**Supplementary Table 1.** Secondary efficacy endpoints over the 12-week double-blind treatment period

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Placebo | *N* | Prucalopride | *N* | *P* value |
| Proportion of patients, *n* (%), with: ≥3 SCBMs/week and an increase of ≥1 SCBM per week for ≥75% of 12-week treatment period and ≥75% of last third of treatment period | 22 (12.2) | 181 | 49 (27.7) | 177 | 0.0002a |
| Proportion of patients, *n* (%), with: |  |  |  |  |  |
| ≥3 SBMs/week | 110 (60.8) | 181 | 137 (77.4) | 177 | 0.0011 |
| ≥3 CBMs/week | 39 (21.5) | 181 | 70 (39.5) | 177 | 0.0001 |
| ≥3 BMs/week | 123 (68.0) | 181 | 143 (80.8) | 177 | 0.0064 |
| an increase of ≥1 SCBM/week | 82 (45.3) | 181 | 95 (53.7) | 177 | 0.0743 |
| Number of SCBMs/week, mean (SD) |  |  |  |  |  |
| Baseline | 0.51 (0.690) | 177 | 0.39 (0.630) | 174 | – |
| Change from baseline to weeks 1–12 | 1.25 (1.899) | 169 | 2.17 (2.371) | 167 | 0.0001b |
| Time to first SCBM, h, median (5%, 95%) |  |  |  |  |  |
| Day 1 (post-dose) | 218.9 (143.93, 291.43) | 135c | 110.3 (70.80, 172.77) | 140c | 0.0090d |
| Day 29 (post-dose) | 122.9 (73.60, 192.95) | 131c | 72.2 (49.67, 104.50) | 126c | 0.0519d |
| Percentage of SBMs with hard/very hard consistency, mean (SD) |  |  |  |  |  |
| Baseline | 51.2 (39.6) | 159 | 56.2 (39.8) | 157 | – |
| Change from baseline to weeks 1–12 | –19.2 (38.7) | 150 | –28.9 (42.1) | 150 | – |
| Percentage of SBMs with severe/very severe straining, mean (SD) |  |  |  |  |  |
| Baseline | 39.4 (36.2) | 159 | 46.3 (38.9) | 157 | – |
| Change from baseline to weeks 1–12 | –16.0 (38.9) | 150 | –24.8 (37.3) | 150 | – |
| Number of bisacodyl tablets taken/week (SD)  Weeks 1–12  Change from run-in to weeks 1–12 | 1.0 (1.76)  0.7 (1.84) | 172  169 | 0.6 (1.56)  1.0 (1.96) | 170  167 | –  – |
| PAC-SYM overall score, mean (SD) |  |  |  |  |  |
| Baseline | 1.75 (0.668) | 178 | 1.84 (0.657) | 175 | – |
| Change from baseline to final on-treatment assessment | –0.59 (0.760) | 168 | –0.76 (0.765) | 167 | 0.0623b |
| Patient global evaluation of constipation severity, *n* (%)  Baseline  Absent  Mild  Moderate  Severe  Very severe | 1 (0.6)  9 (5.1)  68 (38.2)  78 (43.8)  22 (12.4) | 178 | 0 (0)  5 (2.8)  52 (29.5)  93 (52.8)  26 (14.8) | 176 | 0.0308 |
| At final on-treatment assessment  Absent  Mild  Moderate  Severe  Very severe | 19 (11.1)  37 (21.6)  63 (36.8)  44 (25.7)  8 (4.7) | 171 | 26 (15.4)  50 (29.6)  56 (33.1)  29 (17.2)  8 (4.7) | 169 | 0.0101 |
| Patient global evaluation of efficacy of treatment, *n* (%)  At FOTA  Not at all effective  A little bit effective  Moderately effective  Quite a bit effective  Extremely effective | 52 (30.4)  29 (17.0)  38 (22.2)  37 (21.6)  15 (8.8) | 171 | 25 (14.8)  18 (10.7)  47 (27.8)  58 (34.3)  21 (12.4) | 169 | <0.0001 |
| PAC-QOL overall score, mean (SD) |  |  |  |  |  |
| Baseline | 1.90 (0.750) | 178 | 1.97 (0.684) | 175 | – |
| Change from baseline to final on-treatment assessement | –0.59 (0.817) | 168 | –0.79 (0.840) | 167 | 0.0158b |

–, no statistical report.

a*P* value results from a Cochran–Mantel–Haenszel test adjusted for country and average number of CBMs/week during run-in (0 or >0).

b*P* value results from an ANCOVA model comparison of least-squares means with treatment, average number of CBMs/week during the run-in phase, and country as factors and baseline SCBM as a covariate.

c*n*=number of patients with an SCBM.

d*P* value based on a stratified log-rank test containing country and average number of CBMs/week during the run-in phase as stratification factors.

BM, bowel movement; CBM, complete bowel movement; FOTA, final on-treatment assessment; PAC-QOL, Patient Assessment of Constipation – Quality of Life questionnaire; PAC-SYM, Patient Assessment of Constipation – Symptom questionnaire; SBM, spontaneous bowel movement; SCBM, spontaneous complete bowel movement; SD, standard deviation.

**Supplementary Table 2.** All treatment-emergent adverse events (TEAEs)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **TEAE** | **Placebo (*N*=186)** | | | **Prucalopride (*N*=184)** | | |
|  | ***n*** | **%** | **M** | ***n*** | **%** | **M** |
| Total |  |  |  |  |  |  |
| Number of patients with ≥1 TEAE | 64 | 34.4 | 120 | 78 | 42.4 | 152 |
| **Blood and lymphatic system disorders** |  |  |  |  |  |  |
| Total | 2 | 1.1 | 2 | 3 | 1.6 | 3 |
| Anemia | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Iron deficiency anemia | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Leukocytosis | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Thrombocytopenia | 0 | 0 | 0 | 2 | 1.1 | 2 |
| **Cardiac disorders** |  |  |  |  |  |  |
| Total | 4 | 2.2 | 8 | 5 | 2.7 | 5 |
| Angina pectoris | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Atrial fibrillation | 0 | 0 | 0 | 2 | 1.1 | 2 |
| Atrioventricular block first degree | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Bundle branch block right | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Coronary artery occlusion | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Left atrial dilatation | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Left ventricular dysfunction | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Mitral valve incompetence | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Myocardial ischemia | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Palpitations | 1 | 0.5 | 1 | 1 | 0.5 | 1 |
| Supraventricular extrasystoles | 1 | 0.5 | 1 | 0 | 0 | 0 |
| **Ear and labyrinth disorders** |  |  |  |  |  |  |
| Total | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Vertigo | 0 | 0 | 0 | 1 | 0.5 | 1 |
| **Endocrine disorders** |  |  |  |  |  |  |
| Total | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Hyperprolactinemia | 0 | 0 | 0 | 1 | 0.5 | 1 |
| **Eye disorders** |  |  |  |  |  |  |
| Total | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Photophobia | 1 | 0.5 | 1 | 0 | 0 | 0 |
| **Gastrointestinal disorders** |  |  |  |  |  |  |
| Total | 26 | 14.0 | 37 | 37 | 20.1 | 58 |
| Abdominal discomfort | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Abdominal distension | 2 | 1.1 | 2 | 2 | 1.1 | 3 |
| Abdominal pain | 11 | 5.9 | 12 | 8 | 4.3 | 11 |
| Abdominal pain upper | 3 | 1.6 | 3 | 2 | 1.1 | 2 |
| Anal fissure | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Constipation | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Defecation urgency | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Dental caries | 1 | 0.5 | 1 | 1 | 0.5 | 1 |
| Diarrhea | 3 | 1.6 | 3 | 12 | 6.5 | 16 |
| Dry mouth | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Dyspepsia | 1 | 0.5 | 1 | 1 | 0.5 | 1 |
| Flatulence | 2 | 1.1 | 3 | 1 | 0.5 | 1 |
| Frequent bowel movements | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Gastritis | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Gastrointestinal pain | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Gastroesophageal reflux disease | 2 | 1.1 | 2 | 0 | 0 | 0 |
| Hemorrhoids | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Hiatus hernia | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Nausea | 4 | 2.2 | 4 | 11 | 6.0 | 12 |
| Rectal hemorrhage | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Regurgitation | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Vomiting | 3 | 1.6 | 3 | 1 | 0.5 | 2 |
| **General disorders and administration site conditions** |  |  |  |  |  |  |
| Total | 4 | 2.2 | 4 | 8 | 4.3 | 9 |
| Asthenia | 1 | 0.5 | 1 | 2 | 1.1 | 2 |
| Chest discomfort | 0 | 0 | 0 | 2 | 1.1 | 3 |
| Chest pain | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Edema peripheral | 0 | 0 | 0 | 2 | 1.1 | 2 |
| Fatigue | 0 | 0 | 0 | 2 | 1.1 | 2 |
| Influenza-like illness | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Pyrexia | 1 | 0.5 | 1 | 0 | 0 | 0 |
| **Hepatobiliary disorders** |  |  |  |  |  |  |
| Total | 0 | 0 | 0 | 3 | 1.6 | 4 |
| Biliary colic | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Cholelithiasis | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Hyperbilirubinemia | 0 | 0 | 0 | 2 | 1.1 | 2 |
| **Infections and infestations** |  |  |  |  |  |  |
| Total | 16 | 8.6 | 17 | 10 | 5.4 | 10 |
| Cystitis | 1 | 0.5 | 2 | 0 | 0 | 0 |
| Gastroenteritis | 0 | 0 | 0 | 2 | 1.1 | 2 |
| Gingival abscess | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Influenza | 4 | 2.2 | 4 | 1 | 0.5 | 1 |
| Lung infection | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Nasopharyngitis | 5 | 2.7 | 5 | 1 | 0.5 | 1 |
| Pharyngitis | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Sinusitis | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Tracheitis | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Upper respiratory tract infection | 2 | 1.1 | 2 | 1 | 0.5 | 1 |
| Urinary tract infection | 1 | 0.5 | 1 | 2 | 1.1 | 2 |
| Viral infection | 0 | 0 | 0 | 1 | 0.5 | 1 |
| **Injury, poisoning, and procedural complications** |  |  |  |  |  |  |
| Total | 1 | 0.5 | 1 | 1 | 0.5 | 1 |
| Hand fracture | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Lower limb fracture | 1 | 0.5 | 1 | 0 | 0 | 0 |
| **Investigations** |  |  |  |  |  |  |
| Total | 4 | 2.2 | 8 | 4 | 2.2 | 7 |
| Alanine aminotransferase increased | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Aspartate aminotransferase increased | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Blood creatine phosphokinase increased | 1 | 0.5 | 1 | 1 | 0.5 | 1 |
| Blood creatinine increased | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Blood lactate dehydrogenase increased | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Blood potassium decreased | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Blood pressure increased | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Blood urine present | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Body temperature increased | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Electrocardiogram QT prolonged | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Hepatic enzyme increased | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Protein urine | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Weight decreased | 1 | 0.5 | 1 | 0 | 0 | 0 |
| White blood cell count decreased | 0 | 0 | 0 | 1 | 0.5 | 1 |
| **Metabolism and nutrition disorders** |  |  |  |  |  |  |
| Total | 3 | 1.6 | 3 | 4 | 2.2 | 4 |
| Decreased appetite | 1 | 0.5 | 1 | 1 | 0.5 | 1 |
| Dyslipidemia | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Hypertriglyceridemia | 2 | 1.1 | 2 | 1 | 0.5 | 1 |
| Vitamin B12 deficiency | 0 | 0 | 0 | 1 | 0.5 | 1 |
| **Musculoskeletal and connective tissue disorders** |  |  |  |  |  |  |
| Total | 5 | 2.7 | 6 | 5 | 2.7 | 5 |
| Arthralgia | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Back pain | 3 | 1.6 | 3 | 2 | 1.1 | 2 |
| Exostosis | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Medial tibial stress syndrome | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Musculoskeletal chest pain | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Osteoarthritis | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Periarthritis | 0 | 0 | 0 | 1 | 0.5 | 1 |
| **Neoplasms benign, malignant, and unspecified (including cysts and polyps)** |  |  |  |  |  |  |
| Total | 2 | 1.1 | 2 | 0 | 0 | 0 |
| Glottis carcinoma | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Prolactinoma | 1 | 0.5 | 1 | 0 | 0 | 0 |
| **Nervous system disorders** |  |  |  |  |  |  |
| Total | 11 | 5.9 | 12 | 22 | 12.0 | 25 |
| Dizziness | 3 | 1.6 | 3 | 4 | 2.2 | 4 |
| Headache | 7 | 3.8 | 8 | 17 | 9.2 | 18 |
| Occipital neuralgia | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Tremor | 1 | 0.5 | 1 | 2 | 1.1 | 2 |
| **Psychiatric disorders** |  |  |  |  |  |  |
| Total | 2 | 1.1 | 2 | 4 | 2.2 | 4 |
| Anxiety | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Anxiety disorder | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Depression | 0 | 0 | 0 | 2 | 1.1 | 2 |
| Insomnia | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Nightmare | 0 | 0 | 0 | 1 | 0.5 | 1 |
| **Renal and urinary disorders** |  |  |  |  |  |  |
| Total | 3 | 1.6 | 3 | 6 | 3.3 | 9 |
| Dysuria | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Hematuria | 2 | 1.1 | 2 | 3 | 1.6 | 3 |
| Leukocyturia | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Nephrolithiasis | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Pollakiuria | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Polyuria | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Renal colic | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Urine odor abnormal | 0 | 0 | 0 | 1 | 0.5 | 1 |
| **Respiratory, thoracic, and mediastinal disorders** |  |  |  |  |  |  |
| Total | 4 | 2.2 | 5 | 0 | 0 | 0 |
| Atelectasis | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Cough | 3 | 1.6 | 3 | 0 | 0 | 0 |
| Oropharyngeal pain | 1 | 0.5 | 1 | 0 | 0 | 0 |
| **Skin and subcutaneous tissue disorders** |  |  |  |  |  |  |
| Total | 7 | 3.8 | 8 | 2 | 1.1 | 2 |
| Cold sweat | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Dermal cyst | 0 | 0 | 0 | 1 | 0.5 | 1 |
| Dermatosis | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Dry skin | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Pruritus | 2 | 1.1 | 3 | 0 | 0 | 0 |
| Psoriasis | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Skin lesion | 1 | 0.5 | 1 | 0 | 0 | 0 |
| Skin reaction | 0 | 0 | 0 | 1 | 0.5 | 1 |
| **Vascular disorders** |  |  |  |  |  |  |
| Total | 1 | 0.5 | 1 | 3 | 1.6 | 4 |
| Hypertension | 1 | 0.5 | 1 | 1 | 0.5 | 1 |
| Hypotension | 0 | 0 | 0 | 2 | 1.1 | 3 |

TEAE, treatment-emergent adverse event

n = number of subjects; M = number of events; % = percentage of subjects.

Percentages are based on all subjects in the safety population

**Supplementary Figure 1.** Patient flow.



GCP, good clinical practice; mITT, modified intent-to-treat; TEAE, treatment-emergent adverse event.