Prucalopride in Gastroparesis: A Randomized Placebo-Controlled Crossover Study

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OBJECTIVES: **Prokinetics are considered the preferred treatment option for gastroparesis, but evidence of their efficacy is scarce. Prucalopride, a selective 5-hydroxytryptamine 4 receptor agonist used in the treatment of constipation, is able to enhance the gastric emptying rate. In a double-blind, randomized, placebo-controlled crossover study, we evaluated the efficacy of prucalopride to improve the gastric emptying rate and symptoms in patients with gastroparesis.**

METHODS: **Thirty-four patients with gastroparesis (28 idiopathic, 7 men, mean age 42 ± 13 years) were evaluated in a double-blind crossover trial of 4-week treatment periods with placebo or prucalopride 2 mg q.d., separated by 2 weeks of washout. The primary end point was the change in symptom severity, assessed by the Gastroparesis Cardinal Symptom Index; secondary end points comprised the Patient Assessment of Upper Gastrointestinal Disorders–Symptom Severity Index, the Patient Assessment of Upper Gastrointestinal Disorders–Quality of Life, and daily diaries, and the gastric emptying rate was assessed by the ^{13}C-octanoic acid breath test.**

RESULTS: **Three patients were lost to follow-up. One serious adverse event occurred (small bowel volvulus in the prucalopride group), and 3 patients dropped out because of adverse events of nausea and headache (all prucalopride). For the entire patient group, compared with placebo, prucalopride significantly improved the total Gastroparesis Cardinal Symptom Index (1.65 ± 0.19 vs 2.28 ± 0.20, $P < 0.0001$) and the subscales of fullness/satiety, nausea/vomiting, and bloating/distention. Prucalopride significantly improved the overall Patient Assessment of Upper Gastrointestinal Disorders–Quality of Life score (1.15 ± 0.16 vs 1.44 ± 0.16, $P < 0.05$) and the domains of clothing and diet. The gastric half emptying time was significantly enhanced by prucalopride compared with placebo and baseline (98 ± 10 vs 143 ± 11 and 126 ± 13 minutes, $P = 0.005$ and <0.001, respectively). These significant improvements were also found when considering only the idiopathic gastroparesis subgroup.**

DISCUSSION: **In a cohort of patients with predominantly idiopathic gastroparesis, 4 weeks of prucalopride treatment significantly improved symptoms and quality of life and enhanced gastric emptying compared with placebo.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/A644

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INTRODUCTION

Gastroparesis is defined as the presence of delayed gastric emptying in the absence of mechanical obstruction and is associated with symptoms of postprandial fullness, early satiety, nausea, vomiting, and upper abdominal bloating (1,2). Gastroparesis can occur as a complication of diabetes mellitus, but in most cases, no underlying causes can be found, and gastroparesis is defined as idiopathic (3,4). Gastroprokinetic drugs are considered the treatment of choice for gastroparesis, aiming at improving symptoms through stimulation of gastric motility and gastric emptying rate (3). However, a systematic analysis of prokinetic agent trials in idiopathic and diabetic gastroparesis to date failed to find a significant association between the improvement in emptying rate and symptomatic benefit (4). More recent studies have focused on ghrelin receptor agonists in diabetic gastroparesis, showing symptomatic benefit but no consistent relationship between symptomatic benefit and changes in emptying rate (5–7).

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5-hydroxytryptamine 4 (5-HT_4) receptor agonists are probably the best-studied class of agents for the treatment of gastroparesis (3). Prucalopride, a highly selective 5-HT_4 receptor agonist, is approved for the treatment of chronic constipation with insufficient response to laxatives (8,9). After oral administration, prucalopride is well absorbed in the gastrointestinal (GI) tract, and it has an absolute bioavailability of more than 90% (10). The plasma half-life of prucalopride (2 mg) is 24 hours, and it reaches the maximum serum concentration between 2 and 3 hours after intake (10). Furthermore, prucalopride has shown a favorable safety profile in studies and in clinical practice, and it does not affect the QT interval (11,12). Prucalopride stimulates colonic transit, and this is the basis for its effectiveness in chronic constipation (13,14). However, prucalopride was also shown to enhance gastric emptying in a dog model, in healthy volunteers, and in patients with chronic constipation (14–16).

Our aim was to evaluate the efficacy of prucalopride in patients with idiopathic or diabetic gastroparesis in a randomized, double-blind crossover study.

METHODS

Patients

Consecutive idiopathic or diabetic patients with symptoms suggestive of gastroparesis and with established delayed gastric emptying for solids (17) were eligible for this double-blind randomized crossover study. Patients presented to the motility outpatient clinic because of symptoms suggestive of gastroparesis, and all underwent careful history taking and clinical examination, routine biochemistry, upper GI endoscopy, upper abdominal ultrasound, and a gastric emptying breath test (18,19). Exclusion criteria were the presence of reflux esophagitis grade B or higher, gastric atrophy or erosive gastroduodenal lesions on endoscopy, suspected small bowel obstruction, major abdominal surgery, underlying psychiatric illness, and the use of nonsteroidal anti-inflammatory drugs, steroids, or opioids.

Study protocol

The study was registered on clinicaltrials.gov as NCT02510976. An overview of the study design is shown in Figure 1. During a 2-week run-in period, patients filled daily diaries evaluating gastroparesis symptoms and stool pattern (see below) and underwent a gastric emptying breath test study (details outlined below). At the end of the run-in period, they filled the Patient Assessment of Upper Gastrointestinal Disorders–Symptom Severity Index (PAGI-SYM) questionnaire, a broad upper GI symptom questionnaire, which comprises the Gastroparesis Cardinal Symptom Index (GCSI), and the Patient Assessment of Upper Gastrointestinal Disorders–Quality of Life (PAGI-QOL) QOL questionnaires (details outlined below) (20–23). The primary outcome variable is the GCSI at the end of treatment; secondary outcomes are GCSI, PAGI-QOL, and gastric emptying rates.

For this investigator-initiated study, active drug (prucalopride 2 mg) and identically looking placebo tablets were provided by Shire Pharmaceuticals. The randomization and delivery of the study drugs in blinded coded boxes was provided by the Leuven University Hospital Pharmacy. After the run-in period, patients were randomized to a double-blind controlled treatment phase of 4 weeks with prucalopride 2 mg or matching placebo, taken in the morning. This was followed by a 2-week washout period and another 4-week double-blind controlled treatment period in which the patient was crossed over to the other treatment arm in a blinded fashion. A diary was filled throughout the entire study period, and the gastric emptying test, PAGI-SYM/GCSI, and PAGI-QUOL questionnaires were repeated at the end of each treatment period and at the end of the washout period.

All drugs potentially affecting GI motility or sensitivity were discontinued at least 1 week before the start of the study. Informed consent was obtained from each participant. The protocol had been previously approved by the Ethics Committee of the Leuven University Hospital.

Gastric emptying breath test and meal-related symptoms

Gastric emptying rates for solids and liquids were determined using the ^{14}C octanoic acid and ^{13}C glycine breath tests (17,18).

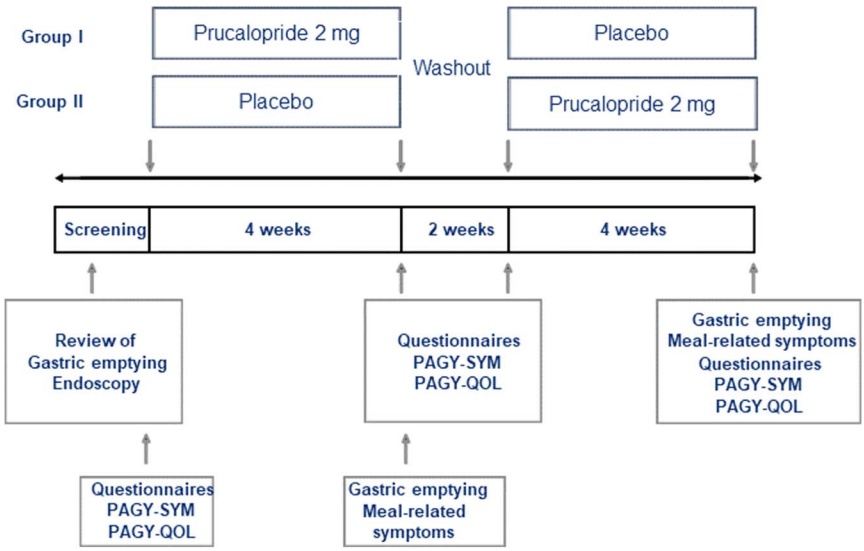

Figure 1. Schematic outline of the study. PAGI-QOL = Patient Assessment of Upper Gastrointestinal Disorders–Quality of Life; PAGI-SYM = Patient Assessment of Upper Gastrointestinal Disorders–Symptom Severity Index.

The test meal consisted of 60 g of white bread, an egg, the yolk of which was doped with 74 kBq of ^{14}C octanoic acid sodium salt (DuPont; NEN Research, Boston, MA), and 300 mL of water in which 100 mg ^{13}C glycine (99% enrichment; Isotec, Miamisburg, OH) was dissolved. All meals were consumed within a 5-minute period. The total caloric value of the test meal was 250 kcal. Breath samples were taken before the meal and at 15-minute intervals for a period of 240 minutes postprandially. At each sampling point, the subject exhaled into 2 different containers for measuring exhaled ^{13}C and ^{14}C, respectively, with sample characteristics, as previously reported (17,18).

Meal-related symptoms were also assessed during the gastric emptying tests at the end of each treatment period. At each breath sampling, the patient was asked to grade the intensity (0–3: 0 = absent; 1 = mild: present in a nonbothersome intensity; 2 = relevant: clearly present and bothersome but not of such intensity that it would interfere with normal daily activities; and 3 = severe: clearly present and of such intensity that it would interfere with normal daily activities) of 6 different symptoms (epigastric pain, bloating, postprandial fullness, nausea, belching, and epigastric burning), as previously reported (17).

Patient Assessment of Gastrointestinal Symptoms

The self-reported PAGI-SYM questionnaire is a broad upper GI symptom questionnaire, composed of 20 items and 6 subscales: heartburn/regurgitation (7 items), nausea/vomiting (3 items), postprandial fullness/early satiety (4 items), bloating (2 items), upper abdominal pain (2 items), and lower abdominal pain (2 items). The severity of each symptom item over a 2-week recall period is scored from 0 (none or absent) to 5 (very severe) (19,20). Subscale scores for the PAGI-SYM are calculated by averaging across items comprising the subscale; scores vary from 0 (none or absent) to 5 (very severe).

Gastroparesis Cardinal Symptom Index

The GCSI score consists of the nausea/vomiting (3 items), postprandial fullness/early satiety (4 items) and bloating (2 items) domains of the PAGI-SYM. The severity of each subdomain is calculated as above. The total GCSI score was obtained by averaging the 3 symptom subscale scores (21,22).

Patient Assessment of Gastrointestinal Quality of Life

The PAGI-QOL is a validated scale to assess QOL in upper GI disorders (23). The questionnaire uses 30 questions, measured on a 0–5 scale (none of the time to all of the time) to cover 5 domains (daily activities, clothing, diet and food habits, relationship, psychological well-being, and distress).

Daily diaries

During the entire study, patients completed a daily diary, incorporating a separate horizontal 100-mm visual analog scale for each of 9 upper abdominal symptoms (postprandial fullness, early satiation, upper abdominal bloating, epigastric pain, nausea, vomiting, heartburn, belching, and overall upper abdominal symptom severity). The diary also collected stool frequency and stool type (Bristol stool scale) on a daily basis (24).

Data analysis

The results of the $^{13}CO_2$ and $^{14}CO_2$ breath tests were expressed as the percentage $^{13}CO_2$ and $^{14}CO_2$, respectively, excreted per hour by calculating procedures described elsewhere (17,18). For both carbon labels, CO_2 production was assumed 300 mmol/m^2 of body surface per hour. The gastric half emptying time (t1/2) was calculated from the $^{13}CO_2$ and $^{14}CO_2$ excretion curves, as previously described (17,18). Solid gastric emptying was considered severely delayed if t1/2 was more than 109 minutes and, liquid emptying was considered severely delayed if t1/2 was more than 75 minutes (17). Symptom scores were obtained before and for 4 hours after the standardized meal. For each symptom, a meal-related severity score was obtained by adding scores at all time points. A cumulative meal-related symptom score was obtained by adding individual symptom severity scores.

The questionnaires were scored as described above. Using the daily diaries, weekly mean severity scores for symptoms and stool consistency and stool frequency scores were calculated. In case of missing values for symptom scores, the last observation was carried forward for numerical analyses on the patients who started study treatment. Data are shown as mean ± SD or as median (interquartile ranges).

Statistical analysis

The primary outcome variable for this proof-of-concept trial was the comparison of the GCSI scores after 4 weeks of treatment with prucalopride or placebo. Results are shown as mean ± SEM. The sample size was originally set at 30 based on the ability to detect a 30% difference in GCSI scores after 4 weeks of treatment with prucalopride or placebo, with 85% using a paired *t*-test at a $P < 0.05$ significance level, and based on the variability of GCSI observed in a previous study (17). Although the trial was ongoing, we decided to use the more appropriate mixed-model statistical analysis as a higher quality statistical analysis for longitudinal studies. We compared outcomes across prucalopride and placebo using mixed models with adjustment for order effects. Using R version 3.5.1, package "TrialSize", the sample size was calculated *post hoc*. To obtain a power of 0.85 at a 0.05 significance level, a number of 11 subjects was sufficient both for the total and the idiopathic gastroparesis patient group. At the current sample size and variation of the GCSI, the power is 0.99, both for the total and the idiopathic group.

Data were analyzed using R version 3.4.2. We compared outcomes across prucalopride and placebo using mixed models with adjustment for order effects by including a period effect and adjusting for possible period-by-treatment interaction effects. Meal-related symptom scores associated with the emptying test during prucalopride or placebo treatment were compared using the Wilcoxon signed-rank test. Data are first presented for the entire population and then for the idiopathic subgroup, as prespecified. Subanalyses were not performed for the diabetic gastroparesis group because of small numbers.

RESULTS

Patient characteristics

Thirty-four patients (26 women, mean age 43.5 ± 2.3 years, and body mass index [BMI] 23.8 ± 0.7 kg/m^2) entered the study. Twenty-eight patients (21 women, mean age 42.3 ± 2.6 years, and BMI 21.9 ± 1.6 kg/m^2) were idiopathic, and 6 patients (5 women, mean age 49.0 ± 4.0 years, and BMI 24.9 ± 0.8 kg/m^2) were diabetic gastroparesis patients. Gastric half emptying times for solids and liquids were 143 ± 11 and 97 ± 12 minutes, respectively, at baseline.

Table 1. Characteristics of patients

	Entire group, prucalopride first	Entire group, placebo first	*P*	Idiopathic, prucalopride first	Idiopathic, placebo first	*P*
Female/male	14/5	12/3	NS	9/4	12/3	NS
Age, yr	42.5 ± 2.9	44.8 ± 14.5	NS	39.5 ± 13.1	44.8 ± 14.5	NS
BMI, kg/m^2	23.6 ± 0.9	25.8 ± 1.4	NS	22.9 ± 1.2	25.8 ± 1.4	NS
Solid emptying t1/2 (min)	151 ± 15	133 ± 16	NS	161 ± 23	133 ± 16	NS
Liquid emptying t1/2 (min)	98 ± 11	95 ± 16	NS	92 ± 25	95 ± 16	NS
GCSI	2.33 ± 0.26	2.69 ± 0.28	NS	2.784 ± 0.19	2.69 ± 0.28	NS

BMI, body mass index; GCSI, Gastroparesis Cardinal Symptom Index; NS, not significant.

Conduct of the study

Nineteen patients were randomized using a computer-generated list to receive prucalopride first, and 15 were randomized to receive placebo first. Baseline characteristics according to the treatment allocation group are summarized in Table 1. Seven patients dropped out of the study (Figure 2). Three patients did not show up after the screening visit because of lack of time, did not receive the study drug, and were lost to follow-up. Four patients dropped out because of adverse events (3 during the first treatment period). In the placebo-first group, 1 patient stopped participation because of nausea during the first treatment phase. In the prucalopride-first group, 1 patient had a major adverse event (small intestinal volvulus during the first treatment phase), 1 patient stopped participation because of diarrhea, and 1 because of headache during the first treatment phase. All other patients participated in the full study protocol as planned.

Entire gastroparesis study population

Symptom pattern. The values at week 6 did not differ significantly between both arms of randomization, and a significant

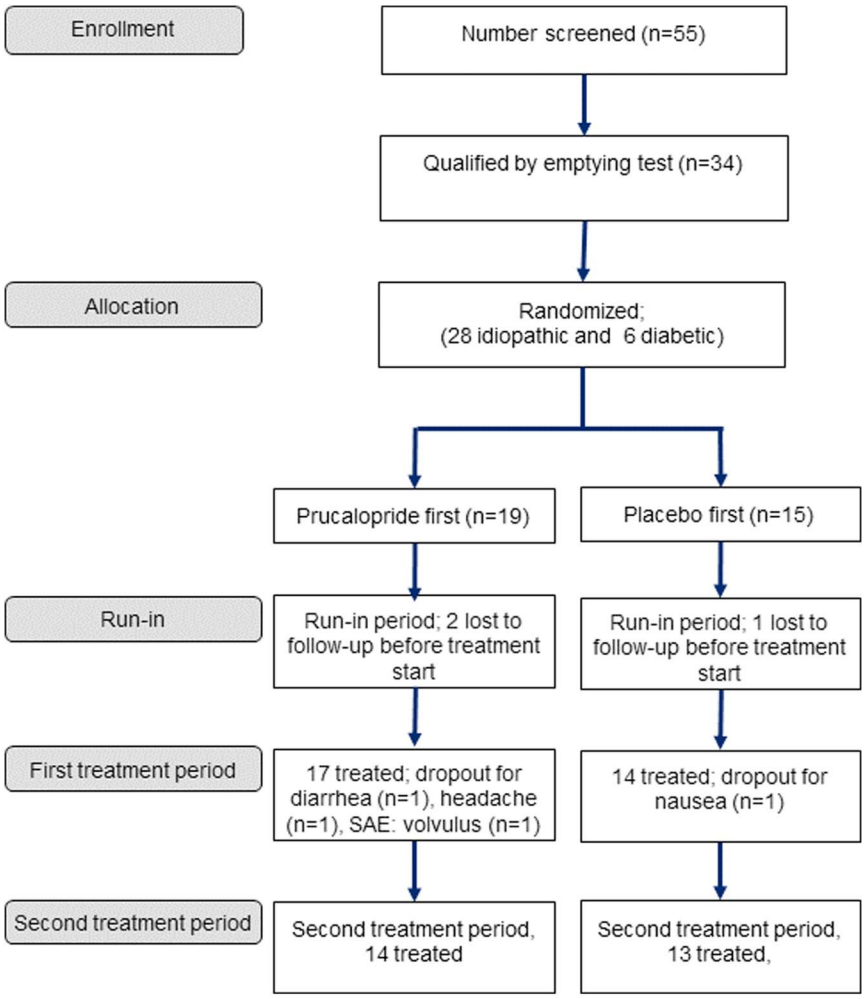

Figure 2. Patient flow diagram. SAE, serious adverse event.

"carryover" effect was not present, allowing pooling of data per treatment modality for analyses and figures (see Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/A644). Figure 3 summarizes the GCSI scores during the different treatment phases according to randomization. After 4 weeks of prucalopride treatment, the GCSI was significantly better in the active treatment group compared with placebo (prucalopride 1.65 ± 0.19 vs 2.28 ± 0.2 during placebo, $P < 0.0001$). All 3 GCSI subscales of nausea/vomiting (1.02 ± 0.20 vs 1.42 ± 0.24, $P = 0.01$), fullness/satiation (2.16 ± 0.26 vs 2.81 ± 0.26, $P < 0.0005$), and bloating/distension (1.58 ± 0.28 vs 2.50 ± 0.29, $P < 0.0005$) were significantly better compared with placebo treatment. The PAGI-SYM subscale of reflux was also significantly lower during prucalopride compared with placebo treatment (1.18 ± 0.22 vs 1.47 ± 0.20, $P = 0.005$, Figure 4a).

Gastric emptying and meal-related symptoms. After 4 weeks of prucalopride treatment, solid and liquid half emptying times were 98 ± 10 and 74 ± 3 minutes, respectively. Solid but not liquid half emptying times with prucalopride were significantly shorter than during placebo treatment (126 ± 13 minutes, $P = 0.02$, and 87 ± 12 minutes, not significant [NS], respectively) or at baseline ($P = 0.00001$ and $P = 0.03$, respectively) (Figure 5). No statistically significant correlation was found between the change in GCSI or PAGI-SYM scores and the change in gastric emptying rate. Meal-related total symptoms (76.3 [7.75; 110.25] vs 47.9 [1.75; 61.25], $P = 0.02$), postprandial fullness (17.65 [0.75; 25.0] vs 9.7 [0.0; 9.25], $P = 0.03$), and bloating (22.0 [1.5; 36.75] vs 12.6 [0.0; 17.75], $P = 0.03$) were significantly lower during prucalopride treatment compared with placebo.

Quality of life. After 4 weeks of prucalopride treatment, the PAGI-QOL and its subscales of clothing and diet were

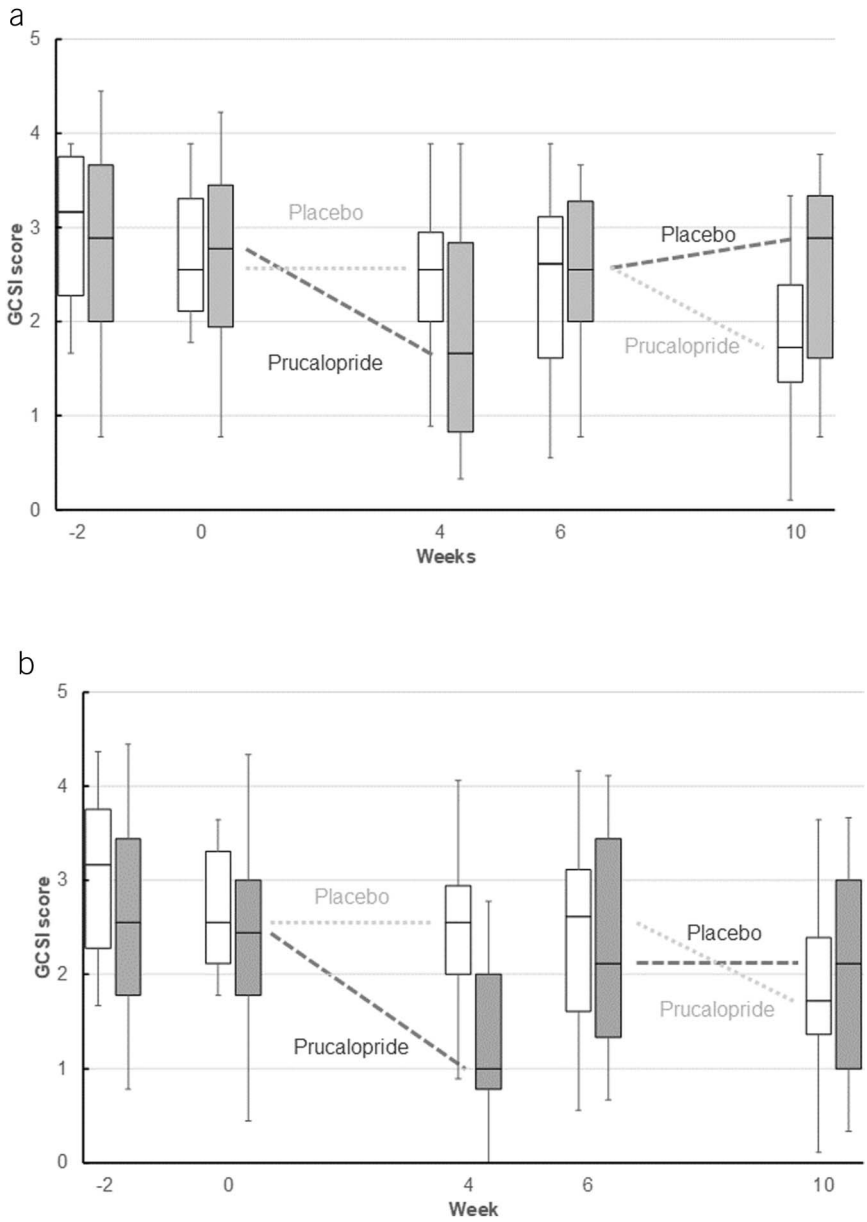

Figure 3. Influence of prucalopride and placebo on the GCSI scores during the double-blind controlled crossover study. Data are separated into 2 groups according to the sequence of treatment. (**a**) Results in the total patient group. (**b**) Results in the idiopathic gastroparesis patient group. GCSI = Gastroparesis Cardinal Symptom Index.

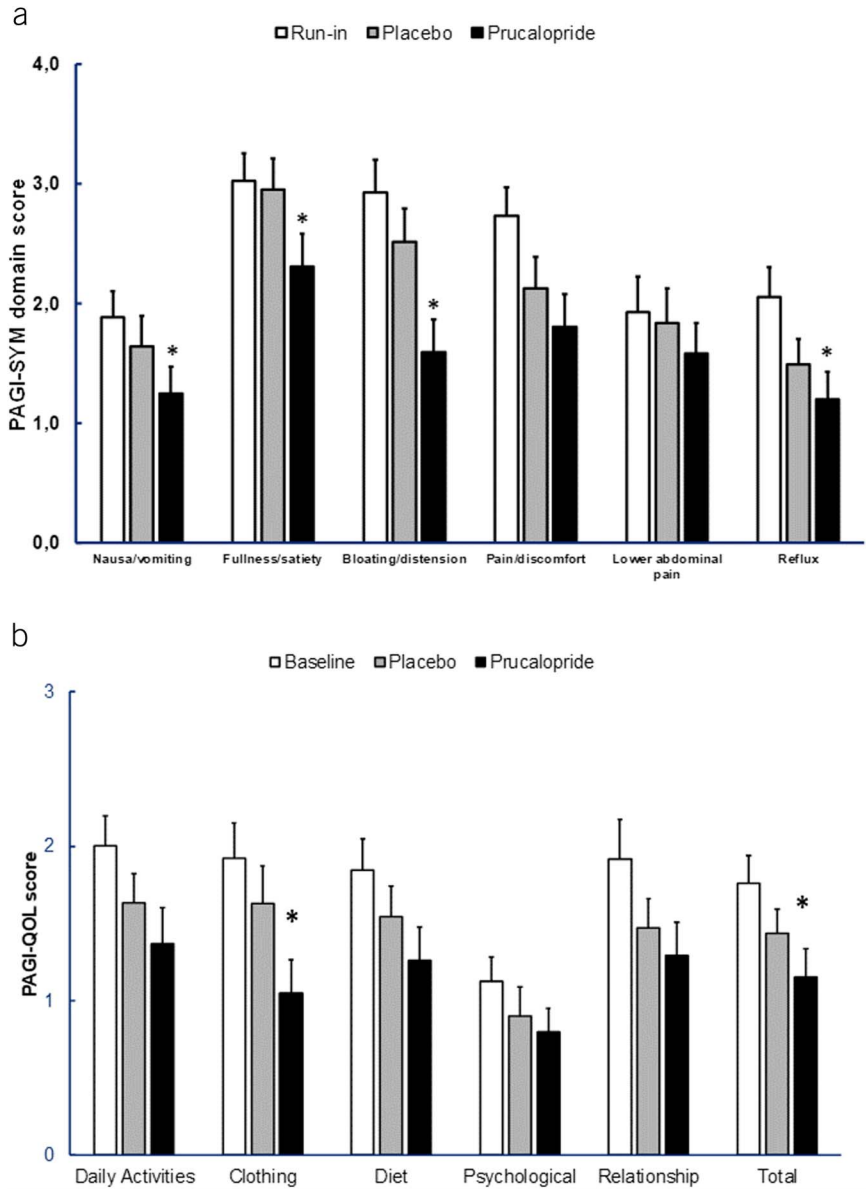

Figure 4. Influence of prucalopride vs placebo on upper gastrointestinal symptoms and quality of life in the total patient group. Data from the 2 crossover treatment groups are pooled for each treatment. (**a**) Results on subscales of the PAGI-SYM questionnaire. (**b**) Results on subscales of the PAGI-QOL questionnaire. * $P < 0.05$ compared with placebo arm. PAGI-QOL = Patient Assessment of Upper Gastrointestinal Disorders–Quality of Life; PAGI-SYM = Patient Assessment of Upper Gastrointestinal Disorders–Symptom Severity Index.

significantly better compared with placebo (1.15 ± 0.16 vs 1.44 ± 0.16, $P < 0.05$) (Figure 4b).

Daily diaries. Daily diaries confirmed significant improvement compared with placebo treatment of symptom severity ratings for abdominal pain, postprandial fullness, bloating, early satiation, nausea, and overall symptom severity (details not shown). Significance over placebo with prucalopride treatment was observed during weeks 3 and 4 (postprandial fullness, early satiation, upper abdominal bloating, nausea, and epigastric pain significantly better than placebo), but not during weeks 1 and 2 (only bloating scores significantly better than placebo).

The number of bowel movements per day rose from a mean of 1.21 ± 0.06 at baseline to 1.57 ± 0.09 during the first 2 weeks of prucalopride therapy ($P = 0.004$) to normalize back to 1.38 ± 0.09 during the second 2 weeks of prucalopride treatment (NS). The proportion of type 1 and 2 bowel movements during prucalopride treatment (8%) was significantly lower compared with placebo or baseline (22 and 13%, both $P < 0.05$, respectively). However, no correlation was found between the change in stool pattern (frequency or consistency) and the change in symptom pattern (GCSI total score and subscales).

Idiopathic gastroparesis subgroup

Symptom pattern. Upper GI symptoms were significantly better during prucalopride compared with placebo treatment: total GCSI (1.81 ± 0.21 vs 2.47 ± 0.19, $P < 0.001$) (Figure 3b) and the PAGI-SYM subscales of fullness/satiety (2.37 ± 0.29 vs 3.14 ± 0.25, $P < 0.0005$), bloating/distension (1.82 ± 0.31 vs 2.66 ± 0.30, $P < 0.0005$), nausea/vomiting (1.07 ± 0.22 vs 1.45 ± 0.25, $P = 0.02$), and reflux (1.38 ± 0.25 vs 1.67 ± 0.22, $P = 0.02$) (Figure 6a).

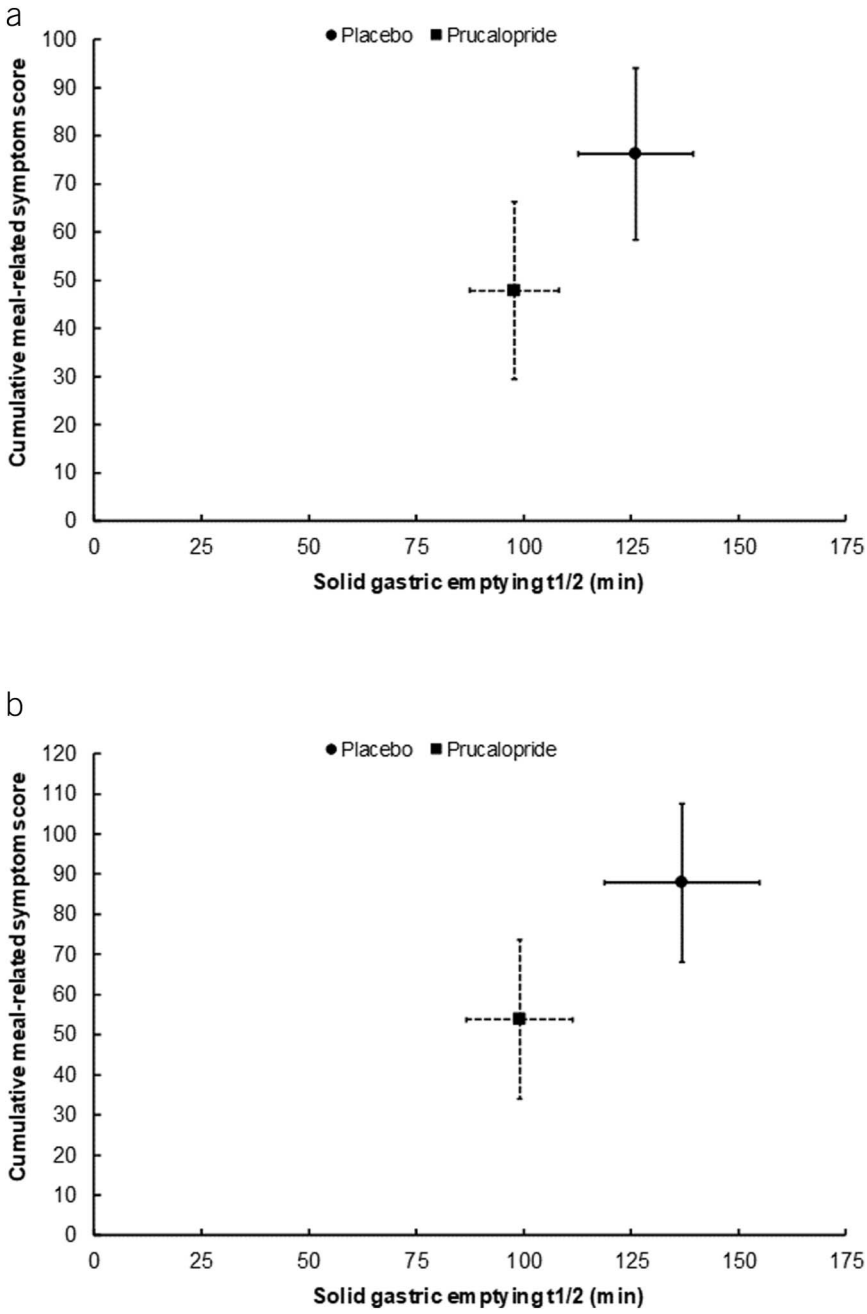

Figure 5. Influence of prucalopride or placebo on solid half emptying time and on total meal-related symptom scores. Data from the 2 crossover treatment groups are pooled for each treatment. Both half emptying time and meal-related symptoms were significantly lower after prucalopride ($P < 0.05$). (**a**) Results in the total patient group. (**b**) Results in the idiopathic gastroparesis patient group. PAGI-QOL = Patient Assessment of Upper Gastrointestinal Disorders–Quality of Life; PAGI-SYM = Patient Assessment of Upper Gastrointestinal Disorders–Symptom Severity Index.

Gastric emptying and meal-related symptoms. In the idiopathic subgroup, prucalopride treatment was associated with a significant improvement of solid but not liquid half emptying times (99 ± 12 and 73 ± 4 minutes, respectively) compared with placebo (137 ± 68 and 87 ± 06 minutes, respectively, $P = 0.005$ and NS) and baseline ($P < 0.0005$ and NS, respectively). Placebo had no significant effect on emptying times compared with baseline. No statistically significant correlation was found between the change in GCSI or PAGI-SYM scores and the change in gastric emptying rate. Meal-related total symptoms (87.8 [22.0; 120.0] vs 53.8 [2.0; 65.0], $P = 0.01$), postprandial fullness (19.8 [4.0; 29.0] vs 11.4 [0.0; 10.0], $P < 0.05$), and bloating (24.9 [5.0; 45.0] vs 12.5 [0.0; 16.0], $P = 0.006$) were significantly lower during prucalopride treatment compared with placebo (Figure 5b).

Quality of life. In the idiopathic subgroup, the PAGI-QOL was significantly better during treatment with prucalopride compared with placebo (1.35 ± 0.18 vs 1.67 ± 0.16, $P = 0.007$). Prucalopride improved the subscales of clothing and diet compared with placebo (Figure 6b).

Daily diaries. Daily diaries in the idiopathic subgroup alone confirmed that prucalopride was superior to placebo in improving severity ratings for abdominal pain, postprandial fullness,

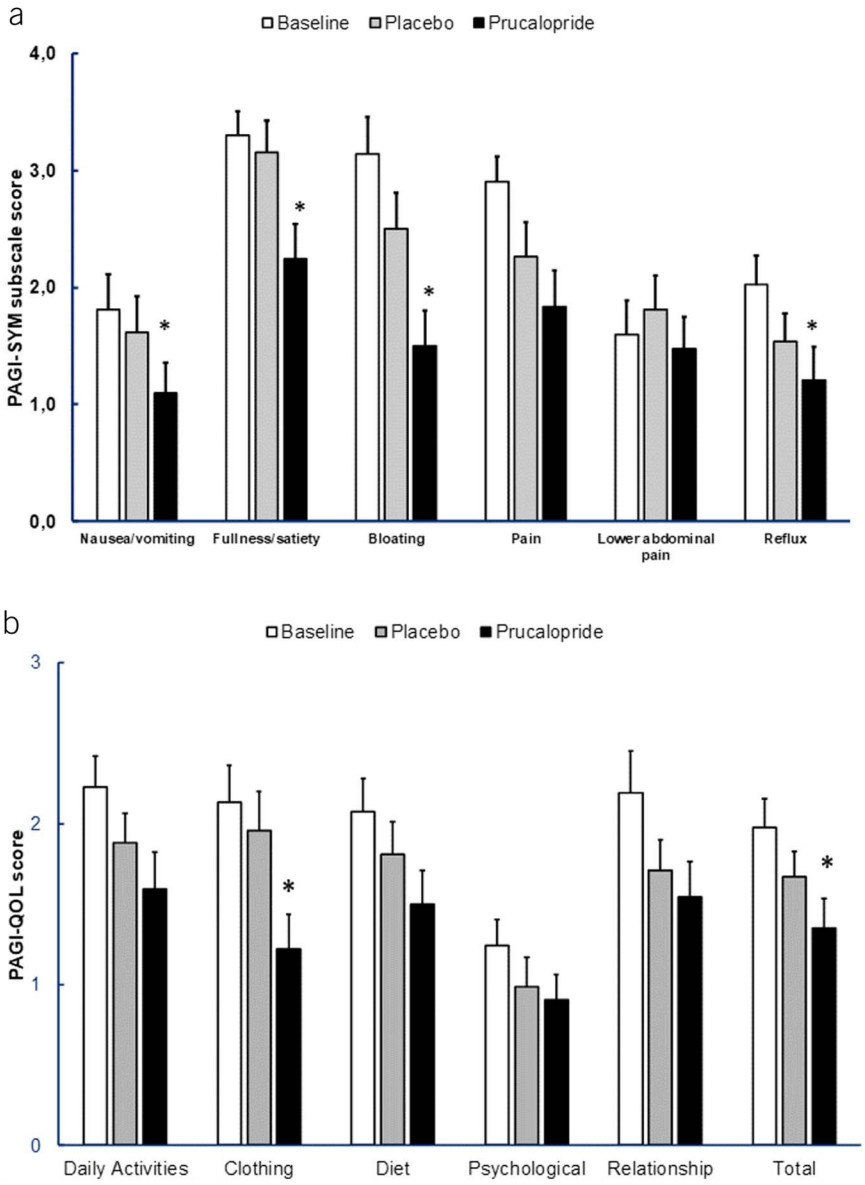

Figure 6. Influence of prucalopride vs placebo on upper gastrointestinal symptoms and quality of life in the idiopathic gastroparesis patient group. Data from the 2 crossover treatment groups are pooled for each treatment. (**a**) Results on subscales of the PAGI-SYM questionnaire. (**b**) Results on subscales of the PAGI-QOL questionnaire. *$P < 0.05$ compared with placebo arm. PAGI-QOL = Patient Assessment of Upper Gastrointestinal Disorders–Quality of Life; PAGI-SYM = Patient Assessment of Upper Gastrointestinal Disorders–Symptom Severity Index.

bloating, early satiation, nausea, and overall symptom severity (details not shown). Stool pattern (frequency and consistency) was not correlated with symptom improvement.

Adverse events

One serious adverse event occurred: 1 patient developed intestinal volvulus 18 days after the start of treatment with prucalopride. Adverse events leading to termination were 1 case of diarrhea and 1 of headache during prucalopride treatment and a case of nausea during placebo treatment.

Transient diarrhea was reported by 9 patients during prucalopride treatment, lasting 1–7 days, and in 1 patient during placebo treatment. Transient headache was reported by 8 patients during prucalopride treatment, lasting 1–7 days, and in 1 patient during placebo treatment. Abdominal cramps were reported during prucalopride and placebo treatment by 1 patient each. Cystitis occurred in 1 patient during each treatment and respiratory infection in 1 patient during prucalopride treatment.

DISCUSSION

In this study, we evaluated the efficacy of the selective 5-HT_4 agonist prucalopride in a placebo-controlled crossover trial in patients with idiopathic and diabetic gastroparesis. Prucalopride treatment improved symptoms, as assessed by the GCSI, compared with placebo and baseline both in the entire population and in the idiopathic subgroup. The beneficial effect of prucalopride was present for all 3 subscales of the GCSI: nausea/vomiting, fullness/satiety, and bloating/distention. In line with the pharmacodynamic properties of 5-HT_4 agonists, prucalopride treatment was also associated with improved solid gastric emptying

rate compared with placebo and baseline. However, there was no correlation between the symptomatic improvement and the enhancement of gastric emptying rate. Prucalopride also improved upper abdominal pain and reflux symptoms, as assessed by the PAGI-SYM questionnaire. Finally, prucalopride improved overall QOL and the subscale of clothing. The improvement in these scales from baseline exceeds the reported minimally important differences (21,25,26).

As revealed by daily diaries, significant symptomatic benefit of prucalopride treatment occurred from week 3 onward. As shown by both the diaries and the PAGI-SYM questionnaire, this improvement included all key dimensions of gastroparesis, namely postprandial fullness/early satiation, upper abdominal bloating/distention, nausea/vomiting, and reflux subscales. This was associated with improved QOL as shown by the PAGI-QOL scale, most clearly in the dimensions of diet and clothing.

The findings are consistent with the overall stimulatory effect of prucalopride on motility, both in the upper and lower GI tract. Indeed, we found significant enhancement of gastric emptying and a (transient) increase in bowel movements during prucalopride treatment. However, the improvement of gastroparesis symptoms was not explained by changes in colonic transit, as assessed using the Bristol stool scale diaries or stool frequency, nor by changes in gastric emptying rate, as assessed by the gastric half emptying time. Gastric motility is a complex phenomenon, including gastric accommodation to store the meal, grinding of solid meal components, and titrated release to the duodenum at a rate that matches intestinal nutrient absorptive capacity. Prucalopride may affect each of these aspects, and this would not necessarily be closely reflected by the gastric half emptying time. Additional studies evaluating the effect of prucalopride on different aspects of gastric and duodenal motor function in gastroparesis seem warranted to further identify the mechanism that underlies symptom improvement.

From its use in chronic constipation, prucalopride is known to be associated with adverse events of diarrhea, headache, and nausea (8–11). The same adverse events occurred more frequently in the prucalopride arm in the present gastroparesis trial and led to a slightly higher discontinuation rate during prucalopride treatment. However, most of the adverse events of diarrhea and headache were transient, as known from prucalopride use in chronic constipation. In addition, scores for nausea/vomiting improved significantly during prucalopride treatment in the entire study population.

Although 5-HT_4 agonists are often considered a preferred pharmacological class of prokinetic drugs for upper GI motility disorders, several recent studies failed to show significant benefit (2–4,27). Most recent treatment trials have focused on diabetic gastroparesis (4–7,27,28), whereas the present study included mainly patients with idiopathic gastroparesis. Subgroup analysis confirmed efficacy in the idiopathic patient group, but the diabetic patient group was too small for a meaningful analysis. It is not inconceivable that the selection of patients with idiopathic gastroparesis, where sensory neuropathy is not an issue, favored a better symptom assessment compared with patients with diabetic gastroparesis, where sensory neuropathy has a potential to confound symptom assessment (1,3,27). Larger-scale studies with prucalopride in both diabetic and idiopathic gastroparesis may clarify this possibility.

The efficacy of prucalopride as observed in this idiopathic gastroparesis trial raises the question whether the drug would also be efficacious in patients with functional dyspepsia/postprandial distress syndrome with normal gastric emptying (2,28,29). The lack of a correlation between the symptomatic benefit of prucalopride and the change in gastric emptying rate suggests that enhanced emptying is not necessarily the mechanism underlying the symptomatic beneficial effect. On the other hand, we recently demonstrated in healthy volunteers that prucalopride may inhibit gastric accommodation and sensitize the stomach to gastric distention (30). As hypersensitivity to gastric distention and impaired accommodation are key mechanisms implicated in symptom generation in functional dyspepsia, it is conceivable that delayed gastric emptying is a marker of a subgroup of patients that may respond to the strong motility stimulatory effects of the selective 5-HT_4 agonist prucalopride (31,32). However, a study exploring the effects of prucalopride in patients with functional dyspepsia/postprandial distress syndrome with normal gastric emptying is worth considering.

The current study has a number of limitations. This is a proof-of-concept study in patients seen at a tertiary care center. The findings are not necessarily applicable to patients seen at other levels of care and patients with organic or drug-induced causes of gastroparesis. In addition, although efficacy can be confirmed in idiopathic gastroparesis, the diabetic subgroup is too small for separate analysis. Relatively short treatment duration of 4 weeks and the crossover design (although no significant carryover effect was found) were other limitations. On the other hand, the crossover design allowed a more accurate evaluation of changes in emptying rate and symptom pattern across treatment arms. Finally, we evaluated only one dose of prucalopride, chosen for its use in chronic constipation, but it is unclear whether this is the optimal dosing for gastroparesis.

In summary, this single-center crossover study of prucalopride showed symptomatic benefit of the drug in gastroparesis and in the subgroup of patients with idiopathic gastroparesis. These encouraging findings should be confirmed in a larger, multi-setting, parallel-group design study, and prucalopride's efficacy in postprandial distress syndrome without delayed emptying also merits studying.

CONFLICTS OF INTEREST

Guarantor of the article: Jan Tack, MD, PhD.

Specific author contributions: J.T., C.J.A., A.P. contributed to the design of the study. J.T. obtained funding. J.T., L.H., P.C., J.A., and T.V. recruited patients. L.H. contributed to data collection. F.C., K.V., E.C., and L.V. contributed to data analysis. J.T., F.C., K.V., and E.G. drafted the manuscript.

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Potential competing interests: J.T. has given scientific advice to AlfaWassermann, Allergan, Christian Hansen, Danone, Grünenthal, Ironwood, Janssen, Kiowa Kirin, Menarini, Mylan, Neutec, Novartis, Noventure, Nutricia, Shionogi, Shire, Takeda, Theravance, Tramedico, Truvion, Tsumura, Zealand and Zeria pharmaceuticals, and has served on the Speaker bureau for Abbott, Allergan, AstraZeneca, Janssen, Kyowa Kirin, Menarini, Mylan, Novartis, Shire, Takeda, Truvion and Zeria. T.V. has given scientific advice to Dr. Falk, Shire, Takeda, Therachon, Tramedico and Zealand, and has served on the speaker bureau for Abbott, Kyowa Kirin, Menarini, Truvion and Will Pharma. Medication for this study was provided by Shire pharmaceuticals, Belgium.

Study Highlights

WHAT IS KNOWN

- ✓ Gastroprokinetic agents are favored for the treatment of gastroparesis, but there is a lack of evidence for their efficacy, and there are no agents of proven efficacy available.
- ✓ Prucalopride is a selective 5-HT_4 agonist, developed for the treatment of chronic constipation, which was shown to enhance the gastric emptying rate.

WHAT IS NEW HERE

- ✓ In this single-center placebo-controlled crossover trial, enrolling patients with predominantly idiopathic gastroparesis, prucalopride 2 mg daily was superior to placebo in improving symptoms, as assessed by the Gastroparesis Cardinal Index.
- ✓ Prucalopride also improved upper GI symptoms in a broad sense and QOL impact, as measured, respectively, by the PAGI-SYM and PAGI-QOL questionnaires.
- ✓ Prucalopride enhanced the gastric emptying rate.
- ✓ Prucalopride was well tolerated.

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