrointestinal Cardinal Symptom Index-Daily Diary (GCSI-DD) scores, as well as physiological changes in electrogastrography and satiety tests.

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 4 weeks of treatment:

Group 1: Aprepitant (125 mg q.d.)
Group 2: Aprepitant-placebo (q.d.)

The randomization scheme will assign patients in randomly permuted blocks of assignments stratified by clinical center and 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 clinic (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 based on the DCC randomization schedule. Patients will be dispensed a medication bottle labeled ***"aprepitant or placebo"***.

Aprepitant or matching placebo will be administered as a single capsule of 125 mg once a day orally with lunch.[30]

3.4. Standard treatment recommendations

During the screening period, patients will receive a standardized set of recommendations to include dietary modification. The patient's medications are reviewed to eliminate drugs that might exacerbate the underlying dysmotility disorder or prevent the beneficial actions of a prokinetic agent. Dietary modification and use of 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 prochlorperazine for nausea and vomiting, and tramadol for abdominal pain. These recommendations have been prepared by the GpCRC Steering Committee as standard of care in the management of patients with gastroparesis or related disorders. This will help ensure that the patients in both treatment groups receive standard of care treatment.

4. Patient selection

4.1. Recruitment

Approximately 120 patients will be recruited from the eight clinical sites of the GpCRC (averaging 15 patients per center) over a 16 month period:

Eligible patients 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 screening procedures, keying of all required data elements, and passing eligibility checks for the APRON trial. Patients may be recruited directly into the APRON trial or may be recruited from other GpCRC studies.

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

4.2. Inclusion criteria

Patients with nausea, vomiting, and other symptoms suggestive of gastroparesis, with or without delayed gastric emptying will be studied. In order to qualify for inclusion in the trial, patients must satisfy the following inclusion criteria:

1. Age 18 years or older at registration
2. Gastric emptying scintigraphy within 2 years of registration
3. Normal upper endoscopy or upper GI series within 2 years of registration
4. Symptoms of chronic nausea or vomiting compatible with gastroparesis or other functional gastric disorder for at least 6 months (does not have to be contiguous) prior to registration with Gastroparesis Cardinal Symptom Index (GCSI) score of ≥ 21
5. Significant nausea defined with a visual analog scale (VAS) score of ≥ 25 mm on a 0 to 100 mm scale
6. Women of child bearing age should have a negative pregnancy test before entry into the study

4.3. Exclusion criteria

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

1. Another active disorder which could explain symptoms in the opinion of the investigator
2. Use of narcotics more than 3 days per week
3. Significant hepatic injury as defined by significant alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations of greater than 2xULN or a Child-Pugh score of 10 or greater
4. Contraindications to aprepitant such as hypersensitivity or allergy
5. Concurrent use of warfarin, pimozide, terfenadine, astemizole, or cisapride
6. Pregnancy or nursing
7. Any other condition, which in the opinion of the investigator would impede compliance or hinder the completion of the study
8. Failure to give informed consent

5. Trial procedures

5.1. Visit schedule overview

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

- Screening for eligibility (1 or 2 screening visits over a maximum of 4 weeks)
- Randomization to treatment (1 visit)
- Treatment phase (2 visits over 4 weeks)
- Post-treatment washout phase (1 visit at 6 weeks)

The trial visit and data collection schedule described below in detail is also summarized in Appendix 10.2.

5.2. Screening visits and baseline data collection

Many of the APRON participants will come from the Gastroparesis Registry 2 Study 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 APRON trial. Patients considered by the clinical center investigator as likely to be eligible for participation in the APRON trial may be consented, registered and screened at a visit that is part of the ongoing clinical care of the patient.

As part of the screening process for the APRON trial, the 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. 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 normal 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 APRON 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 will be reviewed, and patients will be asked to stop specific treatments such as antiemetic medications.

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 APRON 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 visit: 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 and will undergo a history and physical examination to identify other illness and contraindications for participation such as use of antiemetic medications.

The patient will be asked to respond to the clinical global patient impression (CGPI) and mark his or

her nausea on a 0 to 100 mm visual analog scale (VAS) for eligibility evaluation. In addition, the patient will be provided one week supplies of the VAS for nausea assessment and Gastroparesis Cardinal Symptom Index-Daily Diary (GCSI-DD) for completion each night before bed.

Patients will undergo an electrogastrography with satiety testing and will complete the following questionnaires:

- Nausea Profile (NP)
- Gastrointestinal Symptom Rating Scale (GSRS)
- Health-related quality of life questionnaire (SF-36v2)
- Beck Depression Inventory (BDI-II)
- Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM)
- State Trait Anxiety Inventory (STAI)
- Brief Pain Inventory (BPI) focusing on abdominal pain
- Patient Health Questionnaire (PHQ-15)

Anthropomorphic assessments (body weight, body height, body mass index [BMI], waist circumference, hip circumference, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature); and general physical findings will be collected. Patients will have an EKG performed at this visit. Laboratory test results that need to be recorded from chart review or obtained as part of screening include: CBC (complete blood count), metabolic panel (sodium, potassium, chloride, bicarbonate, calcium, BUN, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), magnesium, albumin, total protein). Glucose and hemoglobin A1c will be measured in patients with diabetes.

As part of the electrogastrography and satiety testing, baseline nausea and other symptoms such as stomach fullness, hunger, bloating, and abdominal discomfort will be ascertained by the participant on a 0 to 100 mm VAS, before the study drug is started.

Electrogastrography with satiety testing: Electrogastrography is the recording of electrical activity of the smooth muscle in the stomach using electrodes similar to an electrocardiogram (EKG). On the morning of the electrogastrogram (EGG) and satiety test, the patient will arrive fasting (nothing to eat or drink after midnight the night before the test). Patients may take medications with a small amount of water up to two hours prior to the study, but should refrain from coffee, tea, or juice. Diabetic patients will have blood glucose measured by finger stick. Only patients with glucose levels between 60 and 275 mg/dL and no symptoms to suggest hypo- or hyperglycemia will be allowed to proceed further. Patients who do not meet these criteria will either return on another day or be managed at the site with insulin or other measures, at the discretion of the investigator. 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. Patients will mark their symptoms of nausea, bloating, abdominal discomfort, hunger, and stomach fullness on a 0 to 100 mm VAS before and after the 15 minute baseline EGG recording.

For the satiety test, patients will drink Ensure® (1.1.kcal/mL) every 5 minutes until they feel completely full. Patients will mark their nausea and other symptoms on a 0 to 100 mm VAS immediately after the satiety test. This will be followed by another 30 minute post-satiety EGG recording during which the patients will mark their nausea and other symptoms on a 0 to 100 mm VAS twice: 15 minutes and 30 minutes after the satiety test. 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 can be found in the Standard Operating Procedures, Part I: Clinical Center Operations.

The APRON 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

The randomization visit is the visit at which randomization takes place and the patient is issued the study medication. Randomization is the act of generating the random study drug assignment 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. Women of childbearing potential must have a negative pregnancy test.

The daily VAS nausea measurements and the GCSI-DD completed by the patient each night for one week will be collected by the clinical center staff. After randomization, the patients will be provided three week supplies of the VAS for nausea assessment and GCSI-DD for completion each night before bed. Patients will have approximately 10 mL of blood drawn for plasma banking and 20 mL of blood drawn for DNA banking.

After eligibility is confirmed with the APRON web-based data management system, randomization can occur. 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 study drug assignment will not be generated unless the check finds that the patient is eligible, and the clinic staff indicate that they want to randomize the patient.

The random treatment assignment will consist of a numbered study drug bottle; this number will be unique as well as patient specific. This will correspond to numbered bottles of study drugs which have been sent to the clinical center's research pharmacy by the GpCRC Drug Distribution Center. The research pharmacy 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 will be issued the study drug and instructed about taking the study drug with lunch and monitoring for potential adverse effects. The study drug dispensed at the time of randomization will be either a 125 mg capsule of aprepitant or a similar looking placebo capsule.

The date of randomization is the start (zero) time for reckoning follow-up visits (i.e., 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 2, 4, and 6 weeks after randomization. The specific procedures to be completed at each of the follow-up visits are:

- **Week 2 visit**: Medical history including clinical global patient impression (CGPI) question. The following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Nausea Profile (NP), and Brief Pain Inventory (BPI) focusing on abdominal pain. Review study drug adherence and tolerance of the study drug with the participant. The daily VAS nausea measurements and the GCSI-DD completed by the patient each night since randomization will be collected by the clinical center staff. In addition, the patient will be provided three week supplies of the VAS for nausea assessment and GCSI-DD for completion each night before bed.

- **Week 4 visits**: Patient should be in a fasting state (no food or drink after midnight the night before) in order to complete the EGG with satiety test. The daily VAS nausea measurements and the GCSI-DD completed by the patient each night since the last study visit will be collected by the clinical center staff. Medical history including clinical global patient impression (CGPI) question; physical exam (temperature, heart rate, respiratory rate, blood pressure); 20 mL of blood will be drawn for laboratory test and plasma banking, and the following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Nausea Profile (NP), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II), State Trait Anxiety Inventory (STAI), Brief Pain Inventory (BPI) focusing on abdominal pain, and Patient Health Questionnaire (PHQ-15). Review study drug adherence and tolerance of the study drug with the participant. Collect the medication bottle dispensed at the randomization visit with unused study drug.

Electrogastrography with satiety testing: On the morning of the electrogastrogram (EGG) and satiety test, the patient will arrive fasting (nothing to eat or drink after midnight the night before the test). Patients may take medications with a small amount of water up to two hours prior to the study, but should refrain from coffee, tea, or juice. Diabetic patients will have blood glucose measured by finger stick prior to the test. Only patients with levels between 60 and 275 mg/dL will proceed with the test. 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. Patients will mark their nausea and other symptoms on a 0 to 100 mm VAS before and after the 15 minute baseline EGG recording.

For the satiety test, patients will drink Ensure® (1.1.kcal/mL) every 5 minutes until they feel completely full. Patients will mark their nausea and other symptoms on a 0 to 100 mm VAS immediately after the satiety test. This will be followed by another 30 minute post-satiety EGG recording during which the patients will mark their nausea and other symptoms on a 0 to 100 mm VAS twice: 15 minutes and 30 minutes after the satiety test. 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.

- **Week 6 visit**: Medical history including clinical global patient impression (CGPI) question should be collected.

5.5. Standardized questionnaires

Several standardized questionnaires will be administered to patients enrolled in the APRON 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 information regarding gastroparesis symptoms, side effects, and health-related quality of life.

Patient Assessment of Upper Gastrointestinal Disorders-Symptoms (PAGI-SYM)[31-33] is a validated 20 question questionnaire that quantifies symptoms of gastroparesis, dyspepsia, and gastroesophageal reflux disease on a 0 to 5 scale for each symptom. The PAGI-SYM includes the 9 question Gastroparesis Cardinal Symptom Index (GCSI) - a validated symptom questionnaire that assesses the symptoms of gastroparesis. The GCSI is based on three subscales (postprandial fullness and 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.

Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD)[25-26] is derived from the GCSI with a 24 hour recall

Gastrointestinal Symptom Rating Scale (GSRS)[34] is a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease.

Beck Depression Inventory, Second Edition (BDI - II).[35] The BDI-II is a commonly used, reliable 21-item self-report measure designed to assess for depression.

State Trait Anxiety Inventory.[36] 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).[37] The PHQ-15 is a brief, self-report measure of somatization. This test has good internal consistency and reliability.

Brief Pain Inventory (BPI).[38] The BPI was 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. This assessment will focus on abdomminal pain in gastroparesis patients.

Health Survey (SF-36v2).[39] The SF-36v2 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.

Nausea Profile.[40] The nausea profile (NP) is a subjective symptom checklist with the goal of obtaining a more in-depth description of what patients are experiencing when they report the feeling of nausea. The NP evaluates the experience of 3 dimensions which are involved in the complex feeling of nausea, somatic distress, GI distress and emotional distress..

5.6. Specimen banking

Biological specimens will be collected and stored for use as approved by the Steering Committee of the GpCRC (see Appendix 10.3 for whole blood draw schedule). Specimens to be stored include plasma and DNA. Ten mL of blood will be collected at the randomization visit and at the week 4 follow-up visit for plasma separation and banking. The blood will be drawn in the morning during the study visit while

the participant is still fasting. The blood will be separated into plasma and 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.

For participants who consent to DNA banking, twenty mL of blood will be collected at the randomization visit and will be sent to the NIDDK Genetics Repository for DNA banking. DNA will be extracted and will be stored at -20 degrees C.

5.7. Safety issues

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

Safety concerns related to aprepitant: Study participants will receive aprepitant or placebo. The overall safety of aprepitant has been evaluated in several thousand individuals receiving highly emetogenic cancer chemotherapy and for prevention of postoperative nausea and vomiting. Aprepitant was given in combination with ondansetron and dexamethasone and was generally well tolerated. However, because of the multiple co-morbidities in these patients, it is difficult to form a reliable estimate of adverse events that can be specifically attributed to aprepitant. More meaningful long term use adverse event data come from trials in patients conducted with major depressive disorders with more than 2,000 patients. The dose of aprepitant used in these placebo-controlled trials ranged from 40 to 240 mg per day for a duration of up to 10 months.

During the trial, if a participant develops non-life threatening side effects attributed to the study drug, the study drug will be stopped only if the participant so desires. If the participant chooses to no longer receive the study drug, the participant will be followed in the trial according to the protocol, in keeping with the "intention-to-treat" paradigm. In the event of major dermatological reactions such as generalized urticaria, bullous rashes, exfoliative dermatitis, or Stevens-Johnson Syndrome, study drug will be discontinued immediately.

Safety concerns related to study procedures: EGG with satiety test recording involves placement of EGG electrodes on the abdominal skin. There may be some soreness in removing the EGG electrodes. Otherwise, there are no immediately foreseeable risks to EGG or the consumption of Ensure® during the satiety test. In diabetic patients, blood sugar will be monitored prior to the test. Blood sampling 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, and/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

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

- Counts of capsules in the patient's returned medication bottle
- Conducting a brief, structured interview, in which the study coordinator will assist the patients to identify problems in taking the study drug 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 guidelines described in the Standards of Care for Patients with Gastroparesis (SOP IV) document prepared by the GpCRC Steering Committee.

6. Monitoring for adverse events

The APRON trial will be conducted under the Food and Drug Administration (FDA) Investigational New Drug (IND #108,939) application held by the NIDDK. The investigators will complete a Statement of Investigator (FDA Form 1572) and must obtain IRB approval per the Code of Federal Regulations before the initiation of the APRON trial. The study may not begin until the IND is in effect. 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.

6.1. Definitions[41]

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

***Life-threatening adverse event* or *life-threatening suspected adverse reaction*.** An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

***Unexpected adverse event* or *unexpected suspected adverse reaction*.** An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated

from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

6.2. Adverse event reporting

The APRON 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",[42] shared by 17 Departments and Agencies and (2) 21 CFR 312,[41] the FDA regulation for adverse events. The Common Rule requires written procedures and policies for ensuring reporting of "unanticipated problems" involving risks to participants to IRBs, appropriate institutional officials, and the Department or Agency Head. The FDA regulation requires notification of the FDA and participating investigators of any adverse event associated with the use of a test article that is "both serious and unexpected." Investigators should refer to the 2009 FDA guidance *Improving Human Subjects Protection*,[43] for adverse events reportable to their institutional IRB. Since the definitions and reporting requirements for unanticipated events differ between the two sets of Federal regulations, the APRON trial definitions and procedures for adverse events are designed to satisfy both sets of requirements.

Adverse events will be recorded on the Adverse Event (AE) data forms whether or not they are thought to be associated with the study or with the study drug. Adverse events may be discovered during regularly scheduled visits or through unscheduled 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.[44]

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.

6.3. Serious adverse event reporting

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

If NIDDK determines that the SAE requires an expedited IND Safety Report, the NIDDK Program Official or the NIDDK Regulatory Affairs Specialist will notify the FDA no more than 15 calendar days from the initial receipt of the SAE by the DCC (no later than 7 calendar days if the SAE is fatal or life

threatening). The clinical center investigator may also be responsible for completing an FDA MedWatch 3500 form and additional information for a follow-up SAE report as information becomes available. If the FDA determines that a change to the investigators brochure, IND or protocol is needed, the Data Coordinating Center will send a copy of the IND Safety Report to all clinical centers, with instructions to forward the report to their IRB. NIDDK will determine if the DSMB members should be made aware of the event at that time, or it is appropriate to wait until the next DSMB meeting.

The DCC will maintain a list of all SAEs for reporting and review at Steering Committee meetings and DSMB meetings. The DSMB will review all SAE reports, at least twice a year. On a case-by-case basis, the NIDDK program staff, in conjunction with the DSMB chairperson, will determine whether the DSMB should review SAE reports more expeditiously. The DSMB will review each SAE report and provide comments to the NIDDK Program Official. If requested by any member of the DSMB, a teleconference will be scheduled to discuss the SAE and recommend any actions to the NIDDK. The clinical center must submit to the NIDDK and to the 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 DCC will provide to the pharmaceutical manufacturer copies of all SAEs regardless of association to APRON study drug which involve disability, congenital anomaly/birth defects/fetal losses, hospitalizations, and important medical events, cancers with no other event within five calendar days of receipt. In addition, the DCC will report any pregnancy occurring in association with the use of study drug to the pharmaceutical manufacturer within three calendar days. The DCC will report overdoses of the APRON study drug to the pharmaceutical manufacturer every six months. An overdose that results in an SAE or is associated with an SAE, will follow the normal SAE reporting process and timeframe. The SAE reports described above will be sent to:

ATTN: Global Safety
FAX: (215) 993-1220

6.4. Procedures for unmasking treatment assignment

Treatment assignments are double masked throughout the study until all data collection for the APRON trial has been completed (i.e., after completion of the 2 week post-trial follow-up visit for all patients). Every effort will be made to maintain the masking throughout the study except in emergency situations. The code of specific study drug will not be broken without the knowledge of the clinical center's principal investigator.

Unmasking of study medication will occur under the following conditions:

- **Severe allergic reaction (Stevens-Johnson Syndrome)**: Study medication is stopped indefinitely. The 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.

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.

7. Statistical design and analysis

7.1. Hypotheses

Primary hypothesis:

- In patients with chronic nausea and vomiting of presumed gastric origin, treatment with aprepitant compared to placebo, will result in improvement in nausea symptoms during treatment period (mean of once daily nausea self-ratings from 0 to 100 mm on a visual analog scale (VAS) over a 28 day treatment period) compared to a baseline period (mean of once daily nausea VAS over 7 days before randomization).

Secondary hypotheses:

- Treatment with aprepitant compared to placebo, will result in improved gastrointestinal symptoms during treatment period (mean of GCSI-DD scores over a 28 day treatment period) compared to a baseline period (mean of GCSI-DD scores over 7 days before randomization).
- Treatment with aprepitant compared to placebo, will result in improvement in nausea symptoms after 4 weeks of treatment (self-ratings from 0 to 100 mm VAS during EGG and satiety tests) compared to baseline VAS scores.
- Treatment with aprepitant will result in improved gastrointestinal symptoms as measured by the Gastroparesis Cardinal Symptom Index (GCSI) compared to placebo.
- Patients with gastroparesis in the aprepitant group will have improved satiety testing compared to patients in the placebo group.
- Patients with gastroparesis in the aprepitant group will have improved electrogastrography compared to patients in the placebo group.
- Treatment with aprepitant will result in improved global overall relief of symptoms and Clinical Global Patient Impression (CGPI) compared to placebo.
- Treatment with aprepitant will result in improvement in abdominal pain as measured by the Brief Pain Inventory compared to placebo
- Treatment with aprepitant will result in improvement in nausea symptoms as measured by the Nausea Profile compared to placebo
- Patients in the aprepitant group will have improvements in standardized quality of life scores, compared to placebo.

7.2. Outcomes measures

Primary outcome measure: The primary outcome measure is a binary (0,1) variable indicating improvement or not in the mean of available nausea VAS scores over the 28 day treatment period compared to the mean of VAS scores during the 7 day baseline period. The criteria for improvement are either a 25 mm or more reduction in mean VAS or attaining a mean VAS during the treatment period of < 25 mm.

Secondary outcome measures:

- Change in GCSI-DD score after treatment (mean of scores over a 28 day treatment period) compared to baseline GCSI-DD score (mean of scores over 7 days before randomization). Mean changes in GCSI-DD score will be compared.
- Change in GCSI score (sum of the 9 individual symptoms) after 4 weeks of treatment compared to baseline GCSI score. Mean changes in GCSI score will be compared.

  As noted earlier, a GCSI score of 21 or greater is a requirement for enrollment into the trial. The GCSI 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)

- Change in VAS for other symptoms such as stomach fullness, hunger, bloating, and abdominal discomfort after 4 weeks of treatment compared to baseline VAS. Mean changes in VAS scores will be compared.
- Change in volume of Ensure® consumed during satiety testing after 4 weeks of treatment compared to baseline volume of Ensure® consumed.
- Change in gastric dysrhythmias (outside 2.5-3.75 cycles per minute) during EGG testing after 4 weeks of treatment compared to baseline gastric dysrhythmias.
- Change in global overall relief of symptom after 4 weeks of treatment compared to baseline.
- Change in clinical global patient impression (CGPI) score after 4 weeks of treatment compared to baseline CGPI score. Mean changes in CGPI score will be compared.
- Change in Beck Depression Inventory (BDI-II) scores after 4 weeks of treatment compared to baseline BDI scores. Mean changes in BDI scores will be compared.
- Change in Brief Pain Inventory (BPI) scores focusing on abdominal pain after 4 weeks of treatment compared to baseline BPI scores. Mean changes in BPI scores will be compared.
- Change in State Trait Anxiety Inventory (STAI) scores after 4 weeks of treatment compared to baseline STAI scores. Mean changes in STAI scores will be compared.
- Change in Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM) scores after 4 weeks of treatment compared to baseline PAGI-SYM scores. Mean changes in PAGI-SYM scores will be compared.
- Change in health-related quality of life questionnaire (SF-36v2) scores after 4 weeks of treatment compared to baseline SF-36v2 scores. Mean changes in SF-36v2 scores will be compared.
- Change in Patient Health Questionnaire (PHQ-15) scores after 4 weeks of treatment compared to baseline PHQ-15 scores. Mean changes in PHQ-15 scores will be compared.
- Change in Nausea Profile scores after 4 weeks of treatment compared to baseline NP scores. Mean changes in NP scores will be compared

7.3. Statistical analyses

The primary analysis will be made on "intention to treat" basis,[45] which means that all randomized patients with daily VAS nausea scores at baseline and during the 4 weeks of treatment will be analyzed in the treatment group to which they were assigned. To be randomized, patients must have VAS scores for 7 days prior to randomization; the mean VAS for these 7 scores with be used as the baseline nausea measure for each patient. The mean VAS score during the period of treatment will be calculated based on all available VAS scores during the 28 days of treatment. Patients, who for some reason, do not have any of the VAS nausea scores recorded during the period of treatment will be counted as not improved (i.e., 0) for the primary outcome. Secondary, sensitivity analyses on a per-protocol basis will also be carried out, excluding patients from both groups who do not complete at least 50% (2 weeks) of the 4 weeks on assigned treatment, but conclusions about the primary objective will be based on the intention-to-treat

analysis.

Since the primary outcome measure is a binary indicator of improvement in VAS nausea 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,[46] with stratification by clinic, comparing proportions improved in the group assigned to aprepitant compared to the group assigned to placebo. The two-sided P-values so derived will be reported in the primary results paper of the trial. A two-sided P-value of 0.05 will be considered statistically significant.

Given the randomized design and adequate size planned for the APRON trial, it is unlikely that confounding of the treatment groups by covariates related to the change in VAS nausea score will occur. However, if confounding should occur, sensitivity analyses using logistic regression models with VAS nausea 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.

Analyses related to the secondary hypotheses 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. 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.

7.4. 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 4 week treatment period and the 2 week post-treatment follow-up. In the primary, intention-to-treat analysis, patients with a pattern of missing data that precludes determination in the primary outcome according to its definition will be counted 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 on missing data exceed 10%; however, all such methods involve strong assumptions that cannot be verified from the available data.

7.5. Justification of sample size

The planned sample size for the APRON trial is 120 patients with equal allocation to each of the two treatment groups (60 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 VAS nausea score over the course of treatment. For sample size purposes, the expected proportions improved (0.55 in the aprepitant group compared to 0.25 in the placebo group), were derived from the expert opinions of clinicians on the GpCRC Steering Committee, based on their experience with the VAS nausea score in patients with gastroparesis similar to those meeting the eligibility criteria for the trial. The size of the smallest clinically meaningful effect (0.55 vs. 0.25 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[47] 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 improved VAS nausea score in placebo group (assumed=0.25)

π_2 = expected proportion with improved VAS nausea score in aprepitant group (0.55)

π = 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 54 for a total of 108. To allow for possible mis-specification in the estimated response rates used in the calculation and missing data, we propose a sample size of 60 patients per group, or a total of 120 for the trial.

7.6. Interim analysis

An independent Data and Safety Monitoring Board (DSMB), appointed by the NIDDK, will review the protocol for the APRON trial and make a recommendation to the NIDDK regarding the starting of the study. In addition, the DSMB will meet periodically to monitor 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 makes recommendations 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 NIDDK or 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. Summary data on adverse events will be monitored by the DSMB quarterly and at its

semi-annual meetings or more frequently, as needed. The DSMB will review all SAE reports, at least twice a year. On a case-by-case basis, the NIDDK program staff, in conjunction with the DSMB chairperson, will determine whether the DSMB should review SAE reports more expeditiously. The DSMB will review each SAE report and provide comments to the NIDDK Program Official. If requested by any member of the DSMB, a teleconference will be scheduled to discuss the SAE and recommend any actions to the NIDDK.

The interim analysis of the primary outcome measure will be based on O'Brien-Fleming statistical stopping guidelines with one interim look.[48] This interim efficacy analysis will occur when approximately 50% of the primary outcome measures are complete with both baseline and 28 day treatment period.

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.

8. Human subjects issues

8.1. Overview and IRB approval

The APRON Trial 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 APRON Trial until the center has IRB approval and the DCC has certified the center for initiation of screening. Consent forms must have IRB approval. Clinical 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 APRON Trial 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 patients with chronic nausea and vomiting due to gastroparesis.

All subjects enrolled in the APRON Trial will receive the standard of care for 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.

8.2. Informed Consents

Prototype consents will be prepared for the APRON Trial. Individual clinical centers may add material but may not delete material thought to be necessary for informed consent. Clinical centers may reformat and reword information to conform to their local IRB requirements. A 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 study files.

8.3. 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 participants 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 NIDDK. 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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10. Appendices

10.1. Participating centers

Clinical Centers

- Johns Hopkins University School of Medicine
  - Stanford University
  - California Pacific Medical Center
- Temple University
- Texas Tech University
- University of Louisville
- University of Michigan
- Wake Forest University Medical Sciences

Data Coordinating Center:

- Johns Hopkins University Bloomberg School of Public Health

National Institutes of Health:

- National Institute of Diabetes and Digestive and Kidney Diseases

10.2. Data collection schedule

	Screening and Randomization visits		Follow-up visits: Weeks from randomization		
	S	**RZ**	**2**	**4**	**6**
Consent	X	.	.	.	.
Gastric emptying scintigraphy results review	X	.	.	.	.
Upper endoscopy results review	X	.	.	.	.
Baseline medical history	X	.	.	.	.
Initial VAS nausea assessment	X	.	.	.	.
Provide supplies of VAS and GCSI-DD	X	X	X	.	.
Collection of VAS and GCSI-DD	.	X	X	X	.
PAGI-SYM questionnaire	X	.	X	X	.
GSRS questionnaire	X	.	.	X	.
SF-36v2 Healty Survey questionnaire	X	.	.	X	.
Beck Depression Inventory-II	X	.	.	X	.
State Trait Anxiety Inventory	X	.	.	X	.
Brief Pain Inventory	X		X	X	.
PHQ-15 questionnaire	X	.	.	X	.
Nausea Profile	X		X	X	.
Satiety test with electrogastrography	X	.	.	X	.
Electrocardiogram (EKG)	X	.	.	.	.
Physical exam	X	.	.	X	.
Study drug dispensed	.	X	.	.	.
Follow-up medical history including review of adverse events	.	.	X	X	X
CBC, CMP, glucose, HbA1c*	X	.	.	X	.
Plasma banking	.	X	.	X	.
DNA banking	.	X	.	.	·
Pregnancy test	.	X	.	.	.

Physical exam includes weight, vital signs (temperature, heart rate, blood pressure) and general physical findings
Complete blood conunt (CBC): white blood cells, red blood cells, hemoglobin, hematocrit, platelets
Complete metabolic panel (CMP): sodium, potassium, chloride, carbon dioxide, glucose, calcium, BUN, creatinine, ALT, AST, magnesium, albumin, total protein.
* Glucose, hemoglobin A1c will be obtained in patients with diabetes.

10.3. Whole blood draw schedule

	Study visit (weeks)				
	Screening	rz	2	4	**Total**
Complete blood count	5	.	.	5	**10**
Complete metabolic panel, HbA1c*	5	.	.	5	**10**
Blood for DNA banking	.	20	.	.	**20**
Blood for plasma banking	.	10	.	10	**20**
Total (in mL)	**10**	**30**	**.**	**20**	**60**

Complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets
Complete metabolic panel: sodium, potassium, chloride, carbon dioxide, glucose, calcium, BUN, creatinine, ALT, AST, magnesium, albumin, total protein.
* Glucose, hemoglobin A1c will be obtained in patients with diabetes.

10.4. Glossary

APRON	-	**Ap**repitant for the **R**elief **o**f **N**ausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin: A Multicenter, Randomized, Double-Masked, Placebo-Controlled Trial
BMI	-	body mass index (kg/m^2)
CBC	-	complete blood count
CGPI	-	Clinical Global Patient Impression question
CMP	-	complete metabolic panel
CPM	-	cycles per minute
CTCAE	-	Common Terminology Criteria for Adverse Events
DCC	-	Data Coordinating Center
DSMB	-	Data and Safety Monitoring Board
EGG	-	electrogastrography
FDA	-	Food and Drug Administration
GCSI	-	Gastroparesis Cardinal Symptom Index
GCSI-DD	-	Gastroparesis Cardinal Symptom Index - Daily Diary
GpCRC	-	Gastroparesis Clinical Research Consortium
GpR 2	-	Gastroparesis Registry 2
GSRS	-	Gastrointestinal Symptoms Rating Scale
HIPAA	-	Health Insurance Portability and Accountability Act
IND	-	Investigational New Drug application
IRB	-	Institutional Review Board
NIDDK	-	National Institute of Diabetes and Digestive and Kidney Diseases
NK1	-	neurokinin 1
PAGI-SYM	-	Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index
PHQ	-	Patient Health Questionnaire
SAE	-	serious adverse event
SOP	-	standard operating procedures
VAS	-	visual analog scale

10.5. Document history

Aprepitant for the Relief of Nausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin Trial (APRON) Protocol (01 Mar 10)

Aprepitant for the Relief of Nausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin Trial (APRON) Protocol (07 Jul 10)

- Added IND #108,939
- Corrected the length of time for the EGG recording
- Corrected the amount of water consumed for the gastric emptying scintigraphy
- Clarified details on the handling of missing data
- Added pregnancy testing
- Removed white blood cell differential from complete blood count (CBC)
- Added Section 9.5 Document History

Aprepitant for the Relief of Nausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin Trial (APRON) Protocol (2 Feb 11)

- Clarified the length of recruitment
- Removed gastric emptying breath test
- Removed listing of clinical sites
- Clarified process for serious adverse event reporting
- Clarified text regarding the DSMB's role

Aprepitant for the Relief of Nausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin Trial (APRON) Protocol (26 Nov 12)

- Updated clinical history of aprepitant use
- Added Nausea Profile (NP)
- Removed Investigator Derived Independent Outcome Measure Score (IDIOMS)
- Clarified and expanded procedures for adverse event monitoring and reporting