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Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation – a 12-week, randomized, double-blind, placebo-controlled study

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SUMMARY

Background
Chronic constipation may result in disabling symptoms, is often unsatisfactorily treated by laxatives and negatively impacts quality of life (QoL).

Aim
A randomized, double-blind, placebo-controlled, phase III trial to evaluate the efficacy and safety of a selective, high-affinity 5-HT_4 receptor agonist, prucalopride, in patients with chronic constipation [≤2 spontaneous complete bowel movements (SCBMs)/week].

Methods
Placebo, 2 or 4 mg prucalopride was administered orally once daily, for 12 weeks. The primary efficacy endpoint was the proportion of patients with ≥3 SCBMs/week, averaged over 12 weeks. Other assessments included BM frequency, constipation-related QoL and symptoms and tolerability.

Results
Among 641 patients, significantly more patients taking prucalopride 2 or 4 mg (24%) than placebo (12%), achieved the primary efficacy endpoint (≥3 SCBMs/week) or an increase of ≥1 SCBMs/week; 43% and 47% vs. 28% respectively. Prucalopride-treated patients also achieved significantly greater satisfaction with treatment and bowel function, and improved perception of constipation severity and constipation-related QoL, compared with placebo. Most frequent treatment-related adverse events were headache, abdominal pain, nausea and diarrhoea (mainly during day 1). There were no differences in comparison to placebo in the incidence of serious adverse effects or cardiovascular events.

Conclusion
Over 12 weeks, prucalopride was effective and well tolerated in chronic constipation.

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INTRODUCTION

Constipation is a common disorder that may result in chronic and disabling symptoms.[1] Prevalence estimates range from 10% to 15% in developed countries,[2, 3] but up to 27% of North Americans may be afflicted.[4] Constipation is twice as common in women than in men and it appears to increase with advancing age, particularly after the age of 65.[4]

Constipation is often a long-term and persistent problem and, although half of all constipation sufferers experience symptoms for three or more years, many[3] do not seek medical advice, opting instead for over-the-counter (OTC) remedies that they may continue to take for more than 10 years.[5, 6] However, dissatisfaction with OTC or prescription treatments is high, mainly due to lack of efficacy (82% of participants in a US-based survey) and concerns regarding adverse events (AEs) (16%).[1]

Health-related quality of life (QoL) is lower in constipated than nonconstipated patients,[2] worsening as the severity of constipation-related symptoms increases.[5, 7–10] In addition, the impact of constipation on QoL has been shown to be comparable to that observed among patients with a history of diabetes, hypertension, heart disease or depression.[5, 11] Other consequences of chronic constipation are substantial direct (e.g. related to evaluation and treatment) and indirect (e.g. work absenteeism and presenteeism) costs,[2, 12] making this disorder a major public health issue.[13]

Physicians mainly define constipation based on the number and frequency of stools. However, patients commonly view it as a symptom complex, with bloating, straining, hard stools, abdominal discomfort and a feeling of incomplete evacuation after a bowel movement (BM) being just as bothersome as infrequent BMs.[1] The recently developed Rome III criteria provide a structured framework for the diagnosis and clinical study of chronic constipation, based on the presence of defined symptoms at least 25% of the time for at least 3 months.[14]

Although currently available laxatives have been reported to be more effective than placebo at providing some symptom relief in the short-term,[15] rigorous data from longer-term randomized clinical trials (i.e. 12 weeks or more) are available for very few agents (e.g. PEG 3550), which may not be widely available. Most laxatives do not provide relief for associated symptoms,[16] or directly target the underlying pathophysiology, such as subtle abnormalities of the enteric nervous system (ENS)[17, 18] or colonic smooth muscle.

New approaches to treating constipation include chloride channel activators (which stimulate intestinal fluid secretion), neurotrophins, and serotonergic agents with enterokinetic properties. Serotonin 5-HT_4 receptor agonists (e.g. cisapride, tegaserod, mosapride) have proven useful in enhancing intestinal motility.[19–23] However, these agents lack selectivity for 5-HT_4 receptors, and interact with other receptors, such as 5-$HT_{1B/D}$ (tegaserod), and the cardiac hERG (human ether-a-go-go related gene) potassium channel (cisapride), within the same concentration range which has been suggested to be the basis for cardiac side effects.[24–28]

Prucalopride (a dihydrobenzofurancarboxamide derivative) is the first selective, high-affinity 5-HT_4 agonist; it has potent enterokinetic effects and minimal interactions at nontarget sites (e.g. 5-HT_1, 5-HT_2, hERG potassium channels). Prucalopride is eliminated without extensive metabolism. Therefore, prucalopride has a low potential for drug-drug interactions and the co-administration of drugs that inhibit CYP450 will have no clinically relevant effect on prucalopride plasma concentrations.[29]

Early studies reported significantly improved colonic motility and transit, increased frequency of BMs, and greater satisfaction with bowel function in individuals taking prucalopride.[30–34]

The objective of this phase III, placebo-controlled trial was to evaluate the efficacy of once-daily oral prucalopride (2 and 4 mg tablets), compared with placebo, over 12 weeks of treatment, in providing global relief of symptoms, normalization of bowel function, and patient satisfaction, and in improving QoL in chronic constipation. Safety and tolerability were also investigated.

MATERIALS AND METHODS

This was a multicentre, randomized, double-blind, placebo-controlled, parallel-group trial, consisting of a 2-week placebo run-in period and 12 weeks of treatment with placebo or prucalopride.

The study was conducted at 41 centres in the US from May 1998 to May 1999. Two factors have contributed to the delay between data collection and submission of this study for publication: the transfer of prucalopride (and other assets) from Johnson &

Johnson (Raritan, NJ, USA) to Movetis (Turnhout, Belgium) between 2003 and 2006, and the compilation of an extensive safety and toxicology package between 1999 and 2003.

The study was conducted in accordance with ICH-Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws and regulations. The protocol was approved by the appropriate independent ethics committees of participating centres and patients gave written informed consent. The trial was registered on http://clinicaltrials.gov (number: NCT00485940).

Patients

The study enrolled men and women over 18 years of age (excluding women who were pregnant or breast feeding), with a history of self-reported chronic constipation for at least 6 months that was not secondary to drug use, surgery, organic disorders of the large bowel or other disorders.

Chronic constipation was defined as an average of ≤2 spontaneous complete BMs (SCBMs)/week over the past 6 months or more as well as the occurrence of one or more of the following for at least 6 months before the selection visit:

(i) very hard (like little pellets) and/or hard stools for at least 25% of the time

(ii) sensation of incomplete evacuation at least 25% of the time or

(iii) straining during defecation at least 25% of the time.

Additional exclusion criteria included presence of severe or clinically uncontrolled cardiovascular, liver, or lung disease, neurological or psychiatric disorders, cancer or AIDS, other gastrointestinal or endocrine disorders, impaired renal function and previous treatment with prucalopride. Women of child-bearing potential were required to have adequate contraceptive protection during the study. Patients with no BMs for 3 consecutive days were allowed up to 15 mg (three tablets) of bisacodyl (Dulcolax, Boehringer Ingelheim Consumer Healthcare, Ridgefield, CT, USA); an enema could be administered after unsuccessful bisacodyl treatment. Rescue medication was not allowed within 48 h before, or after the first dose of trial medication.

Following screening for inclusion eligibility, patients underwent a 2-week placebo run-in (to monitor frequency of BMs), and patients with an average of ≤2 SCBMs/week during run-in were eligible for randomization to one of three treatment groups, according to a randomization code generated by the study sponsor (Janssen Research Foundation, Beerse, Belgium). Balancing using a block size of 3 ensured that approximately equal numbers of patients entered each treatment group.

Patients were allocated to receive 2 mg prucalopride, 4 mg prucalopride or placebo, which they were instructed to take as one tablet daily before breakfast. All study medication was supplied in identical containers; tablets were identical in appearance, taste and smell. All study personnel and patients were blinded to the study treatments.

Daily diaries. From the start of the 2-week run-in period until the end of the trial, patients recorded laxative and study drug intake and details of BMs (rating straining, consistency and feeling of incomplete evacuation for each BM) in a daily diary.

For patients who did not complete all 84 days (12 weeks) of their diary, provided they had ≥7 completed diary days after week 1, the diary information from the last week with available data was copied and imputed up to day 84. The average number of SCBMs over these 84 days was used to assess whether the primary endpoint (≥3 SCBMs/week) was met. Patients with <7 completed days of diary information were considered nonresponders.

A BM was considered spontaneous if it occurred >24 h after the last laxative intake. Baseline values for diary endpoints were the weekly averaged scores over the entire run-in period. Baseline values for data collected at the visits were the predose values obtained at the randomization visit.

Patient global assessments. Patient global assessments (of the severity of constipation over the past 2 weeks and of the efficacy of treatment) on five-point Likert scales were conducted at 2, 4, 8 and 12 weeks. Higher scores reflect greater severity of constipation and greater efficacy of treatment. The severity of constipation was also rated at baseline.

Self-rated questionnaires. Patient symptom assessments, using the validated Patient Assessment of Constipation – Symptoms (PAC-SYM) questionnaire,[35] were conducted at baseline, 2, 4, 8 and 12 weeks. The severity of 12 constipation-related symptoms was scored on a five-point Likert scale and the items were

grouped into three subscales: stool, abdominal and rectal symptoms. Higher scores reflect greater severity.

Disease-related QoL and general health status were assessed at baseline, 4 and 12 weeks, with the validated Patient Assessment of Constipation – QoL (PAC-QoL) self-report questionnaire[36] and the Medical Outcomes Study Short-Form 36 (SF-36™) questionnaire[37] respectively. The PAC-QoL allows the scoring of 28 items related to the effects of constipation on day-to-day life within four subscales: physical discomfort, psychosocial discomfort, worries and concerns, and satisfaction. Higher scores reflect greater impairment or dissatisfaction. The SF-36™ is a generic health status instrument consisting of eight domains: physical function, role-physical, vitality, general health perceptions, pain, social function, role-emotional and mental health. Summary scores for physical and mental health components were calculated. Total possible scores range from 0 to 100, with higher scores reflecting better QoL.

Safety and tolerability. Adverse events were recorded at 2, 4, 8 and 12 weeks. Vital signs were evaluated at the screening visit, baseline, 2, 4, 8 and 12 weeks. Electrocardiograms (ECGs), clinical laboratory tests and physical examinations were evaluated at screening, 4 and 12 weeks.

Statistical analysis

All randomized patients who took at least one dose of study medication were included in the analyses of safety, demographics and baseline characteristics. Patients who also had at least one postbaseline assessment for one or more key efficacy endpoints were included in the analyses of efficacy and QoL data (intention-to-treat).

Sample size calculations were based on results from dose-finding Phase II trials. A sample size of 594 patients (198 per treatment group) was calculated to be required to detect a significant difference in response rates (assuming 30% response rate for prucalopride, 15% for placebo and a 5% correction for patients providing an insufficient amount of diary data), with a power of 90% and a two-sided, type-1 error rate of 2.5% (correction for two comparisons vs. placebo).

For binary endpoints, the Cochrane–Mantel–Haenszel test, which controls for (pooled) centres, was used to test differences between treatment groups. Holm's step-down procedure was used to correct for the multiple pairwise comparisons. For continuous endpoints, the analysis of covariance was used (with baseline, treatment and centre as factors) to test differences between treatment groups. Dunnett's *t*-test was used to correct for multiple comparisons. All tests were performed with a 5% level of significance.

RESULTS

Patient demographics and disposition

Figure 1 summarizes the trial flow, number of patients in each group, and number of (and reasons for) withdrawals. Between March 1998 and March 1999, 651 patients were randomized to treatment with prucalopride or placebo. Of the 651 patients randomized, 641 patients received study medication (and were included in the study population for analyses of efficacy, safety and QoL) and 567 (89%) completed the study and the 12-week diary. There were comparable rates of discontinuation in the three treatment groups (Figure 1).

Demographic data for the treated patients are shown in Table 1. There were no significant differences between the treatment groups. The average duration of constipation was 22 years, 44% of patients had a history of no spontaneous stools per week, and 80% of patients who had previously taken treatment for their constipation found it inadequate (Table 1).

Primary efficacy endpoint

Proportion of patients reporting ≥3 SCBMs/week, averaged over 12 weeks. Over the run-in period, patients were required to have ≤2 SCBMs/week. A few (1%) patients were found to have ≥3 SCBMs/week during the run-in. During the 12-week treatment period, significantly more patients in the prucalopride 2- and 4-mg groups, compared with the placebo group, reported ≥3 SCBMs/week, averaged over 12 weeks of treatment ($P \leq 0.01$, in both cases; Table 2, Figure 2). Averaged over the first 4 weeks of treatment, a significantly higher proportion of patients in the prucalopride 2- and 4-mg groups (29%) reported an average of ≥3 SCBMs/week than in the placebo group (12%; $P \leq 0.001$, in both cases) (Table 2).

Secondary efficacy endpoints

Endpoints from diaries. Over the run-in period, patients reported an average of 0.4–0.5 SCBM/week.

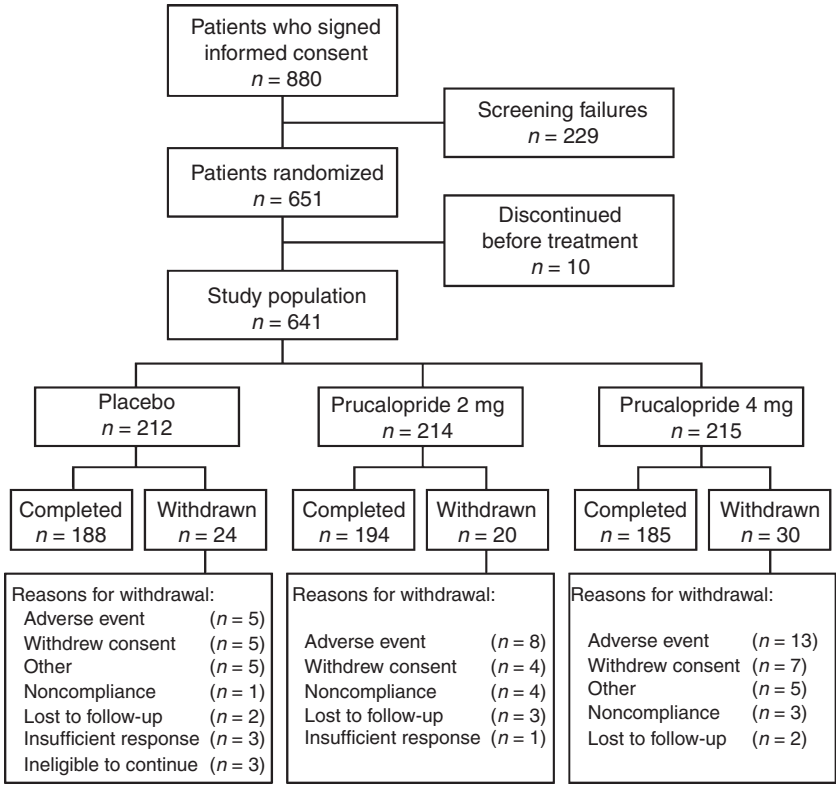

Figure 1. The disposition of patients over time.

Averaged over 12 weeks of treatment, significantly more patients treated with prucalopride than placebo reported an increase from baseline of ≥1 SCBM/week, the key secondary efficacy endpoint ($P \leq 0.001$, prucalopride vs. placebo; Figure 2). Over weeks 1–4, the response rate was 49% (2 mg) and 52% (4 mg) compared with 26% of placebo patients ($P \leq 0.001$, in both cases) (Table 2).

Compared with placebo, other secondary efficacy endpoints (as derived from daily diaries) also improved significantly with prucalopride (2 and 4 mg) (Table 2). Specifically, when averaged over the entire study period (and also over the first 4 weeks of treatment), prucalopride significantly improved: the proportions of patients reporting an increase of ≥1 spontaneous bowel movements (SBM)/week ($P \leq 0.001$, in all cases), the number of SCBM per week ($P \leq 0.001$, in all cases), the percentage of BMs with normal consistency ($P \leq 0.05$, in all cases) and the percentage of BMs with no straining ($P \leq 0.01$, in all cases). In addition, compared with placebo, patients in the prucalopride groups reported using significantly fewer laxatives (bisacodyl) per week ($P \leq 0.01$, in all cases), and significantly fewer days with laxative use or enema per week ($P \leq 0.05$, in all cases). Lastly, both doses of prucalopride significantly reduced the time to first SCBM following the first dose of study medication, compared with placebo ($P \leq 0.001$, in both cases; Table 2).

Patient global assessments. Overall, the patients treated with prucalopride rated the effectiveness of their treatment significantly better than did the placebo group, both at weeks 4 and 12 ($P \leq 0.001$, in both cases; Table 2). In contrast, more patients in the placebo group rated their treatment as 'not at all effective'.

At baseline, the majority of patients in the prucalopride 2- and 4-mg groups (64% and 60% respectively) and the placebo group (58%) rated their constipation as being 'severe' or 'very severe'. At weeks 4 and 12, the prucalopride groups rated their constipation as being significantly less severe than did the placebo group ($P \leq 0.001$, in all cases; Table 2).

Self-rated questionnaires. PAC-SYM: Compared with placebo, patients treated with prucalopride (2 and 4 mg) had significantly greater mean changes from baseline (i.e. improvements) in the overall, stool, and abdominal patient-rated PAC-SYM scores at both week 4 and week 12 ($P \leq 0.05$, in all cases, except for 4 mg

Table 1. Patient demographics and 6-month history of constipation (all treated patients)

Parameter	Placebo (N = 212)	Prucalopride 2 mg (N = 214)	Prucalopride 4 mg (N = 215)	Overall (N = 641)
Race, *n* (%)				
Caucasian	197 (92.9)	183 (85.5)	184 (85.6)	564 (88.0)
Black	9 (4.2)	24 (11.2)	21 (9.8)	54 (8.4)
Hispanic	5 (2.4)	3 (1.4)	7 (3.3)	15 (2.3)
Other	1 (0.5)	1 (0.5)	3 (1.4)	5 (0.8)
Oriental	0	3 (1.4)	0	3 (0.5)
Sex, *n* (%)				
Female	189 (89.2)	181 (84.6)	185 (86.0)	555 (86.6)
Male	23 (10.8)	33 (15.4)	30 (14.0)	86 (13.4)
Age (years)				
Mean (S.E.)	46.2 (0.89)	48.6 (0.97)	49.1 (0.93)	47.9 (0.54)
Range (min–max)	(18–82)	(20–95)	(21–86)	(18–95)
Height (cm)				
Mean (S.E.)	165.3 (0.58)	165.2 (0.6)	165.7 (0.62)	165.4 (0.35)
Range (min–max)	(125–196)	(145–189)	(134–191)	(125–196)
Weight (kg)				
Mean (S.E.)	70.7 (0.99)	71.1 (1.04)	69.6 (1.03)	70.5 (0.59)
Range (min–max)	(45–129)	(40–125)	(41–131)	(40–131)
Duration of constipation (years)				
Mean (S.E.)	21.4 (1.06)	22.7 (1.08)	22.0 (1.17)	22.0 (0.64)
Range (min–max)	(1–71)	(1–63)	(0–82)	(0–82)
Distribution of patients, number of spontaneous stools per week, *n* (%)				
No spontaneous stools	85 (40.1)	96 (44.9)	101 (47.0)	282 (44.0)
>0 and ≤1	65 (30.7)	73 (34.1)	66 (30.7)	204 (31.8)
>1 and ≤3	60 (28.3)	43 (20.1)	43 (20.0)	146 (22.8)
>3	2 (0.9)	2 (0.9)	5 (2.3)	9 (1.4)
Use of previous therapy (laxative, enema), *n* (%)				
Yes	189 (89.2)	189 (88.3)	192 (89.3)	570 (88.9)
No	23 (10.8)	25 (11.7)	23 (10.7)	71 (11.1)
Overall assessment of therapeutic efficacy of previous constipation treatment,* *n* (% of patients with previous treatment)				
Adequate	46 (22.1)	39 (18.6)	39 (18.4)	124 (19.7)
Inadequate	162 (77.9)	171 (81.4)	173 (81.6)	506 (80.3)

* Note: not applicable for 11 patients as they did not use previous therapy.

at week 12 for stool symptoms) (Table 3). In addition, patients in the prucalopride 2-mg group reported significantly greater improvements in rectal symptom scores at week 12 than did patients in the placebo group ($P \leq 0.05$). The proportions of patients with an improvement from baseline of ≥1 point in the overall PAC-SYM score were also significantly higher in the prucalopride groups than in the placebo group at week 4 ($P \leq 0.001$, in both cases), and week 12 in the 2-mg group ($P \leq 0.001$) (Table 3).

PAC-QoL: At week 12, the proportions of patients with an improvement from baseline of ≥1 point in the PAC-QoL satisfaction subscale score (primary QoL endpoint) were significantly higher in the prucalopride 2-mg and 4-mg groups, compared with placebo ($P \leq 0.001$, in both cases; Figure 2). This was also the case at week 4 ($P \leq 0.001$, in both cases; Table 4). Similarly, patients treated with prucalopride (2 or 4 mg) reported significantly greater improvements than patients treated with placebo in overall scores, as well as scores on the 'physical discomfort' and 'worries and concerns' subscales, at weeks 4 and 12 ($P \leq 0.001$, in all cases) (Table 4). Patients treated with 4 mg prucalopride also reported significantly greater

Table 2. Efficacy endpoints (diary data)

	Placebo (N = 212)	Prucalopride 2 mg (N = 214)	Prucalopride 4 mg (N = 215)
Number of patients with an average ≥3 SCBM/week, *n/N* (%)			
Run-in	2/212 (0.9)	1/213 (0.5)	3/215 (1.4)
Weeks 1–12	25/207 (12.1)	50/209 (23.9)**	48/204 (23.5)**
Weeks 1–4	24/208 (11.5)	61/209 (29.2)***	59/204 (28.9)***
Number of patients with an average increase ≥1 SCBM/week, *n/N* (%)			
Weeks 1–12	57/207 (27.5)	89/209 (42.6)***	95/204 (46.6)***
Weeks 1–4	53/208 (25.5)	102/209 (48.8)***	105/204 (51.5)***
Number of patients with an average increase ≥1 SBM/week, *n/N* (%)			
Weeks 1–12	83/207 (40.1)	131/209 (62.7)***	149/207 (73.0)***
Weeks 1–4	89/208 (42.8)	155/209 (74.2)***	167/204 (81.9)***
Average SCBM/week, mean (mean change)			
Run-in	0.4	0.4	0.5
Weeks 1–12	1.2 (0.8)	1.9 (1.5)***	2.0 (1.5)***
Weeks 1–4	1.0 (0.6)	2.1 (1.6)***	2.4 (1.9)***
Percentage of BM with normal consistency, mean (mean change)			
Run-in	23.4	21.6	26.0
Weeks 1–12	35.7 (12.4)	41.7 (19.5)**	46.4 (20.1)***
Weeks 1–4	32.8 (9.6)	38.5 (16.4)*	45.6 (19.3)***
Percentage of BM with no straining, mean (mean change)			
Run-in	20.0	23.0	26.5*
Weeks 1–12	19.0 (−1.4)	26.6 (3.9)**	27.3 (1.2)**
Weeks 1–4	18.0 (−2.3)	28.1 (5.4)***	28.5 (2.4)***
Number of bisacodyl tablets taken/week, mean (mean change)			
Run-in	1.8	2.1	2.2
Weeks 1–12	1.7 (−0.1)	1.4 (−0.7)**	1.2 (−1.0)***
Weeks 1–4	1.8 (−0.1)	1.2 (−0.8)***	1.0 (−1.2)***
Number of days with laxative use [bisacodyl (Dulcolax)] or enema/week, mean (mean change)			
Run-in	0.8	0.9	1.0
Weeks 1–12	0.7 (−0.1)	0.6 (−0.3)*	0.5 (−0.4)***
Weeks 1–4	0.8 (−0.1)	0.5 (−0.3)***	0.4 (−0.5)***
Time to onset of first SCBM (median)			
First SCBM after day 1 dose, h:min	311:00	54:50***	46:15***
Number of patients rating treatment quite a bit or extremely effective, *n/N* (%)			
Week 4	29/199 (14.6)	71/200 (35.5)***	61/196 (31.1)***
Week 12	37/184 (20.1)	75/193 (38.9)***	67/181 (37.0)***
Patient assessment of constipation severity,† mean (mean change)			
Baseline	2.69	2.85	2.72
Week 4	2.34 (−0.36)	1.94 (−0.92)***	1.78 (−0.93)***
Week 12	2.30 (−0.37)	1.86 (−0.98)***	1.90 (−0.80)***

Prucalopride vs. placebo: * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$.
SCBM, spontaneous complete bowel movement; BM, bowel movement.
† None/absent = 0; mild = 1; moderate = 2; severe = 3; very severe = 4.

improvements than did patients on placebo in scores on the 'psychosocial discomfort' subscale at both weeks 4 and 12 ($P \leq 0.01$, in both cases).

SF-36™: At weeks 4 and 12, significantly greater improvements from baseline were seen with 4 mg prucalopride, compared with placebo ($P \leq 0.05$, in

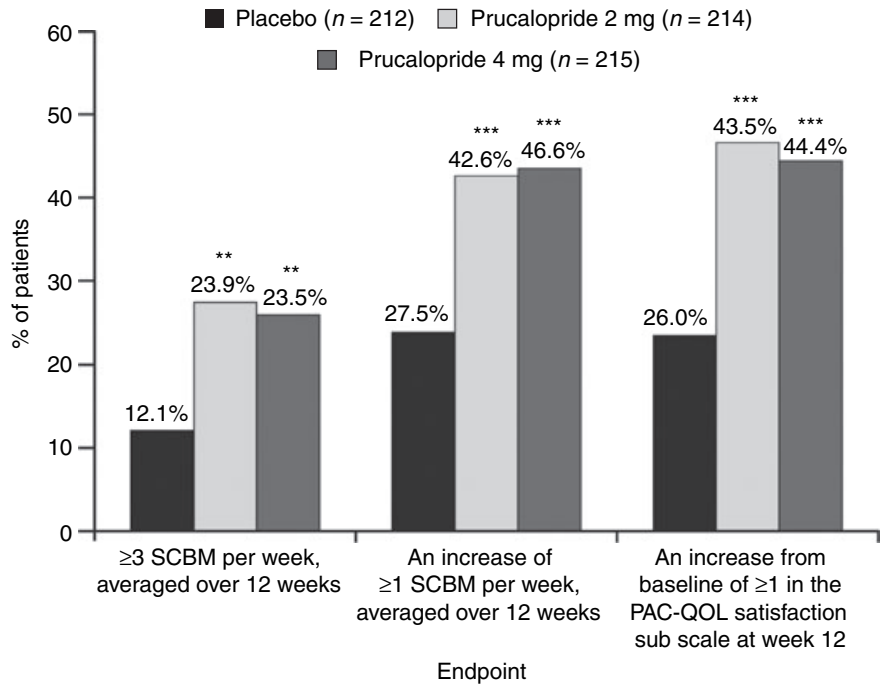

Figure 2. Responder rates for efficacy and quality of life (QoL) endpoints (the proportions of patients achieving: ≥3 spontaneous complete bowel movements (SCBMs)/week; an increase from baseline of ≥1 SCBM/week; an increase from baseline of ≥1 point on the Patient Assessment of Constipation (PAC)-QoL satisfaction subscale). $^{**}P \leq 0.01$; $^{***}P \leq 0.001$, prucalopride (2- and 4-mg groups) vs. placebo.

Table 3. Efficacy endpoints (patient global symptom assessments)

	Placebo (N = 212)	Prucalopride 2 mg (N = 214)	Prucalopride 4 mg (N = 215)
Overall PAC-SYM symptoms score, mean (mean change)			
Baseline	1.97	2.04	1.84
Week 4	1.59 (−0.38)	1.40 (−0.65)***	1.23 (−0.61)***
Week 12	1.52 (−0.45)	1.26 (−0.78)***	1.28 (−0.56)*
Improvement ≥1 overall PAC-SYM score from baseline, n/N (%)			
Week 4	31/199 (15.6)	60/199 (30.2)***	62/194 (32.0)***
Week 12	43/182 (23.6)	73/192 (38.0)***	52/179 (29.1)
PAC-SYM stool symptoms score, mean (mean change)			
Baseline	2.51	2.56	2.29 *
Week 4	2.15 (−0.37)	1.86 (−0.72)***	1.72 (−0.57)***
Week 12	2.07 (−0.45)	1.75 (−0.83)***	1.77 (−0.51)
PAC-SYM abdominal symptoms score, mean (mean change)			
Baseline	1.97	2.02	1.93
Week 4	1.51 (−0.46)	1.32 (−0.71)**	1.11 (−0.82)***
Week 12	1.44 (−0.53)	1.18 (−0.86)***	1.18 (−0.76)**
PAC-SYM rectal symptoms score, mean (mean change)			
Baseline	1.05	1.21	0.98
Week 4	0.76 (−0.28)	0.74 (−0.46)	0.58 (−0.39)
Week 12	0.72 (−0.32)	0.58 (−0.61)*	0.60 (−0.36)

Prucalopride vs. placebo: * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$.
PAC-SYM, Patient Assessment of Constipation – Symptoms questionnaire.

Table 4. Quality of life endpoints

	Placebo (N = 212)	Prucalopride 2 mg (N = 214)	Prucalopride 4 mg (N = 215)
PAC-QOL satisfaction scale score, mean (mean change)			
Baseline	3.43	3.38	3.37
Week 4	3.06 (−0.39)	2.51 (−0.86)***	2.42 (−0.97)***
Week 12	3.01 (−0.44)	2.43 (−0.93)***	2.45 (−0.97)***
Improvement ≥1 PAC-QOL satisfaction score from baseline, n/N (%)			
Week 4	43/193 (22.3)	83/195 (42.6)***	87/194 (44.8)***
Week 12	47/181 (26.0)	83/191 (43.5)***	79/178 (44.4)***
Overall PAC-QOL score, mean (mean change)			
Baseline	2.11	2.18	2.09
Week 4	1.67 (−0.43)	1.43 (−0.77)***	1.29 (−0.80)***
Week 12	1.65 (−0.47)	1.34 (−0.85)***	1.25 (−0.86)***
PAC-QOL Physical discomfort scale score, mean (mean change)			
Baseline	2.40	2.47	2.35
Week 4	1.92 (−0.47)	1.61 (−0.89)***	1.41 (−0.94)***
Week 12	1.85 (−0.55)	1.46 (−1.02)***	1.44 (−0.92)***
PAC-QOL Psychosocial discomfort scale score, mean (mean change)			
Baseline	1.14	1.27	1.18
Week 4	0.79 (−0.34)	0.80 (−0.50)	0.62 (−0.55)**
Week 12	0.77 (−0.38)	0.73 (−0.55)	0.59 (−0.61)**
PAC-QOL Worries and concerns scale score, mean (mean change)			
Baseline	2.12	2.19	2.09
Week 4	1.61 (−0.49)	1.34 (−0.88)***	1.24 (−0.86)***
Week 12	1.60 (−0.54)	1.25 (−0.97)***	1.13 (−0.96)***
SF-36™ PCS scale score, mean (mean change)			
Baseline	46.7	46.4	46.7
Week 4	48.7 (1.6)	48.9 (2.5)	49.5 (2.3)
Week 12	49.4 (2.5)	49.1 (2.7)	49.0 (2.1)
SF-36™ MCS scale score, mean (mean change)			
Baseline	45.9	45.3	46.0
Week 4	47.4 (1.3)	47.6 (2.7)	49.1 (3.3)*
Week 12	47.3 (1.4)	48.6 (3.4)	49.8 (3.8)*

Prucalopride vs. placebo: * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$
PAC-QOL, Patient Assessment of Constipation – Quality of Life questionnaire; SF-36™, 36-item Short Form Health Survey™; PCS, physical component summary of the SF-36™ questionnaire; MCS, mental component summary of the SF-36™ questionnaire.

both cases) on the mental health summary scores of the SF-36™. No other significant differences were observed (Table 4).

Overall efficacy

For each patient, best responses were derived from the three major efficacy endpoints: (i) the primary efficacy endpoint (≥3 SCBM/week, averaged over 12 weeks); (ii) the key secondary efficacy endpoint (an increase from baseline of ≥1 SCBM/week, averaged over 12 weeks) and (iii) the primary QoL endpoint (≥1 point improvement at week 12 on the PAC-QoL satisfaction subscale). The cumulative response rates for these best responses are shown in Figure 3 ($P < 0.001$ for prucalopride groups vs. placebo).

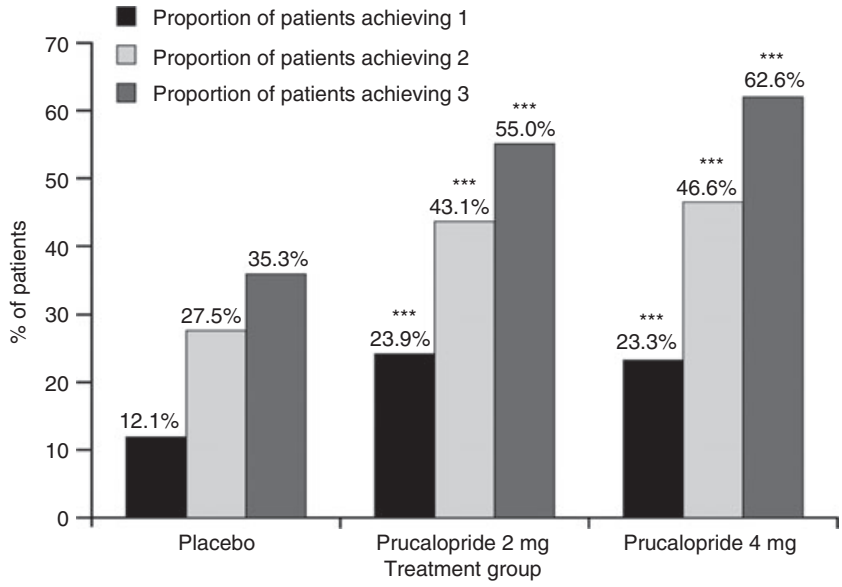

Figure 3. The cumulative response rates for the best responses, derived from the three major efficacy endpoints: (1) the primary efficacy endpoint [≥3 spontaneous complete bowel movements (SCBMs)/week, averaged over 12 weeks]; (2) the key secondary efficacy endpoint (an increase from baseline of ≥1 SCBM/week, averaged over 12 weeks) and (3) the primary quality of life (QoL) endpoint [≥1 point improvement at week 12 on the Patient Assessment of Constipation (PAC)-QoL satisfaction subscale]. ***$P < 0.001$, prucalopride (2- and 4-mg groups) vs. placebo.

Safety and tolerability

Treatment-related AEs were observed in 173 patients (81%) taking 2 mg prucalopride, 163 patients (76%) taking 4 mg prucalopride and 140 patients (66%) taking placebo. The majority were mild or moderate in severity. There were no deaths during the study.

The most frequently reported AEs (>10% in any prucalopride group) were headache, nausea, abdominal pain, diarrhoea and flatulence. These were more commonly reported by patients in the prucalopride groups than patients in the placebo group, mainly on the first day of treatment. Excluding the events occurring on day 1, the incidence of these AEs was similar in the three treatment groups (Figure 4).

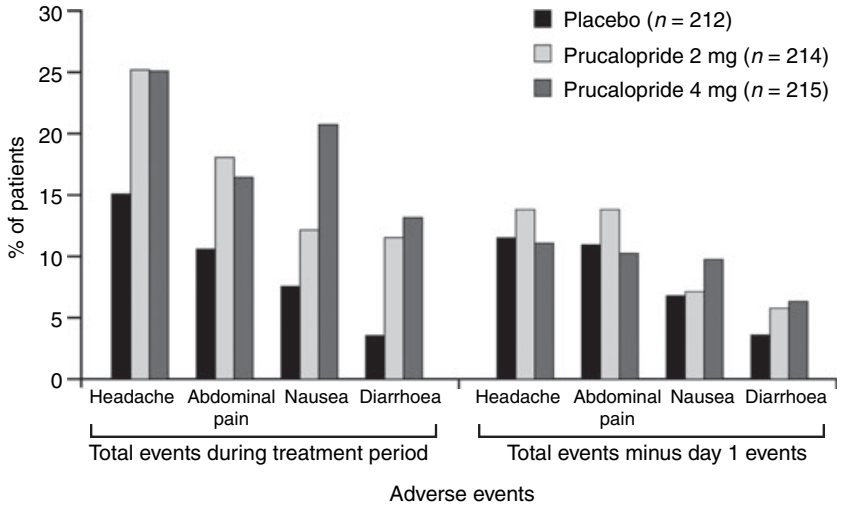

Figure 4. Rates of most frequently reported adverse events over the entire treatment period (left panel) and excluding events reported on day 1 of treatment (right panel).

Table 5. Incidence of prolonged QTc interval at week 12 interval – all (treated) patients

	Placebo		Prucalopride 2 mg		Prucalopride 4 mg	
Corrected QT classification	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)
QTcF	183	0	175	0	172	1 (0.6)
QTcB	164	2 (1.2)	165	1 (0.6)	165	1 (0.6)

N, patients with normal baseline value; *n*, patients with abnormal postbaseline value.
Corrected QT classification was according to Committee for Proprietary Medicinal Products Guidelines.[50]
Normal: <430 ms (M) or <450 ms (F).
Prolonged: >450 ms (M) or >470 ms (F).

Severe AEs were observed in 33 patients (15%) in the 2-mg prucalopride group, 45 patients (21%) in the 4-mg group and 21 patients (10%) in the placebo group. Most severe AEs occurred in the GI system (abdominal pain, diarrhoea, nausea, vomiting, flatulence) and the overall incidence of GI system disorders was comparable in the prucalopride (2 mg: 7.5%; 4 mg: 8.8%) and placebo (5.7%) groups. There was a higher incidence of severe headache in the prucalopride groups (2 mg: 6.5%; 4 mg: 7.4%), compared with placebo (1.9%).

Serious AEs (SAEs) were reported by approximately 2% of patients in each treatment group: four and five patients in the prucalopride 2- and 4-mg groups respectively, and five patients in the placebo group. All SAEs were considered moderate or severe and unrelated or doubtfully related to prucalopride, as there was no consistent pattern in the incidence.

A total of 25 patients permanently discontinued treatment due to treatment-related AEs, and the rate was slightly higher in the prucalopride 4-mg group (6%), compared with the prucalopride 2-mg and placebo groups (4% and 2% respectively).

There were no clinically relevant changes over time in vital signs or ECG parameters. The overall incidence of patients with normal corrected QT intervals at baseline and prolonged corrected QT intervals postbaseline was low and comparable between the treatment groups (Table 5). In addition, no clinically meaningful changes over time were observed in haematology, clinical chemistry or urinalysis parameters in any of the three treatment groups. Furthermore, there were no important differences in the incidence of treatment-emergent laboratory abnormalities between the treatment groups.

DISCUSSION

This 12-week multicentre, randomized, double-blind, placebo-controlled study demonstrates that once daily oral prucalopride (2 or 4 mg) is effective and well tolerated among patients with chronic, severe constipation, including those patients who do not experience adequate relief with prior therapies. Effects on bowel function, associated symptoms, satisfaction with treatment and QoL were prominent at 4 weeks and sustained over the entire 12 weeks of the study.

Our results are consistent with those of Camilleri *et al.*[38] who recently reported that significantly more patients on prucalopride 2 and 4 mg achieved ≥3 SCBMs/week than those on placebo (30.9% and 28.4% vs. 12% respectively) over the 12 weeks of their study; here we report a response rate of 24% for both doses. The placebo response rates for this primary endpoint were low at just 12% in both studies. In both studies, prucalopride resulted in more patients experiencing an increase of ≥1 SCBM/week and an improvement of ≥1 point on the PAC-QoL satisfaction subscale, as well as increases in the number of SCBM per week and improvements in associated symptoms that are regarded as relevant to patient experience and satisfaction.[38] While these responses were sustained over the 3-month study period and could predict longer-term efficacy, this latter issue can only be addressed in truly long-term studies.

Importantly, prucalopride also significantly improved stool consistency, reduced straining and the sensation of complete evacuation (many SCBMs were associated with no straining and with a normal stool consistency), and led to improvements in the PAC-SYM overall, stool and abdominal symptom scores, as compared to placebo. These results are noteworthy as

more than 70% of constipated patients rate hard stool, straining, bloating, abdominal discomfort and feelings of incomplete evacuation as 'extremely', 'very' or 'somewhat' severe.[1] The documented improvements in symptoms such as straining and incomplete evacuation are also deserving of comment given that this was a heterogenous population and not selected on the basis of underlying pathophysiology.

Johanson *et al.*[1] recommend that therapies for constipation should address 'at least several' of the following attributes rated as most important by patients: relief of constipation symptoms (straining; hard/-lumpy, infrequent stools), improved quality of BMs, tolerability, predictable response time, multisymptom relief, long-term use and efficacy in alleviating bloating.

The stringent primary efficacy endpoint of ≥3 SCBMs/week is considered clinically meaningful, as it reflects not only normalization of bowel function in terms of frequency but it also identifies those BMs that fully relieve one of the key symptoms of chronic constipation (i.e. sense of incomplete evacuation). A BM was only defined as spontaneous if no rescue laxatives were taken in the 24 h preceding that BM, which added to the challenge of reaching three or more SCBM in any particular week. Almost half (47%) of the patients in the prucalopride group achieved the key secondary efficacy endpoint (increase of ≥1 SCBM/week), a threshold that is considered appropriate as a primary efficacy endpoint in constipation trials.[39] An improvement of one point in the PAC-QoL questionnaire is considered to be a clinically relevant therapeutic response.[36] The effects on QoL, as assessed by the SF-36, were limited, as might be expected when using a generic rather than a disease-specific instrument.

Traditional laxatives have little consistent evidence of satisfactory treatment of the multiple symptoms associated with chronic constipation, beyond BM frequency.[1, 16] Hence, a goal of new therapies is more effective relief of the full range of constipation symptoms. The results we report herein with prucalopride are difficult to compare with other agents because of differences in study design, study duration and endpoints. We demonstrated an increase in SCBM frequency of 1.5 SCBMs, compared to 0.8 SCBMs/week with placebo. Tegaserod in a dose of 6 mg b.d. was reported to increase SCBM by 1.3 per week, compared with 0.7 with its placebo.[40] Lubiprostone (24 μg b.d.), a chloride channel activator, has been shown to: improve the frequency of spontaneous BMs (SCBMs were not investigated); improve a range of patient-reported constipation symptoms (stool consistency, straining, constipation severity, abdominal bloating and abdominal discomfort); and improve scores for patient-rated global treatment effectiveness, compared with placebo, over 4 weeks.[41] It remains to be determined whether its benefits are maintained with longer treatment. Rigorous QoL data on current therapies are limited.[42–45] We readily acknowledge that only direct comparisons of prucalopride with traditional or newer remedies will provide a precise assessment of the relative efficacy of all of these agents in chronic constipation.

Both doses of prucalopride were well tolerated, and the most frequently reported treatment-related AEs (headache, abdominal pain, nausea and diarrhoea) occurred mainly on the first day of treatment. The rates of occurrence of these AEs after day 1 were similar between placebo and prucalopride. The incidence of nausea was lower with prucalopride (12% with 2 mg, 21% with 4 mg) in comparison to a rate of 31.7% that has been reported with lubiprostone.[41]

Cardiovascular effects have been a concern with nonselective 5-HT_4 receptor agonists. *In vitro* studies with prucalopride have shown no relevant interactions with the hERG potassium channel or other nontarget sites (e.g. 5-HT_{2A}, 5-HT_{2B}, 5-HT_3 receptors) within the same concentration range as interactions with the 5-HT_4 receptor.[28, 46] Extensive safety data has been accumulated from human studies on prucalopride. Such studies have included the evaluation of cardiovascular safety at doses of up to 20 mg/day[47] as well as ECG measurements in efficacy trials;[32, 34, 38, 48, 49] none have revealed any evidence to date of QTc prolongation or related sequelae with prucalopride. In the current study, in which 25% of patients had stable cardiovascular disease at entry, no differences were observed in the incidence of clinically relevant cardiac events between prucalopride and placebo. Among patients with normal QTc at baseline, the incidence of prolonged QTc at 4 and 12 weeks was low in both prucalopride and placebo groups (~1%). Recognizing the limitations of any clinical trial to detect very rare events, continued cardiovascular monitoring in larger samples may be valuable to fully confirm the cardiovascular safety identified thus far.

In conclusion, in patients with an average 22-year history of constipation, 80% of whom found previous treatment inadequate, prucalopride significantly

improved symptoms associated with chronic constipation and normalized bowel function in more patients, compared to placebo. These effects were sustained over the 12 week study period and prucalopride was well tolerated. Prucalopride also improved QoL and satisfaction with bowel function and treatment, in patients with chronic constipation.

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