# PCS12852, A NOVEL 5-HT4 AGONIST, IMPROVES GCSI SYMPTOM SCORES AND GASTRIC EMPTYING IN GASTROPARESIS PATIENTS

Das, Maya; Smythe-Peterkin, Shanique; McCallum, Richard W.; Parks, Kayla; Franks, Peter; Young, David; Bigora, Sian

# Author and Disclosures

- Maya Das, MD, JD
  - Heliconia West, LLC, CA
  - Processa Pharmaceuticals (consultant)
- Shanique Smythe-Peterkin
  - Processa Pharmaceuticals (employee)
- Richard W McCallum, MD
  - Texas Tech University School of Medicine, TX
  - Study PI
- Kayla Parks
  - Processa Pharmaceuticals (employee)
- Peter Franks
  - Processa Pharmaceuticals (employee)
- David Young, PharmD, PhD
  - Processa Pharmaceuticals (employee)
- Sian Bigora, PharmD
  - Processa Pharmaceuticals (employee)

# Abstract


- **INTRODUCTION:** Gastroparesis is a chronic disorder characterized by delayed gastric emptying of solid food in the absence of a mechanical obstruction and is a condition with unmet needs due to the limited available treatment options for patients. This study investigated the effects of PCS12852 (a potent and selective 5-$HT_4$ receptor agonist) on gastric emptying and core gastroparesis symptoms in patients with idiopathic or diabetic gastroparesis.

- **BACKGROUND & AIMS**: We performed a double-blind placebo-controlled trial of patients with delayed gastric emptying and moderate to severe symptoms of idiopathic or diabetic gastroparesis. Patients were randomized 1:1:1 to PCS12852 0.1 mg, PCS12852 0.5 mg, or placebo given once daily for 28 days. The change in gastric emptying rate from baseline was determined by the gastric emptying rate half time ($t_{50}$) and the area under the curve (AUC) as assessed by the Gastric Emptying Breath Test (GEBT). Other endpoints included change from baseline in the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD), a patient-reported outcome measurement that assesses symptoms (i.e., nausea, vomiting, early satiety, postprandial fullness, and upper abdominal pain) associated with gastroparesis.

- **RESULTS:** Twenty-five (25) patients were enrolled (64% white; 88% female; 24% idiopathic, 76% diabetic) at 8 clinical sites. Although patients were only treated for 28 days, the gastric emptying rate improved as compared to baseline for PCS12852 0.5 mg while no significant improvement was seen with placebo. The mean (±SD) $t_{50}$ declined by -31.90 ± 50.53 minutes in the PCS12852 0.5 mg group vs -9.36 ± 42.43 minutes in the placebo group from baseline to day 28. The PCS12852 0.5 mg group demonstrated a clinically meaningful reduction in the total ANMS GCSI-DD score (>0.5) on day 28 as compared to baseline. Similarly, the PCS12852 0.5 mg group showed a positive improvement in all of the ANMS GSCI-DD subscales over the treatment period. There was no significant improvement in the 0.1 mg group as compared to placebo in gastric emptying or symptom scales. PCS12852 was generally well-tolerated. Adverse events were mild to moderate and resolved without sequalae. There were no serious adverse events, and specifically no cardiac adverse events reported during the study.

- **CONCLUSIONS:** PCS12852 0.5 mg, a potent and selective 5-$HT_4$ agonist given once daily for 28 days, improved gastric emptying in patients with gastroparesis as compared to placebo. A clinically meaningful reduction in the total ANMS GSCI-DD score and improvements in individual symptom scores were observed in the PCS12852 0.5 mg group. No significant adverse events were noted. This data supports further investigation of PCS12852 as a treatment for gastroparesis.

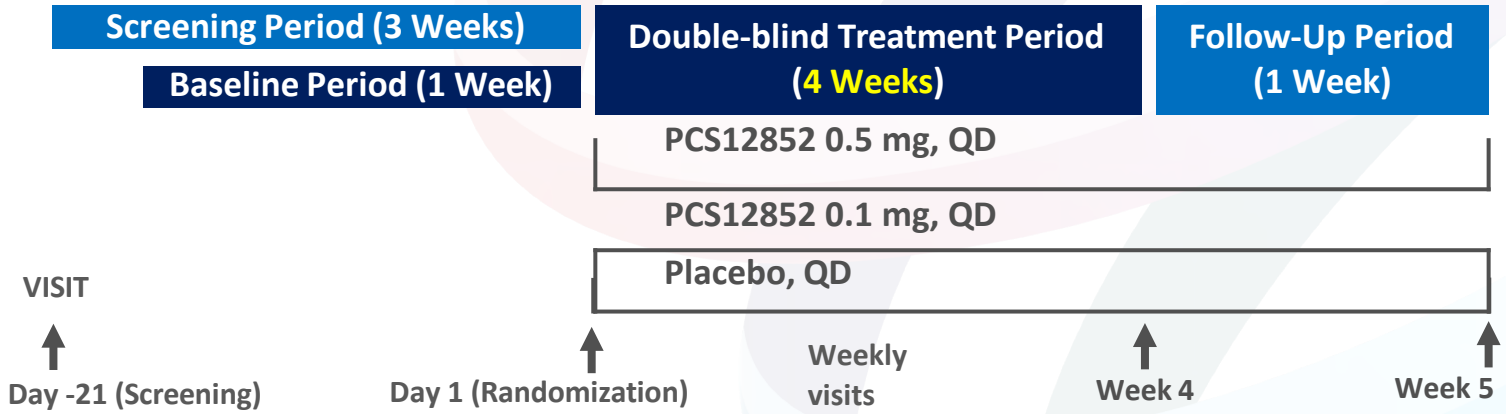
# Background

- PCS12852, a new 5-HT4 receptor agonist
  - Superior potency and efficacy in animals and humans
  - High selectivity for 5-HT4 receptors with no evidence of cardiac toxicity
  - Excellent safety and tolerability profile in nonclinical and Phase 1 studies
  - Currently being investigated for the treatment of gastroparesis

# Phase 2A: Proof of Concept Study Design

**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**

| | |
|---|---|
| **Eligibility criteria** | • Moderate to severe IG or DG according to ANMS GCSI-DD<br>• Male or female 18 to 80 years of age<br>• Moderate to severe delay in gastric emptying measured by GEBT |
| **Primary endpoints** | • Change in gastric emptying rate from baseline assessed by GEBT (AUC and $t_{50}$)<br>• Pharmacokinetics |
| **Secondary endpoints** | • Change from baseline in ANMS GCSI-DD and Day 7, 14, 21 and 28 |
| **Sample size** | • 24<br>• Randomized 1:1:1 |



# Patient and Disease Characteristics

| Characteristic | PCS12852 0.1 mg (N=9) | PCS12852 0.5 mg (N=8) | Placebo (N=8) | Total (N=25) |
|---|---|---|---|---|
| Age (Yrs :Mean±SD) | 58.6±7.3 | 58.0±6.4 | 60.5±5.8 | 59.0±6.4 |
| Sex (M:F) | 2:7 | 0:8 | 1:7 | 3:22 |
| Height (cm: Mean±SD) | 163.0±6.8 | 161.6±7.2 | 163.3±7.8 | 162.6±7.0 |
| Weight(kg: Mean±SD) | 80.7±14.1 | 78.6±17.8 | 80.71±13.9 | 80.0±14.7 |
| BMI ($kg/m^2$:Mean±SD) | 30.5±5.8 | 30.0±6.1 | 30.1±3.4 | 30.2±5.1 |
| Time Since Diagnosis (Yrs :Mean±SD) | 5.0±2.8 | 4.4±2.6 | 6.2±7.0 | 5.2±4.4 |
| Type of Gastroparesis (IG:DG) | 2:7 | 2:6 | 3:5 | 7:18 |

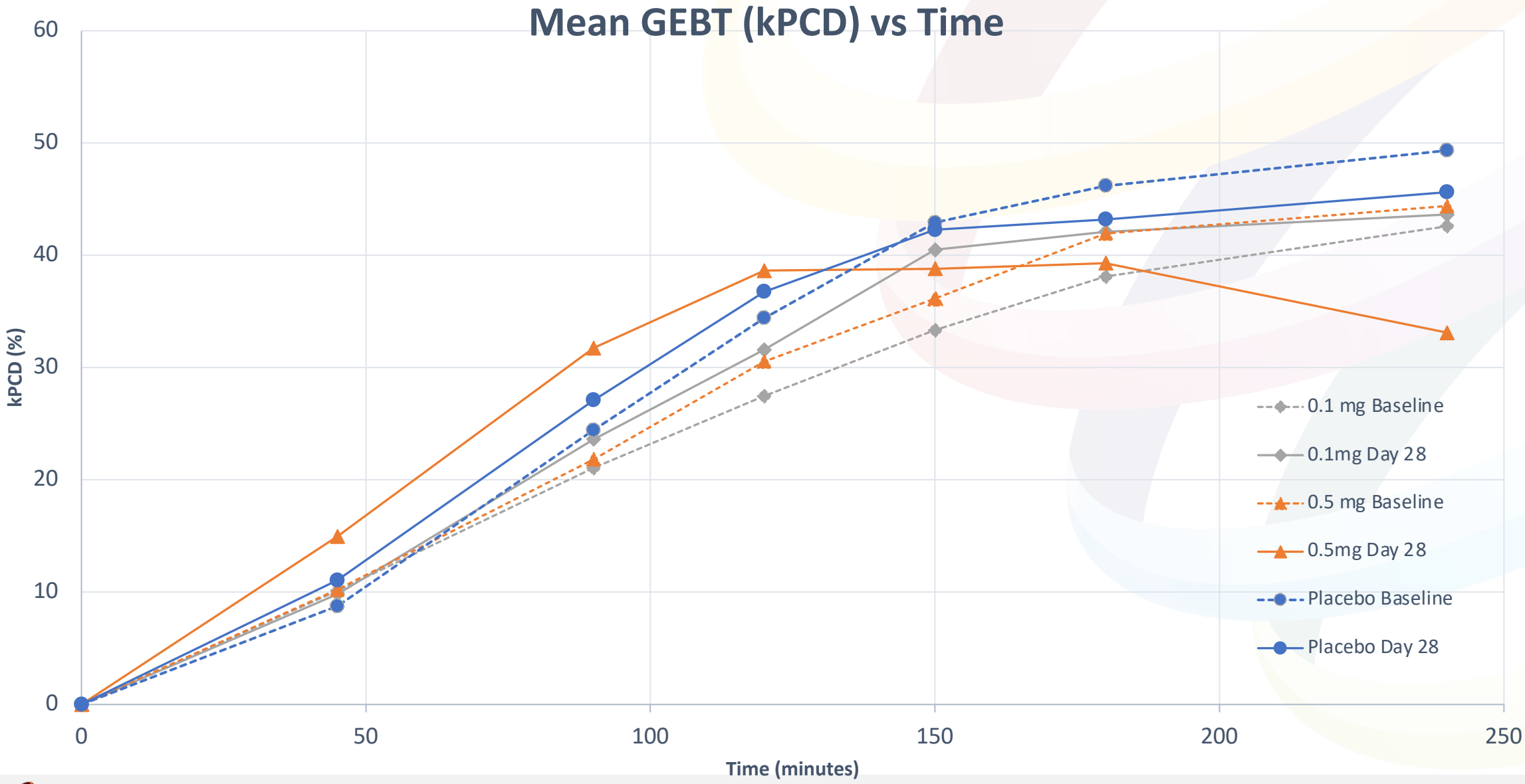
# Phase 2A Study: GEBT Results

## $^{13}$C-Spirulina GEBT Data: Changes from Baseline to Day 28

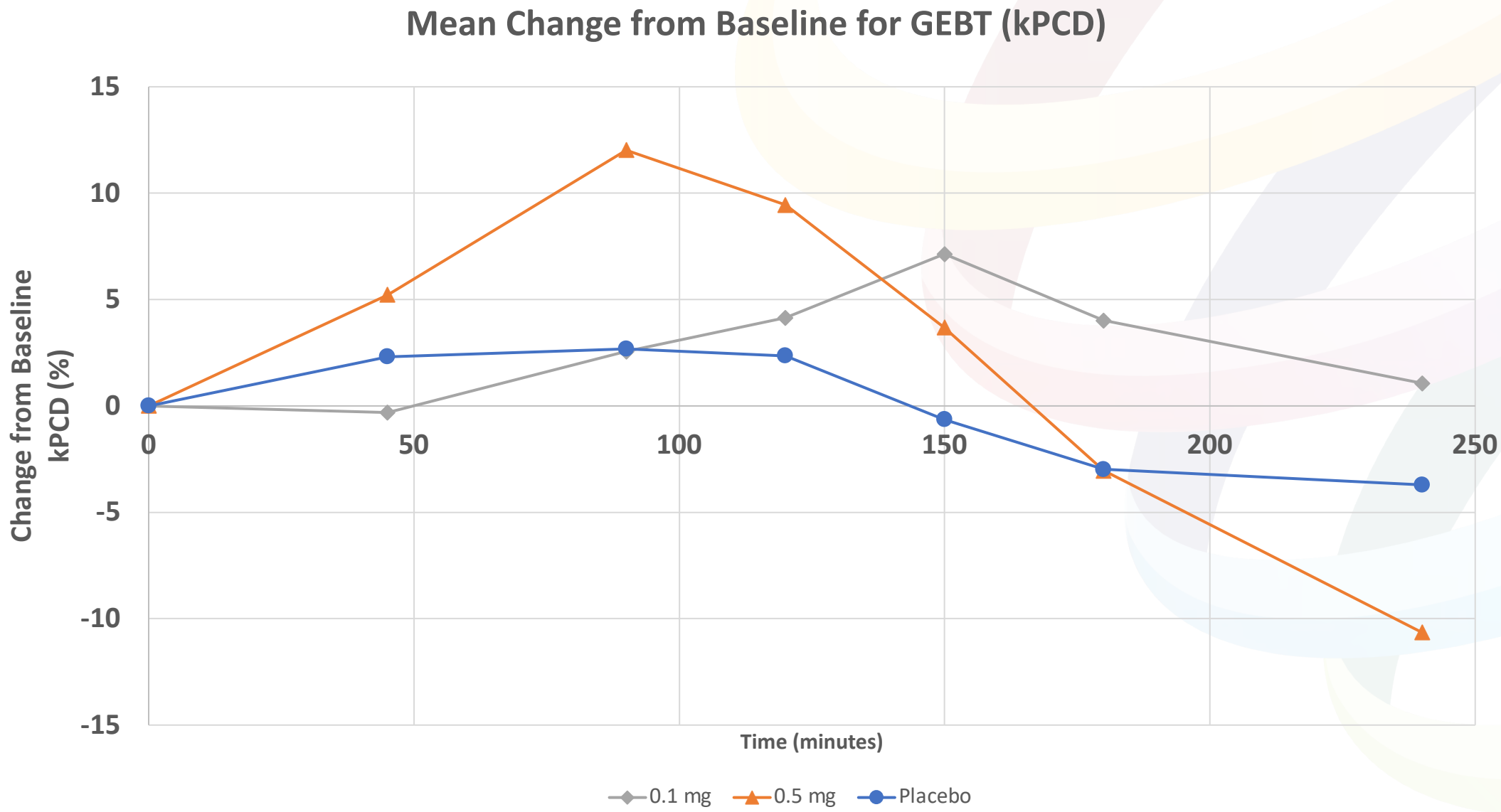
| Mean GEBT Parameter** (SD) | PCS12852-GP-01 Study | | |
|---|---|---|---|
| | PCS12852 0.1 mg (n=9) | PCS12852 0.5 mg (n=6) | Placebo (n=8) |
| $t_{50}$ (minutes) | -7.4±20.2 | -31.9.±50.5† | -9.4±42.4 |
| AUC | 632.7±1881.5 | 597.1±2635.8 | 37.4±2022.8 |
| $t_{10}$ (minutes) | 2.4±4.7 | -9.7±13.7* | -7.8±7.2* |

* P value<0.05 vs baseline (ANCOVA analysis)
† p value<0.1 vs baseline (ANCOVA analysis)
** $t_{50}$ and AUC were primary endpoints; $t_{10}$ was an exploratory endpoint

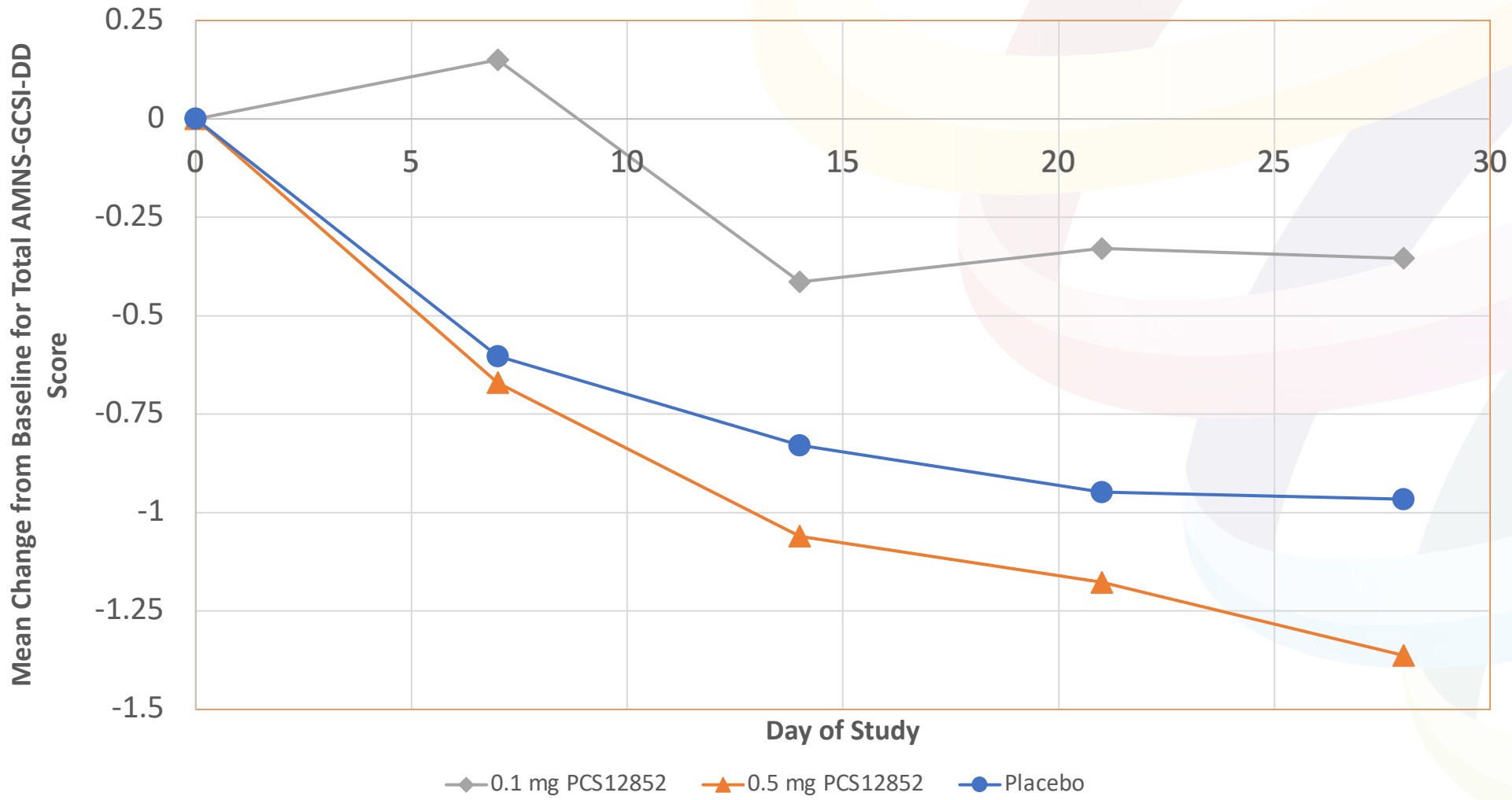
# Phase 2a Study: GEBT Results



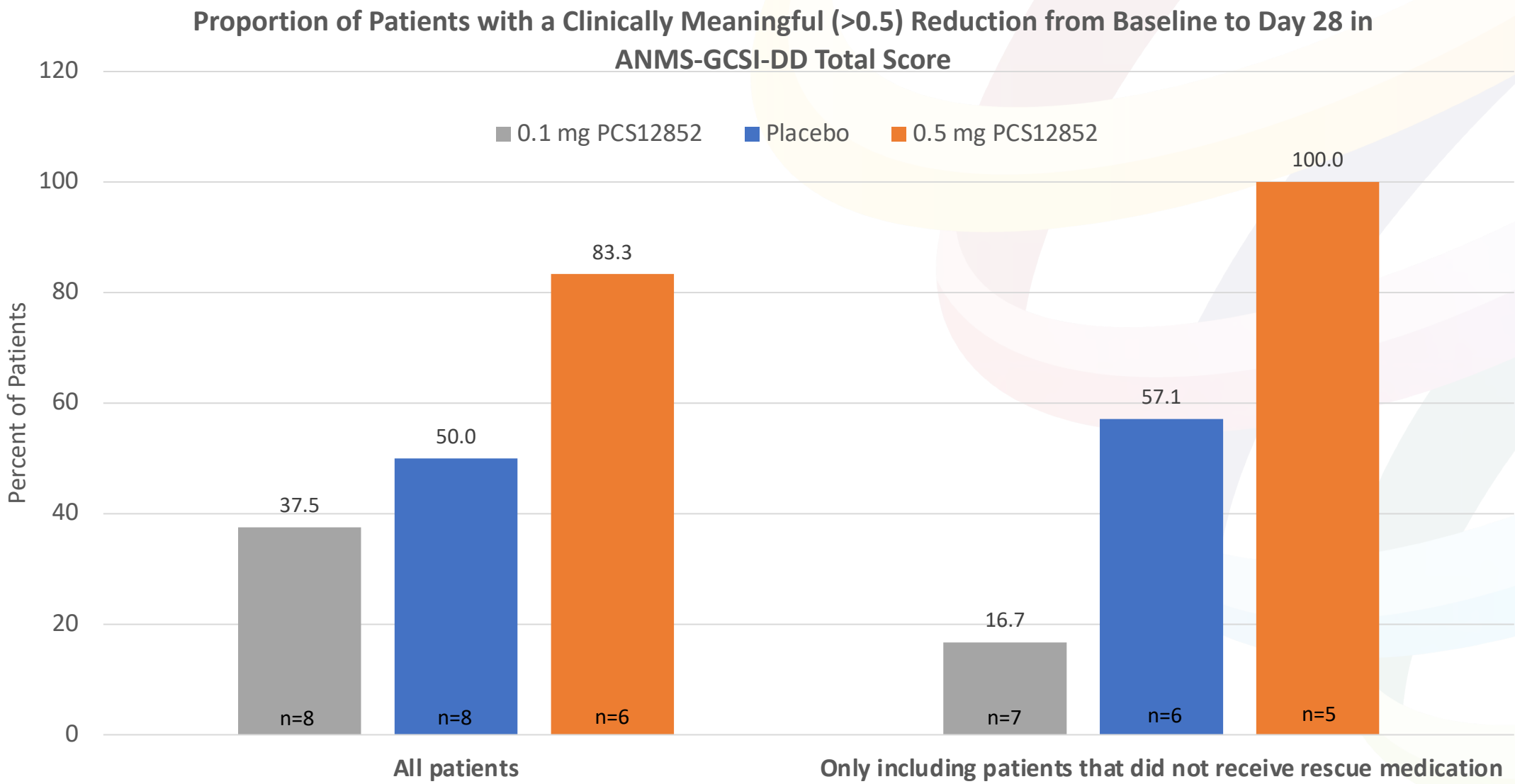
# Phase 2a Study: GEBT Results



# Phase 2a Study: Efficacy Results – Change from Baseline for Total GCSI Score at Day 28

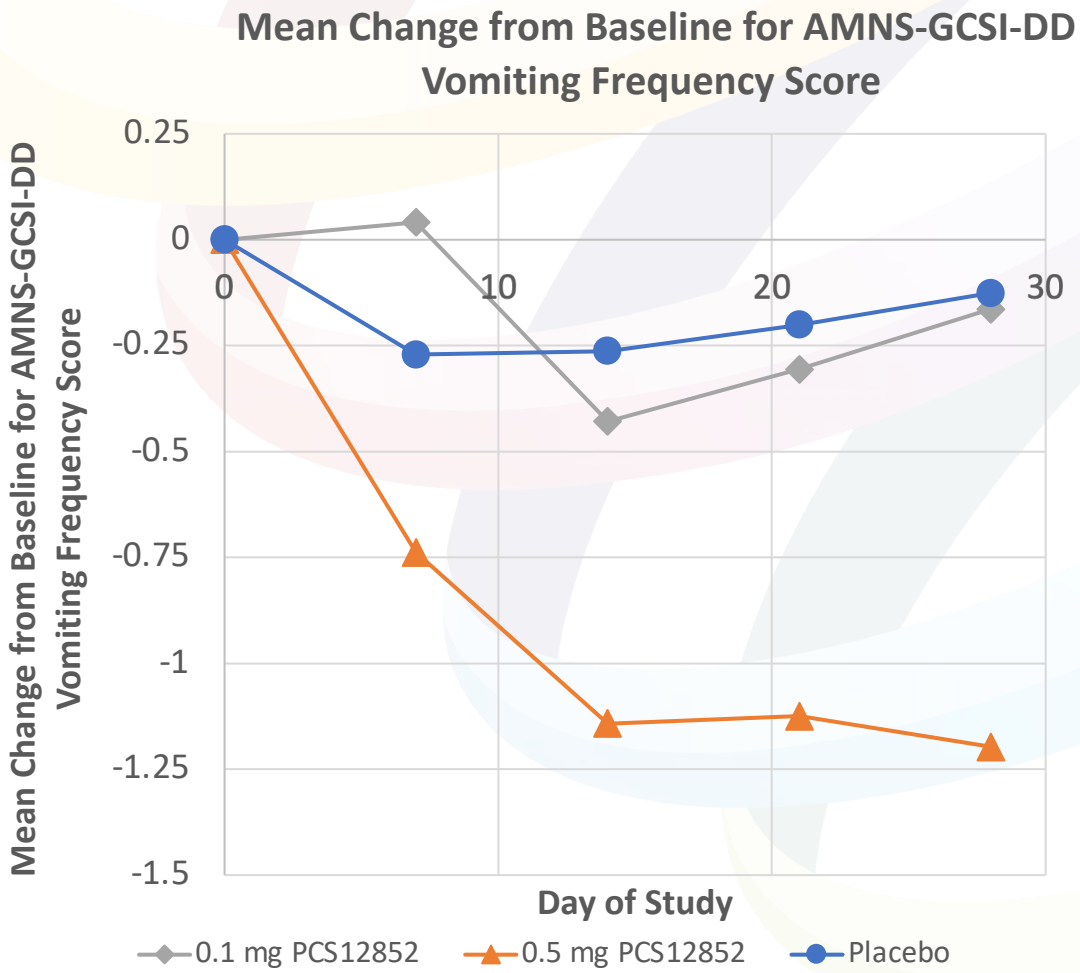


# Phase 2a Study: Efficacy Results- Responders Assessment



# Phase 2a Study: Efficacy Results – AMNS-GCSI-DD Subscores

- For the 0.5 mg PCS12852 group compared to placebo, greater improvements were noted in 4 of the 5 subscores – vomiting, nausea, abdominal pain and feeling excessively full.
- No differences were noted between the 0.1 mg PCS12852 and placebo groups.
- The changes were mostly noted in the DG patients and not the IG patients



# Phase 2a Study: Safety Results

- A total of 12 Treatment Emergent Adverse Events (TEAEs) occurred in 6 subjects, all in the 0.5 mg PCS12852 group
  - All TEAEs were either mild or moderate, with no severe cases, and resolved without sequelae
  - AEs were the following:
    - Diarrhea (5)
    - GERD (1)
    - Dizziness (1)
    - Increased WBC counts (1)
    - Abdominal Pain (1)
    - Nausea (1)
    - Headache (1)
    - Concussion (1)
  - 1 subject experienced mild nausea, dizziness, headache, upper abdominal pain, and GERD, as well as moderate diarrhea, and withdrew from the study
- There were no cardiac events reported during the study
- There were no serious adverse events reported during the study

# Phase 2A: Pharmacokinetic Results

| Mean (±SD) Pharmacokinetic Parameters | PCS12852 0.1 mg | | PCS12852 0.5 mg | |
|---|---|---|---|---|
| | Day 1 | Day 28 | Day 1 | Day 28 |
| Cmax (ng/ml) | 0.12±0.04 | 0.11±0.69 | 0.59±0.33 | 0.48±0.26 |
| Tmax (h) | 2.58±0.95 | 3.32±2.07 | 2.10±1.44 | 3.35±2.06 |
| AUC(0-last) (h*ng/mL) | 0.63±0.28 | 1.10±1.23 | 3.06±1.59 | 7.42±7.11 |
| t½ (h) | NC | 15.91±3.70 | NC | 27.97±15.76 |

NC = Not Calculated

# Phase 2a: Summary

- GEBT results demonstrated a significant improvement in gastric emptying in patients receiving 0.5 mg of PCS12852
- PCS12852 0.5 mg administered daily over 28 days in gastroparesis patients successfully improved gastroparesis symptoms in a clinically meaningful way as defined by > 0.5 reduction in the total ANMS GCSI-DD score compared to baseline
  - Patients in the 0.5 mg group showed a greater improvement than placebo in 4 out of the 5 ANMS-GCSI-DD subscores
  - The PCS12852 0.1 mg daily dose group showed little to no improvement in gastroparesis symptoms
- Greater improvement in the GEBT results and the symptomology results were observed in the DG group compared to the IG group
- Overall, PCS12852 was well tolerated, showed a very low risk of any off-target cardiovascular effects, and demonstrated a favorable safety profile
- These data suggest that a longer treatment than 28 days, as well as a higher dose of PCS12852, may result in even greater differences in the gastroparesis symptoms when compared to placebo

# QUESTIONS?