Protocol Title:	A Phase 2A, Placebo-controlled, Randomized, Dose Response Study of the Safety, Pharmacokinetics and Efficacy of PCS12852 on Gastric Emptying Rate Assessed by ^{13}C Spirulina GEBT in Patients with Moderate to Severe Gastroparesis
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Title Page

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Compound:	PCS12852
Indication:	Moderate to Severe Gastroparesis
Study Sponsor:	Processa Pharmaceuticals, Inc. 7380 Coca Cola Drive, Suite 106 Hanover MD 21076
Protocol Number.:	PCS12852-GP-01
Study Phase:	2A
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Sponsor Signatory:

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Chief Development Officer, Processa Pharmaceuticals, Inc.

4/20/22
Date

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1 Protocol Summary

1.1 Synopsis

Name of Sponsor/Company: Processa Pharmaceuticals, Inc.
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Title of Study: A Phase 2A Placebo-controlled, Randomized Dose Response Study of the Safety, Pharmacokinetics and Efficacy of PCS12852 on Gastric Emptying Rate Assessed by ^{13}C Spirulina GEBT in Patients with Moderate to Severe Gastroparesis.
Study center(s): Approximately 8 centers in the United States (US)
Phase of Development: Phase 2a
Objectives: **Primary Objective**: • To evaluate the effect of different doses of PCS12852 on the gastric emptying rate, as measured by the Gastric Emptying Breath Test (GEBT), in patients with moderate to severe idiopathic gastroparesis (IG) or diabetic gastroparesis (DG). • To evaluate the safety and tolerability of different doses of PCS12852 in IG and DG patients. • To evaluate the PK profile of PCS12852 at different dose levels. **Secondary Objective:** • To evaluate the effect of different doses of PCS12852 on symptoms, as measured by the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD), in patients with moderate to severe IG or DG.
Methodology: This is a randomized, double-blind, placebo-controlled study that will compare the effect of 2 different dosage regimens of PCS12852 on gastric emptying time to placebo in both IG and DG patients. In this Phase 2A study, gastroparesis patients who have successfully completed Screening criteria (Visit 1) will return for a second Screening Visit (Visit 2) where the inclusion/exclusion criteria will be re-evaluated. Visit 1 will include all safety labs and procedures (including an electrocardiogram [ECG]). The investigator will complete the Columbia-Suicide Severity Rating Scales (C-SSRS) to confirm that there are no suicidal tendencies or ideation. If the patients still meet study criteria when returning for Visit 2, patients will have a GEBT performed and will be educated on completion of the ANMS

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GCSI-DD. Patients will complete the ANMS GCSI-DD for 7 days. The results from both the GEBT and the ANMS GCSI-DD during the Screening period will be considered the baseline values for these assessments.

Patients will return to the site for Visit 3 (Randomization) where patients who meet the criteria based on having moderate to severe symptoms based on the ANMS GCSI-DD and moderate to severe delay in gastric emptying will be randomized in a 1:1:1 ratio into three treatment groups, PCS12852 0.1 mg, PCS12852 0.5 mg or placebo.

At Visit 3, patients will answer a series of assessments including the following: Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM), Patient Assessment of Upper Gastrointestinal Disorders – Quality of Life (PAGI-QOL), Patient Global Impression of Severity (PGI-S) and the Patient Global Impression of Change (PGI-C). Patients will arrive fasting and have PK samples drawn prior to receiving the first dose and at the following times after the first dose: 0.5, 1, 2, 4, 6, and 8 hours. The investigator will assess the patient through the C-SSRS as well as the Clinical Global Impression- Severity scale (CGI-S) and Clinical Global Impression – Improvement scale (CGI-I).

Patients will take their assigned treatment for 28 days. During the treatment period, the patients will also complete the ANMS GCSI-DD. Each patient will be told to take one tablet from their assigned kit at approximately the same time each morning, at least 30 minutes prior to a meal (actual dosing times will be captured via a dosing diary), starting on Day 1 for 28 days. Patients will return to the clinic on Day 7 and Day 14 to be assessed in a blinded manner for safety and tolerability of the study treatment as well as have the investigator assess the patient for suicidal tendencies or ideations via the C-SSRS.

On the morning of Day 28, after fasting overnight, the patient will return to the site for Visit 6. At Visit 6, the patient will again complete the patient assessments and will have a PK sample drawn prior to receiving their final dose of PCS12852 or placebo and then have PK samples drawn at 0.5, 1, 2, 4, 6, and 8 hours post-dose. The ECG should be performed prior to the 4-hour PK draw between the 2- and 4- hour samples. The patient's fasting blood glucose (FBG) of $\leq$ 275 mg/dL is required to proceed with the GEBT. If the patient's FBG is not within range, the patient will be sent home with an additional dose of study drug and asked to return the next day to perform the GEBT. The GEBT test will be performed for 4 hours and will be administered approximately 30-60 minutes after the patient's final dose of study treatment. During the GEBT test, the site will prioritize taking the GEBT samples and then the PK samples. After the test is complete the patients will be discharged and will return approximately 48-72 hours after Day 28 (Visit 6) to have a PK blood sample drawn. The patient will also return to the site 1 week after the Day 28 visit for a follow-up visit (Day 35/Visit 8).

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The GEBT at Visit 2 and Visit 6 will be performed at the sites. Patients will be told to fast overnight prior to coming to the site for the test. The patient will have their glucose tested via fingerstick both before and after the GEBT. The patient must have a fasting blood glucose (FBG) of ≤ 275 mg/dL to proceed with the GEBT. If the patient does not have a FBG of ≤ 275 mg/dL prior to the GEBT, the patient may come in the following day to take the GEBT. The GEBT is a nonradioactive, noninvasive test that measures gastric emptying. Patients provide baseline (premeal) breath samples and then consume a standardized 230 kCal (kilocalorie) meal, consisting of a proprietary standardized ^{13}C labeled egg component (which is rehydrated and then microwaved for 1.5 minutes) and 6 saltine crackers, accompanied by 6 ounces of water. The meal is to be consumed within 10 minutes. Single post meal breath samples are collected in capped glass tubes at 45, 90, 120, 150, 180, and 240 minutes after the meal is consumed and sent to the specified local laboratory for analysis by Gas Isotope Ratio Mass Spectrometry. By adding ^{13}C to the test meal, the GEBT can determine how fast the stomach empties the meal by measuring the rate of carbon-13 dioxide ($^{13}CO_2$) excretion arising from the digested test meal. The rate of $^{13}CO_2$ excretion found in the patient's breath is proportional to the patient's rate of gastric emptying.

The total study duration for each patient will be approximately 8 weeks.

Number of patients (planned):

Total number randomized into this study: 24 patients with moderate to severe gastroparesis who have documented delayed gastric emptying. The randomization to treatment groups will be stratified by type (IG, DG), enrolling at least 2 patients of each type in each treatment group.

Diagnosis and Main criteria for Eligibility:

Inclusion criteria:

1. Has a documented diagnosis of moderate to severe IG or DG according to the ANMS GCSI-DD score during the Screening Period (Score of > 2 on average of the screening days).
2. Moderate to severe delay in gastric emptying rate as measured by GEBT at Screening defined as GE half-time (t1/2) ≥ the 80th percentile of normative data as determined by Cairn Diagnostics.
3. Male or female patients 18 to 80 years of age, inclusive, at baseline.
4. Has continuous moderate to severe symptoms for gastroparesis (that is, chronic postprandial fullness, abdominal pain, postprandial nausea, vomiting, loss of appetite and/or early satiety) as assessed by the investigator for at least the past 3 months.

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5. Has hemoglobin A1c (HbA1c) less than (<) 11%.
6. Has Body Mass Index (BMI) range between 18- 40.
7. Women of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at baseline before dosing.
8. Women of childbearing potential must use one of the following acceptable methods of contraception throughout the study (from 1 month prior to Screening through 1 month after last dose of study medication): oral contraceptive medication, intrauterine device (IUD), hormonal implants, injectable contraceptive medications, double-barrier methods, or tubal ligation.
9. Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL. If necessary, to confirm postmenopausal status, an FSH will be drawn at Screening) or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.
10. Male patients must be willing to use acceptable contraceptive measures such as vasectomy or double barrier method and refrain from sexual activity with any female who is pregnant or lactating. Female partners of male participants should use acceptable methods of contraception stated in Inclusion #8 above.
11. Patient must be willing and able to swallow whole tablets.
12. Patient must be willing and able to comply with study procedures.
13. Compliance with the completion of the ANMS GCSI-DD, defined as approximately 80% diary completions, during the screening period. For those patients whose compliance is measured to be <80%, the final decision to randomize a patient will be made by the Investigator and the Sponsor (or designee).
14. Patient must be willing and able to provide signed, informed consent.

Exclusion criteria:

1. Has acute, severe gastroenteritis and pronounced dehydration in the past 48 hours prior to Screening, chronic parenteral feeding or persistent severe vomiting.
2. Has known hypersensitivity to Spirulina, egg, milk products or wheat allergens.
3. Has a known disturbance of small intestinal absorption, exocrine pancreatic function, liver metabolism or pulmonary function.
4. Has a history of anorexia nervosa or bulimia.

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5. Previous history of bezoars (the presence of retained liquid, bile, or small amounts of poorly organized food residue is permitted).
6. Prior surgery involving any gastrointestinal (GI) surgery, including the luminal GI tract (cholecystectomy and appendectomy, are permitted if performed greater than 3 months prior to the baseline GEBT test).
7. Any abdominal or pelvic surgery within the past 3 months.
8. Known or history of the following GI conditions: inflammatory bowel disease; irritable bowel syndrome with diarrhea; or any other active disorder that could explain symptoms in the opinion of the investigator.
9. Has active diverticulitis, diverticular stricture, and other intestinal strictures.
10. Has feeding or decompression tubes and/or a gastric pacemaker.
11. Has had Botox pyloric injections within the prior 3 months.
12. Has had diabetic ketoacidosis (within the prior 4 weeks).
13. Currently taking Glucagon-like peptide-1 (GLP-1) agonists, e.g. exenatide, liraglutide, semaglutide or dulaglutide; or pramlintide.
14. Has severe psychiatric illness (including suicidal tendencies or ideation) or neurological illness.
15. History or suspicion of alcohol, barbiturate, amphetamine or narcotic abuse.
16. Use of narcotics/opioids, drugs used to treat gastroparesis within 3 days of the Screening GEBT test.
17. Anticipated concurrent use of a strong Cytochrome P450 (CYP) inhibiting or inducing drug (listed in Section 6.7.1) that would significantly alter the metabolism of PCS12852 and/or its metabolites during the course of the study (after Screening)
18. Fever (>38°C), or chronic, persistent, or recurring infection(s) at Screening or baseline.
19. Clinically significant cardiac disease including but not limited to unstable angina, acute myocardial infarction within 6 months of baseline, and arrhythmia requiring therapy.
20. Patient has QTcF interval ≥ 480 milliseconds on Screening ECG; a second Screening ECG may be done at the Investigator's discretion but the average of the two QTcF screening intervals must not be ≥ 480 milliseconds.

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21. History of cerebral hemorrhage, cerebrovascular accident, transient ischemic attack, gastrointestinal bleeding, or retinal hemorrhage within 6 months of baseline.
22. Patient has active or history of neoplastic disease (except for adequately treated non-invasive basal cell and/or squamous cell carcinoma of the skin or carcinoma in situ of the cervix) within the past 5 years prior to baseline.
23. Presence of clinically significant medical condition(s) including but not limited to: renal, hepatic, cardiovascular, hematological, gastrointestinal, endocrine, pulmonary, neurological, psychiatric, substance abuse, and/or any other clinically significant disease or disorder, which in the opinion of the Investigator (by its nature or by being inadequately controlled), may put the patient at risk due to participation in the study, influence the results of the study, and/or affect the patient's ability to complete the study.
24. History of or current diagnosis of active tuberculosis (TB); undergoing treatment for latent TB infection (LTBI); untreated LTBI (as determined by documented results within 3 months of the Screening Visit of a positive TB skin test with purified protein derivative with induration >= 5 mm, a positive QuantiFERON-TB test or positive or borderline T-SPOT [Elispot] test); or positive TB test at Screening. Patients with documented completion of appropriate LTBI treatment would not be excluded and are not required to be tested.
25. Vaccination with live or live-attenuated virus vaccine within 1 month prior to baseline. Vaccines for COVID-19 are allowed.
26. The results of the following laboratory tests performed at the central laboratory at Screening meet any of the criteria below:
    a. Hemoglobin < 8.0 g/dL (International System of Units: < 80 g/L)
    b. White blood cells < 3.0 x 10^3 cells/mm^3 (SI: < 3.0 x 10^9 cells/L)
    c. Neutrophils < 1.0 x 10^3 cells/mm^3 (SI: < 1.0 x 10^9 cells/L)
    d. Lymphocytes < 0.5 x 10^3 cells/mm^3 (SI: < 0.5 x 10^9 cells/L)
    e. Platelets < 100 x 10^3 cells/mm^3 (SI: < 100 x 10^9 cells/L)
    f. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or alkaline phosphatase (ALP) ≥ 2 x upper limit of normal (ULN)
    g. Total bilirubin level ≥ 2 x ULN unless the individual has been diagnosed with Gilbert's disease and this is clearly documented
    h. Estimated glomerular filtration rate < 40 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease formula
    i. Creatinine ≥ 3 mg/dL
    j. Positive human immunodeficiency virus serology
    k. Evidence of active Hepatitis B Virus infection

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l. Evidence of active Hepatitis C Virus infection

27. Women who are pregnant or breastfeeding.
28. Any other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, would preclude participation in the study.
29. Use of any investigational product within 30 days prior to baseline or currently enrolled in another study that involves clinical intervention.
30. Currently taking known P-gp and BCRP inhibitors or inducers and gastric acid reducing agents. e.g., proton pump inhibitors or H2 receptor antagonists.

Investigational product, dosage and mode of administration

Group	Dosage Forms
PCS12852	0.1 mg tablet
PCS12852	0.5 mg tablet
Placebo	Matching tablet

Patients in each assigned treatment group, will take one tablet, once daily by mouth at approximately the same time each morning, and at least 30 minutes prior to a meal) during the treatment period of the study. The patient will be asked to complete a dosing diary to document actual dosing times.

Criteria for Evaluation:

Primary Endpoints

- Change in gastric emptying rate from baseline as determined by the AUC of the gastric emptying rate over time as assessed by the GEBT at Visit 6 (Day 28) after administration of the PCS12852 or placebo.
- Change in gastric emptying rate from baseline using the t_{10} and t_{50} metric for gastric emptying rate.
- Concentrations of PCS12852 in plasma; PK parameters will be estimated from concentration-time data using noncompartmental methods, as data permit.

Secondary Endpoints

- Change from baseline in the ANMS GCSI-DD (i.e., Day-7 to Day -1) (predose) and Day 7 (Day 1 to Day 7).

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- Change from baseline in the ANMS GCSI-DD (i.e., Day-7 to Day -1) (predose) and Day 14 (Day 8 to Day 14).
- Change from baseline in the ANMS GCSI-DD (i.e., Day-7 to Day -1) (predose) and Day 21 (Day 15 to Day 21).
- Change from baseline in the ANMS GCSI-DD (i.e., Day-7 to Day -1) (predose) and Day 28 (Day 22 to Day 28).

Exploratory Endpoints

- Change from baseline in ANMS GCSI-DD score over time (Day 7, 14, 21, 28) by comparing Day 7 to Day 14, Day 14 to Day 21 and Day 21 to Day 28.
- Change from baseline in the subscores (nausea, early satiety, postprandial fullness, upper abdominal pain and number of vomiting episodes) of the ANMS-GCSI-DD over time (Day 7, 14 ,21, 28) by comparing Day 7 to Day 14, Day 14 to Day 21 and Day 21 to Day 28.
- Change from baseline in PAGI-SYM and PAGI-QOL scores over time by comparing Day 1 to Day 28.
- Change from baseline in Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) scores over time by comparing Day 1 to Day 28.
- Change from baseline in PGI-S and PGI-C scores over time by comparing Day 1 to Day 28.

Safety Endpoints

- Adverse Events (AEs) (by type, severity, and relatedness) at each visit.
- Changes in safety clinical laboratory testing and vital signs at each site visit.
- Changes in ECGs at each site visit and the potential correlation of the PK with changes in the ECG.
- Change from baseline in the C-SSRS scores over time by comparing Day 1 to Day 28.

STATISTICAL ANALYSES:

Analysis Sets:

- Safety Set: All patients enrolled in the study who received at least 1 dose of treatment.
- PK Analysis Population: Patients in the Safety Set with at least 1 plasma sample with a quantifiable concentration of PCS12852.

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- Full Analysis Set (FAS): All patients who are randomized.

Other populations (e.g., Per Protocol) may be defined and used as supportive evidence of treatment benefit.

Patient Characteristics:

Baseline demographics and disease characteristics will be presented for each treatment group by descriptive statistics. All descriptive summary statistics of continuous variables will include n, mean, median, standard deviation (SD), minimum and maximum. All descriptive summaries presenting frequencies and incidences will include n, percent of total, and N, where N is the total number of patients with recorded values in the corresponding group. Patient completion status and exposure outcomes will be similarly presented.

Primary Efficacy Analyses:

The change in the gastric emptying rate AUC from baseline to Day 28 will be analyzed in the FAS using an analysis of covariance (ANCOVA) model with treatment group (three levels) and types (IG, DG) as a factor and the baseline GEBT as a covariate. Each of the two primary comparisons (0.1 mg versus placebo, 0.5 mg versus placebo) will be conducted using a two-sided Dunnett's test at the overall alpha=0.05 significance level.

Other efficacy analyses:

All secondary endpoints will be analyzed using the same types of ANCOVA models as described for the primary analysis. Each treated group will be compared to placebo. All secondary analyses will be conducted with no adjustment for multiplicity.

Subgroup analysis:

A subgroup analysis of idiopathic gastroparesis patients compared to diabetic gastroparesis patients will be performed for all efficacy analysis endpoints.

Pharmacokinetic Assessment

Plasma concentrations will be used to estimate the pharmacokinetic parameters for PCS12852 on Day 1 and Day 28 using noncompartmental methods in WinNonlin®. The following parameters will be calculated as data permit:

- C_{max}: maximum observed plasma concentration
- T_{max}: time at which the maximum plasma concentration was observed
- $t_{½}$: (the apparent first-order terminal elimination half-life)

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- $AUC_{0\text{-last}}$: the area under the plasma concentration versus time curve, from time 0 to the last measurable concentration
- AUC_{∞}: the area under the plasma concentration vs. time curve from time 0 to infinity
- λ_z: apparent first order terminal elimination rate constant

A dose proportionality analysis will be conducted for log-transformed $C_{max,}$ $AUC_{0\text{-last}}$, and AUC_{∞} using the power model. In addition, the relationship between gastric emptying rate and drug exposure will be assessed, as data permit. Exposure-response for safety measures may also be explored. Details of these analysis will be provided in the Statistical Analysis Plan.

In addition, a population PK model may be used to describe the PK of PCS12852, if appropriate based on the data collected. A previously developed population PK model describing the PK of PCS12852 in patients with functional constipation, using a two-compartment model with first order absorption, may be used to predict the PK in patients in this study.

Safety Analyses:

The safety analyses will be performed using the Safety Population and include AEs, changes in physical exam findings, vital signs, ECGs and clinical laboratory values.

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA version 23.0 or higher). The number and percent of patients reporting at least one AE will be summarized by System Organ Class (SOC) and Preferred Term (PT) and presented by severity, relationship to study treatment, amount of drug exposure, and time. Each patient will contribute only once (i.e., first occurrence) to each of the incidence rates, regardless of the number of occurrences. Severity of AEs will be assessed based on the National Cancer Institute (NCI) CTCAE Version 5.0. For reporting of AE severity in patients with more than one occurrence of the same AE, the patient will only be reported once based on the highest severity of the AE observed. Patients who have a serious adverse event (SAE) or who discontinue the study due to an AE deemed to be related to study treatment will be described in patient narratives.

Vital signs, clinical laboratory, and ECG results will also be presented and summarized by dose level and summarized by descriptive statistics with change from baseline values calculated. All safety data collected in the clinical database, including physical exam findings and abnormal ECG results, will be presented in data listings.

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SAMPLE SIZE CALCULATION: Based on the results of a prior study (Study 102), estimates of the SD of the AUC of the gastric emptying rate over time as assessed by the GEBT change from baseline range from 10 to 35. Assuming a true SD of 15 and based on a two-sided test at the alpha=0.025 level of significance, a sample size of 8 patients per arm (24 total patients) will provide 80% power to detect a between-group mean difference of 25.

1.2 Schedule of Activities (SoA)

Table 1 Schedule of Activities (SoA)

Procedure	Visit 1 (Screening)	Visit 2 (Screening) (Baseline)	Visit 3 (Randomization) Day 1	Visit 4 Day 7	Visit 5 Day 14	Visit 6 Day 28	Visit 7 48-72 hrs after Day 28 visit	Visit 8/ET Day 35
Visit Window	**Days -21 to -1**			**±2 days**	**+3 days**	**+1 day**		**±1 day**
Informed consent	X							
Demographic information	X							
Medical history	X							
Inclusion/ Exclusion criteria	X	X	X					
Screening Lab testing (inc. Hep B/C, HIV and TB)	X							
Concomitant Medications	X	X	X	X	X	X		X
Vital signs	X	X	X	X		X		X
Physical exam[g]	X		X	X	X	X		X
^{13}C GEBT		X				X[d]		

Procedure	Visit 1 (Screening)	Visit 2 (Screening) (Baseline)	Visit 3 (Randomization) Day 1	Visit 4 Day 7	Visit 5 Day 14	Visit 6 Day 28	Visit 7 48-72 hrs after Day 28 visit	Visit 8/ET Day 35
Visit Window	**Days -21 to -1**			**±2 days**	**+3 days**	**+1 day**		**±1 day**
ANMS GCSI-DD[a]		X	X	X	X	X		
Safety laboratory testing				X		X		X
Pregnancy test[b]	X		X	X	X	X		X
ECG[h]	X		X[i]	X[j]	X[j]	X		X[e]
C-SSRS	X		X	X	X	X		X
PGI-S			X			X		X
PGI-C			X			X		X
PAGI-SYM			X			X		
PAGI-QOL			X			X		
CGI-S			X			X		X
CGI-I			X			X		X
Adverse Events	X	X	X	X	X	X		X
Study Drug Dispensed			X	X	X	X		

Procedure	**Visit 1 (Screening)**	**Visit 2 (Screening) (Baseline)**	**Visit 3 (Randomization) Day 1**	**Visit 4 Day 7**	**Visit 5 Day 14**	**Visit 6 Day 28**	**Visit 7 48-72 hrs after Day 28 visit**	**Visit 8/ET Day 35**
Visit Window	**Days -21 to -1**			**±2 days**	**+3 days**	**+1 day**		**±1 day**
Study Drug Instructions	X	X	X					
Study Drug Administered			X			X[c]		
PK sample[f]			X			X	X[k]	
Drug Accountability				X	X	X		

a. ANMS GCSI-DD will be collected for 7 consecutive days after Screening Visit 2, but prior to randomization (i.e. from Days -7 to -1) as well as from Day 1 to Day 28.

b. For WOCBP: Serum β-HCG at Screening Visit 1; Urine pregnancy test at subsequent visits

c. Patients will take the dose of PCS12852 or placebo in clinic on Day 28.

d. A blood glucose finger stick will be taken both before and at the completion of the GEBT.

e. Repeat ECG at Visit 8, only if ECG at Visit 6 was abnormal.

f. PK blood samples will be drawn at both Visit 3 (Day 1) and Visit 6 (Day 28) at the following timepoints: pre-dose (trough) and at 0.5h, 1h, 2h, 4h, 6h and 8h post dose. Clinical staff are encouraged to take the blood samples for PK analysis at the scheduled time point; however, deviations from the scheduled sample times are not considered protocol deviations. The exact time and date of the blood draw must be recorded.

g. A symptom driven physical exam will be done on Visit 3 (Day 1), Visit 4 (Day 7), Visit 5 (Day 14) and Visit 8 (Day 35).

h. Clinical staff are encouraged to perform ECGs prior to any blood draws at a given visit.

i. ECGs should be performed prior to the 4 hour PK draw.

j. ECGs should be performed approximately 4 hours after patient's dose.

k. The single PK sample drawn between 48-72 hours after the Day 28 visit can either be done in the office or by a home health nurse.

2 Introduction

Gastroparesis is a disorder characterized by delayed gastric emptying of solid food in the absence of a mechanical obstruction, particularly pyloric stenosis (Camilleri, 2013). This delay may result in the cardinal symptoms of early satiety, postprandial fullness, nausea, vomiting, belching and bloating. The syndrome is caused by neuromuscular dysfunction that leads to delayed gastric emptying (Camilleri, 2018).

Gastroparesis can be idiopathic, associated with diabetes mellitus, can occur after a medical intervention (iatrogenic or post-surgical), may be associated with neurological disorders or may occur after a bacterial or viral infection. In one series of 146 patients, the etiology of gastroparesis was 36% idiopathic, 29% diabetic, 13% postsurgical, 7.5% Parkinson's Disease, 4.8% collagen vascular disorders, 4.1% intestinal pseudo obstruction and 6% miscellaneous (Soykan, 1998). The majority of patients (up to 80%) with gastroparesis are women (Parkman, 2019).

The symptoms of gastroparesis are nonspecific and may mimic other disorders such as functional dyspepsia.

Treatment of symptomatic gastroparesis generally follow these principles (Quigley, 2001):

1. Dietary recommendations to correct fluid, electrolyte or nutritional deficiencies;

2. Identify and rectify the underlying cause of gastroparesis, if possible; and

3. Reduce the symptoms of gastroparesis.

For diabetic patients with gastroparesis, improvement of glucose control has been shown to increase antral contractility, correct gastric dysrhythmias and accelerate gastric emptying although there have been no long-term studies confirming the beneficial effects of maintaining euglycemia on gastroparetic symptoms (Parkman, 2004).

Treatments are based on the symptom presentation and usually include antiemetic agents or prokinetic agents. Currently the only treatment approved in the United States (US) for gastroparesis is metoclopramide (Prescribing information for Reglan, ANI Pharmaceuticals, Inc., Baudette, MN 2017; Prescribing information for Gimoti, Evoke Pharma, 2021). The currently approved indication for metoclopramide oral or nasal spray is relief of symptoms in adults with acute and recurrent diabetic gastroparesis (DG), although this medication has a black-box warning limiting treatment to no more than 12 weeks because of the risk of related side effects

including tardive dyskinesia. The 5-HT_4 agonist, cisapride, was previously used for the treatment of gastroparesis but was removed from the US market in 2000 because of cardiovascular risks.

Gastroparesis is a disease that affects a large number of people and can significantly impact the quality of life for those patients. With the limitation on currently approved treatments for gastroparesis there still is a need for new, effective treatments for this disorder.

2.1 Study Rationale

PCS12852 is a novel, potent, and highly selective 5-HT_4 receptor agonist. Approximately 80% of the total body 5-HT is found in the gut where it plays a central role in the initiation of the peristaltic reflex on enteric neurons. Serotonergic drugs have been developed for gastric motility disorders, but these products were not selective, e.g. cisapride and tegaserod were withdrawn from the market due to adverse events (AEs). PCS12852 has a high binding affinity for the 5-HT_4 receptor with more than 200-fold selectivity over other 5-HT receptors. It has also been shown to have more potent 5-HT_4 agonistic activity than other 5-HT agonists, e.g. prucalopride.

In vitro pharmacological models have shown that PCS12852 was able to induce a concentration-dependent contraction of guinea pig colon, confirming its agonistic effects on the 5-HT_4 receptor. *In vivo* models have also demonstrated the effect of PCS12852 on gastric motility, showing significant increases in the gastric emptying rate in rats, restoring gastric emptying in clonidine-induced gastroparesis in male beagle dogs and decreasing the gastric emptying time at all dose levels in cynomolgus monkeys.

Cardiovascular effects were reported with earlier 5-HT_4 agonists (prolonged QTc increasing risk for arrythmias) resulting in the withdrawal of these products from the market possibly due to their off target effects. The safety pharmacology studies conducted with PCS12852 showed a low risk of any off-target effects on the cardiovascular, central or respiratory systems.

A previous study (Study 102) evaluated the single and multiple dose pharmacokinetics (PK) and pharmacodynamics (PD) in healthy patients and in patients with functional constipation.

Study 102 was a randomized, double-blind/open label, placebo/active controlled study. Prucalopride was the active control included in the 102 study. An immediate release (IR) and a modified release formulation (DR) of PCS12852 were studied over the 0.3 mg to 3 mg dose range for the IR and 0.5 mg to 2 mg for the DR. Systemic exposures following administration of the IR formulation increased linearly over the 0.3 mg to 3 mg dose range. Steady state concentrations were achieved by approximately Day 5, consistent with the half-life of

approximately 24 hours. Only the IR formulation is currently being evaluated in the development of PCS12852.

In terms of PD, PCS12852 resulted in pharmacologic activity related to stool assessments. There was a trend in improvement over placebo and comparable to prucalopride in terms of average weekly spontaneous bowel movements over the 2-week treatment period. PCS12852 was safe and generally well-tolerated with single and multiple doses under fasted and fed conditions in the healthy male and female patients and in patients with functional constipation.

In the 102 study, an exploratory evaluation was also performed to investigate the change from baseline in gastric emptying measured by the GEBT on Day 7 for the low dose-immediate release cohort (IRM) at 0.05 mg and 0.1 mg, as well as the delayed release multiple dose cohort (DRM) at the various doses between 0.5 to 2 mg doses. The gastric emptying rate was estimated from the GEBT for each patient over time (45, 90, 120, 150, 180, and 240 minutes). The Area Under the Curve (AUC) for gastric emptying for each patient was determined as well as the change in the AUC from baseline for each patient. The time for 10% and 50% of the gastric emptying was also estimated from the GEBT. In the IRM cohort, the change from baseline in gastric emptying rate increased in both PCS12852 IR 0.05 mg and 0.1 mg groups. Additionally, the AUC of the 13C-Spirulina rate showed a statistically significant change from baseline in the PCS12852 IR 0.1 mg group. The IR 0.05 mg group showed a difference from baseline that was not statistically different. All the DRM treatment groups showed a significant difference from baseline. These results along with the pharmacology data provide the rationale for looking further into PCS12852 as a treatment for gastroparesis.

The efficacy of PCS12852 in gastroparesis will be investigated in this Phase 2A study. Preliminary data from the PCS12852-102 study showed a significant effect of PCS12852 at the 0.1 mg QD dose level on the gastric emptying rate assessed by the Gastric Emptying Breath Test (GEBT), but less effect was noted with the 0.05 mg daily dose. Safety for multiple dosing up to 3 mg daily has been well tolerated in the Phase 1 studies. This Phase 2A study will evaluate the effects of PCS12852 at the 0.1 and 0.5 mg dose levels vs. placebo on gastric emptying rate after 28 days of treatment. The study will also evaluate the effects of PCS12852 treatment on the symptoms of gastroparesis assessed by the AMNI-GCSI-DD scale.

2.2 Background

PCS12852 (formerly known as YH12852) was previously developed by Yuhan Corporation (Korea) for the treatment of gastrointestinal motility disorders including chronic constipation, constipation-predominant irritable bowel syndrome, functional dyspepsia and gastroparesis.

Recently the product was acquired by Processa Pharmaceuticals, Inc. (Processa) and is being further developed for the treatment of gastroparesis.

Although there have been advances in understanding the mechanisms and pathophysiology of gastroparesis, there are still significant gaps in knowledge, inconsistencies across studies, and potential differences between different etiological groups (for example, diabetic versus idiopathic). Currently, the only FDA approved treatment for gastroparesis is metoclopramide. However, it carries a black box warning, as it is generally not well-tolerated and chronic use (>12 weeks) may lead to extrapyramidal side effects and potential irreversible tardive dyskinesia. Based on the limitations in currently available products for the treatment of gastroparesis, there still remains an unmet need for new treatments for these patients.

In support of the clinical development program for PCS12852, *in vitro, ex vivo* and *in vivo* pharmacology, safety pharmacology, pharmacokinetic and toxicology studies have been conducted. PCS12852 has been shown to have a high binding affinity for the 5-HT_4 receptor with more than 200-fold selectivity over other 5-HT receptors, as well as for 80 targets including receptors, ion channels and transporters. PCS12852 also exhibits 3.4 times more potent agonistic activity than tegaserod to human 5-HT_{4A} receptors stably expressed in Chinese hamster ovaries (CHO). In studies of *ex vivo* contractile activity in guinea pig colon, PCS12852 was found to be 17 times more potent than 5-HT.

The i*n vivo* prokinetic effects of PCS12852 in the upper GI tract were evaluated in various models including rat, dog and monkey. Single oral administration of PCS12852 at doses of 3 to 10 mg/kg in rats significantly increased the gastric emptying rate and PCS12852 at 3 mg/kg showed a comparable effect to that of another selective 5-HT_4 agonist, mosapride at 10 mg/kg. In rat models of delayed gastric emptying and feeding inhibition induced by restraint stress, single oral administration of PCS12852 at doses of 1, 2 and 3 mg/kg dose-dependently improved gastric emptying, and doses of 1 and 2 mg/kg led to significant restoration of food intake. Single oral administration of PCS12852 at 1.0 μg/kg, significantly restored gastric emptying up to normal levels under conditions of clonidine-induced delayed gastric emptying in conscious beagle dogs. Single oral administration of PCS12852 at doses of 0.2, 0.4 and 1 mg/kg also significantly shortened the gastric emptying time as measured by real-time fluoroscopy imaging in monkeys. In addition to the efficacy shown in the gastroparesis models, PCS12852 significantly increased fecal pellet output at 0.1, 0.3, 1, 3 and 10 mg/kg in male guinea pigs as well as significantly shortening the time to the first giant migrating contraction at 3, 10 and 30 μg/kg and significantly increased giant migrating contraction frequency at 30 μg/kg in female dogs. These data demonstrate that PCS12852 possesses excellent prokinetic effects in the upper and lower GI tracts.

In cardiovascular safety studies, PCS12852 decreased hERG K^+ currents in a dose-dependent manner, with an IC_{50} value of 0.71 μM in CHO cells and increased action potential duration (APD) at concentrations of 4.52 μM in isolated rabbit Purkinje fibers. Considering the affinity of PCS12852 for the human 5-HT_{4A} receptor (IC_{50}, 0.05 nM) and the expected C_{max} at doses up to 10 mg in human subjects, (free-drug C_{max} = 2.89 nM, total-drug C_{max} = 72.26 nM), it is estimated that there is little risk of hERG inhibition, action potential duration (APD) prolongation or cardiovascular contractility exists at the projected therapeutic clinical dose levels. In a telemetry study conducted with conscious monkeys, there were no abnormal electrocardiograms (ECG), blood pressure or heart rate findings after administration of single oral doses up to 60 mg/kg. In addition, no abnormalities were detected in ECG findings in 4-week and 13-week repeat-dose oral toxicity studies in monkeys treated with doses up to 60 mg/kg/day. Additionally, in a telemetry study performed in conscious dogs, there were no abnormal changes in heart rate or ECG parameters after single intravenous administration up to 1 mg/kg. Additional safety pharmacology studies did not show any significant effects on neurobehavioral function or respiratory function.

Non-clinical toxicology studies of PCS12852 conducted so far include single-dose (rats and monkeys) and repeat-dose (rats and monkeys up to 13 weeks) toxicity studies, as well as *in vitro*/*in vivo* genetic toxicology studies, carcinogenicity studies, developmental and reproductive studies. In the 13-week toxicology study in rats there were no treatment-related findings up to 100 mg/kg/day. The No Observable Adverse Effect Level (NOAEL) was determined to be 100 mg/kg/day for both sexes. A 13-week repeat-dose oral toxicity study in monkeys, demonstrated treatment-related clinical signs including vomiting and soft/watery feces with increased neutrophil counts in both sexes at 60 mg/kg/day. Based on these findings, the NOAEL was determined to be 60 mg/kg/day for both sexes. No evidence for genotoxicity has been observed for PCS12852. In the carcinogenicity studies in rats and mice, no PCS12852-related neoplasms were noted. In fertility and early embryonic developmental toxicology studies in rats, there were no abnormal outcomes of mating, fertility or pregnancy. In addition, in embryo–fetal development studies in rats and rabbits, there has been no evidence suggesting that PCS12852 is dysmorphogenic.

Two clinical phase 1 studies that include pharmacokinetic (PK) and pharmacodynamic (PD) information for PCS12852 have been conducted in healthy volunteers and patients. The first study, Study 101 was a randomized, double-blind, placebo/active-controlled, single/multiple dose Phase 1 study. This study evaluated the PK and PD of single and multiple ascending doses of PCS12852 over the range of 0.5 mg to 10 mg and 0.5 mg to 3 mg, respectively. In addition, the effect of food was evaluated over the 0.5 mg to 3 mg single dose range. The systemic exposure for PCS12852 increased in a dose-proportional manner following single and multiple

administrations under fed conditions; although peak exposure was increased in a slightly greater than dose-proportional manner at multiple doses of 0.5 to 3 mg. Food intake decreased PCS12852 C_{max} by 75% and $AUC_{(0-\tau)}$ by 61%, and delayed T_{max} from 1.5 to 6 hours in females with no change in $t_{½}$. In terms of PD, PCS12852 increased the frequency of defecation and decreased the stool consistency with fast onset of spontaneous bowel movements following single and multiple doses.

A second study, Study 102, evaluated the single and multiple dose PK and PD in healthy patients and in patients with functional constipation. This was a randomized, double-blind/open label, placebo/active controlled study. Prucalopride was the active control. An immediate release (IR) and a delayed release formulation (DR) of PCS12852 were studied over the 0.3 mg to 3 mg dose range for the IR and 0.5 mg to 2 mg for the DR. Systemic exposures following administration of the IR formulation increased linearly over the 0.3 mg to 3 mg dose range. Steady state concentrations were achieved by approximately Day 5, consistent with the half-life of approximately 24 hours. In the groups that evaluated the modified release formulation (DR), a delay in T_{max} for PCS12852 was noted, as expected. In terms of PD, PCS12852 resulted in pharmacologic activity related to stool assessments. There was a trend in improvement over placebo and comparable to prucalopride in terms of average weekly spontaneous bowel movements over the 2-week treatment period. PCS12852 was safe and generally well-tolerated with single and multiple doses under fasted and fed conditions in the healthy male and female patients and in patients with functional constipation.

In the 102 study, an exploratory evaluation was also performed to investigate the change from baseline in gastric emptying measured by GEBT on Day 7 (for the low dose-immediate release cohort (IRM) and the delayed release multiple dose cohort (DRM) only). The time for 10% and 50% gastric emptying was analyzed, along with the area under the curve (AUC) of the ^{13}C rate measured in breaths and the analysis of the gastric emptying rate over time (45, 90, 120, 150, 180, and 240 minutes). In the IRM cohort, the change from baseline in gastric emptying rate increased in both PCS12852 IR 0.1 mg and 0.05 mg groups. Additionally, the AUC of the ^{13}C rate showed a statistically significant change from baseline in the PCS12852 IR 0.1 mg group. Similar results were noted for DRM cohort.

All doses of PCS12852 in both of the clinical studies were well tolerated and no serious adverse events (SAEs) occurred. The most frequent treatment-emergent adverse events were diarrhea, headache, and nausea. There were no changes in vital signs, platelet aggregation or ECG parameters including no sign of QTc prolongation in time-matched ECGs monitored in the single ascending dose cohort.

The non-clinical and limited clinical safety and efficacy data accumulated thus far support further investigation on the efficacy, safety and tolerability of multiple doses of PCS12852 IR formulation for the treatment of gastroparesis.

2.3 Benefit/Risk Assessment

The clinical benefit/risk profiles of these 5-HT_4 receptor agonists, some of which exhibit poor 5-HT_4 receptor selectivity, have been complicated by the occurrence of rare but serious side effects related to the binding of the agonists to unintended target receptors or channels. For example, the marketing of both cisapride and tegaserod was discontinued due to cardiovascular concerns (cardiac arrhythmias with cisapride and ischemic events with tegaserod, respectively). Tegaserod, which is used for the treatment of irritable bowel syndrome-constipation and chronic constipation, was also found to be an agonist for the 5-HT_{1B} and 5-HT_{1D} receptors, as well as an antagonist for 5-HT_{2B} receptors. This nonselectivity may explain its association with rare, but serious, instances of ischemic AEs, including stroke and angina. Therefore, more highly selective 5-HT_4 receptor agonists are expected to exhibit favorable safety profiles with a lower risk of cardiovascular side effects (Manabe, 2010; FDA Briefing Document, 2011). Prucalopride, a recently developed selective 5-HT_4 receptor agonist, is intended to be used by laxative non-responders (NICE, 2010). However, it has been found that in several clinical trials, the most common reason for discontinuation of prucalopride medication was its poor response rate (Movetis, 2008 [PRU-USA-22]; Movetis, 2008 [PRU-INT-17]; Movetis, 2008 [PRU-INT-10]). This implies that a significant number of refractory patients still exist. In addition, recently-developed IBS and chronic constipation drugs such as linaclotide are considered expensive compared to traditional laxatives. Linaclotide at 1,000 µg doses had no effect on upper gastrointestinal motility, as measured by gastric emptying and small bowel transit.

A series of *in vitro* and *in vivo* safety pharmacology studies were conducted to assess PCS12852 for evidence of off-target receptor binding and adverse effects on the central nervous, cardiovascular and respiratory systems. Exposure multiples were estimated based on the human C_{max} (free-drug C_{max} = 2.89 nM, total-drug C_{max} 72.26 nM) at the highest dose of 10 mg in the SAD study. PCS12852 decreased hERG K^+ current in a dose-dependent manner with an IC_{50} value of 710 nM, obtained using the whole-cell patch clamp technique to measure peak hERG tail current in CHO cells (G12070). An isolated rabbit Purkinje fiber assay (G12171), revealed that PCS12852 increased APD at a concentration of 4.52 µM. *Ex vivo* contractility testing using tissue chambers with isolated rat aorta and canine coronary artery demonstrated that PCS12852 did not significantly influence canine coronary artery or aorta isometric tone in sham-operated or DOCA-salt hypertensive rats at concentrations of 0.1 to 100 µM. Considering the affinity of PCS12852 for the human 5-HT_{4A} receptor (IC_{50}, 0.05 nM) and C_{max} (free-drug C_{max} = 2.89 nM,

total-drug C_{max} = 72.26 nM) at 10 mg in the SAD study, it is estimated that little or no risk of hERG inhibition, APD prolongation or cardiovascular contractility exists at the projected therapeutic clinical dose levels.

In summary, PCS12852 at the doses of 3 and 10 mg/kg significantly increased solid gastric emptying rates in rats, and its effect appears to be comparable to that of mosapride, indicating that PCS12852 may accelerate gastric emptying in patients with gastroparesis or functional dyspepsia.

More detailed information about the known and expected benefits and risks and reasonably expected AEs associated with PCS12852 are provided in the Investigator's Brochure.

3 Objectives and Endpoints

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of different doses of PCS12852 on the gastric emptying rate, as measured by the GEBT, in patients with moderate to severe idiopathic gastroparesis (IG) or DG • To evaluate the PK profile of PCS12852 at different dose levels.	• Change in gastric emptying rate from baseline as determined by the AUC of the gastric emptying rate over time as assessed by the GEBT at Visit 6 (Day 28) after administration of the PCS12852 or placebo. • Change in gastric emptying rate from baseline using the t_{10} and t_{50} metric for gastric emptying rate. • Concentrations of PCS12852 in plasma; PK parameters will be estimated from concentration-time data using noncompartmental methods, as data permit.
Secondary	
• To evaluate the effects of different doses of PCS12852 on symptoms, as measured by the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD), in patients with moderate to severe idiopathic and diabetic gastroparesis	• Change from baseline in the ANMS GCSI-DD) (i.e., Day-7 to Day -1) (predose) and Day 7 (Day 1 to Day 7) • Change from baseline in the ANMS GCSI-DD (i.e., Day-7 to Day -1) (predose) and Day 14 (Day 8 to Day 14) • Change from baseline in the ANMS GCSI-DD (i.e., Day-7 to Day -1) (predose) and Day 21 (Day 15 to Day 21) • Change from baseline in the ANMS GCSI-DD (i.e., Day-7 to Day -1) (predose) and Day 28 (Day 22 to Day 28)
Exploratory Efficacy • To evaluate the effects of different doses of PCS12852 on symptoms or QOL, as measured by the PAGI-SYM, PAGI-QOL, PGI-S, PGI-C, CGI-S and CGI-I, in patients with moderate to severe idiopathic or diabetic gastroparesis	• Change from baseline in ANMS GCSI-DD score over time (Day 7, 14, 21, 28) by comparing Day 7 to Day 14, Day 14 to Day 21 and Day 21 to Day 28. • Change from baseline in the sub scores (nausea, early satiety, postprandial fullness, upper abdominal pain and number of vomiting episodes) of the

Objectives	Endpoints
	ANMS-GCSI-DD over time (Day 7, 14, 21, 28) by comparing Day 7 to Day 14, Day 14 to Day 21 and Day 21 to Day 28. • Change from baseline in PAGI-SYM and PAGI-QOL scores over time by comparing Day 1 to Day 28. • Change from baseline in Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) scores over time by comparing Day 1 to Day 28. • Change from baseline in PGI-S and PGI-C scores over time by comparing Day 1 to Day 28.
Safety To evaluate the safety and tolerability of different doses of PCS12852 in idiopathic and diabetic gastroparesis patients.	• Adverse Events (by type, severity, and relatedness) at each visit. • Changes in safety clinical laboratory testing and vital signs at each site visit. • Changes in ECGs at each site visit and the potential correlation of the PK with changes in the ECG. • Change from baseline in the C-SSRS scores over time by comparing Day 1 to Day 28.

4 Study Design

4.1 Overall Design

This is a Phase 2A, placebo-controlled, randomized dose response study of the safety, PK, and efficacy of PCS12852 on gastric emptying rate assessed by the GEBT in patients with moderate to severe gastroparesis.

In this study, gastroparesis patients who have successfully completed Screening criteria (Visit 1) will return for a second Screening Visit (Visit 2) where the inclusion/exclusion criteria will be re-evaluated.

Visit 1 will include all safety labs and procedures (including an ECG) as well as the Columbia-Suicide Severity Rating Scales (C-SSRS) assessed by the investigator to confirm that the patient does not have any suicidal tendencies or ideation. If patients still meet study criteria when returning for Visit 2, a GEBT will be performed and the patient will be educated on completion of the ANMS GCSI-DD. Patients will complete the ANMS GCSI-DD for 7 days. The results from both the GEBT and the ANMS GCSI-DD during the Screening period will be considered the baseline values for these assessments.

The GEBT at Visit 2 and Visit 6 will be performed at the sites. Patients will be told to fast overnight (at least 8 hours) prior to coming to the site for the test. The patient will have their glucose tested both before and after the GEBT. The patient must have a fasting blood glucose of ≤275 mg/dL to proceed with the GEBT. If the patient does not have a FBG ≤ 275 mg/dL, they are permitted to come in the following day to perform the GEBT test. If the patient's FBG is not within range at Visit 6, the patient will be sent home with an additional dose of study medication and asked to return the next day to perform the GEBT.

Patients will return to the site for Day 1 (Visit 3 [Randomization]) where patients who meet the criteria for having moderate to severe symptoms based on the ANMS GCSI-DD will be randomized in a 1:1:1 ratio into three treatment groups, PCS12852 0.1 mg, PCS12852 0.5 mg or placebo. At Visit 3, patients will answer a series of questionnaires including the Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM), Patient Assessment of Upper Gastrointestinal Disorders – Quality of Life (PAGI-QOL), Patient Global Impression of Severity (PGI-S) and the Patient Global Impression of Change (PGI-C). Patients will arrive in a fasted condition and have PK samples drawn prior to receiving the first dose and at the following times after the first dose, 0.5, 1, 2, 4, 6, and 8 hours. The ECG should be performed prior to the 4-hour PK draw between the 2- and 4-hour samples. The investigator will assess the patient through the C-SSRS as well as the CGI-S and CGI-I.

Patients will return to the site on Day 7 (Visit 4) and Day 14 (Visit 5) to undergo safety and tolerability assessments as per the Schedule of Assessments, along with the investigator assessing the patient for the C-SSRS to ensure the patient does not have any suicidal tendencies

or ideation. Sites will be asked to schedule the patient's visit so that the ECG can be performed approximately 4 hours after the patient's dose.

Patients will take their assigned treatment once daily for 28 days and will return to the site on Day 28 (Visit 6) for their final dose. On Visit 6, PK samples will be drawn and the GEBT will be repeated. During the treatment period, the patients will also complete the ANMS GCSI-DD. Each patient will be told to take one tablet from their assigned kit each day at approximately the same time each morning, at least 30 minutes prior to a meal (actual dosing times will be captured via a dosing diary), while fasting starting on Day 1 for 28 days.

On the morning of Day 28, after fasting overnight (for at least 8 hours), the patient will return to the site for Visit 6. At Visit 6, the patient will again compete the patient assessments and will have a PK sample drawn prior to receiving the final dose of PCS12852 or placebo and then have PK samples drawn at 0.5, 1, 2, 4, 6, and 8 hours post-dose. The ECG should be performed prior to the 4-hour PK draw between the 2- and 4-hour samples. The patient must have a fasting blood glucose (FBG) of ≤275 mg/dL to proceed with the GEBT. If the patient's FBG is not within range, the patient will be sent home with an additional dose of study drug and asked to return the next day to perform the GEBT and PK sampling. The GEBT test will be performed for 4 hours and will be administered approximately 30-60 minutes after the patient's final dose of study treatment. During the GEBT test, the site will prioritize taking the GEBT samples and then the PK samples. After the test is complete the patients will be discharged and then will return approximately 48-72 hours after Day 28 (Visit 6) to have a PK blood sample drawn. The patient will also return to the site 1 week after the Day 28 visit for a follow-up visit (Day 35/Visit 8).

The total study duration for each patient is expected to be approximately 8 weeks (3 weeks for Screening, 4 weeks for treatment, and 1 week for follow-up).

The SoA displaying assessments/tasks and time points is presented in Table 1.

4.2 Scientific Rationale for Study Design

This study has been designed to comply with recommendations in the FDA Guidance: Gastroparesis: Clinical Evaluation of Drugs for Treatment Guidance for Industry.

Several design features have been incorporated in the study in an effort to minimize bias, including double-blind design and random assignment of patients, helping to ensure that both known and unknown risk factors are distributed evenly among treatment groups. The use of a placebo control permits prospective comparison between the PCS12852 0.1 mg group and the PCS12852 0.5 mg group.

4.3 Justification for Dose

In the Phase 1 studies conducted with PCS12852, the product appeared to be safe and generally well-tolerated after both single (0.5 to 10 mg) and multiple doses (0.05 to 3 mg QD) (Section 2.1). The most frequently reported AE was headache. All AEs were generally mild and resolved without treatment. Therefore, the doses to be administered in the proposed Phase 2A study are 0.1 mg and 0.5 mg QD.

Data from the PCS12852-102 study showed a significant effect of PCS12852 at the 0.1 mg QD dose level on the gastric emptying rate assessed by the GEBT, but less effect was noted with the 0.05 mg daily dose. Safety for multiple dosing up to 3 mg daily has been well tolerated in the Phase 1 studies. In this Phase 2A study the effects of PCS12852 at the 0.1 and 0.5 mg dose levels vs. placebo will be evaluated on gastric emptying rate after 28 days of treatment.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last patient in the study.

A patient is considered to have completed the study if he/she has completed all 4 weeks of the study treatment and has had the last visit (Visit 8).

Independent of the end of study definition, all laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical safety physician.

The overall study will be stopped if ≥ 2 patients develop the same Grade 3 CTCAE (Common Terminology Criteria for Adverse Events) cardiac event or 1 patient develops a CTCAE ≥ Grade 4 cardiac event.

5 Study Population

The study population will consist of male and female patients 18 to 80 years of age with moderate to severe IG or DG.

The patients must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria based on Screening.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Has a documented diagnosis of moderate to severe DG or IG according to the ANMS GCSI-DD score during the Screening period (Score of >2 on average of the screening days).
2. Moderate to severe delay in gastric emptying rate as measured by the GEBT at Screening defined as GE half-time (t1/2) ≥ the 80th percentile of normative data as determined by Cairn Diagnostics.
3. Male or female patients 18 to 80 years of age, inclusive, at baseline.
4. Has continuous moderate to severe symptoms for gastroparesis (that is, chronic postprandial fullness, abdominal pain, postprandial nausea, vomiting, loss of appetite and/or early satiety) as assessed by the investigator for at least the past 3 months.
5. Has hemoglobin A1c (HbA1c) less than (<) 11 percent (%).
6. Has Body Mass Index range between 18 - 40.
7. Women of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at baseline before dosing.
8. Women of childbearing potential must use one of the following acceptable methods of contraception throughout the study (1 month prior to Screening through 1 month after last dose of study medication): oral contraceptive medication, intrauterine device (IUD), hormonal implants, injectable contraceptive medications, double-barrier methods, or tubal ligation.
9. Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL. If necessary, to confirm postmenopausal status, an FSH will be drawn at Screening) or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.
10. Male patients must be willing to use acceptable contraceptive measures such as vasectomy or double barrier method and refrain from sexual activity with any

female who is pregnant or lactating. Female partners of study participants are asked to use acceptable methods of contraception as listed in Inclusion #8 above.

11. Patient must be willing and able to swallow whole tablets.
12. Patient must be willing and able to comply with study procedures.
13. Compliance with the completion of the ANMS GCSI-DD, defined as approximately 80% diary completions, during the screening period. For those patients whose compliance is measured to be <80%, the final decision to randomize a patient will be made by the Investigator and the Sponsor (or designee).
14. Patient must be willing and able to provide signed, informed consent.

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Has acute, severe gastroenteritis and pronounced dehydration in the past 48 hours prior to Screening, chronic parenteral feeding or persistent severe vomiting.
2. Has known hypersensitivity to Spirulina, egg, milk products or wheat allergens.
3. Has a known disturbance of small intestinal absorption, exocrine pancreatic function, liver metabolism or pulmonary function.
4. Has a history of anorexia nervosa or bulimia.
5. Previous history of bezoars (the presence of retained liquid, bile, or small amounts of poorly organized food residue is permitted).
6. Prior surgery involving any gastrointestinal surgery, including the luminal gastrointestinal (GI) tract (cholecystectomy and appendectomy are permitted if performed greater than (>) 3 months prior to baseline GEBT).
7. Any abdominal or pelvic surgery within the past 3 months.
8. Known or history of the following GI conditions: inflammatory bowel disease; irritable bowel syndrome with diarrhea; or any other active disorder that could explain symptoms in the opinion of the investigator.
9. Has active diverticulitis, diverticular stricture, and other intestinal strictures.
10. Has feeding or decompression tubes and/or a gastric pacemaker.
11. Has had Botox pyloric injections within the prior 3 months.
12. Has had diabetic ketoacidosis (within the prior 4 weeks).
13. Currently taking Glucagon-like peptide-1 (GLP-1) agonists, e.g. exenatide, liraglutide, semaglutide or dulaglutide, or pramlintide.
14. Has severe psychiatric illness (including suicidal tendencies or ideation) or neurological illness.
15. History or suspicion of alcohol, barbiturate, amphetamine or narcotic abuse.

16. Use of narcotics/opioids, drugs used to treat gastroparesis within 3 days of the Screening GEBT test.
17. Anticipated concurrent use of a strong Cytochrome P450 (CYP) inhibiting or inducing drug (listed in Section 6.7.1) that would significantly alter the metabolism of PCS12852 and/or its metabolites during the course of the study (after Screening)
18. Fever (> 38°C), or chronic, persistent, or recurring infection(s) at Screening or baseline.
19. Clinically significant cardiac disease including but not limited to unstable angina, acute myocardial infarction within 6 months of baseline, and arrhythmia requiring therapy.
20. Patient has QTcF interval ≥ 480 milliseconds on Screening ECG; a second Screening ECG may be done at the Investigator's discretion but the average of the two QTcF screening intervals must not be ≥ 480 milliseconds.
21. History of cerebral hemorrhage, cerebrovascular accident, transient ischemic attack, gastrointestinal bleeding, or retinal hemorrhage within 6 months of baseline.
22. Patient has active or history of neoplastic disease (except for adequately treated non-invasive basal cell and/or squamous cell carcinoma of the skin or carcinoma in situ of the cervix) within the past 5 years prior to baseline.
23. Presence of clinically significant medical condition(s) including but not limited to: renal, hepatic, cardiovascular, hematological, gastrointestinal, endocrine, pulmonary, neurological, psychiatric, substance abuse, and/or any other clinically significant disease or disorder, which in the opinion of the Investigator (by its nature or by being inadequately controlled), may put the patient at risk due to participation in the study, influence the results of the study, and/or affect the patient's ability to complete the study.
24. History of or current diagnosis of active tuberculosis (TB); undergoing treatment for latent TB infection (LTBI); untreated LTBI (as determined by documented results within 3 months of the Screening Visit of a positive TB skin test with purified protein derivative with induration > = 5 mm, a positive QuantiFERON-TB test or positive or borderline T-SPOT [Elispot] test); or positive TB test at Screening. Patients with documented completion of appropriate LTBI treatment would not be excluded and are not required to be tested.
25. Vaccination with live or live-attenuated virus vaccine within 1 month prior to baseline. Vaccines for COVID-19 are allowed.

26. The results of the following laboratory tests performed at the central laboratory at Screening meet any of the criteria below:
    a. Hemoglobin < 8.0 g/dL (International System of Units: < 80 g/L)
    b. White blood cells < 3.0 x 10^3 cells/mm^3 (SI: < 3.0 x 10^9 cells/L)
    c. Neutrophils < 1.0 x 10^3 cells/mm^3 (SI: < 1.0 x 10^9 cells/L)
    d. Lymphocytes < 0.5 x 10^3 cells/mm^3 (SI: < 0.5 x 10^9 cells/L)
    e. Platelets < 100 x 10^3 cells/mm^3 (SI: < 100 x 10^9 cells/L)
    f. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or alkaline phosphatase (ALP) ≥ 2 x upper limit of normal (ULN)
    g. Total bilirubin level ≥ 2 x ULN unless the individual has been diagnosed with Gilbert's disease and this is clearly documented
    h. Estimated glomerular filtration rate < 40 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease formula
    i. Creatinine ≥ 3 mg/dL
    j. Positive human immunodeficiency virus serology
    k. Evidence of active Hepatitis B Virus infection
    l. Evidence of active Hepatitis C Virus infection
27. Women who are pregnant or breastfeeding.
28. Any other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, would preclude participation in the study.
29. Use of any investigational product within 30 days prior to baseline or currently enrolled in another study that involves clinical interventions.
30. Currently taking known P-gp and BCRP inhibitors or inducers and gastric acid reducing agents. E.g., proton pump inhibitors or H2 receptor antagonists

5.3 Lifestyle Considerations

Abuse of alcohol, barbiturates, amphetamines or narcotics is restricted as indicated in Section 5.2. Smoking is prohibited at least 24 hours prior to the Screening GEBT and during the conduct of the study. There are no other specific lifestyle restrictions in the study.

5.3.1 Meals and Dietary Restrictions

Please refer to Section 4.1 for details regarding the standardized low calorie meal that the patients will consume at Visits 2 and 6. Please refer to the SoA (Table 1) for timing of the GEBT.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study.

Individuals who do not meet certain criteria (e.g. lab values) for participation in this study (screen failure) may be rescreened. The GEBT test will not be repeated on a patient that does not meet GEBT entry criteria.

6 Study Treatment and Concomitant Therapy

Study treatment is defined as any investigational treatments, marketed product, or placebo, or intended to be administered to a study patient according to the study protocol.

6.1 Treatments Administered

Table 3 Study Treatments Administered

Study Treatment	PCS12852	Placebo
Dosage Formulation	Tablet	Tablet
Unit Dose Strengths	0.1 mg and 0.5 mg	N/A
Route of Administration	Oral	Oral
Packaging and Labeling PCS12852 tablets and matching placebo tablets will be packaged in high density polyethylene bottles respectively. Each patient's study medication will be packaged in a study-specific box (kit) and shipped to the study site by a central distribution site.		
Treatment Schedule Regardless of the patient's assigned treatment group, each patient will take one tablet from their assigned kit at approximately the same time each morning and at least 30 minutes prior to a meal starting on Day 1 for 28 days. For Day 28, the patients will be asked to fast overnight prior to the morning dose on Day 28 and the subsequent GEBT. The patient will be asked to document the timing of each dosing via a dosing diary.		

6.2 Preparation, Handling, Storage, and Accountability

The Investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during transit for all study treatment received, and any discrepancies are reported and resolved before use of the study treatment. Study treatment must be stored in the original packaging between 20 to 25° C (68 to 77° F), with deviations permitted between 15 to 30°C (59 to 86° F) and protected from extreme conditions of temperature, light, and humidity.

Only patients enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

Patients who have successfully completed Screening criteria (Visit 1 and Visit 2) will return for a Randomization visit (Visit 3) where the inclusion/exclusion criteria will be evaluated and patients who meet the criteria will be randomized in a 1:1:1 ratio into one of the three treatment groups, PCS12852 0.1mg, PCS12852 0.5mg or placebo via Interactive Response Technology (IRT). The planned sample size to be randomized is 24 patients. The randomization to treatment groups will be stratified by type (IG, DG), enrolling at least 2 patients of each type in each treatment group.

The list of treatment allocations will be kept in a secure location by the CRO until approval to unblind is provided for the final analysis. Access to the treatment allocations will be monitored by Regulatory Affairs/Quality Assurance; any access to the allocations prior to unblinding the study will be documented by Regulatory Affairs/Quality Assurance and included in the Clinical Study Report.

Table 4 Measures to Minimize Bias

Study using IRT	All patients will be centrally randomized using an Interactive Response Technology (IRT). Each patient will be assigned a unique number (randomization number) that encodes the patient's assignment to one of the 3 arms of the study, according to the randomization schedule using a validated computer program. Details of the procedure are described in the IRT Manual provided to all sites. Study treatment will be administered/dispensed at the study visits as summarized in the SoA (Table 1). Returned study treatment should not be re-dispensed to the patients.

Blind break (IRT)	This is a double-blind study in which patients are blinded to study treatment. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's study treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor prior to unblinding a patient's study treatment assignment unless this could delay emergency treatment for the patient. If a patient's study treatment assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

The Sponsor may unblind the treatment assignment for any patient with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the patient's treatment assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

6.4 Study Treatment Compliance

When patients are dosed at the site, study treatment will be administered directly by the Investigator or designee. All dosing by the patient throughout the treatment period will also be documented in the patient's dosing diary. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

For self-administration of the study treatment at home by the patient, compliance with study treatment will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits and documented in the source documents and relevant form. Deviations from the prescribed dosage regimen should be recorded. Final drug accountability will be done by counting returned tablets at the patient's final visit.

A record of the quantity of study treatment dispensed to and administered by each patient must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded.

6.5 Continued Access to Study Treatment After the End of the Study

The study treatment will not be available to the patients at the end of the study.

6.6 Treatment of Overdose

For this study, any dose of study treatment greater than 20 tablets within a 24-hour time period will be considered an overdose.

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately.
- Evaluate the patient to determine, in consultation with the medical monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically.

6.7 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

As much as possible, the dose and frequency of all concomitant medications taken for chronic conditions except for diabetes mellitus (see Section 6.7.2) should be held stable during the study. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.1 Prohibited Treatments

The class of drugs prohibited in the study are those that affect GI motility, either positively or negatively, and therefore could confound the assessment of the efficacy of the study treatment on the signs and symptoms of gastroparesis.

Prohibited concomitant treatment includes cannabis, opioids, GLP-1 agonists (e.g. exenatide, liraglutide, semaglutide or dulaglutide, or pramlintide), cisapride, tegaserod, prucalopride, metoclopramide, bethanechol, domperidone and erythromycin or any other medications that are contraindicated for patients with gastroparesis.

IMPORTANT: Patients should be instructed to consult with the Investigator before taking any new medication or changing medications and/or dosing regimens throughout the study.

Drugs that are known to be strong inhibitors or inducers of Cytochrome P450 (CYP) (most likely CYP3A4 and CYP1A2) may significantly alter exposure to the investigational product, and as such, are strictly prohibited while on the study. Examples of CYP inhibitors include cimetidine, ciprofloxacin, fluvoxamine, clarithromycin, diltiazem, grapefruit juice, and itraconazole. Examples of CYP inducers include carbamazepine, phenobarbital, tobacco, and St. John's wort.

P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and gastric acid reducing agents may also significantly alter the exposure of the investigational product and as such, are strictly prohibited while on study. Examples of P-gp inhibitors include cyclosporine, amiodarone, and itraconazole as well as BCRP inhibitors include novobiocin, sulfasalazine and cyclosporine A which may potentially increase the systemic exposure. Examples of P-gp inducers include carbamazepine, phenytoin and rifampin. Examples of BCRP inducers and gastric acid reducing agents include venlafaxine, apalutamide and dovitinib as well as PPIs (esomeprazole, lansoprazole, omeprazole, etc), H2 blockers (ranitidine, famotidine, nizatidine) which may potentially decrease the systemic exposure.

6.7.2 Permitted Treatments

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded in the eCRF along with:

- indication
- dates of administration including start and end dates
- dosage information including dose and frequency

Diabetic gastroparesis patients enrolled in the study will likely consist mostly of patients receiving one or more prescription medications for blood-glucose control. Good clinical practice allows for frequent adjustment of medication by patients and their health care providers to minimize large fluctuations in glycemia, and this practice is encouraged in this study.

It should be remembered that certain diabetic drugs (see Section 6.7.1) delay gastric emptying and are prohibited during this study. Other therapy considered necessary for the patient's welfare

may be given at the discretion of the Investigator. If the permissibility of a specific medication/treatment is in question, please contact the Medical Monitor.

The Medical Monitor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.3 Rescue Medicine

Use of medications that may impact efficacy evaluations is strongly discouraged at any time after Visit 1 in the study. However, patients who experience severe symptoms of gastroparesis after entering the Treatment Period may receive a single day of treatment per week with an anti-emetic drug, but should avoid such treatment, if possible, on the day prior to and day of treatment visits. If a patient requires an anti-emetic drug (e.g., 5-HT_3 receptor antagonists, NK1 receptor antagonists) for more than 1 day a week, or requires an antiemetic drug once weekly repeatedly (i.e., more than 2 weeks while on study), the Investigator should contact the Medical Monitor to discuss the safety of the patient continuing in the study.

The following rescue medications may be used:

- ondansetron or promethazine (tablet, syrup or suppositories) for emesis
- loperamide for diarrhea
- Tramadol for pain

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7 Discontinuation/Withdrawal Criteria

It may be necessary for a patient to permanently discontinue study treatment. Reasons for discontinuation from study treatment and/or the study may include the following:

- Adverse event
- Death
- Failure to meet randomization criteria
- Lack of efficacy
- Lost to follow-up
- Investigator decision
- Pregnancy

- Protocol deviation
- Screen failure
- Site terminated by the Sponsor
- Study terminated by the Sponsor
- Withdrawal by the patient

The reason for discontinuation should be clearly documented on the appropriate eCRF. Discontinuation of study treatment also requires discontinuation from the study. If study treatment is permanently discontinued, the patient will not remain in the study. See the SoA (Table 1) for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed.

A patient may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. The patient will be permanently discontinued from the study treatment and the study at that time.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Table 1). Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Stopping Criteria

PCS12852 is a highly selective 5-hydroxytryptamine receptor 4 (5-HT_4 receptor) agonist. As such, the stopping rules focus on the known cardiac safety concerns identified for the drug class of 5-HT_4 receptor agonists. The overall study will be stopped if ≥ 2 patients develop the same Grade 3 CTCAE cardiac event or 1 patient develops a CTCAE ≥ Grade 4 cardiac event.

For cardiac adverse events classified as CTCAE ≥ Grade 3, if the same cardiac safety concern is seen on two separate ECGs, the patient should be withdrawn from the study and will be referred to a cardiologist for the appropriate treatment.

7.2 Loss to Follow-Up/Early Discontinuation from Study Drug

A patient will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible (and within the visit window, where one is defined), counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record/eCRF.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

If a patient discontinues study drug prior to study termination, the patient will be asked to return to the clinic for an Early Termination visit. This visit will include all the study procedures of the Day 35/Visit 8 clinic visit. The Day 35 study procedures and their timing are summarized in the SoA (Table 1).

8 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Table 1).

Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator should maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Patient Identification Card

All patients will be given a patient identification card identifying them as patients in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The Investigator or qualified designee will provide the patient with a patient identification card immediately after the patient provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the patient identification card.

Medical History

A medical history will be obtained by the Investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 5 years that the Investigator considers to be clinically relevant. Details regarding the disease for which the patient has enrolled in this study will be recorded separately and not listed as medical history.

8.1 Efficacy Assessments

8.1.1 Primary Efficacy Assessment – Gastric Emptying Breath Test

The GEBT is a nonradioactive noninvasive test that measures gastric emptying. Patients will provide baseline (premeal) breath samples and then consume a standardized 230 kCal meal, consisting of a proprietary standardized ^{13}C labeled egg component (which is rehydrated and then microwaved for 1.5 minutes) and 6 saltine crackers, accompanied by 6 ounces of water. The meal is to be consumed within 10 minutes. Single post meal breath samples are collected in capped glass tubes at 45, 90, 120, 150, 180, and 240 minutes after the meal is consumed and sent to the specified local laboratory for analysis by Gas Isotope Ratio Mass Spectrometry. By adding ^{13}C to the test meal, the GEBT can determine how fast the stomach empties the meal by measuring the rate of carbon-13 dioxide ($^{13}CO2$) excretion arising from the digested test meal.

The GEBT measures the rate of $^{13}CO_2$ excretion after consumption of a ^{13}C-enriched test meal. As the ^{13}C enriched meal is emptied from the stomach it is digested, assimilated and $^{13}CO_2$ is excreted in the breath. At any given measurement time t, the $^{13}CO_2$ excretion rate is related to the rate of gastric emptying. A larger kPCD value means a faster $^{13}CO_2$ excretion rate which is proportional to a faster rate of gastric emptying.

In subjects with normal gastric emptying, $^{13}CO2$ excretion rates obtained by GEBT generally rise to a maximum between 120 and 180 minutes and then start to decrease because nearly all of the of the ^{13}C-labeled test meal has been emptied from the stomach. In subjects with delayed emptying, $^{13}CO2$ excretion rates likewise start to rise after ingestion of the meal, but rates are lower and rarely reach a maximum before the end of the evaluation period (240 minutes) as a significant portion of the meal remains in the stomach and digestion and assimilation are incomplete.

Planned timepoints for all efficacy assessments are provided in the SoA (Table 1).

8.1.2 Secondary Efficacy Assessment – ANMS GCSI-DD

The ANMS GCSI-DD is designed to assess gastrointestinal symptoms associated with IG and DG. The ANMS GCSI-DD symptom assessments are based on a 24-hour recall period to minimize bias in patient recall. The instrument asks patients to rate the severity of five symptoms: bloating (feeling like you need to loosen your clothes), nausea, not able to finish a normal-sized meal, feeling excessively full after meals, and upper abdominal pain. The severity response is rated by the patient as the worst severity of the symptom over the previous 24 hours. The severity of symptom response scale ranges from 0 (“none”), 1 (“mild”), 2 (“moderate”), 3 (“severe”) to 4 (“very severe”). In the scoring of vomiting episodes, the number of episodes of vomiting per day is used, with the episodes capped at 4, so that the scoring is similar to the symptom severity scores of the other items. Therefore, vomiting episodes are scored as 0=none; 1=one episode; 2=two episodes; 3= three episodes and 4= four or more episodes.

The ANMS GCSI-DD total gastroparesis symptom daily score is generated by summing the scores on each of the five symptom items and then dividing by 5, that is the number of items within the gastroparesis related symptom score. Thus, the maximum total symptom score could be (5 symptoms * maximum score 4 divided by 5); hence, the maximum score is 20/5=4. The ANMS GCSI-DD gastroparesis symptom daily score can range from 0 to 4. High scores on the ANMS GCSI-DD reflect greater symptom severity. The minimum clinically important difference in the ANMS GCSI-DD score has been estimated to be 0.50.

In addition, overall severity of gastroparesis is assessed. The overall severity of gastroparesis takes into account that other symptoms might impact on a patient’s condition.

In this study, the change from baseline over time for the ANMS-GCSI-DD score will be assessed by comparing the following:

Change from baseline in the ANMS GCSI-DD) (i.e. Day-7 to Day -1) (predose) and Day 7 (Day 1 to Day 7)

Change from baseline in the ANMS GCSI-DD (i.e., Day-7 to Day -1) (predose) and Day 14 (Day 8 to Day 14)

Change from baseline in the ANMS GCSI-DD (i.e., Day-7 to Day -1) (predose) and Day 21 (Day 15 to Day 21)

Change from baseline in the ANMS GCSI-DD (i.e., Day-7 to Day -1) (predose) and Day 28 (Day 22 to Day 28)

The ANMS-GCSI-DD sub scores will also be assessed as an Exploratory Endpoint:

Change from baseline in the sub scores (nausea, early satiety, postprandial fullness, upper abdominal pain and number of vomiting episodes) of the ANMS-GCSI-DD over time (Day 7, 14, 21, 28) by comparing Day 7 to Day 14, Day 14 to Day 21 and Day 21 to Day 28.

The patients will complete these assessments using an electronic diary.

8.1.3 Exploratory Efficacy Assessments

8.1.3.1 PAGI-SYM and PAGI-QOL

The PAGI-SYM will assess the patient's severity of symptoms related to the GI problem. The PAGI-SYM is a 20-question assessment (Rentz, 2004). The patient will circle the number that best describes how severe the symptom has been during the past 2 weeks. PAGI-SYM subscale scores are calculated by taking the mean of the items in each subscale; the subscale scores vary from 0 (none or absent) to 5 (very severe). The half-scale rule is applied for missing data (i.e., the subscale score is calculated using the mean of non-missing items; when more than 50% of items are missing, the score is set to missing). The total score is calculated by taking the mean of the subscales. If a subscale score is missing, the PAGI-SYM total score is set to missing.

If the patient has not experienced the symptom, they would circle 0. If the symptom has been very mild, mild, moderate, or severe, they would circle 1, 2, 3 or 4, respectively.

The PAGI-QOL will assess the patient's current GI problems such as pain, discomfort or other problems and evaluate how these symptoms have affected the patient's quality of life and well-being in the past 2 weeks. There are 30 questions in the assessment, with questions such as "Have you had to depend on others to do your daily activities?" and "Have you felt helpless?" with answer options including "none of the time," "a little of the time," "some of the time," "a good bit of the time," and "all of the time." The PAGI-QOL contains 30 items covering five subscales: Daily Activities (10 items), Clothing (2 items), Diet and Food Habits (7 items), Relationships (3 items), and Psychological Well-Being (8 items). Subjects are asked to respond

to each item on a 6-point Likert scale, ranging from 0 (none of the time) to 5 (all of the time). Subscale scores are calculated by averaging across the items within the specific subscale after reversing item scores. The range of scores is 0–5; higher scores indicate better HRQL (de la Loge, 2004)

In this study, the change from baseline over time for the PAGI-SYM and PAGI-QOL scores will be assessed by comparing Day 1 to Day 28. The patients will complete these assessments using an electronic diary.

8.1.3.2 CGI-S and CGI-I

The CGI-S provides an overall clinician-determined summary measure that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. The CGI actually comprises two companion one-item measures evaluating the following: (a) severity of psychopathology from 1 to 7 and (b) change from the initiation of treatment on a similar seven-point scale (Busner, 2007).

The CGI-S asks the Investigator the question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time? This is rated on the following 7-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5= markedly ill; 6=severely ill; and 7=among the most extremely ill patients. The rating is based upon observed and reported symptoms, behavior and function in the past 7 days.

The CGI-I will ask the Investigator the question: "Compared to the patient's condition at admission to the study, this patient's condition is 1=very much improved since the initiation of study treatment; 2=much improved; 3=minimally improved; 4=no change from baseline (the initiation of study treatment); 5=minimally worse; 6=much worse; and 7=very much worse since the initiation of study treatment.

In this study, the change from baseline over time for the CGI-S and CGI-I scores will be assessed by comparing Day 1 to Day 28. The investigator will complete these assessments using an electronic diary.

8.1.3.3 PGI-S and PGI-C

Consistent with the recommendations in the FDA Draft Guidance: Gastroparesis: Clinical Evaluation of Drugs for Treatment, 2019, multiple anchor scales will also be used to assess the impact of treatment on the patient's disease. The patient global impression of severity (PGI-S)

and patient global impression of change (PGI-C) scales will be used in the proposed Phase 2A study, with the intent of providing accumulated evidence to help interpret a clinically meaningful within-patient score change.

The PGI-S will assess the patient's severity of symptoms. The choices are: "none," "mild," "moderate," "severe" and "very severe."

The PGI-C will assess the patient's impression of how their GI symptoms have changed. The patient will choose 1 of 7 answers, including: "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse" and "very much worse."

In this study, the change from baseline over time for the PGI-S and PGI-C scores will be assessed by comparing Day 1 to Day 28. The patients will complete these assessments using an electronic diary.

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1).

- AEs (by type, severity, and relatedness) at each visit.
- Changes in safety clinical laboratory testing and vital signs at each site visit.
- Changes in ECGs at each site visit and the potential correlation of the PK with changes in the ECG.
- Change from baseline in the C-SSRS scores over time by comparing Day 1 to Day 28.

8.2.1 Physical Examinations

Complete physical examinations (excluding pelvic exam in women and genital exam in men, and rectal exam in both genders) are to be performed at Screening (Visit 1) and Day 28 (Visit 6). Symptom-directed (abbreviated) physical examinations may be conducted as required at Visit 3 (Day 1) Visit 4 (Day 7), Visit 5 (Day 14), and Visit 8 (Day 35).

Patients should be weighed with no shoes, in light clothing, without any outerwear. Height should be measured only at the first study visit. Any abnormality noted on the physical examination done at or following Visit 3 or the early termination visit that was not present on the physical examination at screening should be reported as an AE if considered by the Investigator to be clinically significant.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Heart rate (HR), respiratory rate, systolic and diastolic blood pressure (BP), weight and temperature will be assessed; the method for measuring temperature will be per the site's preference.
- BP and HR measurements will be assessed in the sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP and HR measurements should be preceded by at least 3 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).
- Vital signs are to be taken before blood collection for laboratory tests.

8.2.3 Electrocardiograms

A 12-lead ECG will be obtained as outlined in the SoA (Table 1) using an ECG machine after the patient has rested for 5 minutes in supine position. At Visit 3 (Randomization) and Visit 6 (Day 28), the ECG will be performed prior to the 4-hour PK draw. At Visit 4 and Visit 5, the ECG will be performed approximately 4 hours after the patient's dose. The Investigator will report whether the ECG is normal or abnormal and if the result is considered clinically significant or not.

All clinically significant ECG abnormalities occurring during the study should be documented as AEs. The ECG performed at Screening will be recorded as the baseline assessment. Standard ECG parameters, including heart rate, QRS, PR, QT, Bazett's correction for QT (QTcB), and Fridericia's correction for QT (QTcF) intervals will be measured. The ECGs will be overread by the Investigator to assess any abnormalities.

8.2.4 Clinical Safety Laboratory Tests

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Table 1) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, where possible, and the Sponsor notified.
- All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Table 1).
- If laboratory values from laboratory tests not specified in the protocol and performed at the institution's local laboratory result in the need for a change in patient management or are considered clinically relevant by the Investigator (e.g., are considered to be an SAE or an AE or require dose modification), then the results must be recorded in the eCRF.

8.2.5 Pregnancy Testing

Women of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at baseline before dosing. A serum β-HCG test will be performed at Screening (Visit 1) and a urine pregnancy test at subsequent visits. Refer to the SoA (Table 1) for testing timepoints.

Details of all pregnancies in females and female partners of male patients will be collected after the start of study treatment and until the end of the study period (Visit 7). If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs.

8.2.6 Suicidal Ideation and Behavior Risk Monitoring

Although no increased risk of suicide ideation or behavior has been documented with PCS12852, it is in a class of products that have an increased risk of suicidal ideation or behavior.

Patients being treated with PCS12852 should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior, especially at

the beginning and end of the course of study treatment. Patients who experience signs of suicidal ideation or behavior should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study treatment.

Baseline assessment of SIB will be monitored during the study using the C-SSRS by comparing Day 1 to Day 7, Day 14 and Day 28 scores. Refer to the SoA (Table 1) for timepoints.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

Adverse events will be reported by the patient or noted by the Investigator.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the patient to discontinue the study treatment (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the ICF. All SAEs will be collected and followed until 30 days after the final Visit (Visit 8), at the timepoints specified in the SoA (Table 1).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of awareness, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obliged to actively seek information on AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrence.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs and SAEs, (as defined in Appendix 3), will be followed until resolution, stabilization, until the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.2). Further information on follow-up procedures is given in Appendix 3.

8.3.4 Regulatory Reporting Requirements for SAE

Prompt notification within 24 hours (see Appendix 3) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female patients and female partners of male patients will be collected after the start of study treatment and until 7 days after the last dose.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs and will be reported as such.

8.4 Pharmacokinetics

Blood samples will be collected for measurement of PCS12852 in plasma via a specific and sensitive validation bioanalytical method, at timepoints as specified in the SoA (Table 1). Clinical staff are encouraged to take the blood samples for PK analysis at the scheduled time point; however, deviations from the scheduled sample times are not considered protocol deviations. The actual date and time (24-hour clock time) of sample collections will be recorded in the source document and transcribed into the eCRF. Instructions for the collection and handling of biological samples will be provided in the Study Manual.

Samples will be used to evaluate the PK of PCS12852. Samples collected for analyses of PCS12852 plasma concentration may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the study.

Genetic analyses will not be performed on these blood samples. Subject confidentiality will be maintained.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

9 Statistical Considerations

The statistical analysis plan (SAP) will be developed and finalized before database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Analysis Sets

The analysis populations will consist of patients as defined in Table 5.

Table 5 Analysis Data Sets

Analysis Data Sets	Description
Safety Analysis Set	Patients enrolled in the study who received at least 1 dose of treatment.
PK Analysis Set	Patients in the Safety Set with at least 1 plasma sample with a quantifiable concentration of PCS12852.
Full Analysis Set	Patients who are randomized.

9.2 Statistical Analyses

9.2.1 General Considerations

Approximately 24 patients (approximately 8 patients in each of the three treatment groups) with moderate to severe gastroparesis who have documented delayed gastric emptying are planned to be randomized (1:1:1) in the study. The randomization to treatment groups will be stratified by type of gastroparesis (idiopathic, diabetic), enrolling at least 2 patients of each type of gastroparesis (idiopathic, diabetic) in each treatment group.

9.2.2 Primary Efficacy Analysis

The change in the gastric emptying rate AUC as measured by the GEBT, from baseline to Day 28 will be analyzed in the FAS using an analysis of covariance (ANCOVA) model with treatment group (three levels) as a factor and the baseline GEBT as a covariate. Each of the two primary comparisons (0.1 mg versus placebo, 0.5 mg versus placebo), will be conducted using a two-sided Dunnett's test at the overall alpha=0.05 significance level.

Other efficacy analyses:

All secondary endpoints will be conducted using the same approach as described for the primary analysis. Each treated group will be compared to placebo using Dunnett's test. All secondary analyses will be based on the use of two-sided tests at the alpha=0.05 overall level of significance, with no adjustment for multiplicity.

Subgroup analysis:

A subgroup analysis of idiopathic gastroparesis patients compared to diabetic gastroparesis patients will be done for all efficacy analysis endpoints.

Pharmacokinetic analysis:

Plasma concentrations will be used to estimate the pharmacokinetic parameters for PCS12852 on Day 1 and Day 28 using noncompartmental methods in WinNonlin®. The following parameters will be calculated as data permits:

- C_{max}: maximum observed plasma concentration
- T_{max}: time at which the maximum plasma concentration was observed
- $t_{½}$: (the apparent first-order terminal elimination half-life)
- $AUC_{0\text{-last}}$: the area under the plasma concentration versus time curve, from time 0 to the last measurable concentration
- AUC_{∞}: the area under the plasma concentration vs. time curve from time 0 to infinity
- λ_z: apparent first order terminal elimination rate constant

A dose proportionality analysis will be conducted for log-transformed Cmax, AUC0-last, and AUC∞ using the power model. . In addition, the relationship between gastric emptying rate and drug exposure will be assessed, as data permit. Exposure-response for safety measures may also be explored.

In addition, a population PK model may be used to describe the PK of PCS12852, if appropriate based on the data collected. A previously developed population PK model describing the PK of PCS12852 in patients with functional constipation, using a two-compartment model with first order absorption, may be used to predict the PK in patients in this study.

Further details of all analyses will be described in the SAP.

9.2.3 Secondary Efficacy Analysis

This study will enroll gastroparesis patients with documented delayed gastric emptying and at least moderate symptom severity. The ANMS GCSI-DD scale will be used to assess the change from baseline in symptoms.

The ANMS GCSI-DD symptom assessments are based on a 24-hour recall period to minimize bias in patient recall. The ANMS GCSI-DD total gastroparesis symptom daily score is generated by summing the scores on each of the five symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain, and number of vomiting episodes) and then dividing by 5, that is the number of items within the gastroparesis related symptom score. Thus, the maximum total symptom score could be (5 symptoms x maximum score 4 divided by 5); hence, the maximum score is 20/5=4. The ANMS GCSI-DD gastroparesis symptom daily score can range from 0 to 4. High scores on the ANMS GCSI-DD reflect greater symptom severity.

9.2.4 Other Patient-reported outcomes (PRO) Assessments – Exploratory Endpoints

The PAGI-SYM is a patient-reported outcome that asks patients the severity of their symptoms over the last 2 weeks. The PAGI-SYM was developed to measure symptom severity for gastroparesis, functional dyspepsia, and gastroesophageal reflux disease. The PAGI-SYM is composed of 20 items and 6 subscales: heartburn/regurgitation (7 items), nausea/vomiting (3 items), postprandial fullness/early satiety (4 items), bloating (2 items), upper abdominal pain (2 items), and lower abdominal pain (2 items). Subscale scores are calculated by averaging across items comprising the subscale; scores vary from 0 (none or absent) to 5 (very severe). The half-scale rule is applied for missing data (i.e., the subscale score is calculated by using the mean of non-missing items; when more than 50% of items are missing, the score is set to missing). The change from baseline in the PAGI-SYM will be analyzed using the same statistical approach as described for other analyses.

The PGI-C is a patient-reported questionnaire with a 7-point rating scale where the participant rates his/her own improvement in overall symptoms relative to the baseline assessment. It is rated as 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

The PGI-S is a patient reported questionnaire with a single question to measure disease severity on a 5-point rating scale. It is rated as “none,” “mild,” “moderate,” “severe,” and “very severe.”

The PAGI-QOL is a 30-item instrument assessing quality of life in patients with gastroparesis. The questionnaire covers 5 domains: Daily Activities, Clothing, Diet and Food Habits, Relationship, and Psychological Well-Being and Distress. The effect on overall quality of life and well-being over the past 2 weeks is rated on a scale of 0 (none of the time) to 5 (all of the time) for each item.

Clinicians complete the CGI-S, which is a 7-point scale on which the clinician rates the severity of the patient's gastroparesis at the time of assessment and refers to the degree of illness at the time of the visit and during the 2 weeks before the visit. The CGI-S is rated on the following 7-point scale: 1: normal, not at all ill; 2: borderline ill; 3: mildly ill; 4: moderately ill; 5: markedly ill; 6: severely ill; 7: among the most extremely ill patients.

The CGI-I is a 7-point scale in which the clinician rates the change from the initiation of treatment. The CGI-I is rated as: 1: very much improved since the initiation of study treatment; 2: much improved; 3: minimally improved; 4: no change from baseline (the initiation of study treatment); 5: minimally worse; 6: much worse; and 7: very much worse since the initiation of study treatment.

9.2.5 Safety Analyses

The safety analyses will be performed using the Safety Population and include AEs, changes in physical exam findings, vital signs, ECGs and clinical laboratory values.

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA version 23.0 or higher). The number and percent of patients reporting at least one AE will be summarized by System Organ Class and Preferred Term and presented by severity, relationship to study treatment, amount of drug exposure, and time. Each patient will contribute only once (i.e., first occurrence) to each of the incidence rates, regardless of the number of occurrences. Severity of AEs will be assessed based on the National Cancer Institute (NCI) CTCAE Version 5.0. For reporting of AE severity in patients with more than one occurrence of the same AE, the patient will only be reported once based on the highest severity of the AE observed. Patients who have an SAE or who discontinue the study due to an AE deemed to be related to study treatment will be described in patient narratives.

Vital signs, clinical laboratory, and ECG results will also be presented and summarized by dose level and summarized by descriptive statistics with change from baseline values calculated. All safety data collected in the clinical database, including physical exam findings and abnormal ECG results, will be presented in data listings. The safety categories will be summarized as appropriate (eg, categorial or continuous descriptives, shift tables) and will be fully defined in

the SAP. The potential relationship between abnormal ECG results and PK will also be evaluated and fully defined in the SAP.

9.3 Sample Size Determination

Based on the results of a prior study (Study 102), estimates of the standard deviation (SD) of the AUC change from baseline range from 10 to 35. Assuming a true SD of 15 and based on a two-sided test at the alpha=0.025 level of significance, a sample size of 8 patients per arm (24 total patients) will provide 80% power to detect a between-group mean difference of 25.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines.
- Applicable ICH Good Clinical Practice (GCP) guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the overall conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the patient and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

10.1.3 Data Protection

Patients will be assigned a unique identifier by the Sponsor via the IRT system. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.

The patient must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4 Dissemination of Clinical Study Data

A summary of the results of the clinical study together with a summary that is understandable to a layperson will be provided after the global end (or early termination) of the study in all countries concerned to ensure full availability of all clinical data under this protocol, within 12 months.

10.1.5 Data Quality Assurance

All patient data relating to the study will be recorded on electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and Regulatory Agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request

previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the eCRF.

10.1.6 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.7 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the Investigator.
- Total number of patients included earlier than expected.
- Discontinuation of further study treatment development.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the US: Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug Application under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.8.1 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual patient's medical records, assess drug accountability, and ensure that the

study is being conducted according to pertinent regulatory requirements. The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical QA Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor of the necessary support at all times.

10.2 Appendix 2: Clinical Laboratory Tests

- All clinical laboratory tests should be done after patients have fasted for at least 8 hours.
- The tests will be performed by the central laboratory, unless prior approval is received from the Sponsor.
- Protocol-specific requirements for inclusion or exclusion of patients are details in Sections 5.1 and 5.2.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 6 Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters	
Hematology	Platelet count RBC count Hemoglobin Hematocrit RBC indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) % Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry	BUN Potassium Creatinine Sodium Glucose, fasting Calcium Phosphorus Bicarbonate	AST/SGOT Total and direct bilirubin ALT/SGPT Total protein Alkaline phosphatase Chloride Albumin

Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones, by dipstick Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	Highly sensitive serum and/or urine hCG pregnancy test (as needed for women of childbearing potential) at timepoints detailed in Section 8.3.5.
Other screening tests	HbA1c and TSH will be done at Screening only Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, THC and benzodiazepines) Serology (HIV antibody, hepatitis B surface antigen (HbsAg), and HCV antibody) [HCV PCR will be done for any HCV Ab positive result] All study required laboratory assessments will be performed by a central laboratory.
NOTES: 1. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.	

ALT= alanine aminotransferase; AST= aspartate aminotransferase; BUN=blood urea nitrogen; hCG= human chorionic gonadotropin; HCV = hepatitis C; HIV = human immunodeficiency virus; IEC= independent ethics committee; INR= international normalized ration; IRB= institutional review board; RBC= red blood cell; SGOT= serum glutamic-oxaloacetic transaminase; SGPT= serum glutamic-pyruvic transaminase; THC = tetrahydrocannabinol; TSH = thyroid stimulating hormone; WBC= white blood cell.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected treatment-treatment interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs,

symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is an AE that:
a. Results in death
b. Is life-threatening The term *life-threatening* in the definition of *serious* refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations

Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the patient or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-up of AE and SAE

AE and SAE Recording
When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE information. It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page. There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be blinded on the copies of the medical records before submission to the Sponsor. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity
The clinical severity of an AE will be graded using the NCI CTCAE Version 5.0. The severity of all adverse events should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. These criteria can be found at http://ctep.cancer.gov/reporting/ctc.html. For those adverse event terms not listed in the CTCAE, the following grading system should be used: • *CTCAE Grade 1:* Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. • CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- CTCAE Grade 4: Life threatening consequences; urgent intervention indicated.
- CTCAE Grade 5: Death related to the adverse event.

The investigator is to evaluate whether the AE meets serious criteria. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.

A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in their assessment.

For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report in the electronic data collection tool. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the electronic data collection tool.**

The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The following "binary" decision choice will be used by the Investigator to describe the initial causality assessment:

- Related: Reasonable possibility of a relatedness
- Not related: No reasonable possibility of relatedness.

The following factors should also be considered:

- The temporal sequence from study drug administration-
  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant drug-
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug-
  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed form.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAE

SAE Reporting to the Sponsor via email, fax or telephone

Initial Reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to Medpace Clinical Safety **within 24 hours** of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the investigator considers related to study must be reported to Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Medpace SAE hotline – USA:

Telephone: +1-800-730-5779, dial “3” or +1-513-579-9911, dial “3”

Facsimile: +1-866-336-5320 or +1-1-513-570-5196

E-mail: medpace-safetynotification@medpace.com

Follow-Up Reports

The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies.

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy

    - Documented bilateral salpingectomy

    - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.

3. Premenopausal female

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. An FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female Patients

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective or accepted effective method of contraception consistently and correctly as described below.

Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] Failure rate of < 1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Highly Effective Contraceptive Methods That Are User Independent[a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.*

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.

Accepted Effective Contraceptive Methods

Acceptable birth control methods that result in a failure of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- Nonhormonal intrauterine device

A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Pregnancy Testing

At a minimum, a pregnancy test should be performed as per the SoA (Table 1).

- Women of childbearing potential (WOCBP) should only be included in the study after a confirmed menstrual period and a negative highly sensitive serum pregnancy test

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Female Patients Who Become Pregnant

- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are always considered to be SAEs and will be reported as such. Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be

reported to the Sponsor as described in Section 10.3.4. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

- Any female patient who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

10.5 Appendix 5: Abbreviations

Abbreviation	Description
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANMS GCSI-DD	American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary
APD	action potential duration
AST	aspartate aminotransferase
AUC	Area Under the Curve
$AUC_{0\text{-last}}$	the area under the plasma concentration versus time curve, from time 0 to the last measurable concentration
AUC_{∞}	the area under the plasma concentration vs. time curve from time 0 to infinity
BP	Blood Pressure
BCRP	Breast cancer resistance protein
BMI	Body mass index
BUN	Blood urea nitrogen
C_{max}	maximum observed plasma concentration
eCRF	electronic case report form
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CHO	Chinese hamster ovary
C-SSRS	Columbia–Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DG	diabetic gastroparesis
DRM	delayed release multiple dose cohort
ECG	electrocardiogram
FAS	full analysis set
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FGID	Functional gastrointestinal disorders
FSH	follicle-stimulating hormone

GCP	Good Clinical Practice
GEBT	Gastric Emptying Breath Test
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
hCG	human chorionic gonadotropin
HbA1c	hemoglobin A1c
HCV	hepatitis C
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Conference for Harmonisation
IG	idiopathic gastroparesis
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ration
IR	immediate release
IRB	Institutional Review Board
IRM	Low dose immediate release cohort
IRT	interactive response technology
IUD	intrauterine device
LTBI	latent TB infection
NCI	National Cancer Institute
NOAEL	No Observable Adverse Effect Level
PAGI-SYM	Patient Assessment of Gastrointestinal Disorders Symptom Severity Index
PAGI-QOL	Patient Assessment of Upper Gastrointestinal Disorders – Quality of Life
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
PRO	Patient-Reported Outcomes
PT	preferred term
QD	once daily
QTcB	Bazett's correction for QT

QTcF	Fridericia's correction for QT
RBC	Red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SIB	suicidal ideation and behavior
SoA	schedule of activities
SOC	System organ class
TB	tuberculosis
T_{max}	time at which the maximum plasma concentration was observed
$t_{½}$	the apparent first-order terminal elimination half-life
ULN	upper limit of normal
US	United States
WBC	White blood cell
WOCBP	woman of childbearing potential
λ_z	apparent first order terminal elimination rate constant
5-HT receptor	5-hydroxytryptamine receptor
5-HT_4 receptor	5-hydroxytryptamine receptor 4

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12 Declaration of the Investigator

Title: A Phase 2A Placebo-controlled, Randomized Dose Response Study of the Safety, Pharmacokinetics and Efficacy of PCS12852 on Gastric Emptying Rate Assessed by 13C Spirulina GEBT in Patients with Moderate to Severe Gastroparesis.

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, electronic CRF (eCRF), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted IRB or IEC. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the patients.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the Local Study Center

_____ _____

Signature Date

_____

Name (print letters)

_____

Title (print letters)

_____

Institution (print letters)

_____

Phone number