

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Prucalopride for Severe Chronic Constipation

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ABSTRACT

BACKGROUND

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In this 12-week trial, we aimed to determine the efficacy of prucalopride, a selective, high-affinity 5-hydroxytryptamine₄ receptor agonist, in patients with severe chronic constipation.

METHODS

In our multicenter, randomized, placebo-controlled, parallel-group, phase 3 trial, patients with severe chronic constipation (≤ 2 spontaneous, complete bowel movements per week) received placebo or 2 or 4 mg of prucalopride, once daily, for 12 weeks. The primary efficacy end point was the proportion of patients having three or more spontaneous, complete bowel movements per week, averaged over 12 weeks. Secondary efficacy end points were derived from daily diaries and validated questionnaires completed by patients. Adverse events, clinical laboratory values, and cardiovascular effects were monitored.

RESULTS

Efficacy was analyzed in 620 patients. The proportion of patients with three or more spontaneous, complete bowel movements per week was 30.9% of those receiving 2 mg of prucalopride and 28.4% of those receiving 4 mg of prucalopride, as compared with 12.0% in the placebo group ($P < 0.001$ for both comparisons). Over 12 weeks, 47.3% of patients receiving 2 mg of prucalopride and 46.6% of those receiving 4 mg of prucalopride had an increase in the number of spontaneous, complete bowel movements of one or more per week, on average, as compared with 25.8% in the placebo group ($P < 0.001$ for both comparisons). All other secondary efficacy end points, including patients' satisfaction with their bowel function and treatment and their perception of the severity of their constipation symptoms, were significantly improved with the use of 2 or 4 mg of prucalopride as compared with placebo, at week 12. The most frequent treatment-related adverse events were headache and abdominal pain. There were no significant cardiovascular effects of treatment.

CONCLUSION

Over 12 weeks, prucalopride significantly improved bowel function and reduced the severity of symptoms in patients with severe chronic constipation. Larger and longer trials are required to further assess the risks and benefits of the use of prucalopride for chronic constipation. (ClinicalTrials.gov number, NCT00483886.)

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CONSTIPATION AFFECTS 14.7% OF THE U.S. population,¹ specifically 16% of children² and 15 to 50% of the elderly,³ and it is more common in women than in men.⁴ Patients associate constipation with several symptoms: infrequent bowel movements, hard or lumpy stools, straining, bloating, the feeling of incomplete evacuation after a bowel movement, and abdominal discomfort.⁵ Health-related quality of life is negatively affected by the presence of chronic constipation⁶ and by its severity.^{7,8} Reduced colonic motility is one of the pathophysiological mechanisms in severe chronic constipation.⁵

There is insufficient evidence from randomized, controlled trials to assess the long-term effectiveness and side-effect profile of laxatives in patients with severe chronic constipation.⁹⁻¹¹ In recent years, the nonselective serotonin 5-hydroxytryptamine₄ (5-HT₄) receptor agonist tegaserod and the chloride-channel activator lubiprostone have been used in the United States to treat chronic constipation.^{12,13}

Prucalopride, a dihydrobenzofurancarboxamide derivative, is a selective, high-affinity 5-HT₄ receptor agonist, which accounts for its enterokinetic effects.^{14,15} It differs from cisapride, tegaserod, mosapride, and renzapride, which — in contrast with prucalopride and other 5-HT₄ receptor agonists — interact in part with one or more other receptors (such as 5-hydroxytryptamine₃, 5-hydroxytryptamine_{1B} [5-HT_{1B}], and the human ether-a-go-go-related protein [hERG] channel) at levels relevant to their action on 5-HT₄ receptors.¹⁶ The effects on the hERG channel or the 5-HT_{1B} receptor may lead to an unfavorable cardiovascular profile.

Prucalopride increases colonic motility and transit.¹⁷⁻²⁰ In phase 2B, placebo-controlled trials, the frequency of bowel movements and satisfaction with bowel function were both significantly improved with the use of prucalopride.^{19,20}

In our phase 3, placebo-controlled trial, we aimed to determine the efficacy, safety, and effect on quality of life of 2-mg and 4-mg doses of oral prucalopride, given once daily for 12 weeks, in patients with severe chronic constipation.

METHODS

STUDY DESIGN

A multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial was conducted at 38 centers in the United States during

a period of 12 months, from April 1998 to May 1999. For all evaluations, participants were asked to attend the research centers after having fasted in the morning.

The trial was conducted in accordance with the Good Clinical Practice Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Declaration of Helsinki, and local laws and regulations, and the protocol was reviewed and approved by the ethics committees of participating centers. Participants gave written informed consent.

The study was designed by Johnson & Johnson, and the academic author and one industry author participated in the development of the study design and protocol in 1998. Data gathering and analysis were performed by Johnson & Johnson, and the analysis was finalized by Movetis. Since the data had never been published, in 2007, Movetis sought collaboration of the academic author to review the study files and data, and a joint decision was made that these data were of general interest and should be published. The authors vouch for the completeness and veracity of the data and data analyses.

ELIGIBILITY OF PATIENTS

For inclusion, adult patients (≥18 years of age) of either sex had to have a history of chronic constipation, defined as two or fewer spontaneous, complete bowel movements per week for a minimum of 6 months before the screening visit. In addition, patients had to have very hard or hard stools, a sensation of incomplete evacuation, or straining during defecation with at least 25% of bowel movements. A bowel movement was considered spontaneous when it occurred more than 24 hours after the last intake of a laxative.

Patients were ineligible if the constipation was secondary to drugs, to endocrine, metabolic, or neurologic disorders, to surgery, or to organic disorders of the large intestine or megacolon or if they had uncontrolled cardiovascular, liver, psychiatric, or lung diseases, a serum creatinine level of more than 180 μmol per liter (2.0 mg per deciliter), or abnormal laboratory values that were deemed clinically significant on the basis of pre-specified values.

RANDOMIZATION

The 12-week treatment period was preceded by a 2-week run-in phase after the screening visit. To

undergo randomization at the end of the run-in period, patients had to have an average of two or fewer spontaneous, complete bowel movements per week during the run-in period. At each center, patients were assigned consecutive numbers, starting with the lowest number available, and were randomly assigned, with the use of a block size of three, to receive one of three treatments: placebo, 2 mg of prucalopride, or 4 mg of prucalopride. The study drug was taken orally before breakfast. Group assignment was concealed from participants and investigators.

DISALLOWED MEDICATION

The use of laxatives was not permitted, except as follows. If patients did not have a bowel movement for 3 or more consecutive days during the trial, they were permitted to take up to 15 mg of bisacodyl (Dulcolax, Boehringer Ingelheim) as rescue medication, followed by the use of an enema if the bisacodyl was ineffective. Such use of rescue medication was documented. Bisacodyl and enemas were disallowed during the 48-hour periods before and after the start of double-blind treatment, in order not to compromise assessment of the time to the first bowel movement after the start of treatment.

ASSESSMENTS

Diaries

From the start of the 2-week run-in period through the end of the trial, patients recorded in daily diaries the timing of bowel movements, stool consistency, degree of straining during defecation, sensation of complete or incomplete evacuation, and date and time of intake of the study drug and of bisacodyl.

The primary efficacy end point was the proportion of patients having, on average, three or more spontaneous, complete bowel movements per week during the 12 weeks of the trial. Thus, the total number of spontaneous bowel movements associated with a feeling of complete evacuation was summed and divided by 12 (the number of weeks of treatment). The data were also summarized for each of the three 4-week periods of the 12-week study, to assess the response over time. Imputations were performed for patients who did not complete the diary through day 84 but who had at least 7 nonmissing diary days after week 1. The last 7 diary days with available data were used to fill the missing diary days

through day 84. Such imputations were performed in about 15% of patients, equally distributed among the three study groups. Patients with fewer than 7 diary days after week 1 were considered nonresponders.

The main secondary efficacy end point was the proportion of patients with an average increase of one or more spontaneous, complete bowel movements per week as compared with the baseline number. Other secondary end points were the average number of spontaneous, complete bowel movements per week; the percentage of bowel movements with normal consistency; the percentage of bowel movements with severe or very severe straining during defecation; the median time to the first spontaneous, complete bowel movement after intake of the first dose of trial medication; the average number of bisacodyl tablets or enemas used per week; and the patient's global assessment of efficacy of treatment at baseline and at weeks 2, 4, 8, and 12 with the use of a 5-point Likert scale, ranging from "not at all effective" (0) to "extremely effective" (4).

Questionnaires

On the basis of the validated Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaire²¹ at baseline and at weeks 2, 4, 8, and 12, data about 12 constipation-related symptoms were obtained and scored on three subscales: stool, abdominal, or rectal symptoms. For the overall scale and for each subscale, scores can range from 0 (symptoms absent) through 4 (symptoms very severe).

At baseline and at weeks 4 and 12, the validated Patient Assessment of Constipation Quality of Life (PAC-QOL) self-report questionnaire²² permitted patients to score 28 items related to the effects of constipation on their daily lives, on four subscales: physical discomfort, psychosocial discomfort, worries and concerns, and satisfaction. For each item, scores can range from 0 through 4, with lower scores indicating a better quality of life. The primary quality-of-life end point was the satisfaction score, and the main analysis assessed the proportion of patients with an improvement in the score of more than 1 point.

The Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36)²³ was used to assess the general health status of patients on a scale of 0 to 100. Higher scores indicate better health status.

Safety Assessments

Data from patients who took at least one dose of the trial medication were included in the assessment of drug safety. Adverse events were reported at 2, 4, 8, and 12 weeks. Vital signs were evaluated at the screening visit, at baseline, and at 2, 4, 8 and 12 weeks. Results of electrocardiography, clinical laboratory tests, and physical examinations were evaluated at screening and at weeks 4 and 12. The heart rate, the QT interval corrected with the use of Fridericia's formula (QTcF), and the proportions of patients with a QTcF of 471 to 500 msec and those with a QTcF of more than 500 msec were tabulated for the three study groups. The cutoff value was 470 msec because the vast majority of patients were women, and the risk of cardiac arrhythmias associated with prolongation of the corrected QT interval (QTc) in women appears to be associated with a QTc of more than 470 msec.²⁴

STATISTICAL ANALYSIS

The study population for the analysis of efficacy and health-related quality-of-life variables comprised the patients who received at least one dose of trial medication and had at least one post-baseline diary assessment. In addition, a separate per-protocol analysis excluded data from patients with an average of more than two spontaneous, complete bowel movements per week during the run-in period, those who used laxatives on more than 3 days per week on average, and those whose compliance with the trial medication was less than 75%.

The primary evaluation was based on pairwise comparisons of the groups receiving each dose of prucalopride with the placebo group. The Cochran–Mantel–Haenszel test controlling for differences between centers was used to test differences between the three study groups in the binary responses regarding efficacy. Holm's procedure was used to correct for the multiple pairwise comparisons. For continuous data, analysis of covariance was used, including factors for study group, baseline value, and center, to evaluate differences among the three groups. Dunnett's test was used to correct for the multiple comparisons. There were no interim analyses of efficacy. All reported P values are two-sided and were not adjusted for multiple testing, unless otherwise indicated. P values of less than 0.05

were considered to indicate statistical significance.

On the basis of results from dose-finding phase 2 trials,^{19,20} we calculated that 188 patients were required in each of the three groups, assuming response rates of 15% for patients receiving placebo and 30% for those receiving either the 2-mg or 4-mg dose of prucalopride, a statistical power of 90%, and a two-sided type I error rate of 2.5% (for the comparison of each prucalopride group with the placebo group). Assuming that 5% of patients would provide insufficient diary data, we planned to enroll 198 patients in each of the three study groups.

RESULTS

ENROLLMENT AND BASELINE CHARACTERISTICS OF THE PATIENTS

Between April 1998 and February 1999, 628 patients were randomly assigned to receive one of three study drugs once daily: placebo (213 patients), 2 mg of prucalopride (210), or 4 mg of prucalopride (205). Eight patients discontinued the study before the 12-week treatment period began; thus, 620 patients were included in the study population for analyses of efficacy, safety, and quality of life (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

There were no significant differences in baseline characteristics among the three groups (Table 1). A total of 85% of patients completed the trial and the 12-week diary. Imputations for diary data for 4 or more weeks were needed in 11% of patients receiving placebo, 15% of those receiving 2 mg of prucalopride, and 13% of those receiving 4 mg of prucalopride.

PRIMARY EFFICACY END POINT

During the run-in period, patients reported an average of 0.5 spontaneous, complete bowel movement per week. The percentage of patients having three or more spontaneous, complete bowel movements per week, averaged over 12 weeks of treatment, was 30.9% (64 of 207 patients) in the group receiving 2 mg of prucalopride, 28.4% (58 of 204) for the group receiving 4 mg of prucalopride, and 12.0% (25 of 209) for the group receiving placebo (P<0.001 for both comparisons with the placebo group) (Fig. 1 and Table 2).

Table 1. Baseline Characteristics of the Patients and Characteristics of Their History of Constipation during the Previous 6 Months.

Characteristic	Prucalopride, 2 mg (N=207)	Prucalopride, 4 mg (N=204)	Placebo (N=209)	All (N=620)
Race or ethnic group — no. (%) [*]				
White	188 (90.8)	186 (91.2)	182 (87.1)	556 (89.7)
Black	13 (6.3)	9 (4.4)	18 (8.6)	40 (6.5)
Hispanic	5 (2.4)	8 (3.9)	4 (1.9)	17 (2.7)
Asian	1 (0.5)	1 (0.5)	2 (1.0)	4 (0.6)
Other	0	0	3 (1.4)	3 (0.5)
Sex — no. (%)				
Female	188 (90.8)	174 (85.3)	183 (87.6)	545 (87.9)
Male	19 (9.2)	30 (14.7)	26 (12.4)	75 (12.1)
Age — yr				
Mean (±SE)	48.2±1.0	47.8±1.0	48.9±0.9	48.3±0.6
Range	20–83	18–85	18–81	18–85
Height — cm				
Mean (±SE)	164.7±0.6	165.0±0.6	164.7±0.6	164.8±0.4
Range	132–193	137–185	107–191	107–193
Weight — kg				
Mean (±SE)	69.3±1.0	68.6±1.0	68.4±1.0	68.8±0.6
Range	45–141	40–141	42–131	40–141
Duration of constipation — yr				
Mean (±SE)	21.1±1.1	20.5±1.1	21.6±1.2	21.1±0.7
Range	1–78	1–79	1–77	1–79
Average frequency of spontaneous stools per week, 6 mo before study entry — no. (%)				
0	77 (37.2)	76 (37.3)	79 (37.8)	232 (37.4)
>0 to ≤1	79 (38.2)	77 (37.7)	78 (37.3)	234 (37.7)
>1 to ≤3	50 (24.2)	46 (22.5)	49 (23.4)	145 (23.4)
>3	1 (0.5)	5 (2.5)	3 (1.4)	9 (1.5)
Overall assessment of therapeutic efficacy of previous treatment of constipation — no. (%) [†]				
Adequate	34 (16.9)	32 (16.1)	32 (15.8)	98 (16.3)
Inadequate	167 (83.1)	167 (83.9)	170 (84.2)	504 (83.7)

* Race or ethnic group was reported by the investigator.

† Data on the therapeutic efficacy of previous treatment were not applicable for the 18 patients who had not received previous treatment (7 in the placebo group, 6 in the group receiving 2 mg of prucalopride, and 5 in the group receiving 4 mg of prucalopride).

Over the first 4 weeks of treatment, there was an average of three or more spontaneous, complete bowel movements per week in 33.8% of patients receiving 2 mg of prucalopride and 36.3% of those receiving 4 mg of prucalopride, as compared with 10.0% in the placebo group ($P<0.001$ for both comparisons) (Fig. 1). Similar efficacy was observed during weeks 5 through 8 and 9 through 12 (Fig. 1). The per-protocol analysis of data averaged over the 12 weeks of treatment showed

similar response rates (31.6% of patients receiving 2 mg of prucalopride, 29.0% of those receiving 4 mg of prucalopride, and 12.1% of those receiving placebo).

SECONDARY EFFICACY END POINTS

Averaged over 12 weeks, the percentage of patients with an increase by one or more in the number of spontaneous, complete bowel movements per week was 47.3% for 2 mg of prucalo-

pride and 46.6% for 4 mg of prucalopride, as compared with 25.8% of those in the placebo group ($P < 0.001$ for both comparisons) (Table 2).

Several end points were significantly improved in each of the prucalopride groups as compared with the placebo group ($P < 0.001$ for each comparison) (Table 2): the average number of spontaneous, complete bowel movements per week, the percentage of bowel movements with normal consistency or with severe or very severe straining during defecation over the 12-week period, the median time to the first spontaneous, complete bowel movement, and the percentage of patients quite satisfied or extremely satisfied with treatment efficacy during the 12-week period. In addition, the use of prucalopride (2 mg or 4 mg), as compared with placebo, significantly reduced the use of laxative during the treatment period ($P < 0.001$) (Table 2).

PAC-SYM SCORES

The mean reduction (at week 12 as compared with baseline) in the overall PAC-SYM score, the stool symptoms subscore, and the abdominal symptoms subscore (but not the rectal symptoms subscore) was significantly greater in the prucalopride groups than in the placebo group (Table 3).

QUALITY-OF-LIFE SCORES

At week 12, the proportions of patients with an improvement of 1 or more points on the PAC-QOL satisfaction score were significantly higher among the patients receiving 2 mg of prucalopride (89 of 198 patients [44.9%]) or 4 mg of prucalopride (94 of 193 patients [48.7%]) than among those receiving placebo (47 of 195 patients [24.1%]) ($P < 0.001$ for both comparisons). Similarly, mean overall PAC-QOL scores showed significantly greater improvements with 2 mg or 4 mg of prucalopride than with placebo at week 12 ($P < 0.001$ for both comparisons). There were no treatment-associated differences in scores on the SF-36 (overall scale or subscales).

SAFETY

Treatment-emergent adverse events were reported by 166 of the 207 patients (80.2%) receiving 2 mg of prucalopride, 160 of the 204 patients (78.4%) receiving 4 mg of prucalopride, and 149 of the 209 patients (71.3%) receiving placebo. The most frequently reported adverse events were headache, nausea, abdominal pain, and diarrhea (Table 4). The majority were mild or moderate in severity,

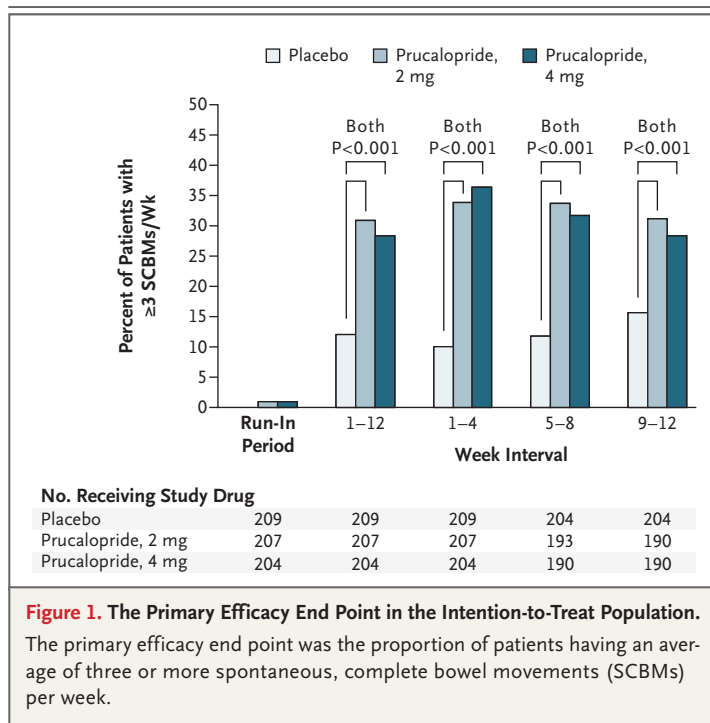


Figure 1. The Primary Efficacy End Point in the Intention-to-Treat Population.

The primary efficacy end point was the proportion of patients having an average of three or more spontaneous, complete bowel movements (SCBMs) per week.

occurred primarily during the first day of treatment, and were transient. There were no deaths during the study and no clinically significant cardiovascular events, except in one patient with known mitral-valve prolapse and a history of supraventricular tachycardia in whom that condition developed during treatment with 2 mg of prucalopride. Serious adverse events were reported by 3 of the 207 patients (1.4%, including the patient with supraventricular tachycardia) receiving 2 mg of prucalopride, 7 of the 204 patients (3.4%) receiving 4 mg of prucalopride, and 8 of the 209 patients (3.8%) receiving placebo.

Trial medication was permanently stopped owing to the adverse events in 17 of the 207 patients (8.2%) receiving 2 mg of prucalopride, 16 of the 204 (7.8%) receiving 4 mg of prucalopride, and 4 of the 209 (1.9%) receiving placebo. Diarrhea led to permanent discontinuation in 1.5% of the patients receiving 2 mg of prucalopride and in 4.4% of those receiving 4 mg of prucalopride but in none of the patients in the placebo group. There were three cases of discontinuation for adverse events that included cardiovascular events.

There were no significant differences among the three groups in hematologic findings, clinical chemical data, results of urinalysis or electrocardiography, or vital signs (Table 5). The overall incidence of prolonged QTcF (>470 msec) during

Table 2. Efficacy End Points.*

End Point	Prucalopride, 2 mg (N=207)	Prucalopride, 4 mg (N=204)	Placebo (N=209)
Mean of ≥ 3 SCBMs/wk, wk 1–12 — no. (%)	64 (30.9)†	58 (28.4)†	25 (12.0)
Average increase of ≥ 1 SCBM/wk, wk 1–12 — no. (%)	98 (47.3)†	95 (46.6)†	54 (25.8)
Average increase of ≥ 1 SBM/wk, wk 1–12 — no. (%)	143 (69.1)†	126 (61.8)†	76 (36.4)
No. of SCBMs/wk			
Mean at baseline	0.5	0.5	0.4
Wk 1–12 — mean (change from baseline)	2.6 (2.2)†	3.0 (2.5)†	1.2 (0.8)
Percent of BMs with normal consistency			
Mean at baseline	23.5	23.7	21.9
Wk 1–12 — mean (change from baseline)	46.6 (22.9)†	45.4 (21.6)†	35.5 (13.5)
Percent of BMs with severe or very severe straining			
Mean at baseline	28.6	29.5	27.0
Wk 1–12 — mean (change from baseline)	14.9 (–13.7)†	16.0 (–13.5)†	21.8 (–5.1)
Median days to first SCBM after first intake of trial medication	1.3†	1.0†	12.6
No. of bisacodyl tablets taken/wk			
Mean at baseline	1.9	1.8	2.1
Wk 1–12 — mean (change from baseline)	0.9 (–1.0)†	1.0 (–0.8)†	1.9 (–0.1)
Treatment self-rated as quite effective or extremely effective, wk 12 — no./total no. (%)	67/201 (33.3)†	75/199 (37.7)†	35/207 (17.0)

* Continuous data were analyzed with the use of a t-test with Dunnett's adjustment for multiple comparisons. Binary end points (uncorrected) were analyzed with the use of the Cochran–Mantel–Haenszel test. BM denotes bowel movement, SBM spontaneous bowel movement, and SCBM spontaneous, complete bowel movement.

† $P < 0.001$ for the comparison with the placebo group.

the treatment period was not significantly different between the placebo group and either prucalopride group (Table 5).

DISCUSSION

In this randomized, placebo-controlled trial of patients with severe chronic constipation, the proportion of patients in whom the primary end point of an average of three or more spontaneous, complete bowel movements per week was achieved was significantly higher in both prucalopride groups than in the placebo group during the 12 weeks of treatment. This primary end point is considered to be clinically meaningful, since it combines a subjective measure of the completeness of evacuation with an objective measure of the number of bowel movements and reflects the relief of chronic constipation. Since three or more spontaneous, complete bowel movements per week is considered the low end of the range that defines normal bowel function, the end point also reflects the normalization of bowel function.

In clinical practice, patients with severe chronic constipation report spontaneous bowel movement twice a month. The increase of 2.2 and 2.5 spontaneous, complete bowel movements per week among patients receiving 2 mg and 4 mg of prucalopride, respectively, was in contrast with an increase of 0.8 spontaneous, complete bowel movement per week in the placebo group. This was associated with a 50% reduction, on average, in the use of rescue medication. In a clinical trial of tegaserod¹² that used the same definition of spontaneous, complete bowel movements, the increase from baseline was 1.3 spontaneous, complete bowel movements per week with the use of 6 mg of tegaserod twice daily, as compared with an increase of 0.7 spontaneous, complete bowel movement with the use of placebo.

There was a slight decrease in the efficacy of 4 mg of prucalopride, but not 2 mg of prucalopride, during the 12-week period. However, among patients who had a response after 4 weeks of treatment, more than 74% still had a response after 12 weeks of treatment, suggesting that phy-

Table 3. Summary of Overall and Subscale Symptom Scores on the Patient Assessment of Constipation Symptoms (PAC-SYM) Questionnaire.*

Score	Prucalopride, 2 mg			Prucalopride, 4 mg			Placebo		
	No. of Patients	Mean Score	Mean Change from Baseline	No. of Patients	Mean Score	Mean Change from Baseline	No. of Patients	Mean Score	Mean Change from Baseline
Overall PAC-SYM score									
At baseline	207	1.9		203	1.9		206	2.0	
At wk 12	200	1.3	-0.6	198	1.2	-0.7	207	1.6	-0.4
P value vs. placebo			0.001			<0.001			
Stool symptoms subscore (5 items)									
At baseline	207	2.4		203	2.5		206	2.5	
At wk 12	200	1.7	-0.6	198	1.7	-0.8	207	2.1	-0.5
P value vs. placebo			0.008			0.001			
Abdominal symptoms subscore (4 items)									
At baseline	207	1.9		203	1.8		206	2.0	
At wk 12	200	1.2	-0.7	198	1.1	-0.7	207	1.6	-0.4
P value vs. placebo			<0.001			<0.001			
Rectal symptoms subscore (3 items)									
At baseline	207	1.2		203	1.0		204	1.0	
At wk 12	200	0.6	-0.5	198	0.6	-0.4	207	0.6	-0.4
P value vs. placebo			0.5			0.6			

* Scores on the Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaire can range from 0 (symptoms absent) through 4 (symptoms very severe). Lower scores reflect improvement. P values were calculated with the use of the t-test with Dunnett's adjustment for multiple comparisons.

Table 4. Treatment-Emergent Adverse Events Reported by at Least 10% of Patients Receiving the Trial Medication in Any Group.*

Variable	Prucalopride, 2 mg (N=207)	Prucalopride, 4 mg (N=204)	Placebo (N=209)
Patients with adverse event — no. (%)	166 (80.2)	160 (78.4)	149 (71.3)
Gastrointestinal system disorder	103 (49.8)	103 (50.5)	79 (37.8)
Nausea	46 (22.2)	44 (21.6)	17 (8.1)
Abdominal pain	40 (19.3)	46 (22.5)	40 (19.1)
Diarrhea	28 (13.5)	38 (18.6)	11 (5.3)
Flatulence	23 (11.1)	17 (8.3)	18 (8.6)
Vomiting	14 (6.8)	10 (4.9)	4 (1.9)
Central and peripheral nervous system disorder			
Any	68 (32.9)	76 (37.3)	35 (16.7)
Headache	55 (26.6)	60 (29.4)	25 (12.0)

* Adverse events were those reported at any time during the study or within 5 days after the trial medication was stopped. Events are named on the basis of the preferred terms of the World Health Organization.

sicians can assess at 4 weeks whether a longer treatment period is warranted.

Prucalopride significantly improved the values of several prespecified secondary efficacy end points, including satisfaction with bowel function and treatment, perception of the severity of constipation, and disease-related quality of life. Thus, there was an improvement of 1 point or more on the 5-point overall PAC-QOL scale in more patients in either prucalopride group than in the placebo group. The minimal clinically important difference for responses on a 7-point Likert scale is reported to be 0.5 per item.²⁵

One approach to treating severe chronic constipation is to enhance colonic propulsion,^{26,27} which accelerates transit¹⁷⁻¹⁹ and delivers stool from the proximal colon, where it is most commonly retained in severe constipation.²⁸ In patients with normal colonic motility and constipation, such propulsion may deliver the more liquid contents of the proximal colon to the distal colon, facilitating the passage of stool of looser consistency. In animals, prucalopride induces giant colonic contractions that start in the proximal colon¹⁴ through selective action on 5-HT₄ receptors. Prucalopride also enhances gastroduodenal motility and accelerates delayed gastric emptying.

The incidences of adverse events were similar among all three treatment groups, except for

diarrhea, which is a predictable pharmacologic result of prucalopride use, and headache. There were no clinically relevant changes over time in vital signs or electrocardiographic variables.

Prucalopride has a high affinity and selectivity for 5-HT₄ receptors; its affinity for 5-HT₄ receptors is at least 150 times that for other receptors. The affinities of renzapride, mosapride, tegaserod, and prucalopride for the hERG channel are all in the micromolar range and contrast with cisapride, which has a selectivity for 5-HT₄ receptors that is approximately 10 times less than that for hERG.^{29,30} Other compounds at an earlier stage of development, such as ATI-7505,³¹ also appear to be highly selective for 5-HT₄ receptors. In contrast, other 5-HT₄ receptor agonists such as cisapride, mosapride, tegaserod, and renzapride act on other receptors, within their therapeutic ranges. The affinities of cisapride (for hERG) and tegaserod (for 5-HT_{1B}) may contribute to the less favorable benefit-risk profile attributed to these drugs.^{16,29}

The electrocardiographic responses (including QTc) reported in this study are consistent with the large number of cardiovascular tests specifically designed to monitor possible cardiovascular events conducted in healthy volunteers, the elderly, and patients with spinal-cord injury.^{19,20,32,33} However, a relatively small number of patients were treated with prucalopride in our trial, and

Table 5. Effect of Treatment on Heart Rate and Corrected QT Interval by Fridericia's Formula (QTcF).*

Variable	Prucalopride, 2 mg		Prucalopride, 4 mg		Placebo	
	No. of Patients	Mean \pm SE	No. of Patients	Mean \pm SE	No. of Patients	Mean \pm SE
Heart rate (beats/min)						
At baseline	206	68.3 \pm 0.8	202	66.8 \pm 0.8	208	66.4 \pm 0.7
At wk 4	184	70.5 \pm 0.8	182	68.6 \pm 0.8	187	67.5 \pm 0.8
Change from baseline	183	2.2 \pm 0.7	181	1.8 \pm 0.7	186	1.1 \pm 0.6
At wk 12	170	69.7 \pm 0.8	169	69.9 \pm 0.8	176	67.3 \pm 0.8
Change from baseline	169	1.1 \pm 0.8	168	2.7 \pm 0.8	176	1.0 \pm 0.6
QTcF (msec)						
At baseline	206	405.9 \pm 2.2	202	405.7 \pm 2.4	208	409.1 \pm 2.0
At wk 4	184	403.9 \pm 1.7	182	405.5 \pm 1.8	187	404.3 \pm 1.8
Change from baseline	183	-2.3 \pm 1.6	181	-0.7 \pm 2.3	186	-4.8 \pm 1.7
At wk 4	170	404.0 \pm 1.8	169	406.5 \pm 2.0	176	403.4 \pm 1.7
Change from baseline	169	-2.2 \pm 2.0	168	0.7 \pm 2.3	176	-6.2 \pm 1.9
	No./Total No. (%)		No./Total No. (%)		No./Total No. (%)	
Maximum QTcF at any time during study	206		202		208	
<470 msec	200/201 (99.5)		197/199 (99.0)		198/200 (99.0)	
470–500 msec	1/201 (0.5)		2/199 (1.0)		1/200 (0.5)	
>500 msec	0		0		1/200 (0.5)	

* None of the changes from baseline were significant.

concerns about the potential cardiac toxic effects of tegaserod emerged after the analysis of data from 29 clinical studies.³⁴ Further assessment of the cardiovascular safety of prucalopride in other trials is required to ensure that rare adverse cardiovascular effects are ruled out.

Limitations of the current study include an inadequate number of male patients to prove efficacy for men, an insufficient duration to assess fully the long-term benefit–risk ratio, a failure to record 24-hour electrocardiograms, and an insufficient prospective validation of the magnitude of responses to understand the clinical significance of the effects. In our placebo-controlled trial, we were also unable to assess the efficacy of prucalopride as compared with other treatments for constipation.

In conclusion, during a treatment period of 12 weeks, prucalopride significantly increased the number of spontaneous, complete bowel movements, reduced the severity of symptoms, and

improved the disease-related quality of life in patients with severe chronic constipation. Prucalopride given at a dose of 4 mg did not provide an incremental benefit over the 2-mg dose. Earlier studies suggest that a dose lower than 2 mg is not efficacious for the relief of severe chronic constipation³² or for accelerating colonic transit.¹⁸ Larger and longer-term trials are required to fully assess the risks and benefits of the use of prucalopride for chronic constipation.

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