# Aprepitant has Mixed Effects on Nausea and Reduces Other Symptoms in Patients With Gastroparesis and Related Disorders

## Online Supplement

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**Members of the NIDDK Gastroparesis Clinical Research Consortium are listed in Appendix 1.

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## Author Contributions

**Pankaj J. Pasricha:** study concept and design, acquisition of data, writing of manuscript

**Katherine P. Yates**: statistical analysis and presentation of data, writing and revision of manuscript

**Irene Sarosiek:** acquisition of data, critical revision of the manuscript for important intellectual content

**Richard W McCallum:** acquisition of data, critical revision of the manuscript for important intellectual content

**Thomas L. Abell:** study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content

**Kenneth L. Koch:** study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content

**Linda Nguyen:** acquisition of data; critical revision of the manuscript for important intellectual content

**William J. Snape:** acquisition of data, critical revision of the manuscript for important intellectual content

**William L. Hasler:** acquisition of data, critical revision of the manuscript for important intellectual content

**John Clarke:** acquisition of data

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**Ellen Stein:** acquisition of data

**Linda Lee:** review of safety data, technical support

**Laura Miriel:** technical support

**Mark Van Natta:** statistical analysis

**Madhusudan Grover:** critical revision of the manuscript for important intellectual content

**Gianrico Farrugia:** critical revision of the manuscript for important intellectual content

**James Tonascia:** study concept and design, statistical analysis, critical revision of the manuscript for important intellectual content

**Frank Hamilton:** study supervision, critical revision of the manuscript for important intellectual content

**Henry P. Parkman:** study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content

## Appendix 1. Members of the Gastroparesis Clinical Research Center

**Members of the Gastroparesis Clinical Research Consortium (GpCRC) are as follows:**

***Clinical Centers*:**
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***Resource Centers*:**
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**National Institute of Diabetes, Digestive and Kidney Diseases, Bethesda, MD**: Frank Hamilton, MD, MPH (Project Scientist); Jose Serrano, MD, PhD (Program Official); Stephen James, MD; Rebecca Torrance, RN MSN; Sherry Hall, MS

**Johns Hopkins University, Bloomberg School of Public Health (Data Coordinating Center), Baltimore, MD**: James Tonascia, PhD (Principal Investigator); Patricia Belt; John Dodge; Michele Donithan, MHS; Erin Hallinan, MHS; Milana Isaacson; Linda A. Lee, MD; Patrick K. May, MS; Laura Miriel; Alice Sternberg, ScM; Mark Van Natta, MHS; Annette Wagoner; Laura Wilson, ScM; Katherine P. Yates, ScM

# Appendix 2. List of GpCRC centers participating in APRON

### Clinical Centers

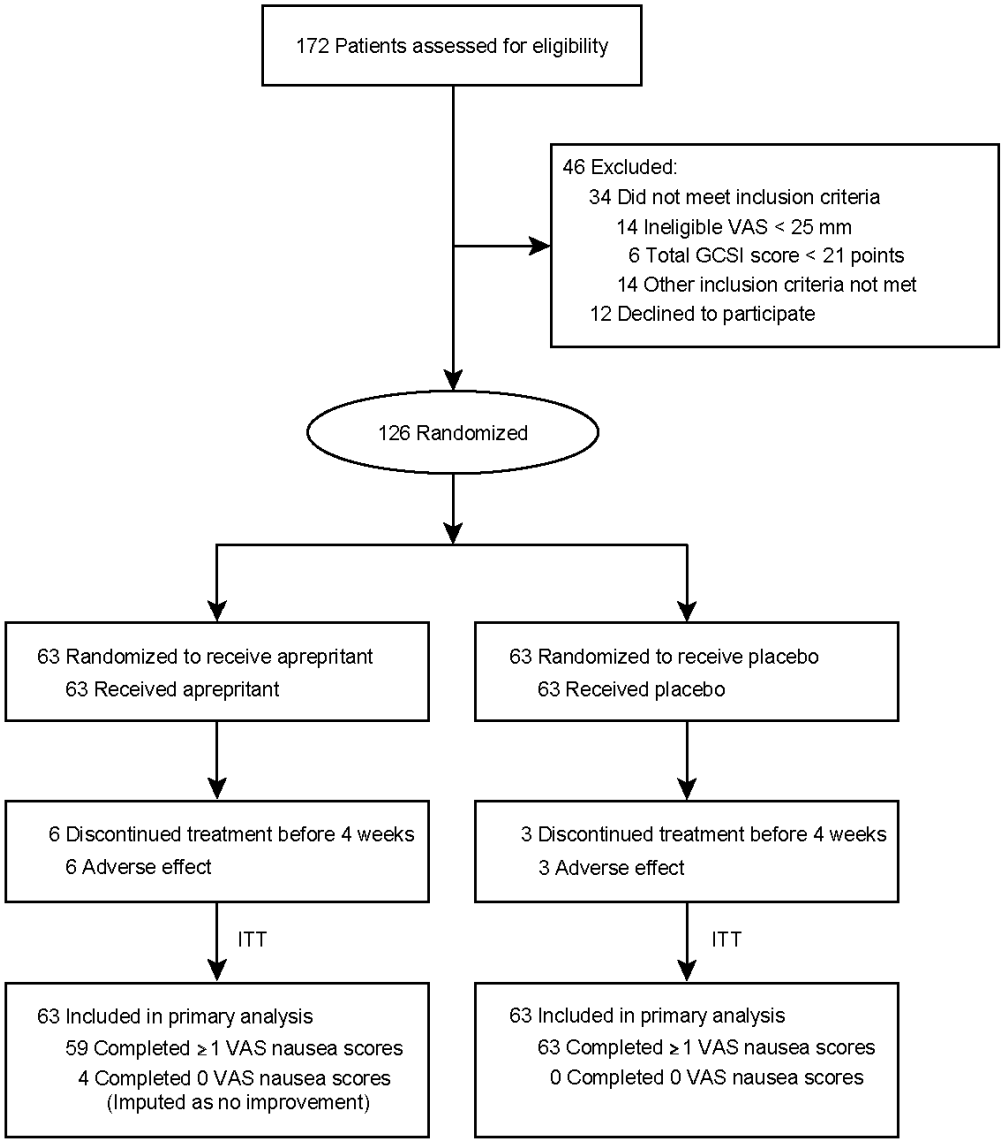
- Johns Hopkins University, Baltimore, MD (Pankaj Jay Pasricha, MD)
    - California Pacific Medical Center, San Francisco, CA (William J. Snape, Jr., MD)
    - Stanford University, Stanford, CA (Pankaj Jay Pasricha, MD)
- Temple University, Philadelphia, PA (Henry P. Parkman, MD)
- Texas Tech University Health Science Center, El Paso, TX (Richard W. McCallum, MD)
- University of Louisville, Louisville, KY (Thomas Abell, MD)
- University of Michigan, Ann Arbor, MI (Willam Hasler, MD)
- Wake Forest University, Winston-Salem, NC (Kenneth Koch, MD)

### Data Coordinating Center

- Johns Hopkins University, Baltimore, MD (James Tonascia, PhD)

# Appendix 3. Additional Figures and Tables

## Figure S1. CONSORT Flow Diagram of APRON Trial Participants




Note: ITT denotes Intention-to-treat

**Figure S2.** Changes from baseline in Gastroparesis Cardinal Symptom Index (GCSI), 6 individual GCSI component severity scores, and the upper abdominal pain and GERD subscores by treatment group

GCSI total score, each severity score, and the upper abdominal pain/discomfort and the gastroesophageal reflux disease (GERD) subscores range from 0 (no symptoms) to 5 (very severe). There was an overall significant decrease in total GCSI (P=0.001) (A) between the aprepitant group compared to placebo; however, there were no differences in changes during the trial in 5 of the remaining 6 individual severity scores (fullness (B), early satiety (C), excessive fullness (D), loss of appetite (E), and stomach distention (G)) between the aprepitant group compared with the placebo group. There were significant decreases in bloating (P=0.01) (F), the upper abdominal pain/discomfort severity subscore (P=0.02) (H) and the GERD subscore (P=0.03) (I) comparing the aprepitant group with the placebo. P-values shown are for the overall treatment effect over the trial from a repeated-measures analysis adjusting for the baseline value of the outcome.

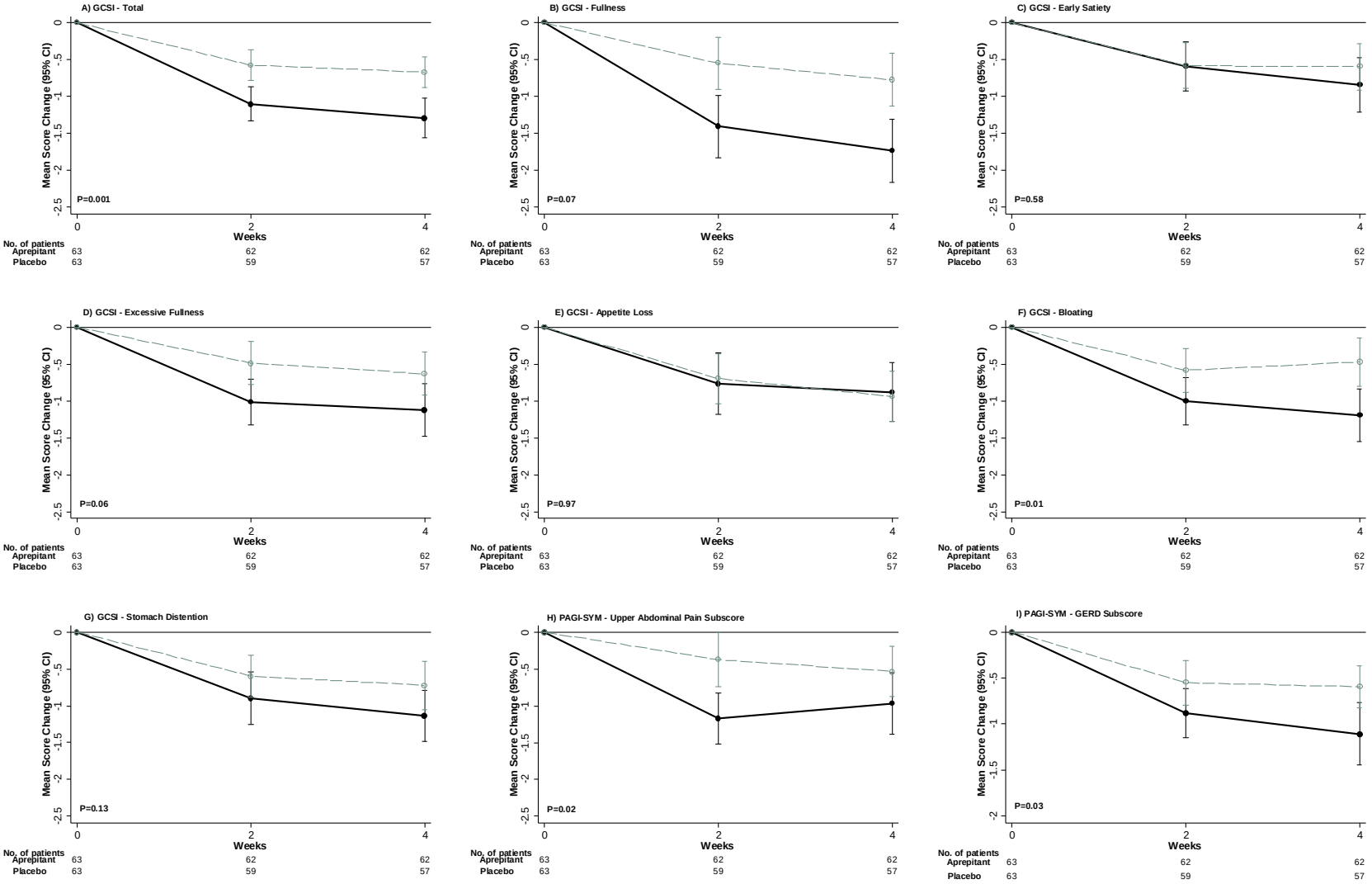

A) GCSI - Total
P=0.001
B) GCSI - Fullness
P=0.07
C) GCSI - Early Satiety
P=0.58
D) GCSI - Excessive Fullness
P=0.06
E) GCSI - Appetite Loss
P=0.97
F) GCSI - Bloating
P=0.01
G) GCSI - Stomach Distention
P=0.13
H) PAGI-SYM - Upper Abdominal Pain Subscore
P=0.02
I) PAGI-SYM - GERD Subscore
P=0.03
Mean Score Change (95% CI)
0
-.5
-1
-1.5
-2
-2.5
Weeks
0
2
4
No. of patients
Aprepitant 63 62 62
Placebo 63 59 57
Aprepitant
Placebo

**Table S1.** Additional baseline patient characteristics: physical exam, medications, co-morbidities, laboratory measures, patient symptom inventories, quality of life and psychological inventories, and satiety and electrogastrography tests

| Characteristic | Mean (SD)* | | |
|---|---|---|---|
| | Aprepitant (N=63) | Placebo (N=63) | Total (N=126) |
| **Physical exam** | | | |
| BMI classification, No. (%) | | | |
| Underweight | 5 (8%) | 1 (2%) | 6 (5%) |
| Normal | 24 (38%) | 22 (35%) | 46 (37%) |
| Overweight | 12 (19%) | 23 (37%) | 35 (28%) |
| Obese | 22 (35%) | 17 (27%) | 39 (31%) |
| Systolic blood pressure (mmHg) | 121.1 (17.8) | 122.1 (15.0) | 121.6 (16.4) |
| Diastolic blood pressure (mmHg) | 73.6 (11.6) | 75.0 (11.3) | 74.3 (11.4) |
| **Medications taken in past month, No. (%)** | | | |
| Selective serotonin reuptake inhibitors (SSRI) | 9 (14%) | 18 (29%) | 27 (21%) |
| Tricyclic antidepressant (TCA) | 11 (17%) | 16 (25%) | 27 (21%) |
| Other antidepressant | 12 (19%) | 10 (16%) | 22 (14%) |
| **Co-morbidities, N (%)** | | | |
| Any comorbidity | 60 (95%) | 61 (97%) | 121 (96%) |
| Number of comorbidities, median (IQR) | 3 (2 - 6) | 5 (2 – 6) | 4 (2 – 6) |
| Fibromyalgia | 7 (11%) | 10 (16%) | 17 (13%) |
| Migraine | 19 (30%) | 25 (40%) | 44 (35%) |
| Hypertension | 14 (22%) | 18 (29%) | 32 (25%) |
| Major depression, schizophrenia, bipolar disorder, OCD or severe anxiety or personality disorder | 16 (25%) | 23 (37%) | 39 (31%) |
| Gastroesophageal reflux disease (GERD) | 34 (54%) | 44 (70%) | 78 (62%) |
| **Laboratory measures: Liver enzymes, glucose, hematology, and chemistries** | | | |
| Alanine aminotransferase (ALT) (U/L) | 25.7 (17.4) | 23.4 (16.3) | 24.5 (116.8) |
| Aspartate aminotransferase (AST) (U/L) | 20.2 (9.3) | 20.0 (18.0) | 20.1 (14.2) |
| HbA1c (%)† | 7.1 (2.2) | 6.3 (1.2) | 6.7 (1.8) |
| Fasting serum glucose (mg/dL) | 124.4 (71.6) | 100.8 (36.0) | 112.6 (57.6) |
| Hemoglobin (g/dL) | 13.4 (1.7) | 13.3 (1.6) | 13.4 (1.6) |
| Hematocrit (%) | 40.3 (4.7) | 40.0 (4.3) | 40.1 (4.4) |
| Red blood cell count (RB) (x$10^6$ cells/µL) | 4.6 (0.6) | 4.5 (0.5) | 4.5 (0.5) |
| Sodium (mEq/L) | 139.4 (2.3) | 140.4 (2.1) | 139.9 (2.2)***** |
| Blood urea nitrogen (BUN) (mg/dL) | 14.2 (8.2) | 13.8 (6.6) | 14.0 (7.4) |
| Creatinine (mg/dL) | 1.2 (2.0) | 0.9 (0.5) | 1.0 (1.4) |
| **Gastroparesis symptom inventories** | | | |
| PAGI-SYM Severity index | | | |
| Stomach fullness severity | 3.9 (1.0) | 3.8 (1.0) | 3.9 (1.0) |
| Unable to finish meal severity | 3.6 (1.4) | 3.8 (1.0) | 3.7 (1.2) |
| Excessive fullness severity | 4.0 (1.0) | 3.9 (0.9) | 4.0 (1.0) |
| Loss of appetite severity | 3.3 (1.4) | 3.3 (1.2) | 3.3 (1.3) |
| Bloating severity | 3.4 (1.4) | 3.5 (1.3) | 3.5 (1.4) |
| Stomach distension severity | 3.1 (1.6) | 3.3 (1.6) | 3.2 (1.6) |
| Upper abdominal pain severity | 3.2 (1.5) | 3.1 (1.5) | 3.2 (1.5) |

| Characteristic | Mean (SD)* | | |
|---|---|---|---|
| | Aprepitant (N=63) | Placebo (N=63) | Total (N=126) |
| Upper abdominal discomfort severity | 3.6 (1.2) | 3.5 (1.2) | 3.6 (1.2) |
| Lower abdominal pain | 2.4 (1.6) | 2.5 (1.4) | 2.5 (1.5) |
| Lower abdominal discomfort | 2.5 (1.6) | 2.6 (1.4) | 2.6 (1.5) |
| Heartburn during the day severity | 2.5 (1.6) | 2.4 (1.7) | 2.5 (1.7) |
| Heartburn when lying down severity | 2.6 (1.6) | 2.4 (1.7) | 2.5 (1.7) |
| Chest discomfort during the day severity | 2.2 (1.4) | 2.1 (1.6) | 2.2 (1.5) |
| Chest discomfort during sleep time severity | 2.0 (1.6) | 2.1 (1.7) | 2.0 (1.7) |
| Regurgitation during the day severity | 2.4 (1.7) | 2.4 (1.6) | 2.4 (1.6) |
| Regurgitation when lying down severity | 2.5 (1.7) | 2.4 (1.6) | 2.4 (1.6) |
| Bitter taste severity | 2.4 (1.8) | 2.4 (1.7) | 2.4 (1.7) |
| **Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD)** *(0=none to 4=very severe)* | | | |
| Early satiety severity | 2.7 (1.0) | 2.7 (0.9) | 2.7 (0.9) |
| Excessive fullness severity | 2.7 (0.1) | 2.8 (0.9) | 2.7 (1.0) |
| Bloating severity | 2.3 (1.4) | 2.5 (1.1) | 2.4 (1.2) |
| Gastrointestinal Symptom Rating Scale (GSRS) (items coded 0 to 7, no to very severe discomfort) | | | |
| Total score | 3.6 (1.1) | 3.7 (1.0) | 3.7 (1.1) |
| Reflux score | 3.5 (1.8) | 3.6 (1.8) | 3.5 (1.8) |
| Abdominal pain score | 4.5 (1.1) | 4.5 (1.2) | 4.5 (1.2) |
| Indigestion score | 3.6 (1.5) | 3.9 (1.5) | 3.8 (1.5) |
| Diarrhea score | 2.8 (1.7) | 2.8 (1.8) | 2.8 (1.8) |
| Constipation score | 3.7 (1.8) | 3.7 (1.7) | 3.7 (1.7) |
| **Depression, anxiety, and quality of life (QOL)** | | | |
| Beck Depression Inventory (BDI) (0 to 63, none to severe) total score | 18.0 (11.8) | 18.3 (12.6) | 18.2 (12.1) |
| State-Trait Anxiety Inventory (STAI) | | | |
| State anxiety score (20 to 80) | 39.6 (13.9) | 41.9 (13.9) | 40.7 (13.9) |
| Trait anxiety score (20 to 80) | 40.3 (14.2) | 43.0 (13.2) | 41.6 (13.7) |
| SF-36 Quality of Life (QOL) (0 to 100, low to high) | | | |
| Physical component summary score | 33.5 (9.5) | 29.8 (8.8) | 31.6 (9.4)***** |
| Mental component summary score | 41.4 (14.3) | 40.5 (13.5) | 40.9 (13.9) |
| **Satiety test**† | | | |
| Volume of Ensure consumed, median (IQR), mL | 240 (150-300) | 237 (150-356) | 238 (150-300) |
| **Electrogastrography (EGG)**† | | | |
| Average power in frequency region, % | | | |
| Bradygastria (1-<2.5 cpm) | | | |
| Baseline | 54 (21%) | 50 (19%) | 52 (20%) |
| 0-30 post-satiety | 48 (18%) | 44 (15%) | 46 (17%) |
| Normogastria (2.5-<3.8 cpm) | | | |
| Baseline | 19 (15%) | 22 (14%) | 21 (14%) |
| 0-30 post-satiety | 23 (14%) | 22 (13%) | 22 (14%) |
| Tachygastria (3.8-10 cpm) | | | |
| Baseline | 19 (10%) | 21 (9%) | 20 (10%) |

| Characteristic | Mean (SD)* | | |
|---|---|---|---|
| | Aprepitant (N=63) | Placebo (N=63) | Total (N=126) |
| 0-30 post-satiety | 24 (11%) | 26 (10%) | 24 (10%) |
| Duodenal (>10-15 cpm) | | | |
| Baseline | 7 (9%) | 8 (6%) | 8 (7%) |
| 0-30 post-satiety | 8 (11%) | 8 (7%) | 8 (9%) |

* Data are mean (SD), unless otherwise noted. There were only 2 significant difference in the above 60 baseline characteristics by treatment group which was: sodium (P=0.02), and the physical component summary score of the SF-36 QOL (P=0.03). P values were determined using the Kruskal-Wallis two sample test, to account for skewness in the lab distributions and t-tests for all other continuous variables; Fisher's exact test was used to determine P values for categorical variables.

† 40 aprepitant, 34 placebo did not report HbA1c; 1 aprepitant, 1 placebo subject did not have SF-36v2 data; 1 aprepitant, 1 placebo subject did not have EGG and satiety results.

**Table S2.** Use of rescue medication over the 28-days of follow-up and at post-treatment by treatment group

| | Apron | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Rescue Medication (any use)** | **Mean weeks 2-4** | **Mean week 6** | **Mean change† (95% CI)** | **P†** | **Mean weeks 2-4** | **Mean week 6** | **Mean change† (95% CI)** | **P†** | **P†** |
| No. patients* | 57 | | | | 63 | | | | |
| Antiemetic | 36 (63%) | 33 (58%) | -5% (-13,2) | 0.25 | 43 (68%) | 39 (62%) | -6% (-14,1) | 0.05 | 1.00 |

* No of patients determined by data for the rescue medication being available at either week 2 or 4 and at 6 weeks.

† Mean change of % medication use (week 6 – treatment phase) reported. P values determined using an exact McNemar's test for paired proportions and 95% confidence intervals (C.I.) determined using a continuity correction.

‡ Exact logistic regression was used to assess whether changes in medication use from 28-days of follow-up to post-treatment phase differed by treatment group.

**Table S3.** Additional secondary and exploratory outcomes: mean changes from baseline in physical exam measures, laboratory measures, gastroparesis symptoms inventories, quality of life and psychological inventories and satiety and electrogastrography tests

| Outcome‡ | Change from baseline to 28 days (mean (SD))* Aprepitant (N=56) | Placebo (N=61) | Adjusted mean changes from baseline (95% CI) Aprepitant vs. placebo† | P† |
|---|---|---|---|---|
| **Physical exam** | | | | |
| Body mass index (BMI) (kg/m$^2$) | 0.3 (2.5) | -0.3 (1.0) | 0.6 (-0.1, 1.2) | 0.09 |
| Weight (kg) | -0.1 (4.5) | -0.7 (2.8) | 0.7 (-0.6, 1.9) | 0.30 |
| Waist circumference (cm) | -0.9 (6.5) | -0.4 (6.0) | -0.5 (-2.8, 1.8) | 0.65 |
| Systolic blood pressure (mmHg) | 1.2 (16.0) | -2.1 (10.7) | 2.6 (-2.0, 7.2) | 0.26 |
| Diastolic blood pressure (mmHg) | 0.4 (10.3) | -0.2 (7.5) | 0.1 (-2.8, 3.0) | 0.94 |
| **Laboratory measures: liver enzymes, glucose, hematology and chemistries** | | | | |
| Alanine aminotransferase (ALT) (U/L) | 2.3 (36.6) | 0.8 (7.6) | 2.6 (-7.0, 12.2) | 0.59 |
| Aspartate aminotransferase (AST) (U/L) | 3.1 (30.2) | 0.9 (7.7) | 2.1 (-5.9, 10.0) | 0.61 |
| HbA1c (%) | -0.1 (1.0) | 0.1 (0.5) | 0.0 (-0.5, 0.5) | 0.97 |
| Glucose (mg/dL) | 9.6 (66.8) | 7.0 (44.8) | 3.1 (-18.0, 24.2) | 0.77 |
| Hemoglobin (g/dL) | -0.1 (0.9) | -0.2 (0.6) | 0.1 (-0.2, 0.4) | 0.44 |
| Hematocrit (%) | -0.4 (2.7) | -0.4 (1.9) | 0.1 (-0.7, 0.9) | 0.77 |
| Red blood cell count (RB) (x10$^6$ cells/µL) | -0.1 (0.3) | -0.1 (0.2) | 0.0 (-0.1, 0.1) | 0.88 |
| Sodium (mEq/L) | -0.3 (2.3) | -0.7 (2.9) | 0.0 (-0.9, 1.0) | 0.93 |
| Blood urea nitrogen (BUN) (mg/dL) | -0.9 (4.6) | -0.3 (3.3) | -0.5 (-2.0, 0.9) | 0.45 |
| Creatinine (mg/dL) | -0.1 (0.2) | 0.0 (0.2) | -0.1 (-0.2, -0) | **0.008** |
| **Symptom Inventories** | | | | |
| **PAGI-SYM Severity index** | | | | |
| *(0=none to 5=very severe)* | | | | |
| Fullness/early satiety subscore | -1.0 (1.3) | -0.7 (1.0) | -0.3 (-0.7, 0.1) | 0.13 |
| Stomach fullness severity | -1.1 (1.6) | -0.5 (1.4) | -0.5 (-1.0, -0.1) | **0.03** |
| Unable to finish meal severity | -0.8 (1.4) | -0.6 (1.3) | -0.3 (-0.8, 0.1) | 0.16 |
| Excessive fullness severity | -1.1 (1.4) | -0.6 (1.2) | -0.5 (-0.9, 0.0) | **0.05** |
| Loss of appetite severity | -0.9 (1.6) | -0.9 (1.4) | 0.1 (-0.4, 0.6) | 0.72 |
| Bloating subscore | -1.2 (1.2) | -0.6 (1.2) | -0.6 (-1.2, -0.2) | **0.004** |
| Bloating severity | -1.2 (1.4) | -0.5 (1.3) | -0.8 (-1.2, -0.3) | **0.001** |
| Stomach distension severity | -1.1 (1.3) | -0.7 (1.3) | -0.5 (-0.9, 0.0) | **0.04** |
| Upper abdominal pain subscore | -1.1 (1.5) | -0.6 (1.2) | -0.4 (-0.9, 0.1) | 0.08 |
| Upper abdominal pain severity | -1.0 (1.6) | -0.5 (1.4) | -0.4 (-0.9, 0.1) | 0.14 |
| Upper abdominal discomfort severity | -1.2 (1.6) | -0.7 (1.3) | -0.5 (-1.0, 0.0) | 0.07 |
| Lower abdominal pain severity | -0.8 (1.4) | -0.6 (1.5) | -0.3 (-0.8, 0.2) | 0.19 |
| Lower abdominal discomfort severity | -1.1 (1.4) | -0.6 (1.5) | -0.5 (-0.9, -0.0) | **0.04** |
| GERD subscore | -1.1 (1.3) | -0.6 (0.9) | -0.5 (-0.8, -0.1) | **0.007** |
| Heartburn during the day severity | -1.2 (1.5) | -0.6 (1.4) | -0.5 (-1.0, -0.1) | **0.02** |

| | | | | |
|---|---|---|---|---|
| Heartburn when lying down severity | -1.2 (1.5) | -0.7 (1.4) | -0.4 (-0.9, 0.0) | 0.06 |
| Chest discomfort during the day severity | -1.1 (1.5) | -0.7 (1.4) | -0.4 (-0.8, 0.1) | 0.09 |
| Chest discomfort during sleep time severity | -0.9 (1.5) | -0.6 (1.4) | -0.3 (-7, 0.1) | 0.17 |
| Regurgitation during the day severity | -1.2 (1.7) | -0.5 (1.5) | -0.6 (-1.1, -0.2) | **0.009** |
| Regurgitation when lying down severity | -1.3 (1.7) | -0.5 (1.3) | -0.7 (-1.2, -0.2) | **0.004** |
| Bitter taste severity | -0.8 (1.6) | -0.5 (1.3) | -0.4 (-0.8, 0.1) | 0.10 |
| Constipation severity | -0.8 (1.6) | -0.3 (1.5) | -0.4 (-0.9, 0.1) | 0.13 |
| Diarrhea severity | -0.1 (1.4) | -0.2 (1.3) | -0.01 (-0.5, 0.4) | 0.98 |
| **Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD)** *(0=none to 4=very severe)* | | | | |
| Early satiety severity | -0.6 (0.9) | -0.4 (0.7) | -0.2 (-0.5, 0.1) | 0.12 |
| Excessive fullness severity | -0.6 (0.9) | -0.4 (0.7) | -0.2 (-0.4, 0.1) | 0.22 |
| Bloating severity | -0.6 (1.0) | -0.4 (0.8) | -0.2 (-0.5, 0.1) | 0.12 |
| Percent of vomiting-free days during 28-day fup (mean, 95% CI) | 69.5% (59.7, 79.2%) | 66.7% (57.7, 75.6%) | 2.8 (-10.3, 15.9) | 0.67 |
| **Gastrointestinal Symptom Rating Scale symptom clusters (GSRS)** (*0=no to 7=very severe discomfort*) | | | | |
| Reflux score | -1.1 (1.5) | -0.7 (1.6) | -0.5 (-0.9, 0.0) | 0.06 |
| Abdominal pain score | -1.3 (1.1) | -0.7 (1.0) | -0.6 (-1.0, -0.2) | **0.001** |
| Indigestion score | -0.7 (1.3) | -0.7 (1.1) | -0.2 (-0.6, 0.2) | 0.28 |
| Diarrhea score | -0.5 (1.6) | 0.1 (1.3) | -0.5 (-1.0, 0.0) | **0.05** |
| Constipation score | -0.8 (1.3) | -0.4 (1.5) | -0.4 (-0.9, 0.1) | 0.08 |
| **Depression and quality of life (QOL)** | | | | |
| Beck Depression Inventory (BDI) score (*0=none to 63=severe*) | -4.6 (8.5) | -2.4 (5.9) | -2.2 (-4.7, 0.4) | 0.09 |
| State-Trait Anxiety Inventory (STAI) | | | | |
| State anxiety score (*20 to 80*) | -3.1 (8.7) | -1.7 (10.6) | -1.8 (-5.2, 1.5) | 0.28 |
| Trait anxiety score (*20 to 80*) | -1.8 (8.8) | -0.7 (8.4) | -1.6 (-4.6, 1.4) | 0.30 |
| SF-36v2 Quality of Life (0 to 100, low to high) | | | | |
| Physical component summary score | 2.3 (6.9) | 3.2 (7.5) | -0.1 (-2.7, 2.5) | 0.95 |
| Mental component summary score | 3.5 (10.8) | 2.6 (9.2) | 1.4 (-1.9, 4.7) | 0.41 |
| **Satiety Test§** | | | | |
| Volume Ensure consumed, mL | -13.0 (125.7) | 9.2 (131.1) | -21.2 (-70.5, 28.1) | 0.40 |
| **Electrogastrography (EGG)§** | | | | |
| Average power in frequency region, % | | | | |
| Bradygastria (1-<2.5 cpm) | | | | |
| Baseline | -5.7 (23.1) | 1.2 (21.2) | -4.5 (-11.9, 2.9) | 0.23 |
| 0-30 post-satiety | -0.7 (16.7) | -1.9 (17.0) | 2.8 (-3.3, 8.9) | 0.37 |

| | | | | |
|---|---|---|---|---|
| Normogastria (2.5-<3.8 cpm) | | | | |
| Baseline | 1.8 (17.9) | -2.0 (15.4) | 2.1 (-3.1, 7.3) | 0.43 |
| 0-30 post-satiety | 2.8 (13.8) | 1.1 (15.4) | 2.1 (-3.3, 7.5) | 0.44 |
| Tachygastria (3.8-10 cpm) | | | | |
| Baseline | 1.5 (9.7) | 0.0 (11.4) | 0.8 (-2.6, 4.2) | 0.65 |
| 0-30 post-satiety | -2.0 (11.0) | 1.3 (12.9) | -5.4 (-9.1, -1.7) | **0.004** |
| Duodenal (>10-15 cpm) | | | | |
| Baseline | 2.3 (13.6) | 0.9 (11.2) | 1.3 (-3.3, 5.9) | 0.58 |
| 0-30 post-satiety | -1.1 (7.8) | -0.7 (6.1) | -0.8 (-2.6, 0.9) | 0.33 |

NOTE: Physical exam and laboratory outcomes are included as part of the safety profile.
Exploratory outcomes include all symptom severity measures from the GCSI-DD and the 5 symptom clusters measured by the GSRS.

* Defined as value at baseline visit subtracted from the value at the 28-day visit.

† P-values and mean changes from baseline were calculated using ANCOVA, regressing change from baseline to 28 days on treatment group and baseline value of the secondary outcome.

‡ 2 aprepitant subjects did not provide 28 day data (NP, GSRS)

§ No. patients with 28-day satiety and EGG data: 49 aprepitant, 55 placebo.

**Table S4.** Post-hoc analysis: Subgroup variation in the odds of nausea improvement between treatment groups using baseline and post-randomization subgroups

| Subgroup§ | Nausea Improvement* Aprepritant % | Aprepritant x/N | Placebo % | Placebo x/N | Odds ratio (95% CI) Aprepitant vs. Placebo† | P | Treatment by Subgoup P‡ |
|---|---|---|---|---|---|---|---|
| Overall | 49% | 29/59 | 40% | 25/63 | | | |
| **Demographic** | | | | | | | |
| Gender | | | | | | | 0.93 |
| Female | 44% | 20/45 | 37% | 19/33 | 1.4 (0.6, 3.1) | 0.43 | |
| Male | 64% | 9/14 | 55% | 6/11 | 1.5 (0.3, 7.5) | 0.62 | |
| Age (years) | | | | | | | 0.19 |
| < 50 | 41% | 16/39 | 40% | 15/35 | 1.0 (0.4, 2.6) | 0.93 | |
| ≥ 50 | 65% | 7/20 | 39% | 11/28 | 2.9 (0.9, 9.4) | 0.08 | |
| **Clinical** | | | | | | | |
| BMI group (kg/m$^2$) | | | | | | | 0.21 |
| < 25 | 57% | 16/28 | 35% | 8/23 | 2.5 (0.8, 7.8) | 0.12 | |
| ≥ 25 | 42% | 13/31 | 42% | 17/40 | 1.0 (0.4, 2.5) | 0.96 | |
| Etiology | | | | | | | 0.78 |
| Diabetic | 57% | 12/21 | 54% | 7/13 | 1.1 (0.3, 4.6) | 0.85 | |
| Not diabetic | 45% | 17/38 | 36% | 18/50 | 1.4 (0.6, 3.4) | 0.41 | |
| **Scintigraphic gastric emptying (GES)¶** | | | | | | | 0.91 |
| Delayed retention | 52% | 14/27 | 42% | 18/43 | 1.5 (0.6, 3.9) | 0.42 | |
| Not delayed | 47% | 15/32 | 35% | 7/20 | 1.6 (0.5, 5.2) | 0.19 | |
| **Medications** | | | | | | | |
| Anti-emetic at BL | | | | | | | 0.40 |
| Any | 48% | 20/42 | 35% | 17/49 | 1.7 (0.7, 4.0) | 0.21 | |
| None | 53% | 9/17 | 57% | 8/14 | 0.8 (0.27, 3.5) | 0.82 | |
| Ondansetron use | 38% | 12/32 | 34% | 10/29 | 1.1 (0.4, 3.2) | 0.81 | 0.40 |
| No use | 63% | 17/27 | 44% | 15/34 | 2.2 (0.4, 1.6) | 0.15 | |
| Proton pump inhibitor use at BL | 48% | 19/40 | 41% | 21/51 | 1.3 (0.6, 3.0) | 0.60 | 0.58 |
| No use | 53% | 10/19 | 33% | 4/12 | 2.2 (0.5, 10.0) | 0.30 | |
| Narcotic use over 28-day follow-up | 57% | 4/7 | 57% | 4/7 | 1.0 (0.1, 8.3) | 1.00 | 0.71 |
| No use | 48% | 25/52 | 38% | 21/56 | 1.5 (0.7, 3.3) | 0.27 | |
| **Symptoms at BL** | | | | | | | |
| Nausea | | | | | | | 0.26 |
| Severe/very severe | 48% | 23/48 | 33% | 16/49 | 1.9 (0.8, 4.3) | 0.13 | |
| None to moderate | 55% | 6/11 | 64% | 9/14 | 0.7 (0.1, 3.3) | 0.62 | |
| Vomiting | | | | | | | 0.40 |

| Subgroup§ | Nausea Improvement* Aprepritant % | Aprepritant x/N | Placebo % | Placebo x/N | Odds ratio (95% CI) Aprepitant vs. Placebo† | P | Treatment by Subgoup P‡ |
|---|---|---|---|---|---|---|---|
| Severe/very severe | 59% | 16/27 | 40% | 4/10 | 2.2 (0.5, 2.6) | 0.30 | |
| None to moderate | 41% | 13/32 | 40% | 21/53 | 1.0 (0.4, 2.6) | 0.09 | |
| Stomach fullness | | | | | | | 0.56 |
| Severe/very severe | 44% | 18/41 | 37% | 15/41 | 1.4 (0.6, 3.3) | 0.50 | |
| None to moderate | 61% | 11/18 | 45% | 10/22 | 1.9 (0.5, 6.7) | 0.33 | |
| Excessive fullness after meal | | | | | | | 0.36 |
| Severe/very severe | 39% | 16/41 | 34% | 14/41 | 1.2 (0.5, 3.0) | 0.65 | |
| None to moderate | 72% | 13/18 | 50% | 22/22 | 2.6 (0.7, 9.8) | 0.16 | |
| Bloating | | | | | | | 0.44 |
| Severe/very severe | 41% | 14/34 | 38% | 14/37 | 1.2 (0.4, 3.0) | 0.77 | |
| None to moderate | 60% | 15/25 | 42% | 11/26 | 2.0 (0.7, 6.2) | 0.21 | |
| Abdominal pain | | | | | | | |
| Severe/very severe | 48% | 16/33 | 37% | 10/27 | 1.6 (0.6, 4.5) | 0.38 | 0.86 |
| None to moderate | 50% | 13/26 | 42% | 15/36 | 1.4 (0.5, 3.9) | 0.52 | |
| **Adherence to prescribed dose‖** | | | | | | | |
| Dose by pill count | | | | | | | |
| Adherent | 52% | 29/56 | 40% | 24/60 | 1.6 (0.8, 3.4) | 0.20 | 0.80 |
| Non-adherent | 0% | 0/3 | 33% | 1/3 | 1.00 (0, 39) | 1.00 | |

* Improvement in nausea is a binary composite outcome defined as either 1) an improvement in the mean of available nausea visual analog scale (VAS) scores over the 28-day treatment period compared to the means of VAS during the 7-day baseline (BL) period being ≤ -25 mm, or 2) the mean VAS after 28-days of treatment was < 25 mm.

† The odds ratio and 95% confidence interval were derived from a logistic regression of the odds of nausea improvement by treatment group within each stratum of the subgroup.

‡ The treatment by subgroup P-value was derived from Wald's test of one or more indicator variables of the interaction of treatment group and subgroup within each stratum of the subgroup. P-value <0.01 is defined as significant.

§ Excludes observations with missing subgroup data.

¶ Delayed gastric emptying defined as gastric emptying scintigraphy of > 60% retention at 2 hours OR >10% retention at 4 hours.

‖ Adherence defined as patient taking the treatment medication 80% of the days during the 28-day follow-up period using pill count determined by the Drug Dispensing case-report form ((pills returned – pills dispensed)/No. days in the trial)*100.

Exact logistic regression is used to compute odds ratios, 95% confidence intervals and the interaction P-value.

**Table S5.** Adverse events by body classification system by treatment group

| | Number of Reports | | | Number of Patients | | |
|---|---|---|---|---|---|---|
| **Body System/Category*** | **Ap** | **Plbo** | **P†** | **Ap (N=63)** | **Plbo (N=63)** | **P‡** |
| Allergy/Immunology | 1 | 1 | 1.00 | 1 | 1 | 1.00 |
| Ocular/Visual | 0 | 1 | 1.00 | 0 | 1 | 1.00 |
| Hepatobiliary/Pancreas | 1 | 0 | 1.00 | 1 | 0 | 1.00 |
| Cardiac general | 0 | 2 | 0.50 | 0 | 2 | 0.50 |
| Dermatology/skin | 1 | 0 | 1.00 | 1 | 0 | 1.00 |
| Endocrine | 1 | 0 | 1.00 | 1 | 0 | 0.50 |
| Gastrointestinal | 11 | 7 | 0.48 | 10 | 6 | 0.42 |
| Musculoskeletal/Soft Tissue | 3 | 1 | 0.63 | 3 | 1 | 0.62 |
| Neurology | 4 | 1 | 0.38 | 4 | 1 | 0.36 |
| Pulmonary/Upper Respiratory | 0 | 1 | 1.00 | 0 | 1 | 1.00 |
| Renal/Genitourinary | 2 | 0 | 0.50 | 2 | 0 | 0.50 |
| Constitutional Symptoms | 2 | 2 | 1.00 | 2 | 2 | 1.00 |
| Hemorrhage/Bleeding | 1 | 1 | 1.00 | 1 | 1 | 1.00 |
| Metabolic/Laboratory | 1 | 0 | 1.00 | 1 | 0 | 1.00 |
| Pain | 4 | 2 | 0.69 | 4 | 2 | 0.68 |
| Other§ | 2 | 2 | 1.00 | 2 | 2 | 1.00 |
| **Total¶** | **26** | **15** | **0.12** | **22** | **11** | **0.04** |

* Derived from adverse events reported on the Adverse Event Report (AE) forms that were completed by the principal investigator.
Ap denotes Aprepitant group and Plbo denotes the Placebo group.

† P-values derived from two-sided Binomial probability test with probability of success=0.5.

‡ P-values derived from Fisher's exact test.

§ Other body systems specified: Aprepitant: fatigue, general disorders and fatigue; Placebo: withdrawal symptoms from anti-depressants, congenital adrenal hyperplasia.

¶ Total number of reports is the total number of unique Adverse Event reports. Multiple body systems may be reported on each form and patients may have multiple Adverse Event Report forms.
Total number of patients is the number of unique patients with one or more Adverse Event Report form. The total is less than the sum across body system because multiple body systems may be reported on each form.