NCT04857281

Non-invasive Vagal Nerve Stimulation (nVNS) for Symptomatic Exacerbation of Nausea in Patients With Gastroparesis and Related Disorders

Date: 11/14/2022

Principal Investigator
Glenn Treisman, MD
Johns Hopkins University
School of Medicine

1

Non-invasive vagal nerve stimulation (nVNS) for symptomatic exacerbation of nausea in patients with gastroparesis and related disorders

CONFIDENTIAL

Version: November 2022

1. Study Rationale

Chronic nausea and vomiting disorders have been referred to by many names in the literature, including chronic unexplained nausea and vomiting (CUNV), gastroparesis-like syndrome (GLS), functional vomiting, and vomiting of unexplained etiology (VUE). Chronic nausea and vomiting disorders are also included in the classification of functional gastrointestinal disorders (FGIDs). [1]

Gastroparesis is a digestive disorder in which the motility of the stomach is either abnormal or absent. [2] The symptoms of gastroparesis can range from mild to severe, requiring prolonged hospitalizations and interventions. Patients may present with predominant nausea, vomiting, bloating and early fullness while eating meals, heartburn, and epigastric pain. The symptoms can cause life-threatening complications can significantly affect the quality of life in affected individuals such as weight loss, dehydration, hypoglycemia, malnutrition, bacterial overgrowth from the fermentation of food and benzoars that may cause and obstruction in the stomach.[3-5]

The causes of gastroparesis are extensive and varied. One of the most common causes of gastroparesis is diabetes probably due to damage to nerves that supply the stomach. Some people with idiopathic gastroparesis report symptoms following a virus infection and sometimes the cause are unknown (idiopathic). [6-8]

Other possible causes include endocrine disorders like hypothyroidism, connective tissue disorders such as scleroderma, autoimmune conditions (systemic lupus erythematosus), some nervous system link disorders such as Parkinson's disease or migraines, neuromuscular diseases, eating disorders, [9-11] certain cancer radiation treatment applied over the chest or abdomen, [12] some chemotherapy agents. Less frequently, gastroparesis is seen to occur after certain medications such as opioids,[13] some antidepressants, and high blood pressure.[8,14]

Any surgery on the esophagus, stomach or duodenum may result in injury to the vagus nerve that is responsible for many sensory and motor (muscle) responses of the intestine.[15] In health, the vagus nerve sends neurotransmitter impulses to the smooth muscle of the stomach that result in contraction and forward propulsion of gastric contents. If the vagus nerve is injured by trauma or during surgery, gastric emptying may be reduced. Symptoms of postoperative gastroparesis may develop immediately, or months to years, after a surgery is performed. The vagus nerve helps manage the complex processes in the digestive tract, including signaling the muscles in the stomach to contract and push food into the small intestine. A damaged vagus nerve cannot send signals normally to the stomach muscles. This may cause food to remain in the stomach longer, rather than move normally into the small intestine to be digested. [16]

Several medications are used to treat gastroparesis and CUNV to control the symptoms specially nausea and vomiting such as the 5-HT3 antagonist (e.g. ondansetron) or D2 receptor antagonist (e.g. Promethazine). [17] Other medications stimulate the stomach muscles and help with digestion with prokinetics. These include metoclopramide, erythromycin and domperidone. [1,18] However, the drugs can cause side effects.

When gastroparesis does not respond to standard medical management, including drugs and dietary changes, the condition is said to refractory. Gastric Electrical Stimulation (GES) uses a device, surgically implanted in the abdomen, to deliver mild electrical pulses to the nerves and smooth muscle of the lower part of the stomach. This procedure reduces the nausea and vomiting and may be considered for compassionate treatment in patients with refractory symptoms, particularly in patients with persisting symptoms and GES.[19]

The vagus nerve plays a key role in regulation of nausea and vomiting, and there is evidence of vagus afferent effects on nociception, which suggests that electrical stimulation modulates nauseas and vomiting. The current proof of concept study explores the possibility that non-invasive vagus nerve stimulation (nVNS) could have clinical effects similar those of an implanted gastric electrical stimulation device in patients with symptoms of gastroparesis. GES report some complications, the main one being the infections of subcutaneous pocket, inflammation over implant site, device migration/erosion, lead penetration, extra-abdominal pain, seroma and hematoma. Less common complications include erosions of the abdominal wall by the device, penetration of the leads through the gastric wall, or tangling of wires in the generator pocket and formation of adhesions. GES is relatively expensive treatment with the high cost of the device and for the surgical procedure. [20-22]

gammaCore (nVNS) is the first non-invasive, handheld medical device[23] applied on the side of the neck and sends gentle, patented mild electrical stimulation through the skin to activate the vagus nerve. nVNS offers a potential alternative to GES that could eliminate significant risks of injury or illness or identify likely responders to implantable neurostimulator including implanted VNS (iVNS). nVNS could provide a more effective and safer alternative to the use of traditional rescue medications.

nVNS primarily stimulates myelinated sensory afferent vagus nerve fibers as they ascend through the neck in the carotid sheath. nVNS has been cleared for the acute and preventive treatment of migraine and the acute and preventive treatment of cluster headache by the Food and Drug Administration (FDA) and is also CE marked and used in several all forms of primary headache. [24, 25]

The hypothesis of the pilot study is that nVNS will result in relief of nausea by modulation of vagal nerve activity.

2. **Objectives** (include all primary and secondary objectives)

- The principal objective of this open label pilot study is to evaluate whether acute treatment of nausea exacerbations with nVNS will be effective in reducing the use of rescue medications.

- Secondary objectives of this study include:
    - Determine the nature and incidence of adverse effects.

- Exploratory objectives
    - Determination of the effects of nVNS (or correlation with response) use on:
        - Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM) and the Gastrointestinal Symptom Rating Scale (GSRS).
        - Depression and anxiety using the Beck Depression Inventory and State-Trait Anxiety Scores.
        - Frequency of migraines and headaches (since many patients with gastroparesis have concomitant migraine) defined as, 'migraine day'= a migraine headache occurring in a 24-hour period, and a 'headache day'= any headache occurring in a single calendar day.
        - Autonomic symptoms as determined by the COMPASS-31 score.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Chronic nausea and vomiting are the clinical hallmarks of gastroparesis and Chronic Unexplained Nausea and Vomiting or CUNV (very similar to Functional Dyspepsia of the postprandial subtype, FD-PPS, by Rome criteria) or related disorders and in most cases, are constant and daily symptoms. However, in addition, the majority of these patients also experience periodic exacerbations of these symptoms either on a daily basis or several times in a week. These exacerbations require them to use "rescue" medications such as 5-HT3 antagonists (e.g. ondansetron) or D2 receptor antagonists (e.g. Promethazine). These are only partially effective at best and often associated with adverse effects. Our hypothesis is that nVNS may provide a more effective and safer alternative to the use of traditional rescue medications. We therefore believe that while nVNS may not necessarily be a stand-alone treatment for gastroparesis, it has the potential for meeting a large unmet "niche" need in this condition.

***4.* Study Procedures**

Patients who appear to be eligible after chart review and completion of standard of care tests and procedures for gastroparesis, CUNV or related disorders will be invited to undergo screening for study. Patients considered by the clinical center investigator as likely to be eligible for participation in the trial may be consented, registered and screened at a visit that is part of the ongoing clinical care of the patient.

After informed consent is obtained, patients will fill out a validated symptom-based questionnaires and assessment daily.

Visit schedule

- At least **2 weeks** of pre-treatment observation (screening).
- **8 weeks** of treatment
- **2 weeks** of post-treatment observation.
- Length of recruitment: **9 months**

1. Screening visit and baseline data collection

Study participants will come from the patient rosters of study physicians. Patients who appear to be eligible after chart review and completion of standard of care test and procedures will be invited to undergo screening for the trial. Patients considered by the clinical center investigator as likely to be eligible for participation in the trial may be consented, registered and screened at a visit that is a part of the ongoing clinical care of the patient.

An open label pilot study to be conducted at Johns Hopkins Bayview Medical Center over 9 months to evaluate with nVNS for the symptomatic exacerbations of nauseas in patients with gastroparesis or CUNV. Approximately 30 patients will be enrolled in the study. Inclusion criteria will include patients 18 years or older with symptomatic nausea, vomiting and other symptoms suggestive of chronic nausea and vomiting of presumed gastric origin (Gastroparesis or CUNV). All the participants will come from the patient roster of the study physicians from the Division of Gastroenterology, Department of medicine: Dr. Glenn Treisman (Principal Investigator), and Dr. Robert Bulat.

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions

Revisions to the informed consent process are being permanently adopted for this research. Teleconsent will be used as opposed to in person consenting where possible to reduce unnecessary in person encounters specifically for a consent procedure. In the event teleconsent is utilized, participants will be provided with a copy of the Informed Consent prior to the teleconsent meeting either via email, fax, mail or previously provided during an in person visit.

Participants will be given adequate time to consider the research study and ask questions prior to signing the consent form. The consent designee must verify the participant physically signed the consent document by either viewing via video conference, obtaining a photo of the signed consent document; or obtaining verbal confirmation from the participant that he/she signed the consent form or agreed to participate electronically. The participant will sign and date/time the informed consent document. The document is then mailed, emailed or faxed to the consent designee. The participant will be asked to return the original signed document on their first in person visit. If the Informed Consent form is mailed to the consent designee by the participant the study coordinator will sign the copy, which they possess after the participant has acknowledged signature on their copy. Once the original is received by the consent designee the copies will be

attached to make a single document. In all other instances, once received, the research coordinator signs, dates/times the informed consent document.

At the time of the first clinical encounter post teleconsent, research coordinator will review any additional study participant questions and discuss the risks, benefits and alternatives of the study in full detail, completing the physician/mid-level component of the consent process. After the Informed Consent process is completed, a study team member will file the consent document in EPIC. The entire consent document is also then filed in the research record.

Only patients who are sufficiently proficient in English will be recruited for this study. All potential study candidates will be able to obtain a consent form in advance and review it at their own time, as needed. All contact information for the lead study coordinator and the study PI will be given to the potential candidate when they are given a copy of the consent form.

As part of the screening process for the trial, the patient must have a diagnosis of gastroparesis or CUNV with delayed gastric emptying documented by gastric emptying scintigraphy (4-hour emptying after a low-fat meal with any combination of 2- and 4-hour retention of >60% and 10% respectively) and ongoing symptoms such as: nausea, vomiting, abdominal pain, etc. for at least 3 months without any other obvious cause. Patients must also have a normal upper endoscopy or standard radiography, 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 informed consent form (ICF). Screening and baseline data collection procedures will include questionnaires, urine pregnancy test, 12 lead EKG, and review of the patient's medical chart.

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

Screening visit:

The patient will undergo a medical history to identify other illness and contraindications for participations such as use of narcotics for more than 3 days per week, previous surgery of the upper gastrointestinal tract, history of prolonged QT interval or clinical significant arrhythmia, etc.

In addition, the patient will be provided with the questionnaires and will be administered on a daily basis for up two weeks before treatment with following questionnaires (delivered electronically):

- Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD)

- Rescue medication uses daily diary- number of pills and type. Rescue medications that will be allowed for this trial are ondansetron, promethazine and prochlorperazine.
- Migraine and headache daily diary
- Gastrointestinal Symptom Rating Scale (GSRS)
- Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM)
- Beck Depression Inventory (BDI-II)
- State- Trait Anxiety Inventory (STAI)
- Average weekly frequency of migraine headaches for the last 4 week period
- COMPASS-31 score.

Anthropomorphic assessments (body weight, body height, body mass index [BMI]. Pregnancy test results that need to be recorded from chart review or obtained as part of the screening and EKG to rule out any abnormal baseline electrocardiogram such as second and third degree heart block, atrial fibrillation, atrial flutter, recent history of ventricular tachycardia or ventricular fibrillation, or clinically significant premature ventricular contraction, history of prolonged QT interval or a history of clinically significant arrhythmia.

Data will be captured on REDCAP and stored on the secure Hopkins server for this purpose.

2. Treatment Start Visit

At this visit, the patient will receive the gammaCore (nVNS) device and a video instruction will be use to explain how to properly handle the device. Treatment can only start after eligibility has been fully checked and all data collected at screening have been keyed into the trial database. Women of childbearing potential must have a negative urine pregnancy test.

After eligibility is confirmed with the clinical center staff the treatment can begin. The date of starting treatment is the start (ZERO) time for the timing of follow-up visits.

Frequency and duration of nVNS treatment.
The treatment will be self-administered using nVNS and will be applied for 8 weeks; 4 weeks will be used on one side of the neck and other 4 weeks in the contralateral side. A member of the study will provide the proper training on the correct use of nVNS. The patient will be instructed to use the nVNS in place of the rescue medications. When the nauseas gets bad enough that they feel to use a rescue medication they will first use the device on one side of the neck for two 2-minute stimulations and wait fifteen minutes to check if the stimulation works. If this does not help either, they will stimulate with an additional 2 stimulations and wait for another fifteen minutes. If there is no improvement rescue medication will be used. nVNS can be used up to, but no more than, 8 times a day.

3. Follow-up Visits

Patients will return for follow-up visits at 4 and 10 weeks after treatment initiation. The specific

procedures to be completed at each of the follow-up visits are:

- **Week 4 visit:** The following questionnaires should be completed and collected:
  - Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD)
  - Rescue medication uses daily diary- number of pills and type
  - Migraine and headache daily diary
  - Gastrointestinal Symptom Rating Scale (GSRS)
  - Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM)
  - Beck Depression Inventory (BDI-II)
  - State- Trait Anxiety Inventory (STAI)
  - Average weekly frequency of migraine for the last 4 week period
  - COMPASS-31 score.
  - Global patient impression (GCPI) questionnaire.

  Laboratory test results that need to be collected are EKG and urine pregnancy test. Review study of adverse events will be addressed.

- **Week 8 visit:** This will be the end of study visit. A medical history, including side effect or symptom profile will be collected. The following questionnaires should be completed and collected:

  - Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD)
  - Rescue medication uses daily diary- number of pills and type
  - Migraine and headache daily diary
  - Gastrointestinal Symptom Rating Scale (GSRS)
  - Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM)
  - Beck Depression Inventory (BDI-II)
  - State- Trait Anxiety Inventory (STAI)
  - COMPASS-31 score.
  - Global patient impression (GCPI) questionnaire.

- **Week 10 visit:** This will be the end of study visit. A medical history, including side effect or symptom profile will be collected. The following questionnaires should be completed and collected:

  - Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD)
  - Rescue medication uses daily diary- number of pills and type
  - Migraine and headache daily diary
  - Gastrointestinal Symptom Rating Scale (GSRS)
  - Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM)
  - Beck Depression Inventory (BDI-II)
  - State- Trait Anxiety Inventory (STAI)
  - COMPASS-31 score.
  - Global patient impression (GCPI) questionnaire.

noninvasive Vagal Nerve Stimulation (nVNS) device Study Data Collection Schedule					
	Screening & GammaCore treatment Visits (Weeks)		**Follow-up Visits: Weeks from start of treatment**		
	Screening (0)	**Treatment initiation (2)**	**4**	**8**	**10**
Consent	X				
Baseline medical history	X				
GCSI-DD	X		X	X	X
Rescue Medication Daily Diary	X		X	X	X
Migraine and Headache Daily Diary	X		X	X	X
Collection of GCSI-DD		X	X	X	X
Collection of Rescue Medication Daily Diary		X	X	X	X
Collection of Migraine and Headache Daily Diary		X	X	X	X
PAGI-SYM questionnaire	X		X	X	X
GSRS questionnaire	X		X	X	X
Beck Depression Inventory-II	X		X	X	X
State Trait Anxiety Inventory	X		X	X	X
COMPASS 31-score			X	X	X
Noninvasive Vagal Neural Stimulation (VNS) device dispensed		X			
Follow-up medical history, including review of adverse events			X		X
12-lead EKG	X		X		
Urine pregnancy test	X		X		

Specific Tests and Questionnaires

- Pregnancy test: Women of childbearing potential must have a negative urine pregnancy test.

- 12-lead EKG: To rule out any abnormal baseline electrocardiogram such as second and third degree heart block, atrial fibrillation, atrial flutter, recent history of ventricular tachycardia or ventricular fibrillation, or clinically significant premature ventricular contraction, history of prolonged QT interval or a history of clinically significant arrhythmia.

- Gastroparesis Cardinal Symptom Index (GCSI) Daily Diary:[26] Consists of five core symptoms (nausea, vomiting, early satiety, postprandial fullness, upper abdominal pain). Each night, participants grade the severity of symptoms over the prior 24 hours. The GCSI-DD core symptom composite score (an average of the five core symptoms) is designed to detect clinical improvement in symptoms of gastroparesis and to be used as a PRO outcome for clinical trials.

- Rescue medication daily diary: Must contain the name of the antiemetic medications, dosage, frequency and number of pills during the day.

- Gastrointestinal Symptom Rating Scale (GSRS): [27] The GSRS is a disease-specific instrument of 15 items combined into five symptom clusters depicting Reflux, Abdominal pain, Indigestion, Diarrhea, and Constipation. The GSRS has a seven-point graded Likert-type scale where 1 represents the absence of troublesome symptoms and 7 represents very troublesome symptoms. The reliability and validity of the GSRS are well-documented and normative values for a general population are available.

- Patient Assessment of Upper Gastrointestinal Disorders-Symptoms (PAGI-SYM): [28] The self-reported questionnaire is composed of 20 items and 6 subscales. The severity of each symptom item over a 2-week recall period is scored from 0 (none or absent) to 5 (very severe). The GCSI, a 9-symptom survey relevant to gastroparesis stratified in 3 subscales – nausea/vomiting, fullness/early satiety, and bloating, is contained in the PAGI-SYM. The GCSI correlates with patient severity ratings and is responsive to changes in overall symptoms. Two additional items for constipation and diarrhea also will be recorded and scored and their main symptom will be determined.

- Beck Depression Inventory, Second Edition (BDI-II): [29] The BDI-II is a commonly used, reliable 21-item self-report measure designated to assess for depression.

- State Trait Anxiety Inventory:[30] 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.

- Migraine and headache daily diary: is going to record various aspects of headache or migraine attacks, monitor the frequency, type, duration, severity, symptoms, possible triggers and track medication use.

- Migraine Frequency: This will be obtained from the Migraine and headache daily diary.

- COMPASS-31:[31] Is a self-report measure for assessing symptoms of dysautonomia. Scale contains 31 questions in six domains, yielding an overall autonomic symptom score from 0 to 100. The domains are orthostatic intolerance (4 questions), vasomotor (3 questions), secretomotor (4 questions), pupillomotor (5 questions), bladder (3 questions), and gastrointestinal (including diarrhea, constipation, and gastroparesis, 12 questions). For each question there is a numeric rating based on factors such as site, consistency, severity, frequency, or trends.

Recruitments Procedures:

Individuals Responsible for Approaching Participants:
Prospective participants will be approached by their own physicians who are study team members Recruitment will take place while the potential participants are present for clinic appointments. Potential participants will be informed that participation is voluntary and that their care at Johns Hopkins will not be affected if they considered not participating it this study.

How Privacy Issues will be addressed:
The study team member will approach the participants when they are alone in the exam rooms to ensure privacy so that others cannot hear the conversation between the participant and study team members. After ensuring that sufficient privacy is achieved and that the potential subjects are at ease and comfortable with their surroundings, the consent designee will obtain informed consent to enter the study and explain the study procedures verbally and encourage the potential subjects to ask questions.

The questionnaires will also be filled out during the treatment and during the 2 weeks after nVNS treatment has been completed. All questionnaires are short and easy to fill out with multiple-choice type responses. Adverse events (AEs) will also diarized.

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

5. Inclusion/Exclusion Criteria

Inclusion criteria

- Age 15 years or older at registration.
- Diagnosis of gastroparesis as documented by gastric emptying scintigraphy (4-hour emptying after a low-fat meal with any combination of 2- and 4-hour retention of >60% and 10%, respectively), or Chronic Unexplained Nausea and Vomiting (CUNV).
- Ongoing symptoms (i.e. Nausea and vomiting, bloating, and abdominal pain) with a nausea score of 3 or more on the PAGI-SYM scale at baseline (moderate to severe nausea).
- Exclusion of other causes of symptoms such as mechanical gastrointestinal obstruction, uncontrolled esophagitis, peptic ulcer disease, etc. By standard radiographic or endoscopic tests.
- Use of the following medications on an as-needed basis: ondansetron, promethazine or prochlorperazine but no more than four times a day.

Exclusion criteria

- Another active disorder, which could explain symptoms in the opinion of the investigator.
- Age < than 15 years.
- Pregnancy or nursing.
- A previous surgery of the upper gastrointestinal tract, including vagotomy.
- Use of narcotics more than 3 days per week.
- History of prolonged QT interval or a history of clinically significant arrhythmia.
- Abnormal baseline ECG (e.g. Second- and third-degree heart block, atrial fibrillation, atrial flutter, recent history of ventricular tachycardia or ventricular fibrillation, or clinically significant premature ventricular contraction).
- Previous bilateral or right cervical vagotomy.
- Uncontrolled high blood pressure.
- Currently implanted with an electrical and/or neurostimulator device, including but not limited to cardiac pacemaker or defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, bone growth stimulator, or cochlear implant.
- History of carotid endarterectomy or vascular neck surgery on the right side.
- Implanted with metal cervical spine hardware or has a metallic implant near the gammaCore stimulation site.
- Any other condition, which in the opinion of the investigator would impede compliance or hinder the completion of the study.
- Failure to give informed consent.

6. Drugs/ Substances/ Devices

gammaCore Sapphire (nVNS) [23-25]

Description:

nVNS is a multi-use, hand-held, rechargeable, portable device consisting of a rechargeable battery, signal-generating and -amplifying electronics, and a control button for the patient to control the signal amplitude. The device provides visible (display) and audible (beep) feedback on the device and stimulation status. A pair of stainless steel surfaces, which are the skin contact surfaces ("stimulation surfaces"), allow the delivery of a proprietary electrical signal. The patient applies electroCore-approved gel to the stimulation surfaces to maintain an uninterrupted conductive path from the stimulation surfaces to the skin on the neck. Tubes of electroCore-approved gel are provided with each unit and refill kit for this purpose. The stimulation surfaces are capped when not in use.

7. Study Statistics

Data analysis will be performed at Mayo Clinic Scottsdale, Arizona by Dr. Jay Pasricha, (Pasricha.Jay@mayo.edu). This site will no recruit participants.
Johns Hopkins will serve as coordinating center, responsible for overall data management, monitoring and communication among both sites, and general oversight of the conduct of this protocol.

Outcome measures

Primary: The primary outcome measure is the average daily use of rescue medications for exacerbation of nausea/vomiting.

Sample size justification

- Primary endpoint: Improvement in nausea control, as defined by a 50% reduction n the number of weekly doses of rescue medications, compared with baseline.
- Total of **45 patients.** This is a pilot study to assess the strength of the signal (improvement) with peripheral VNS for nausea. Since there is evidence that the left and right vagus may have different pathways within the CNS, with the left side being dominant in innervation of center involved in food aversion and nausea (Cell 175, 665–678, 2018), we are proposing to study three groups as follows
  Group 1; Start with left sided stimulation - 15 patients
  Group 2. Start with right sided stimulation - 15 patients
  Group 3. Both sided stimulation - 15 patients
- Our assumptions are as follows, in terms of the number of patients improving in each group
  Group 1: 4/15
  Group 2: 11/15
  Group 3: 7/15
  If these assumptions are true, the type I error will be < 0.05

8. Risks[32-34]

The adverse reactions observed in nVNS studies include:

i. Shortness of breath (dyspnea), hoarseness, or change in voice during treatment.
ii. Muscle twitching, discomfort, or pain during stimulation.
iii. Change in taste (dysgeusia).

These first three reactions resolved after treatment was completed.

iv. Local skin irritation/inflammation.
v. Any progression of headache symptoms.

Adverse reactions not seen in the studies, but associated with implanted vagal nerve stimulation devices include:

vi. Tingling, pricking, or a feeling of “pins and needles” on the skin where the device is applied (paresthesia or dysaesthesia) lasting beyond the treatment period.
vii. Fainting (syncope), light-headedness, and/or dizziness.
viii. Sweating.
ix. Fatigue, depressed mood.
x. Tinnitus.
xi. Diarrhea.
xii. Abnormal heart rhythm.

Adverse events will be evaluated in every follow-up visit. A form of Adverse Event will be completed if the candidate complains of any symptoms, sign, abnormal assessment or any combination of these. An adverse event can be expected side effect that is of a serious nature, or an unexpected side effect/event regardless of severity.

This study will monitor and report adverse events to ensure patient safety to IRB and FDA. Signs and symptoms associated with the adverse event will be graded as to severity by the clinical site staff as mild, moderate, or sever using Version 5.0 of the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE).

9. Benefits

Description of the probable benefits for the participant and for society.

The benefit to the participant includes the opportunity to have their rare, debilitating disease studied and better identified through specific diagnostic testing.

Benefit/Risk Conclusion

nVNS has been cleared as a low-risk Class II treatment. This indicated that the likely benefit outweighs the risks across the cleared indications.

10. Payment and Remuneration

Participation in the study will be voluntary and there will be no additional compensation. There will be no penalties for not completing the protocol.

11. Costs

The study team will cover all the procedures, material and logistics. Electrocore will supply the Sapphire devices at no cost to the Investigator.

12. References:

1. Harer, K; Pasricha PJ. Chronic Unexplained Nausea and Vomiting or Gastric Neuromuscular Dysfunction (GND)? An Update on Nomenclature, Pathophysiology and Treatment and Relationship to Gastroparesis. 2016 Dec; 14 (4): 410-419. [PubMed: 5102760].
2. Camilleri, M; Parkman HP; Shafi MA; Abell T; Gerson L. Clinical guideline: management of gastroparesis. 2013 Jan; 108 (1): 18-37. [PubMed: 3722580].
3. Liu N, Abell T. Gastroparesis Updates on Pathogenesis and Management. Gut Liver. 2017 Sep 15;11 (5): 579-589. doi: 10.5009/gnl16336. [PubMed: 28535580].
4. Camilleri, M; Chedid, V; Ford, AC; Haruma, K; Horowitz, M; Jones KL; et al. Gastroparesis. 2018 Nov 1;4 (1): 41. doi: 10.1038/s41572-018-0038-z. [PubMed: 30385743].
5. Lacy BE; Crowell MD; Mathis C; Bauer D; Heinberg, LJ. Gastroparesis: Quality of Life and Health Care Utilization. J Clin Gastroenterol. 2018 Jan; 52 (1): 20-24. doi: 10.1097/MCG.0000000000000728. [PubMed: 27775961].
6. Parkman, H; Wilson, L; Farrugia, G; Kenneth L; Hasler, W; Pasricha, PJ; et al. Delayed Gastric Emptying Associates With Diabetic Complications in Diabetic Patients With Symptoms of Gastroparesis. Am J Gastroenterol 2019 Nov: 114 (11): 1778-1794.
7. Parkman HP. Idiopathic gastroparesis. Gastroenterol Clin North Am. 2015 Mar; 44 (1): 59-68. doi: 10.1016/j.gtc.2014.11.015. [PubMed: 25667023].
8. Aswath GS; Foris LA; Ashwath AK; Krunal P. Diabetic Gastroparesis. 2019. [PubMed: 28613545].
9. Nassar Y, Richter S. Gastroparesis in Non-Diabetics: Associated Conditions and Possible Risk Factors. Gastroenterology Res. 2018 Oct; 11 (5): 340-345. doi: 10.14740/gr1060w. Epub 2018 Oct 1. [PubMed: 30344804].
10. Lockshin, MD; Levine, AB; Erkan, D. Patients with overlap autoimmune disease differ from those with 'pure' disease. Lupus Sci Med. 2015 May 6;2 (1): e000084. doi: 10.1136/lupus-2015-000084. [PubMed: 25973214].
11. Poirier, AA; Aubé, B; Côté, M; Morin, N; Di Paolo, T; Soulet, D. Gastrointestinal Dysfunctions in Parkinson's Disease: Symptoms and Treatments. Parkinsons Dis. 2016;2016:6762528. doi: 10.1155/2016/6762528. Epub 2016 Dec 6. [PubMed: 28050310].
12. Annede, P; Prieux-Klotz, C; Dubergé, T; Chargari, C; Gisserot, O; de Jaureguiberry, JP. Radiation induced gastroparesis-case report and literature review. J Gastrointest Oncol. 2017 Aug; 8 (4): E52-E55. doi: 10.21037/jgo.2017.04.06. [PubMed: 28890828].
13. Siddiqui MT, Bilal M, Schorr-Lesnick B, Lebovics E, Dworkin B. Opioid use disorder is associated with increased mortality and morbidity in patients with gastroparesis. Ann

Gastroenterol. 2019 Jul-Aug; 32 (4): 370-377. doi: 10.20524/aog.2019.0389. [PubMed: 31263359].

14. Kelly D, Moran C, Maher M, O'Mahony S. Malignancy-associated gastroparesis: an important and overlooked cause of chronic nausea and vomiting. BMJ Case Rep. 2014 Feb 10;2014: bcr2013201815. doi: 10.1136/bcr-2013-201815. [PubMed: 24515229].
15. Camilleri, M; Parkman, HP; Shafi, MA; Abell, TL; Gerson, L; American College of Gastroenterology. Clinical guideline: management of gastroparesis. Am J Gastroenterol. 2013 Jan; 108 (1): 18-37; quiz 38. doi: 10.1038/ajg.2012.373. Epub 2012 Nov 13. [PubMed: 23147521].
16. Browning KN, Verheijden S, Boeckxstaens GE. The Vagus Nerve in Appetite Regulation, Mood, and Intestinal Inflammation. Gastroenterology. 2017 Mar; 152 (4): 730-744. doi: 10.1053/j.gastro.2016.10.046. Epub 2016 Dec 15. [PubMed: 27988382].
17. Lacy, BE; Parkman, HP; Camilleri, M. Chronic nausea and vomiting: evaluation and treatment. Am J Gastroenterol. 2018 May; 113 (5): 647-659. doi: 10.1038/s41395-018-0039-2. Epub 2018 Mar 15. [PubMed: 29545633].
18. Hasler WL. Newest Drugs for Chronic Unexplained Nausea and Vomiting. Curr Treat Options Gastroenterol. 2016 Dec; 14 (4): 371-385. doi: 10.1007/s11938-016-0110-2. [PubMed: 27726068.
19. Lal, N; Livemore, S; Dunne, D; Khan, I. Gastric Electrical Stimulation with the Enterra System: A Systematic Review. Gastroenterol Res Pract. 2015;2015:762972. doi: 10.1155/2015/762972. Epub 2015 Jul 12. [PubMed: 26246804].
20. Abell, TL; Yamada, G; McCallum, RW; Van, Natta, ML; Tonascia, J; Parkman, HP; et al. Effectiveness of gastric electrical stimulation in gastroparesis: Results from a large prospectively collected database of national gastroparesis registries. Neurogastroenterol Motil. 2019 Dec; 31 (12): e13714. doi: 10.1111/nmo.13714. Epub 2019 Oct 4. doi: 10.1111/nmo.13714. [PubMed: 31584238].
21. Oh, JH. Expanding Indications of Gastric Electrical Stimulation. J Neurogastroenterol Motil. 2015 Oct 1;21 (4): 455-6. doi: 10.5056/jnm15144. [PubMed: 26424035].
22. Zoll, B; Jehangir, A; Malik, Z; Edwards, MA; Petrov, RV; Parkman, HP. Gastric Electric Stimulation for Refractory Gastroparesis. J Clin Outcomes Manag. 2019 Jan; 26 (1): 27-38. [PubMed: 31501641].
23. Grazzi L. Non invasive neurostimulation. J Headache Pain. 2015 Dec; 16 (Suppl 1): A18. doi: 10.1186/1129-2377-16-S1-A18. [PubMed: 28132370].
24. Simon, B; Blake, J. Mechanism of action of non-invasive cervical vagus nerve stimulation for the treatment of primary headaches. Am J Manag Care. 2017 Nov; 23 (17 Suppl): S312-S316. [PubMed: 29144716].
25. Mwamburi, M; Liebler, EJ; Tenaglia, AT. Review of non-invasive vagus nerve stimulation (gammaCore): efficacy, safety, potential impact on commodities, and economic burden for episodic and chronic cluster headache. Am J Manag Care. 2017 Nov; 23 (17 Suppl): S317-S325. [PubMed: 29144717]
26. Revicki DA, Camilleri M, Kuo B, Szarka LA, McCormack J, Parkman HP. Evaluating symptom outcomes in gastroparesisclinical trials: validity and responsiveness of the Gastroparesis Cardinal Symptom Index-Daily Diary (GCSI-DD). Neurogastroenterol Motil 2012;24 (5): 456-63. [PubMed: 22284754].

27. Khanna, D; Hays, RD; Shreiner, AB; Melmed, GY; Chang, L; Khanna, PP. et al. Responsiveness to Change and Minimally Important Differences of the Patient-Reported Outcomes Measurement Information System Gastrointestinal Symptoms Scales. Dig Dis Sci. 2017 May; 62 (5): 1186-1192. doi: 10.1007/s10620-017-4499-9. Epub 2017 Mar 1. [PubMed: 28251500].
28. Development and psychometric evaluation of the patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM) in patients with upper gastrointestinal disorders. Qual Life Res. 2004 Dec; 13 (10): 1737-49. doi: 10.1007/s11136-004-9567-x. [PubMed:15651544].
29. Beck, AT; Steer, RA; Ball, R; Ranieri, W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess. 1996 Dec; 67 (3): 588-97. doi: 10.1207/s15327752jpa6703_13. [PubMed: 8991972].
30. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res (Hoboken). 2011 Nov; 63 Suppl 11 (0 11): S467-72. doi: 10.1002/acr.20561. [PubMed: 22588767].
31. Treister, R; O'Neil, K; Downs, HM; Oaklander, AL. Validation of the composite autonomic symptom scale 31 (COMPASS-31) in patients with and without small fiber polyneuropathy. Eur J Neurol. 2015 Jul; 22 (7): 1124-30. doi: 10.1111/ene.12717. Epub 2015 Apr 23. [PubMed: 25907824].
32. Howland RH. Vagus Nerve Stimulation. Curr Behav Neurosci Rep. 2014 Jun; 1 (2): 64-73. doi: 10.1007/s40473-014-0010-5. [PubMed: 24834378].
33. Barbanti P, Grazzi L, Egeo G, Padovan AM, Liebler E, Bussone G. Non-invasive vagus nerve stimulation for acute treatment of high-frequency and chronic migraine: an open-label study. J Headache Pain. 2015;16:61. doi: 10.1186/s10194-015-0542-4. Epub 2015 Jun 30. [PubMed 26123825].
34. Akdemir, B; Benditt, DG. Vagus nerve stimulation: An evolving adjunctive treatment for cardiac disease. Anatol J Cardiol. 2016 Oct; 16 (10): 804-810. doi: 10.14744/AnatolJCardiol.2016.7129. [PubMed: 27723668].