Functional dyspepsia and gastroparesis are interchangeable syndromes with common clinical and pathological features

Online Supplement

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Appendix 2. Inclusion and Exclusion Criteria for the Gastroparesis Registry (GpR) studies

Inclusion criteria

- Symptoms of gastroparesis of at least 12 weeks duration with varying degrees of nausea, vomiting, early satiety, postprandial fullness, and/or abdominal pain (do not need to be contiguous)
- An etiology of either diabetic, idiopathic, or post-Nissen fundoplication gastroparesis
- Gastric emptying scintigraphy of solids and liquids using the 4-hour Egg Beaters® protocol within the last 6 months with either:
    - Abnormal gastric emptying rate defined as an abnormal 2 hour (>60% retention) and/or 4 hour (>10% retention) result based on a 4-hour scintigraphic low fat Egg Beaters® gastric emptying study performed at a GpCRC clinical center. (This group will comprise ~80% of patients in the registry.)
    - Patients with a normal gastric emptying rate, but who have symptoms of gastroparesis. (This group will comprise ~20% of patients in the registry.)
- Age at least 18 years at initial screening visit
- Ability and willingness to participate in follow-up

Exclusion criteria:

- Inability to comply with or complete the gastric emptying test by scintigraphy (including allergy to eggs)
- Presence of other conditions that could explain the patient's symptoms:
    - Pyloric or intestinal obstruction: by EGD, UGI, or Abdominal CT
    - Active inflammatory bowel disease
    - Known eosinophilic gastroenteritis
    - Primary neurological conditions that can cause nausea and vomiting such as increased intracranial pressure, space occupying or inflammatory/infectious lesions
    - Advanced liver disease
    - Chronic renal failure (serum creatinine >3 mg/dL) and/or on hemodialysis or peritoneal dialysis
    - Acute liver failure
    - Advanced liver disease (Child's B or C; a Child-Pugh-Turcotte (CPT) score of ≥7)
    - Acute renal failure
- Total or subtotal (near complete) gastric resection, esophagogastrostomy, gastrojejunostomy, or gastric bypass. **Note:** patients with prior Nissen fundoplication will be eligible for enrollment.
- Any other condition, which in the opinion of the investigator, could explain the symptoms or interfere with study requirements
- Inability to obtain informed consent

Appendix 3. Additional Methods

Assessments

Medical History and Physical Examination

Demographic data as reported by the patient was collected at baseline. Patient self-reported medical histories were collected at each visit through face-to-face interviews. Family history, lifestyle (smoking, drinking alcohol), onset and nature of symptoms, comorbidities and medications (using itemized lists), emergency department visits and hospitalizations, treatments including surgeries, and source of nutrition were collected. Physical exams were conducted at each visit which included assessment of height (m), weight (kg), waist circumference (cm), blood pressure (mmHg) and overall assessment of major organ systems. Body Mass Index (BMI) was computed as weight divided by height squared (kg/m^2). Laboratory tests included assessment of glucose (mg/dL), A1C (%), and measures of inflammation (C-reactive protein (mg/dL), erythrocyte sedimentation rate (mg/dL)). Rome III Classification System for Functional GI Disorders which uses symptom-based diagnostic criteria was used to identify patients with Functional Dyspepsia (FD);[1] Rome IV was not available until after implementation of GpR2.

Gastric emptying scintigraphy test (GES)

All clinics used the same protocol to assess gastric emptying of solids by scintigraphy using a low-fat, egg white meal labeled with radioactive technetium with imaging at 0, 30 minutes, and 1, 2, 3 and 4 hours after meal ingestion (30 minutes and 3 hours optional). For at least 72 hours prior to scintigraphy, patients were instructed to not use opioids, prokinetics, anticholinergics, or cannabinoids. As per this consensus report, delayed gastric emptying was defined as greater than 60% retention at 2-hours and/or 10% at 4-hours.[2,3] Rapid emptying was defined as gastric retention less than 30% at 1-hour. GES was done at baseline and at the annual 48-week visit per protocol for the more recent registry patients in this study.

Symptom scoring

The severity of patients' gastroparesis symptoms were evaluated at every visit using the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) questionnaire to select a severity score from 0 (no symptoms) to 5 (very severe symptoms) for each symptom that "best" indicates the severity of the gastroparesis symptom over the preceding 2 weeks.[4-6] The PAGI-SYM also contains the Gastroparesis Cardinal Symptom Index (GCSI), a validated 9-item scale of symptom severity in patients that uses 3 symptom clusters (nausea/vomiting/retching, postprandial fullness/early satiety, and bloating/stomach distention). To determine each of these clusters or subscales, respectively, the mean of the nausea, retching, vomiting items, the mean of the stomach fullness, inability to finish a meal, excessive fullness post-meal, loss of appetite items, and the mean of the bloating, visible stomach distention items were computed. Additionally, there are 2 items on upper abdominal pain, 2 items on lower abdominal pain (not reported), and 7 items averaged to assess gastroesophageal reflux disease (GERD) symptoms (the heartburn/regurgitation cluster).

The clinical severity of gastroparesis was graded by the investigator as follows: grade 1, mild gastroparesis (symptoms relatively easily controlled and able to maintain weight and nutrition on a regular diet); grade 2, compensated gastroparesis (moderate symptoms with only partial control with use of daily medications, able to maintain nutrition with dietary adjustments); grade 3, gastric failure (refractory symptoms that are not controlled, with the patient having emergency department visits, frequent physician visits, or hospitalizations and/or inability to maintain nutrition via the oral route).[7]

Quality of life and psychological measurements

Psychological characteristics were evaluated at every visit. Quality of life was assessed using 2 questionnaires: 1) The PAGI-Quality of Life (PAGI-QOL), ranging from 0 to 5, a validated 30-item instrument to measure quality of life in the previous 2 weeks in patients with FD or gastroparesis,[8] and 2) the physical and mental components of the Medical Outcomes Study Short-Form V2 (SF-36v2), scored 0 to 100, which measures patients' general quality-of-life in the previous 4 weeks.[9] Higher scores indicate higher QOL. Depression in the previous 2 weeks was assessed using the Beck Depression Inventory (BDI) and current and general anxiety in the previous 2 weeks were evaluated using the State-Trait Anxiety Inventory (STAI).[10,11] Higher scores indicate more severe conditions with depression >20 indicating moderate/severe and anxiety ≥50 indicating severe.

Gastric Pathology

Specimens. Full thickness gastric body biopsies were obtained from 9 idiopathic gastroparesis patients, 9 FD patients with normal gastric emptying (non-diabetic) undergoing implantation of a gastric electrical stimulator and from 9 controls without diabetes or gastroparesis who are undergoing obesity surgery. There were eight females and 1 male in all three groups. All patients were ≥18 years of age and gastroparesis and FD patients had symptoms of at least 12-week duration, a standardized gastric emptying test and no evidence of obstruction. Exclusion criteria included presence of active inflammatory bowel disease, eosinophilic gastroenteritis, neurological conditions, acute liver or renal failure, and history of total or subtotal gastric resection. Tissue collection was done in standardized fashion with established protocols by the participating sites of the GpCRC and was shipped to the histology core at Mayo Clinic. Tissue was fixed in 4% PFA, blocked in OCT and frozen at -80°C until further use.

Light microscopy. Twelve μm sections were cut for H&E and immunofluorescence for enteric nervous system (ENS) markers. Protein gene product 9.5 (PGP9.5) was used as general marker for nerves, neuronal nitric oxide synthase (nNOS), vasoactive intestinal peptide (VIP) for the inhibitory component and substance P for the excitatory component of the ENS. Tyrosine hydroxylase (TH) was used to assess extrinsic innervation, Kit to assess ICC, CD45 to assess overall immune cells and CD206 to assess M2 (alternatively activated) macrophages.

Quantification. For quantitative assessment of PGP9.5 ir fibers (circular muscle), nNOS ir neurons (myenteric plexus) and fibers (circular muscle), VIP ir fibers (circular muscle), substance P ir fibers (circular muscle), TH ir (myenteric plexus), and CD45 and CD206 ir cell bodies (myenteric plexus and circular muscle), 2 nonadjacent sections were analyzed per patient. The antibodies (primary and secondary) used are detailed in Table 6. 20-23 images were randomly collected per patient at 40x magnification. These were then manually counted to

identify positive staining nerve fibers and cell bodies. Each field was 0.0367 mm2 in size. For quantitative assessment of ICC bodies (circular muscle), 2 to 3 nonadjacent sections were analyzed per patient. ICC cell bodies were counted from 38 to 40 fields per patient at 40x magnification. An ICC body was defined as a Kit-positive structure with a DAPI-positive nucleus within the structure. Mast cells were excluded by their larger, more circular appearance and brighter fluorescence. The number of images needed for all markers was determined from previous data from quantification from gastric body[12].

Average counts per subgroup adjusted for multiple measures per subject (Bonferroni corrected) from each patient were used for comparative analysis between the three groups in Figure 1 and Table 6.

Statistical Methods

Baseline characteristics including demographics, lifestyle, gastroparesis symptom severity, clinical factors, depression, anxiety and QOL were compared between FD and gastroparesis patients using either 2-sample t-tests or ANOVA for continuous and Pearson's chi-square test for categorical characteristics. FD and gastroparesis patients were compared for differences for 12 patient outcomes. The mean change of 48-week outcome for each patient subgroup (FD and gastroparesis (Gp)) was computed by subtracting the baseline value from the value at 48-weeks for the GCSI total score, an indicator for GCSI of 1+ points from baseline (as a percent), BMI (kg/m^2), weight (kg), total hospitalizations excluding enterra placement or removal, total parental nutrition (TPN) use (as a percent), BDI score, State anxiety score, Trait anxiety score, PAGI-QOL total score, SF-36v2 physical score, and SF-36v2 mental score for those patients with 48-week visit data. Since ED visits were not reported at baseline, the total number of ED visits from baseline to 48 weeks was tallied and compared using a zero-inflated negative binomial regression with robust variance. *P* values for continuous outcomes determined using multiple regression of each outcome in relation to the subgroup indicator (FD vs Gastroparesis) with adjustment for the baseline value of the characteristic. *P* for 1+ point improvement in GCSI was determined from a generalized linear model (GLM) with binomial distribution. *P* for the total hospitalizations in past year determined from a zero-inflated negative binomial regression of total hospitalizations in relation to subgroup with adjustment for the total hospitalizations in the year prior to baseline. *P* value for TPN as a percent, derived from a Wald test to assess whether change in TPN use varied by delayed retention adjusting for the baseline TPN use using ANCOVA with robust variance. The mean net change between subgroups defined as subtracting the mean change in outcome for gastroparesis from the mean change for FD. 95% confidence intervals (C.I.) for the net mean change between gastric retention groups computed from a t-test. For GCSI 1+ improvement, the difference, 95% C.I. and *P* determined using the 2-group proportion test. GES diagnosis (gastroparesis or FD) at baseline was compared to the patient's diagnosis at 48-weeks to determine whether a patient's diagnosis (DX) stayed the same or converted. A Fisher's exact test was used to test whether the diagnosis changes from baseline to 48-weeks were random. PAGI-SYM symptom changes were analyzed between converter status within 2 subgroups (FD or Gastroparesis (Gp) at baseline) using an ANCOVA regressing the change in symptom score on the subgroup indicator (change in DX at 48 weeks, or no change), adjusting for the baseline value of the symptom. For eight histological biomarkers assessed from the baseline visit, mean counts per subgroup (Control, FD, Gp) and 95% confidence-intervals were adjusted for multiple measures per patient. Each histologic biomarker

was analyzed using a mixed multiple linear regression model regressing each patient's biomarker counts on the 3-category subgroup, accounting for the repeated measures per patient. Pairwise-*P* values are determined with pairwise comparisons of the marginal linear predictions of the subgroups adjusted for Bonferroni multiple comparisons per biomarker. Dot plots for each subgroup of 3 histological biomarkers (ICC (circular muscle), CD206 (myenteric plexus), PGP9.5 (circular muscle) were displayed. Dots represented each patient's mean count of the cells or neuron fibers, and horizontal lines were used to display the adjusted mean count for each subgroup.

All *P* values were 2-sided and nominal. 95% confidence intervals or standard deviation were provided in all tables except for the binary measures in Tables 1 and 3, so that the amount of variation per measure could be considered in result interpretation. Complete case-analysis was used in all tables. Table 1 had some variables with patients' missing data, though the percent of missingness was small (< 5% for several characteristics). All analyses were performed using Stata/MP for Windows release 16.0 (StataCorp, College Station, TX) or SAS software 9.4 (SAS Institute Inc., Cary, NC).

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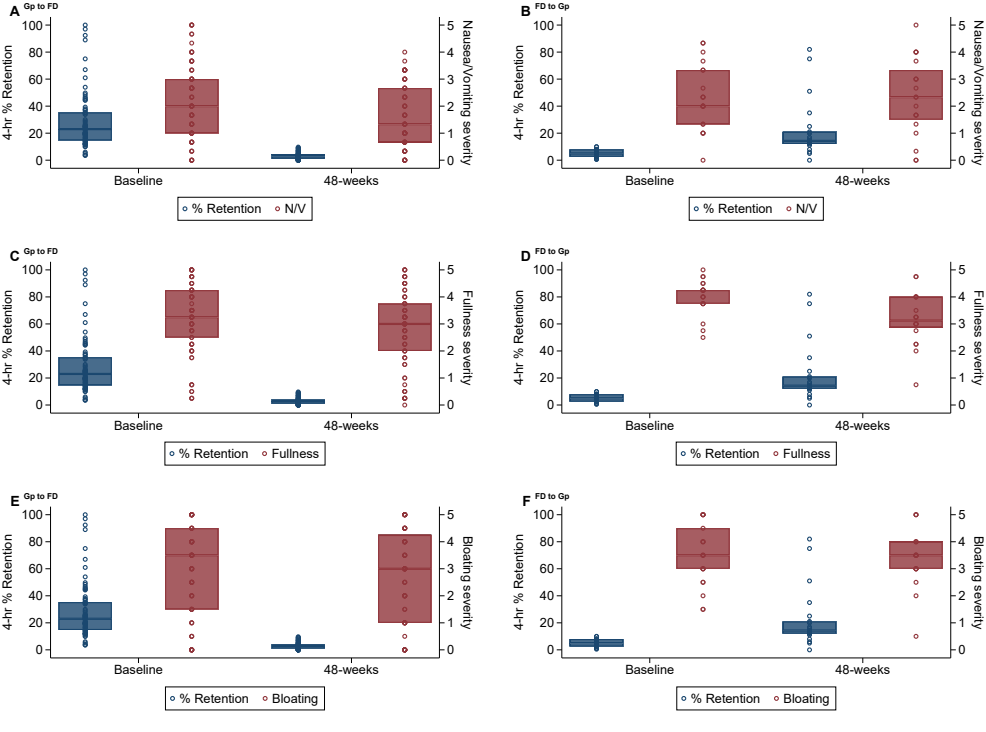
Appendix 4. Additional Figures and Tables

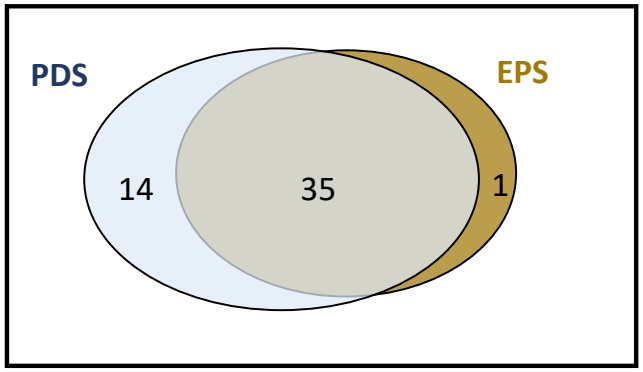
Supplemental Figure legends

Supplemental Figure 1: Boxplots of symptom subscales (in blue font; 0 to 5 where 5 is very severe symptoms) and percent gastric retention at baseline and 48-weeks (red font; 0 to 100% where a greater than 10% indicates delayed retention) for patients with paired baseline and follow-up gastric emptying tests (N=249). Displayed are plots for patients with gastroparesis at baseline and normal emptying at 48-weeks (n=79) (Gp converters: Gp to FD) or with normal emptying results and functional dyspepsia (FD) at baseline and delayed emptying at 48-weeks (n=22) (FD converters: FD to Gp). Each dot represents an individual patient's values (larger dots show multiple patients with the same values). (A): Nausea/vomiting subscales for Gp converters, (B): Nausea/vomiting subscales for FD converters, (C): Fullness severity subscales for Gp converters, (D): Fullness severity subscales for FD converters, (D): Bloating severity subscales for Gp converters, (E): Bloating severity subscales for FD converters. For all symptoms presented, severity is similar at baseline and 48-weeks, while % gastric retention changes from the initial diagnosis.


A
Gp to FD
4-hr % Retention
Nausea/Vomiting severity
Baseline
48-weeks
% Retention
N/V
B
FD to Gp
4-hr % Retention
Nausea/Vomiting severity
Baseline
48-weeks
% Retention
N/V
C
Gp to FD
4-hr % Retention
Fullness severity
Baseline
48-weeks
% Retention
Fullness
D
FD to Gp
4-hr % Retention
Fullness severity
Baseline
48-weeks
% Retention
Fullness
E
Gp to FD
4-hr % Retention
Bloating severity
Baseline
48-weeks
% Retention
Bloating
F
FD to Gp
4-hr % Retention
Bloating severity
Baseline
48-weeks
% Retention
Bloating

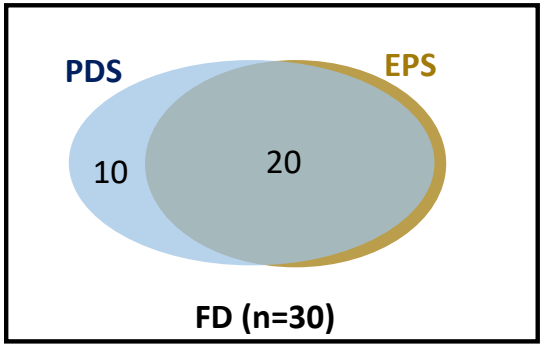
Supplemental Figure 2: Venn diagrams of Rome III classification of patients at baseline and 48-weeks. 168 patients with gastroparesis and 50 with FD at baseline with follow-up gastric emptying and Rome III questionnaire data were classified according to Rome III criteria for Post-Prandial Distress Syndrome (PDS) or Epigastric Pain or Burning (EPS) as subclassifications of Functional Dyspepsia (FD) at the two time points. For patients with gastroparesis, 21 were not classified as either category of FD by Rome III and are shown as "other" (these include "functional nausea", "chronic idiopathic nausea", "cyclic vomiting syndrome" "irritable bowel syndrome").

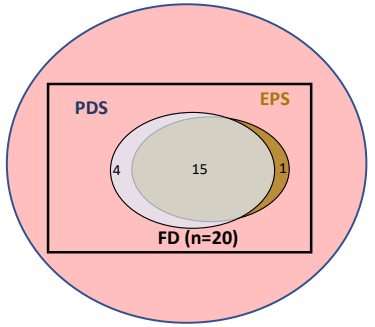
Functional Dyspepsia (FD) Group at Baseline



FD (n=50)

Functional Dyspepsia (FD) Group at 48 weeks

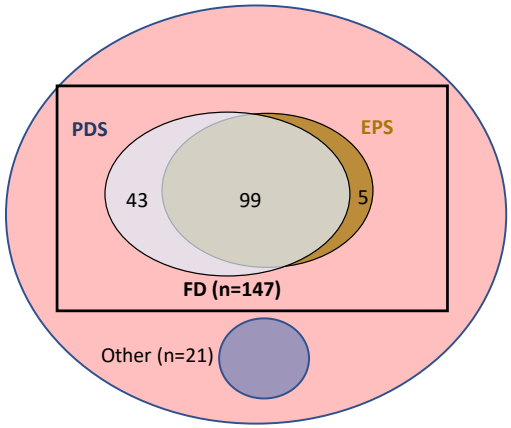




Normal Emptying (n=30)

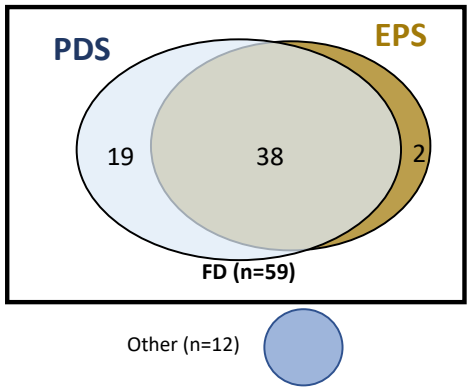
Delayed Emptying (n=20)

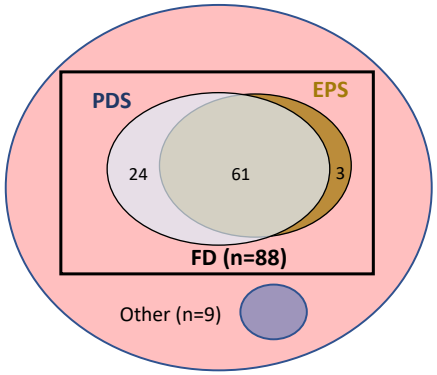
Gastroparesis Group (Gp) at Baseline



Gp (n=168)

Gastroparesis Group at 48 weeks





Normal Emptying (n=71)

Delayed Emptying (n=97)

NOTE: Other category includes: FN, CIN, CVS, IBS, Bloating, Constipation and IBS

Supplemental Table 1: Baseline Rome III classification for patients with FD or gastroparesis

	Patients with symptoms†				
	FD (N=224)		Gastroparesis (N=720)		
Rome III categories*	**No.**	**Percent**	**No.**	**Percent**	***P* value‡**
Functional dyspepsia†, *if no structural disease explains it*:					**<.001**
Yes, pending exam/test	224	100.0%	615	85.4%	
No	0	0%	105	14.6%	
Functional dyspepsia, *Postprandial Distress Syndrome (PDS), if no structural disease explains it*:					**<.001**
Yes	213	95.1%	577	80.1%	
No	11	4.9%	143	19.9%	
Functional dyspepsia, *Epigastric pain or burning (EPS), if no gallbladder & sphincter of Oddi Disorders seen:*					**<.001**
Yes	153	68.3%	436	60.6%	
No	71	31.7%	284	39.4%	
Functional vomiting *(for 6+ months), if no eating disorder/ rumination/major DSM-IV classification:*					.57
Yes, pending exam/test	67	29.9%	232	32.2%	
No	157	70.1%	488	67.8%	
Nausea/Vomiting Disorders for 6+ months, *Chronic Idiopathic Nausea (CIN):*					**<.001**
Yes	113	43.3%	224	31.1%	
No	148	56.7%	496	68.9%	
Nausea/Vomiting Disorders: *Cyclic Vomiting Syndrome (CVS)*					.17
Yes	103	46.0%	370	51.4%	
No	121	54.0%	350	48.6%	
Irritable bowel syndrome (IBS) *(for 6+ months):*					.20
Yes	154	68.8%	461	64.0%	
No	70	31.2%	259	36.0%	
Rumination Syndrome *(for 6+ months):*					.42
Yes	6	2.7%	13	1.8%	
No	218	97.3%	707	98.2%	

* Rome III diagnoses determined from the Rome III Diagnostic Questionnaire analyzed using an analysis program developed by the Rome Foundation (http://www.romecriteria.org/rome_iii_sas/ , accessed 03 February 2010).

† Patients enrolled in either the GpR or GpR2 with idiopathic or diabetic etiology, without rapid emptying met these study inclusion criteria (N=981). If a patient was enrolled in both Registry studies, the GpR2 data was used. Of the 261 total patients with normal emptying, 224 (85.8%) were classified as functional dyspepsia (FD) [85.8% FD vs 85.4% Gp, *P*=.92]. The 37 (14.2%) patients with normal emptying classified as not FD were excluded from the analysis population (N=944).

‡ P (2-sided) determined from Fisher's exact test. Bolded font denotes a *P* <.05.

Supplemental Table 2: Comparison of baseline characteristics of patients meeting the Rome III classification for FD at baseline by gastric emptying test status

Baseline characteristic	Gastric Emptying Test Status* Normal Emptying FD Mean (SD) or No. (Percent) (N=224)	Gastric Emptying Test Status* Gastroparesis FD Mean (SD) or No. (Percent) (N=615)	*P†*
Demographics/lifestyle:			
Sex: female	199 (89%)	530 (86%)	.31
Race: White	200 (89%)	547 (89%)	.89
Ethnicity: Hispanic	22 (10%)	65 (11%)	.75
Age at baseline (≥ 50 years)	64 (29%)	173 (28%)	.90
Age at baseline (years)	42.8 (13.9)	43.1 (13.4)	.76
Smoked (ever regularly)	71 (32%)	198 (32%)	.89
Education: College degree or higher	79 (35%)	203 (33%)	.54
Income (≥ $50,000)	119 (53%)	303 (49%)	.30
Symptom severity (Global and PAGI-SYM‡):			
Global symptom severity (Investigator-rated):			**.03**
Mild	37 (17%)	86 (14%)	
Moderate	150 (67%)	372 (61%)	
Gastric failure	37 (17%)	154 (25%)	
Predominant symptom on presentation:‡			.25
Nausea	88 (39%)	196 (32%)	
Abdominal pain	40 (18%)	124 (20%)	
Vomiting	41 (18%)	123 (20%)	
All other symptoms	55 (25%)	172 (28%)	
GCSI total score	3.0 (0.9)	3.1 (0.9)	.15
Nausea/vomiting subscale	2.2 (1.3)	2.5 (1.4)	**.02**
Post-prandial fullness subscale	3.6 (1.0)	3.6 (1.0)	.47
Bloating subscale	3.2 (1.6)	3.3 (1.5)	.37
Abdominal pain moderate/severe‡	148 (67%)	433 (71%)	.27
Upper abdominal pain subscale	3.0 (1.4)	3.2 (1.4)	.07
Upper abdominal pain severity score	2.9 (1.5)	3.2 (1.6)	.08
Upper abdominal discomfort score	3.1 (1.4)	3.3 (1.4)	.08
GERD subscale	1.9 (1.3)	2.1 (1.4)	**.02**
Gastric Emptying Scintigraphy (GES):			
4-hr % Retention category:			*n/a*
Normal/Mild (<20%)	217 (100%)	236 (38%)	
Moderate (20-35%)	0 (0%)	172 (28%)	
Severe (>35%)	0 (0%)	206 (34%)	
% Retention at 2-hours	33.0 (14.6)	64.5 (18.0)	*n/a*
% Retention at 4-hours	4.3 (3.0)	31.8 (21.2)	*n/a*
Delayed emptying at 2-hours	0 (0%)	382 (62.1)	*n/a*
Delayed emptying at 4-hours‡	0 (0%)	579 (94%)	*n/a*
Clinical factors:			
Etiology:			**.03**
Idiopathic	170 (76%)	413 (67%)	
Diabetes Type 1	22 (10%)	99 (16%)	
Diabetes Type 2	32 (14%)	103 (17%)	
Body Mass Index category:			
Overweight or obese (BMI >25)	117 (52%)	346 (56%)	.30
Body Mass Index (BMI)(kg/m^2) average	27.9 (8.7)	27.4 (7.5)	.35
Acute onset of symptoms	92 (41%)	273 (44%)	.39

Initial infectious prodrome	45 (20%)	111 (18%)	.50
Duration of gastroparesis symptoms at enrollment (years)	6.1 (7.4)	5.8 (7.1)	.61
Inflammation‡	86 (38%)	286 (47%)	**.04**
CRP (mg/dL)	1.0 (1.8)	2.0 (6.5)	**.02**
ESR (mm/hr)	15.8 (15.6)	19.7 (19.7)	**.007**
HbA1c (%)	6.0 (1.4)	6.3 (1.8)	**.049**
Treatment (current use at baseline):			
Narcotics use	78 (35%)	248 (40%)	.15
Proton pump inhibitors	150 (67%)	468 (76%)	**.008**
Prokinetics	66 (29%)	277 (45%)	**<.001**
Antiemetics	138 (62%)	393 (64%)	.57
Antidepressants	116 (52%)	307 (50%)	.63
Anxiolytics	45 (20%)	152 (25%)	.16
Pain modulators	55 (25%)	154 (25%)	.89
On total parental nutrition (TPN)	7 (3%)	46 (7%)	**.02**
Gastric electric stimulation device implantation	17 (8%)	41 (7%)	.64
Psychological & QOL			
Beck Depression Index (BDI) score	18.3 (11.5)	19.3 (11.3)	.29
Moderate to severe depression (BDI>20)‡	91 (41%)	267 (43%)	.47
State-Trait Anxiety Inventory (STAI):	43.4 (13.4)	44.8 (13.8)	.18
State Anxiety score	73 (33%)	221 (36%)	.37
Severe state anxiety (≥ 50)‡	43.0 (12.9)	44.3 (12.6)	.18
Trait Anxiety score	69 (31%)	211 (34%)	.34
Severe trait anxiety (≥ 50)‡	18.3 (11.5)	19.3 (11.3)	.29
Quality of Life total score	2.6 (1.1)	2.5 (1.1)	.20
PAGI-QOL‡ ≥ 3	80 (36%)	201 (33%)	.35
Overall Health Survey‡ (SF-36 v2)			
Physical health component sub-score	33.8 (11.0)	32.2 (10.2)	.05
Mental health component sub-score	40.3 (12.2)	38.5 (13.1)	.07

* No. (percent) or mean (standard deviation) for each characteristic determined from the patients with non-missing data for that characteristic.

Only patients with FD were included in the analysis reported in this table (i.e., 105 patients with delayed gastric emptying at baseline were excluded).

† P value (2-sided) derived from either a t-test or ANOVA for continuous characteristics, or Pearson's chi-square test for categorical predictors. Bolded font denotes a $P < 0.05$. *n/a* denotes not applicable.

‡ PAGI-SYM scores report patient-rated severity of symptoms from 0 (none) to 5 (severe) in the past 2-weeks.

Predominant symptom at presentation (baseline visit) is the main reason for evaluation that the patient reported; it was categorized to report the 3 most frequent issues; the other category includes bloating, early satiety, post-prandial fullness, diarrhea, constipation, anorexia, GERD symptoms, poorly managed diabetes or glycemic control and a weight change (loss or gain).

The 36 patients without delayed emptying at 4-hours (due to missing % retention data) were delayed emptying at 2-hours.

Abdominal pain moderate/severe defined as either upper abdominal pain or discomfort PAGI-SYM symptom score ≥ 3.

Inflammation defined as either CRP > 1.0 mg/dL or ESR > 20 mm/hr.

Beck Depression Inventory (BDI) > 20 indicates moderate or more severe depression

STAI scores ≥ 50 indicate severe state or trait anxiety

PAGI-QOL score increases with increased quality of life due to gastroparesis symptoms in past 2 weeks

SF-36v2 score increases with increased general quality of life in the past 4 weeks

Supplemental Table 3: Baseline characteristics by Functional Dyspepsia (FD) and gastroparesis for the 18 patients with a biopsy used in the biomarker analysis

Baseline characteristic	Gastric Emptying Test Status* Gastroparesis Mean (SD) or No. (Percent) (N=9)	FD (Normal emptying) Mean (SD) or No. (Percent) (N=9)	P†
Demographics/lifestyle:			
Sex: female	8 (89%)	8 (89%)	1.00
Race: White	9 (100%)	9 (100%)	--
Ethnicity: Hispanic	0 (0%)	0 (0%)	--
Age at baseline (≥ 50 yrs)	1 (11%)	0 (0%)	1.00
Age at baseline (yrs)	38.3 [30.1, 41.6]	38.0 [26.2, 42.6]	.56
Smoked (ever regularly)	6 (67%)	4 (44%)	.46
Symptom severity (Global and PAGI-SYM‡):			
Global symptom severity (Investigator-rated):			.15
Mild	0 (0%)	1 (11%)	
Moderate	3 (33%)	6 (67%)	
Gastric failure	6 (67%)	2 (22%)	
Predominant symptom on presentation:‡			1.00
Nausea	5 (56%)	6 (67%)	
Abdominal pain	3 (33%)	2 (22%)	
Vomiting	0 (0%)	1 (11%)	
Constipation	1 (11%)	0 (0%)	
GCSI total score	3.6 (0.8)	3.7 (0.6)	.84
Nausea/vomiting subscale	3.0 (2.0, 4.3)	3.0 (2.3, 4.3)	1.00
Post-prandial fullness subscale	3.8 (3.3, 4.3)	4.0 (3.3, 4.5)	.79
Bloating subscale	4.0 (4.0, 5.0)	4.0 (3.5, 5.0)	.96
Upper abdominal pain subscale	4.0 (4.0, 5.0)	4.0 (3.0, 4.5)	.16
Upper abdominal pain severity score	4.0 (4.0, 5.0)	4.0 (3.0, 4.0)	.14
Upper abdominal discomfort score	4.0 (4.0, 5.0)	4.0 (3.0, 4.0)	.20
GERD subscale	3.3 (1.9, 4.4)	2.4 (2.1, 2.9)	.79
Gastric Emptying Scintigraphy (GES):			
4-hr % Retention category:			*n/a*
Normal/Mild (<20%)	3 (33%)	9 (100%)	
Moderate (20-35%)	2 (22%)	0 (0%)	
Severe (>35%)	4 (44%)	0 (0%)	
% Retention at 1-hours	78.5 (66.0, 88.0)	57.0 (54.0, 61.0)	*n/a*
% Retention at 2-hours	58.0 (50.0, 80.1)	27.0 (26.0, 30.0)	*n/a*
% Retention at 4-hours	24.0 (20.0, 60.0)	2.0 (1.0, 4.0)	*n/a*
Delayed emptying at 2-hours	3 (33%)	0 (0%)	*n/a*
Rapid emptying: <30% at 1-hour	0 (0%)	1 (11%)	*n/a*
Clinical factors:			
Etiology:			--
Idiopathic	9 (100%)	9 (100%)	
Diabetes Type 1 or Type 2	0 (0%)	0 (0%)	
Body Mass Index category:			.26
Underweight	0 (0%)	1 (11%)	
Normal	6 (67%)	2 (22%)	
Overweight	2 (22%)	3 (33%)	
Obese	1 (11%)	3 (33%)	
Body Mass Index (BMI)(kg/m^2)	23.6 (20.4, 25.4)	28.3 (22.2, 32.5)	.20
Acute onset of symptoms	3 (33%)	2 (22%)	1.00
Initial infectious prodrome	4 (44%)	0 (0%)	.08

Duration of gastroparesis symptoms from onset to enrollment (years)	7.6 (5.8)	6.7 (5.7)	.76
Inflammation‡	3 (33%)	4 (44%)	1.00
CRP (mg/dL)	0.3 (0.2, 1.1)	0.5 (0.3, 0.9)	.42
ESR (mm/hr)	6.0 (5.0, 10.0)	10.0 (2.0, 22.0)	.76
HbA1c (%)	5.2 (5.1, 5.8)	5.3 (5.1, 5.5)	.96
Serum glucose (mg/dL)	90.0 (90.0, 95.0)	98.0 (90.0, 101.0)	.14
Treatment (current use at baseline):			
Narcotics use	8 (89%)	4 (44%)	.13
Proton pump inhibitors	8 (89%)	7 (78%)	1.00
Prokinetics	6 (67%)	5 (56%)	1.00
Antiemetics	8 (89%)	7 (78%)	1.00
Antidepressants	4 (44%)	5 (56%)	1.00
Anxiolytics	3 (33%)	1 (11%)	.58
Pain modulators	3 (33%)	2 (22%)	1.00
On total parental nutrition (TPN)	1 (11%)	0 (0%)	1.00
Gastric electric stimulation device implantation	1 (11%)	3 (33%)	.58
Psychological & QOL			
Beck Depression Index (BDI) score	25.3 (10.8)	24.3 (14.2)	.87
Moderate to severe depression (BDI>20)‡	6 (67%)	5 (56%)	1.00
State-Trait Anxiety Inventory (STAI):			
State Anxiety score	44.0 (37.0, 61.0)	43.0 (39.0, 53.0)	.60
Severe state anxiety (≥ 50)‡	4 (44%)	3 (33%)	1.00
Trait Anxiety score	49.0 (33.0, 61.0)	44.0 (42.0, 51.0)	.89
Severe trait anxiety (≥ 50)‡	4 (44%)	3 (33%)	1.00
Quality of Life total score	1.9 (1.1, 2.4)	2.1 (1.0, 2.2)	.96
PAGI-QOL‡ ≥ 3	1 (11%)	0 (0%)	.87
Overall Health Survey‡ (SF-36 v2)			
Physical health component sub-score	24.9 (19.9, 29.5)	33.3 (25.7, 43.4)	**.04**
Mental health component sub-score	41.2 (25.8, 46.0)	36.6 (24.9, 44.0)	.63
Abdominal surgical procedures: any	9 (100%)	8 (89%)	
Cholecystectomy	5 (56%)	4 (44%)	
Gastric surgery: total or subtotal resection, gastric bypass, or stapling	1 (11%)	1 (11%)	
Endoscopy	3 (60%)	4 (80%)	
C-section	1 (20%)	1 (17%)	
Heliamyotomy	0 (0%)	1 (17%)	
Hernia repair	1 (20%)	0 (0%)	
J-tube	0 (0%)	1 (17%)	
Laparoscopic for endometriosis	0 (0%)	1 (17%)	
Liver transplant	1 (20%)	0 (0%)	
Partial hysterectomy	1 (20%)	0 (0%)	
Permanent pacemaker placement	1 (20%)	0 (0%)	
Placement of gastric stimulator	0 (0%)	2 (34%)	
Nissen fundoplication for GERD	1 (11%)	1 (11%)	

* No. (percent) or median [Q1,Q3} for each characteristic determined from the patients with non-missing data for that characteristic.

† P value (2-sided) derived from either a Kruskal-Wallis test for continuous characteristics, or Pearson's chi-square test for categorical predictors. Bolded font denotes a $P < 0.05$. *n/a* denotes not applicable.

Supplemental Table 4: Independent baseline characteristics of patients without and with a gastric emptying test at 48-weeks

Baseline characteristics*	Odds Ratio (No 48-week vs Has 48-wk)	95% C.I.	*P*†
FD (Not delayed) vs Gp	1.07	0.74-1.54	.73
Demographic/lifestyle			
Sex: female	0.60	0.36-0.99	.05
Age at baseline (yrs)	0.99	0.98-1.00	.13
Race: White	0.49	0.26-0.91	**.02**
Ethnicity: Hispanic	0.31	0.20-0.49	**<.001**
Education: College degree or higher (vs < college)	0.95	0.68-1.32	.74
Smoked (ever regularly) vs not smoker	1.44	1.00-2.07	.05
Clinical factors:			
Etiology			.12
Idiopathic (*reference*)	1.00	-	
Diabetes Type 1	1.64	0.97-2.76	.06
Diabetes Type 2	1.38	0.85-2.25	.19
BMI (kg/m^2)	0.98	0.96-1.01	.15
Any hospitalization (vs none)	1.32	0.91-1.916	.14
Duration of symptoms from onset to enrollment	1.01	0.98-1.03	.63
Symptom severity:			
Investigator-rated gastroparesis symptom severity			.11
Mild (*reference*)	1.00	-	
Moderate	0.78	0.50-1.23	.28
Gastric failure	1.23	0.68-2.24	.50
GCSI total score	0.75	0.51-1.10	.14
Nausea/vomiting subscale	1.13	0.94-1.34	.20
Post-prandial fullness/early satiety subscale	1.03	0.80-1.33	.81
Upper abdominal pain subscale	1.04	0.91-1.19	.54
GERD subscale	1.02	0.89-1.17	.78
Quality of Life			
Overall Health Survey (SF-36 v2)			
Physical health component	1.01	1.00-1.04	.15
Mental health component	1.00	0.98-1.02	.84
PAGI-QOL total score	0.80	0.63-1.01	.06

* The total number of patients at enrollment with the reported characteristics without missing data is 923, with a total of 242 (26%) patients with a 48-week GET (2 GpR1 and 5 GpR2 patients were missing data on one or more of the above characteristics and were not included in the regression.)

GpR1 patients were not required to have a follow-up gastric emptying test (GET); however, GpR2 patients were to have a 48-week GET by protocol.

At enrollment, there are 501 GpR1 patients in this analysis with 32 (6%) patients with a 48-week GET. There are 422 GpR2 patients in this analysis with 210 (50%) patients with a 48-week GET.

† Odds ratios, 95% confidence intervals (C.I.) and *P* determined from a logistic regression of Not having a 48-week GET compared to having a 48-week GET in relation to the 20 baseline characteristics reported above. One characteristic is expected to be significant at an alpha < 0.05 level. Bolded font denotes a $P < .05$.

Supplemental Table 5:
Glucose Levels prior to the patient's gastric emptying test at baseline and 48-week followup

	Gastric Emptying Test Status	
	FD	**Gastroparesis**
	Mean (SD) or No. (Percent)	**Mean (SD) or No. (Percent)**
At Baseline:		
Number of patients with GET, N (%)	108	329
For patients with diabetes: N (%)	29 (27%)	121 (37%)
Glucose ≥ 270 mg/dL, N (%)	0 (0%)	3 (2%)
At 48-weeks:		
Number of patients with GET, N (%)	50	166
For patients with diabetes: N (%)	15 (30%)	52 (31%)
Glucose ≥ 270 mg/dL, N (%)	0%	0%

Supplemental Table 6: Histologic biomarkers by control, functional dyspepsia (FD) and gastroparesis patients with a full thickness biopsy of stomach tissue

Histologic Biomarkers* **(Counts per hpf field)**	**Controls**	**Functional Dyspepsia (FD)†**	**Gastroparesis (Gp)†**	***P*‡ FD vs Controls**	***P*‡ Gp vs Controls**	***P* overall§**
Interstitial Cells of Cajal (ICC) (circular muscle)	6.20 (4.63, 7.77)	3.45 (1.79, 5.12)	2.03 (0.47, 3.61)	**.01**	**< .001**	**<.0001**
Protein Gene Product 9.5 (circular muscle)	43.5 (34.6, 52.4)	46.7 (37.2, 56.1)	50.7 (41.8, 59.6)	1.00	.51	.39
CD45+ immune cells (myenteric plexus)	19.7 (14.8, 24.6)	18.4 (13.8, 23.0)	20.7 (15.5, 25.9)	1.00	1.00	.71
CD45+ immune cells (circular muscle)	13.9 (11.3, 16.5)	14.7 (11.9, 17.4)	13.5 (10.9, 16.2)	1.00	1.00	.77
CD206+ cells (myenteric plexus)	6.37 (5.18, 7.55)	3.93 (2.67, 5.19)	4.24 (3.05, 5.43)	**.002**	**.007**	**.0009**
CD206+ cells (circular muscle)	3.60 (2.62, 4.58)	3.32 (2.28, 4.36)	2.98 (1.20, 3.96)	1.00	.85	.56
Neuronal Nitric oxide synthase neurons (myenteric plexus)	0.91 (0.39, 1.43)	0.30 (-0.22, 0.83)	0.97 (0.43, 1.50)	.14	1.00	.06
Neuronal Nitric oxide synthase	19.8 (14.1, 25.5)	19.0 (12.9, 25.0)	19.9 (14.2, 25.5)	1.00	1.00	.96

fibers (circular muscle)						
Substance P (circular muscle)	19.5 (13.6, 25.5)	24.4 (18.4, 30.4)	20.7 (13.6, 27.9)	.50	1.00	.36
Tyrosine Hydroxylase (myenteric plexus)	54.9 (41.3, 68.4)	49.0 (35.4, 62.7)	53.7 (40.2, 67.3)	1.00	1.00	.74
Vasoactive Intestinal Peptide (Circular muscle)	17.1 (12.0, 22.1)	16.3 (11.5, 21.1)	13.6 (8.17, 19.0)	1.00	.78	.50

* Eight histologic biomarkers were analyzed by 3 subgroups, each with 9 subjects per group: Controls, functional dyspepsia (FD with normal gastric emptying), and Gastroparesis (Gp). The biomarkers were determined using stained stomach tissue slides, with multiple counts per circular field under high-powered focus (hpf) per subject. The number of counts per subject varied by the histologic biomarker and between subjects.

Mean counts per subgroup adjusted for multiple measures per subject (Bonferroni corrected) and 95% confidence intervals per subgroup are reported in the table.

† The median % retention at 4-hours (Q1,Q3) for the FD patients is 2.0% (1.0, 4.0) and for the Gp patients is 24.0% (20.0, 60.0).

‡ Pairwise *P* values are determined with pairwise comparisons of the marginal linear predictions of the subgroups. Bold font denotes a $P < .05$.

§ Overall *P* is determined from a mixed multiple linear regression model regressing each subject's biomarker counts on the 3-category subgroup, accounting for the repeated measures per subject. Bold font denotes a $P < .05$.