Pioglitazone for Idiopathic Gastroparesis
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Clinical Protocol Synopsis- Pioglitazone for the Treatment of Gastroparesis

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Title

- **Pioglitazone for the Treatment of Idiopathic Gastroparesis (PIOGAS Study)**

Type of study

- Open label pilot study

Objective

- The principal objective of this pilot study will be to evaluate whether 8 weeks of treatment of pioglitazone will improve symptoms as measured by the Gastrointestinal Symptom Index Daily Diary (GCSI-DD) in patients with Idiopathic Gastroparesis
- Secondary objectives of this study include:
    - To determine the effects of pioglitazone on other symptoms associated with gastroparesis using the Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM) and the Gastrointestinal Symptom Rating Scale (GSRS),
    - To determine the effects of pioglitazone on gastric emptying as measured by the ^{13}C- Spirulina breath test,
    - To determine the effects of pioglitazone on satiety as measured by a liquid caloric test
    - To determine the effects of pioglitazone on depression and anxiety using the Beck Depression Inventory and State-Trait Anxiety Scores,
    - To determine the effects of pioglitazone on Quality of Life using the PAGI-QoL and SF-36 questionnaire,
    - To determine the effects of pioglitazone on markers of inflammation (CRP and ESR) and serum cytokine levels
    - And to determine the nature and incidence of adverse effects from a 12-week course of pioglitazone.

Treatment group

- **Pioglitazone** (**30 mg po qd**)

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 symptomatic gastroparesis.

Study duration

- Up to **4 weeks** of screening prior to pioglitazone treatment
- **8 weeks** of treatment starting at initial dose of pioglitazone
- **4 weeks** of washout period
- Length of recruitment: **16 months**

Sample size justification

- Total of **20 patients**
- Primary comparison: Baseline PAGI-SYM score versus 4, 8, and 12 weeks.

Number of clinical centers

- Johns Hopkins Bayview Medical Center.
- Mayo Clinic – Scottsdale, Arizona – This site will not perform enrollment of patients, It will only intervene as data analysis center under the supervision of Dr. Jay Pasricha.
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Inclusion criteria

- Age 18 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)
- Ongoing symptoms referable to gastroparesis (i.e. nausea and vomiting, bloating, and abdominal pain)
- Exclusion of other causes of symptoms such as mechanical gastrointestinal obstruction, uncontrolled esophagitis, peptic ulcer disease, etc. by standard radiographic or endoscopic tests
- Females will be required to use adequate contraceptive methods during study participation as determined by the Principal Investigator and the study team members

Exclusion criteria

- Another active disorder which could explain symptoms in the opinion of the investigator
- Age < than 18 years
- Pregnancy or nursing
- Previous surgery of the upper gastrointestinal tract including vagotomy
- 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
- Serious systemic disease, such as recent myocardial infarction/unstable angina, decompensated congestive heart failure, severe pulmonary disease with dyspnea at rest, or altered mental status from any cause
- Diabetes as defined by HbA1c >6.5 and/or fasting blood sugar of >125 mg/dL
- Contraindications to pioglitazone such as hypersensitivity or allergy
- Concurrent use of: estradiol, ethynyl estradiol, mestranol, pazopanib, warfarin, digoxin, atorvastatin, ranitidine, gemfibrozil, fexofenadine, midazolam
- Any other condition, which in the opinion of the investigator would impede compliance or hinder completion of the study
- History of bladder cancer or family history of bladder cancer
- Failure to give informed consent

Outcome measures

- ***Primary:*** The primary outcome measure is a binary (0,1) variable indicating improvement as measured by a decline of 1 or more in the total GCSI score

- **Secondary outcome measures** will be defined to address the following areas:

  (1) Gastrointestinal symptoms
    - Subscores for the GCSI: nausea/vomiting, postprandial fullness, bloating
    - Total and Subscores for the GSRS
      NIH Patient Reported Outcome Measurement Information System (PROMIS)

gastrointestinal symptom scales.

(2) Quality of Life
- PAGI-QoL
- SF-36

(3) Inflammatory Markers
- CRP and ESR

(4) Mood and Behavior
- Beck Depression Inventory
- State-Trait Anxiety

(5) Adverse Events
- Biochemical tests
- Symptoms of cardiac or pulmonary disease
- Any other AE reported or noted throughout the study and follow-up

Justification of sample size
This will be a pilot study recruiting 20 candidates.

Statistical analysis
All analyses will be on an intention-to-treat basis. Patients who do not have any of the decline of 1 or more in the total GCSI score recorded during the period of treatment will be counted as not improved (i.e., 0) for the primary outcome. Comparisons will also be made with baseline total GCSI score and other secondary outcomes. 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 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.

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.

Visit schedule
- Screening: at least 1 visit separated by at least 1 calendar day prior pioglitazone treatment; screening period can last no more than **4 weeks** after registration
- Final pre-treatment interview, dispensing of study agent
- Follow-up visits: every **4 weeks** after pioglitazone treatment throughout the **12 week** study
- Post-treatment: follow-up at **16 weeks**

(1) Screening visits and baseline data collection

Many of the PIOGAS participants will come 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 PIOGAS 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.

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.

As part of the screening process for the PIOGAS 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. 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 PIOGAS 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. Baseline and follow up questionnaires can be answered through REDcap.

All participants who sign the consent statement will be registered in the trial database (REDcap). Each participant who starts screening will be accounted for at the end of 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 for the PIOGAS 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 participation in the trial. The reason for screening failure will be recorded 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 form at or prior to the screening visit and will undergo a history and physical examination to identify other illness and contraindications for participation such as use of antiemetic medications.

In addition, the patient will be provided one week supplies of the Gastroparesis Cardinal Symptom index-Daily Diary (GCSI-DD) for completion each night before bed.

The patient will complete the following questionnaires:

- PAGI-SYM
- Gastrointestinal Symptom Rating Scale (GSRS)
- Health-related quality of life questionnaire (SF-36v2)
- Beck Depression Inventory (BDI-II)
- State Trait Anxiety Inventory (STAI)
- NIH Patient Reported Outcome Measurement Information System (PROMIS) gastrointestinal symptom scales.

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. 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.

(2) Treatment Start Visit

At this visit the patient is issued the study medication. Treatment can only start 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. Medication can be delivered to patient home address from the Bayview IDS pharmacy

The GCSI-DD completed by the patient each night for one week will be collected by the clinical center staff. After initial dose of pioglitazone, the patients will be provided thee week supplies of the GCSI-DD for completion each night before bed.

After eligibility is confirmed with the PIOGAS web-based data management system, treatment can begin. The date of starting treatment is the start (zero) time for reckoning follow-up visits.

(3) Follow-up visits

Patients will return for follow-up visits at 4, 8 and 12 weeks after treatment has begun. The specific procedures to be completed at each of the follow-up visits are:

- **Week 4 visit:** Medical history including clinical global patient impression (GCPI) questionnaire. The following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), NIH Patient Reported Outcome Measurement Information System (PROMIS) gastrointestinal symptom scales. Review study drug adherence and tolerance of the study drug with the participant. The daily GCSI-DD completed by the patient each night since beginning treatment will be collected by the clinical center staff.

In addition the patient will be provided 4 weeks of GCSI-DD for completion each night before bed.

- **Week 8 visit**: Medical history including clinical global patient impression (GCPI) questionnaire. The following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), NIH Patient Reported Outcome Measurement Information System (PROMIS) gastrointestinal symptom scales. Review study drug adherence and tolerance of the study drug with the participant. The GCSI-DD completed by the patient each night since the last visit will be collected by the clinical center staff. In addition the patient will be provided 4 weeks GCSI-DD for completion each night before bed. 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). CRP and ESR

- **Week 12 visit**: Medical history, physical exam including clinical global patient impression (GCPI) questionnaire. The following questionnaires should be completed: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptom Rating Scale (GSRS), Health Survey (SF-36v2), Beck Depression Inventory (BDI-II), and State Trait Anxiety Inventory (STAI), NIH Patient Reported Outcome Measurement Information System (PROMIS) gastrointestinal symptom scales. Review study drug adherence and tolerance of the study drug with the participant. The GCSI-DD completed by the patient each night since the last visit.

  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. .

- **Week 16 visit:** This will be a terminal visit. Medical history including side effect or symptom profile, and include a questionnaire for global overall relief of symptoms question and clinical global patient impression question..

PIOGAS Study Data Collection Schedule					
	Screening & Pioglitazone treatment Visits		**Follow-up Visits: Weeks from start of treatment**		
	Screening	**Treatment initiation**	**4**	**8**	**12**
Consent	X				
Gastric emptying scintigraphy results review	X				
Baseline medical history	X				
GCSI-DD	X		X		

Collection of GCSI-DD			X	X	X
PAGI-SYM questionnaire	X		X	X	X
GSRS questionnaire	X				X
SR-36v2 Healthy Survey questionnaire	X				X
Beck Depression Inventory-II	X				X
State Trait Anxiety Inventory	X				X
PROMIS NIH scale	X		X	X	X
Physical exam	X				X
Study drug dispensed		X			
Follow-up medical history, including review of adverse events			X	X	X
CBC, CMP	X			X	
HbA1c	X				
CRP & ESR	X			X	
12-lead EKG	X				
Pregnancy test	X				

Physical exam includes weight, vital signs (temperature, heart rate, blood pressure) and general physical findings
Complete blood count (CBC): white blood cells, red blood cells, hemoglobin, hematocrit, platelets
Complete metabolic panel (CMP): sodium, potassium, chloride, carbon dioxide, glucose, calcium, BUN, creatinine, bilirubin, ALT, AST, alkaline phosphatase, magnesium, albumin, total protein

Specific Tests and Questionnaires

- Laboratory Tests: All laboratory test results may be obtained as archival material from the patient's chart or should be collected as part of standard of care during screening. The etiologic tests required once as part of screening include: high-sensitivity C-reactive protein (hs-CRP); sedimentation rate (ESR); complete blood count (white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, platelet count); comprehensive metabolic panel (sodium, potassium, chloride, carbon dioxide, calcium, BUN, creatinine, glucose, and liver panel including total protein, albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase); and hemoglobin A1c.

- Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QoL): A validated 30 item questionnaire to assess quality of life in patients with dyspepsia, GERD, or gastroparesis. Copyright© 2004 Johnson & Johnson.

- State Trait Anxiety Inventory: 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.

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

- Patient Assessment of Upper Gastrointestinal Disorders-Symptoms (PAGI-SYM): 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.

- Gastrointestinal Symptom Rating Scale (GSRS): 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 absence of troublesome symptoms and 7 represents very troublesome symptoms. The reliability and validity of the GSRS are well-documented and norm values for a general population are available.

- PROMIS NIH Scale: The Patient-Reported Outcomes Measurement Information System (PROMIS®) GI Symptom item bank captures upper and lower GI symptoms (reflux, disrupted swallowing, nausea/vomiting, belly pain, gas /bloating /flatulence, diarrhea, constipation, and fecal incontinence).

Recruitment Procedures

Individuals Responsible for Approaching Participants:
Prospective participants will be approached by either their own physicians who are study members or introduced by their physicians to another member of the study team with consenting privileges. Referring physicians will obtain the patient's approval for referral prior to contacting the GpCRC team. Recruitment will take place while the potential participants are present for clinic appointments. Potential participants will be informed that participation in the GpCRC registry is voluntary and that their care at Hopkins will not be affected if they decide not to join this study.

How Privacy Issues will be Addressed:
The study member will approach participants when they are alone in the exam rooms to ensure privacy so that the conversation between the participant and study member cannot be heard by others. 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.

Online Recruitment:
Web links to the Johns Hopkins Bayview Medical Center Clinical Trials (Gastroenterology) webpage will be posted on professional associations' websites, including the Association for Gastrointestinal Motility Disorders (AGME), for potential recruitment from outside of the Hopkins network. These self-referred patients will, however, be required to be seen by a Hopkins Gastroenterologist for specific research study referral and recommendation prior to being screened or contacted for further study participation. Patients recruited through online recruitment will need to be seen in a regular GI clinic visit and be approached during their GI clinic visit by their physician or study coordinator for informed consent prior to study enrollment.

Due to the length of the proposed study, participants may drop out of the study at any time due to relocation, disinterest, or inability/unwillingness to continue participating in study follow-up visits. Due to the length of the study, relocation is the only anticipated major change in the study population over the course of the study period.

Risks.
The adverse events reported in placebo-controlled clinical trials of pioglitazone are upper respiratory tract infections, headache, sinusitis, myalgia, tooth disorders, Diabetes Mellitus aggravated, pharyngitis, chest pain, decreased urine output, dilated neck veins, extreme fatigue, irregular breathing, irregular heartbeat, swelling of the face, fingers, feet, or lower legs, tightness in the chest, trouble breathing, weight gain, decreased hemoglobin and hematocrit, elevated liver function enzymes and creatine phosphokinase (CPK).

Adverse events will be evaluated in every follow up visit. A form of Adverse Event will be completed if the candidate complains of any symptom, sign, abnormal assessment or any combination of these. An adverse event can be an 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 severe using Version 4.03 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).