**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) | 172169 | 0.6 (1.56)1.0 (1.96) | 170167 | –– |
| 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.