neurogastroenterology & motility

Neurogastroenterol Motil (2010) **22,** 991–e255 doi: 10.1111/j.1365-2982.2010.01533.x

A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation

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Abstract

Background *Constipation affects up to 50% of the elderly; this study evaluates the efficacy, safety, and tolerability of the selective 5-HT_4 agonist prucalopride in chronically constipated elderly patients.* ***Methods*** *Three hundred chronic constipation patients aged ≥65 years were randomized to prucalopride (1, 2, or 4 mg once daily) or placebo for 4 weeks. The primary endpoint was the percentage of patients with ≥3 spontaneous complete bowel movements (SCBM) per week. Secondary endpoints included the percentage with an increase of ≥1 SCBM per week, BM frequency, constipation-related symptoms, quality of life (QoL), safety, and tolerability.* ***Key Results*** *More patients achieved ≥3 SCBM per week with prucalopride than with placebo. This difference was largest and significant during the first week of 4 mg prucalopride ($P \leq 0.05$). Significantly more patients in each prucalopride group achieved an increase of ≥1 SCBM per week from baseline vs placebo (e.g. 60% with 1 mg prucalopride vs 34% with placebo at week 4; $P \leq 0.05$). More patients had improvement in PAC-QOL satisfaction score of ≥1 with 1 mg prucalopride than with placebo ($P \leq 0.05$); the same was true for PAC-SYM stool symptoms (1 and 4 mg prucalopride; $P \leq 0.05$). Treatment-emergent adverse events were similar between groups: the most frequently reported with prucalopride were headache and gastrointestinal events. There were no clinically significant differences between prucalopride and placebo for vital signs, laboratory assessments, or ECG variables.*

Conclusions & Inferences *Prucalopride, in the dose-range tested (1–4 mg once daily), has beneficial effects on bowel movements, symptoms, and QoL, and is safe and well-tolerated in elderly patients with chronic constipation.*

Keywords *5-HT_4 receptors, colon motility, constipation, elderly, enterokinetic, prucalopride.*

Abbreviations: AE, adverse event; BM, bowel movement; CMH, Cochran–Mantel–Haenszel; HR, heart rate; ITT, intent to treat; PAC-QOL, patient assessment of constipation-quality of life; PAC-SYM, patient assessment of constipation-symptom; QTcF, QT interval corrected according to Fridericia; SAE, serious adverse event; SBM, spontaneous bowel movement; SCBM, spontaneous complete bowel movement.

INTRODUCTION

Estimates suggest that constipation affects up to 28% of individuals in the Western World,[1,2] with a two-fold higher prevalence in women than in men.[3] Rome III criteria[4] define constipation on the basis of multi-system symptoms, including straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction, and fewer than three bowel movements (BMs) per week. The symptoms of chronic constipation are unpleasant and have an adverse effect on patients' quality of life (QoL).[5–7]

Longer transit times have been reported in elderly individuals,[8] which may explain why chronic constipation appears to be a particular problem in the elderly, with estimated prevalence of 15–50%.[3] The biological basis of constipation in the elderly is not entirely clear, although there is evidence of enteric neurodegeneration, which affects gut epithelial, muscle and neuronal function.[9] There is evidence of loss of excitatory enteric neurons (e.g. cholinergic) whereas inhibitory enteric neurons appear to be unchanged in aging, leading to decreased motility.[9] In addition, reduced fiber and fluid

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Received: 3 December 2009
Accepted for publication: 7 May 2010

intake, decreased mobility resulting from chronic diseases, and medications with anticholinergic side effects are risk factors for constipation in elderly people.[10]

Many doctors recommend lifestyle changes, such as increasing fluid and fiber in the diet and regular physical activity. However, such advice is often ineffective[11] and pharmacological intervention is required, with many patients using laxatives. The use of stimulant laxatives in elderly patients with chronic constipation may be problematic as these agents can produce a strong and sudden urge to defecate. This can lead to incontinence in elderly individuals with limited mobility.[12] Osmotic laxatives, such as PEG and lactulose, can be unpalatable[13] and can cause bloating.[14] There is therefore a need for alternative treatments.

The urge to defecate usually follows high-amplitude propagated contractions in the colon known as giant migrating contractions that occur a few times a day, especially immediately after waking and after meals.[15] In patients with chronic constipation, the frequency and duration of these giant migrating contractions are lower than in normal individuals.[15] Hence, it would be attractive to stimulate these contractions and to restore the physiologic colonic motility.

Control of giant migrating contractions is suggested to involve release of serotonin and its action at 5-HT_4 receptors.[16] Prucalopride is the first compound of a new class of highly selective 5-HT_4 agonists with strong enterokinetic activity, with greater selectivity for this receptor than previous prokinetic agents, such as tegaserod and cisapride.[17–19] A comprehensive Phase III dataset supports its efficacy in patients with chronic constipation for whom laxatives do not provide adequate relief.[20–24]

In fasted conscious dogs, prucalopride induces giant migrating contractions, stimulates motility in the proximal colon, enhances gastro-pyloro-duodenal motility and accelerates delayed gastric emptying.[25] In Phase III studies, oral treatment with prucalopride, 2–4 mg once daily, normalized the weekly frequency of spontaneous complete bowel movements (SCBMs) in approximately one-quarter of patients and significantly improved QoL and satisfaction with treatment in around 40% of patients.[20–22,24]

The aim of this study was to evaluate the efficacy, effect on patients' QoL, and the safety and tolerability of prucalopride in elderly patients with chronic constipation.

METHOD

This was an international multicenter, parallel-group, placebo-controlled Phase III trial in elderly patients. The study period, from first screening to last follow-up, was October 1998–September 1999. [Clinicaltrials.gov identifier: NCT00487422]

Inclusion criteria

Patients were male or female, aged 65 years or more, with a history of constipation. This was defined as having (in the past 6 months) two or fewer SCBMs per week and one or more of the following for at least a quarter of the stools: stools passed were very hard (little balls) and/or hard; a sensation of incomplete evacuation; straining to defecate. Spontaneous bowel movements (SBM) were defined as BMs not preceded within 24 h by a laxative, enema, or by treatment other than prucalopride. Patients who never had SBMs were considered to be constipated and were eligible for the study.

Exclusion criteria

Patients were excluded if their constipation was considered to be drug-induced or secondary to other medical conditions (e.g. endocrine, metabolic or neurologic disorders not controlled by appropriate therapy, surgery, organic disorders of the large bowel, or other serious illnesses), or if their main complaint was abdominal pain. Patients with uncomplicated diverticulosis were eligible for the study.

Study design

After a 2-week run-in period during which all existing laxative medications were withdrawn, patients were randomly assigned to take either prucalopride (1, 2, or 4 mg) or placebo, once daily before breakfast for 4 weeks. Patients were asked not to change their diet or lifestyle during the study. Allocation to treatment groups was based on a randomization code generated by Janssen Research Foundation, with balancing to insure equal numbers entered each group. In each center, patient numbers were assigned in sequential order starting with the lowest number available. Study medication was supplied in identically appearing containers, and tablets were identical in appearance, taste, and smell. Investigators and patients were blind to treatment allocations, with a sealed envelope containing codes that could be opened only in case of emergency.

Concomitant medication

No medication that might interfere with bowel function (anticholinergics, opioids, spasmolytics, or prokinetics) was allowed with the following exceptions: (i) codeine, as an analgesic or antitussive, as needed but not continuously ($\leq$40 mg day^{-1}); (ii) patients with Parkinson's disease were allowed to take anticholinergics, provided that the patient had been taking the same dose for at least 4 weeks before the study; (iii) tricyclic antidepressants were allowed on the same basis as in (ii). For all three previous exceptions, the constipation had to predate the use of the medication; and (iv) laxatives [bisacodyl, a maximum single dose of 15 mg (3×5 mg tablets)] were only allowed if the patient had had no BM for three or more consecutive days. If no BM was produced following this standard dose of bisacodyl (3×5 mg tablets), the investigator could increase the dose of bisacodyl. If this failed, an enema could be administered. No bisacodyl/enemas could be taken within 48 h prior to and 48 h following the start of the double-blind treatment period.

Efficacy evaluations

Throughout the study, patients kept a daily diary in which they recorded details of their BMs, symptoms, and use of a rescue laxative (bisacodyl tablets) or rescue enema.

The primary efficacy endpoint was the proportion of patients having on average ≥3 SCBMs per week during the 4 weeks of the trial. Secondary endpoints were: (i) the proportion of patients with an average increase from baseline of ≥1 SCBM per week; (ii) the average weekly frequency of SCBM/SBM; and (iii) the number of patients with an improvement of ≥1 on the satisfaction subscale of the patient assessment of constipation-quality of life (PAC-QOL) questionnaire,[26] overall score on the patient assessment of constipation-symptoms (PAC-SYM) scale.[27] The PAC-SYM is a 12-item self-administered assessment instrument, consisting of three subscales, that measures the severity of constipation-related symptoms. Patients rate items on a 5-point Likert scale: 0 = symptoms absent; 1 = mild; 2 = moderate; 3 = severe; and 4 = very severe. The PAC-QOL is a 28-item self-administered questionnaire, consisting of four subscales including satisfaction, in which patients also rate items on a 5-point scale.

In addition, patients' global assessments of treatment efficacy and constipation severity were assessed. For treatment efficacy, each patient was asked to rate the efficacy of his/her treatment (after 2 and 4 weeks of treatment) using the following 5-point scale: not at all effective (0); a little bit effective (1); moderately effective (2); quite a bit effective (3); and extremely effective (4). For severity of constipation, each patient was asked to record his/her severity of constipation at all visits except visit 1, on the following 5-point scale: absent (0); mild (1); moderate (2); severe (3); and very severe (4).

Safety evaluation

A physical examination and laboratory tests (hematology, biochemistry, and urinalysis) were performed at run-in and at the final visit (or at discontinuation). Vital signs and adverse events (AEs) were recorded at each visit.

ECG recordings were taken during the run-in and at the final visit. The following variables were extracted from ECG recordings: (i) heart rate (HR, bpm), (ii) PR interval (ms), (iii) QRS width (ms), and (iv) QT interval (ms). QT intervals were corrected for HR using Fridericia's formula (QTcF). Corrected QT intervals were classified as normal, borderline, or prolonged according to EMEA CPMP guidelines.

Statistical assessments

It was calculated that 64 patients per treatment group would give 80% power (chi-square test) to detect a 25% difference between placebo (15% response) and one of the prucalopride groups (40% response) at a 5% level of significance (with a Bonferroni correction for three comparisons).

The efficacy analyses were performed on data from the intent-to-treat (ITT) population, comprising all patients who took at least one dose of double-blind study medication and who had at least one post-baseline efficacy assessment. All patients who took at least one dose of study medication were included in the safety analysis and descriptive statistics of the baseline characteristics.

The Cochran–Mantel–Haenszel (CMH) test controlling for differences between countries was used to compare treatment groups for binary efficacy variables. Holm's step-down procedure was used to correct for multiple pairwise comparisons. For continuous variables, analysis of covariance was used to analyze differences between treatment groups and Dunnett's test was used to control for multiple comparisons. A 5% level of significance was used.

Subjects who dropped out early (<14 days) or who collected too little diary information for a proper evaluation were considered as non-responders for the primary endpoint. BMs were only considered spontaneous if they occurred more than 24 h after a last laxative intake.

Ethical considerations

This study was conducted in accordance with applicable local regulatory requirements and with the principles of the Declaration of Helsinki and the International Conference on Harmonization requirements for good clinical practice. All participants were informed of the nature and purpose of the study and gave written informed consent before they were admitted to the study. The clinical study protocol, subject information sheet, and informed consent form were reviewed and approved in advance by an independent ethics committee.

RESULTS

Patient disposition

Four hundred and sixty one patients signed consent forms and entered screening (Fig. 1). In total, 303 patients were randomized and received at least one dose of study medication. The ITT population comprised 300 patients who took study medication and who provided follow-up data for one or more of the key efficacy variables. The ITT population was used to assess efficacy and QoL, and the all-(treated) population was used for the safety analysis and to determine the demographics and baseline characteristics. Compliance, measured as the mean daily number of tablets taken during the study, was similar across treatment groups being 0.94, 0.92, 0.91, and 0.90 for placebo, prucalopride 1, 2, and 4 mg, respectively.

Demographics

Patients were recruited from 48 study centers in Austria (2), Canada (9), Germany (7), Great Britain (13), The Netherlands (11), Norway (2), and South Africa (4). The study population had a mean age of 76 years (range 64–95) and 70% of the patients were female. There were no significant differences in the distribution of race, sex, age height, and weight across the treatment groups. The median duration of constipation was around 15 years and around 30% of the patients had no SCBM per week at run-in. The main complaint at baseline of most patients was infrequent defecation (20.8–26.3%) or feeling not completely empty (21.3–23.6%). More than 70% of patients were dissatisfied with previous treatment,

mainly laxatives. Subject demographics and constipation history for the all-(treated) population are summarized in Table 1.

Although the study did not permit the use of laxative-type medications, with the exception of bisacodyl as rescue therapy, 48 (15.8%) patients reported the use of 29 types of laxative during the study. Laxative use was balanced across the treatment groups with 13 (18.1%) patients receiving placebo, 12 (15.8%) patients receiving 1 mg prucalopride, 14 (18.7%) patients receiving 2 mg prucalopride and 9 (11.3%) patients receiving 4 mg prucalopride reporting laxative use.

Concomitant diseases classified as cardiovascular (69.6%), musculoskeletal (64.0%), gastrointestinal (GI) (63.0%), and genito-urinary (50.2%) were reported with a similar frequency across the treatment groups.

Efficacy: BMs

The proportion of patients achieving ≥3 SCBM per week (the primary endpoint) was higher for all prucalopride treatment groups compared with placebo for each individual week[1–4] of treatment (Fig. 2A). The difference was largest and significant during the first week of treatment in the group receiving 4 mg prucalopride ($P \leq 0.05$). The cumulative distribution of the number of SCBM per week over the 4-week treatment period indicates that the three prucalopride treatment groups have similar effects, and all have a greater effect on bowel frequency compared with placebo (Fig. 2B).

More pronounced effects on the number of patients achieving an average increase of ≥1 SCBM per week (secondary endpoint) from baseline (over the 4-week treatment period) were observed in groups receiving prucalopride treatment compared with those receiving placebo (Fig. 2C). This effect was most evident and significant after the first week of treatment for all doses of prucalopride, and at week 4 in the group receiving 1 mg prucalopride ($P \leq 0.05$). The cumulative distribution curve of the change from baseline in number of SCBM per week over the 4-week treatment period shows that the effects of prucalopride are comparable with respect to dose and all doses have a greater effect compared with placebo (Fig. 2D).

Increases in the number of patients achieving ≥1 SBM per week compared with placebo were seen in each of the individual weeks 1, 2, 3, and 4, for all doses of prucalopride and were most pronounced during the first week of treatment ($P \leq 0.05$). Significant effects of prucalopride treatment (1 mg) on the number of patients achieving ≥1 SBM per week were also observed at week 4 ($P \leq 0.05$).

The mean changes from baseline in the average weekly number of SCBM, SBM, and total BM are presented in Table 2. For SCBMs, average increases were significantly greater in each of the prucalopride-treated groups ($P \leq 0.05$).

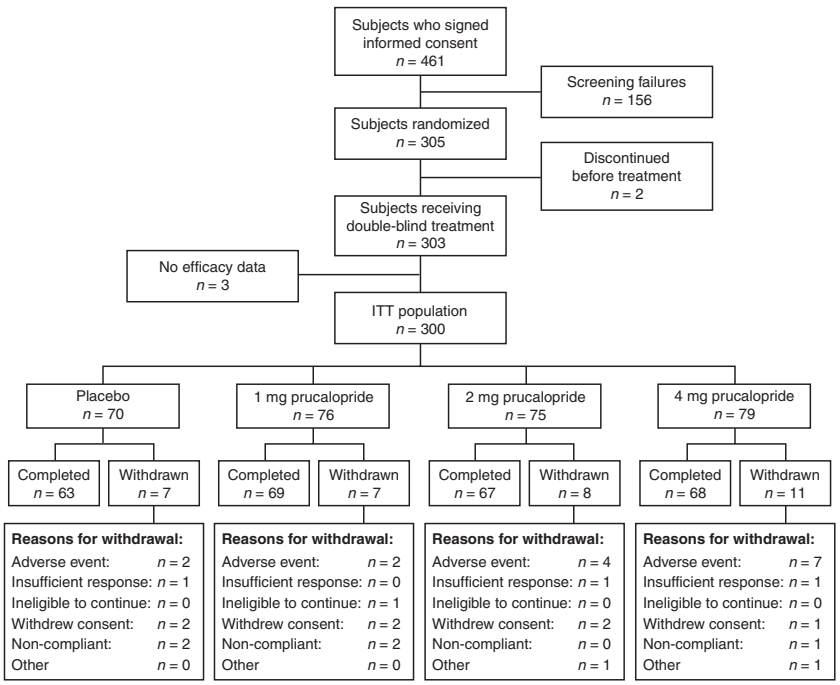

Figure 1 Study flow and disposition of patients.

Table 1 Study demographics and constipation history

Characteristic	Placebo (n = 72)	Prucalopride 1 mg (n = 76)	Prucalopride 2 mg (n = 75)	Prucalopride 4 mg (n = 80)
Females, %	58.3	76.3	68.0	75.0
Age, years				
Mean (SE)	76 (0.87)	76.7 (0.9)	75.6 (0.83)	77.1 (0.91)
Range	65–94	65–92	64–91	65–95
Duration of constipation, years – median (range)	15.5 (1–76)	10.0 (1–60)	15.5 (1–70)	15.0 (1–80)
No SCBM per week at run-in, %	31.4	30.3	21.0	34.2
Previous treatments, %				
Diet	47.2	53.9	45.3	43.8
Bulk-forming agents	54.2	39.5	52.0	47.5
Laxatives	86.1	82.9	80.0	83.8
Previous treatment inadequate, %	87.3	82.7	71.4	76.6

Efficacy: PAC questionnaire scores

The proportion of patients with an improvement in PAC-QOL satisfaction score of ≥1 was significantly higher for the group treated with 1 mg prucalopride once daily compared with the group receiving placebo ($P \leq 0.05$). In addition, the proportion of patients with an improvement in PAC-SYM stool symptoms score ≥1 was significantly higher in patients treated with 1 or 4 mg prucalopride once daily than in patients receiving placebo ($P \leq 0.05$), from mean baseline scores of 2.06, 2.09, and 2.13, respectively (Figure S1A).

Efficacy: patients' global assessment

Prucalopride reduced the overall severity of constipation, as rated by patients using the global constipation severity scale (Figure S1B). Patients treated with 1 or

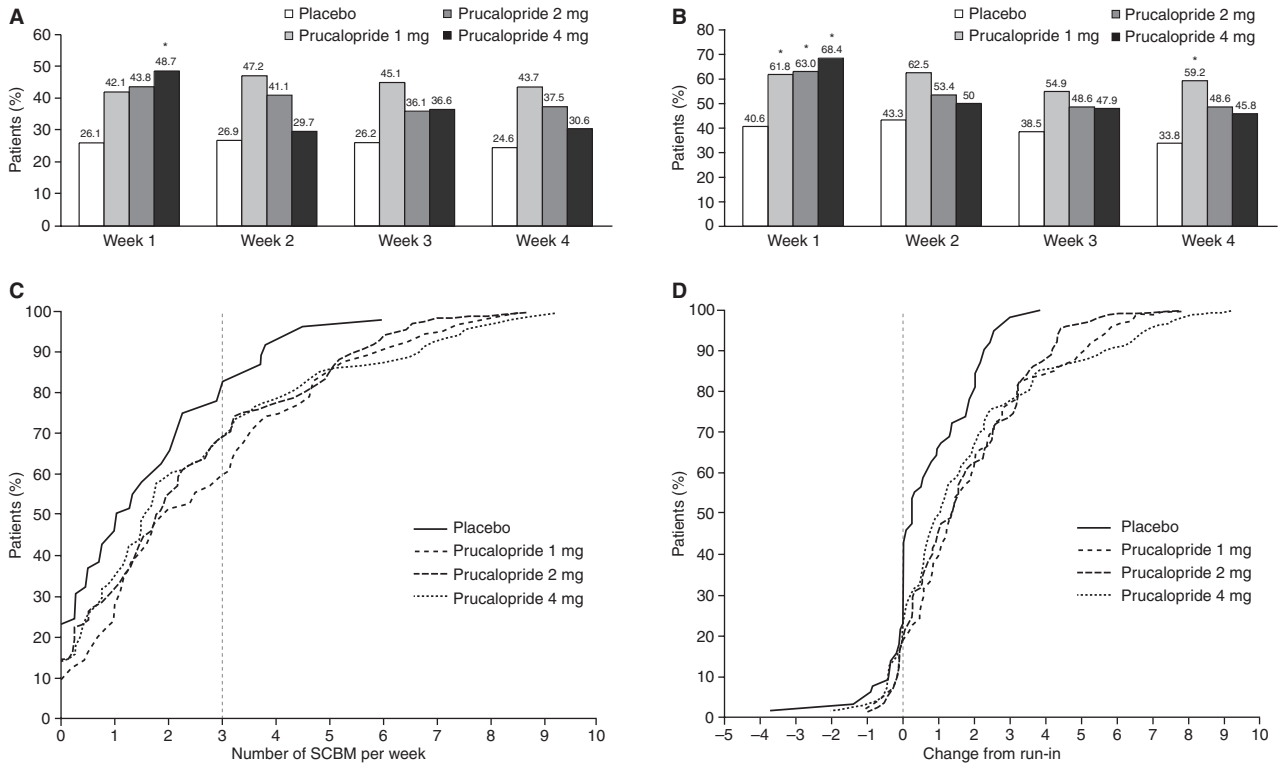

Figure 2 Effect of prucalopride on primary and secondary efficacy measures. (A) Percentage of patients with an average of ≥3 spontaneous complete bowel movement (SCBM) per week [intent-to-treat (ITT) population], at weeks 1–4. *$P < 0.05$ *vs* placebo. (B) Cumulative distribution curve of the number of SCBM week^{-1} over the 4-week treatment period. The dotted line indicates the primary efficacy endpoint (≥3 SCBM week^{-1}. (C) Percentage of patients with an average increase of ≥1 SCBM week^{-1} (ITT population), at weeks 1–4. *$P < 0.05$ *vs* placebo. (D) Cumulative distribution curve of the change from baseline in number of SCBM week^{-1} over the 4-week treatment period.

Table 2 Weekly frequency of BMs, and mean change from baseline, after 4 weeks of treatment (ITT population)

Measure	Placebo (n = 70)	Prucalopride 1 mg (n = 76)	Prucalopride 2 mg (n = 75)	Prucalopride 4 mg (n = 79)
SCBMs per week				
Baseline	1.1	0.8	0.7	0.7
Week 4	1.7	2.7	2.4	2.4
Mean change from baseline	+0.6	+1.9*	+1.7*	+1.8*
SBMs per week				
Baseline	4.2	4.5	4.1	4.3
Week 4	5.1	6.9	6.0	6.2
Mean change from baseline	+1.0	+2.4*	+1.9	+2.0
BMs per week				
Baseline	6.1	5.7	5.7	5.7
Week 4	6.1	7.7	6.9	7.1
Mean change from baseline	+0.2	+2.0*	+1.2	+1.4*

*$P \leq 0.05$ *vs* placebo (CMH test with Holm's multiple comparison adjustment).

4 mg prucalopride once daily for 4 weeks reported a mean improvement in severity of constipation above baseline that was significantly greater than in patients receiving placebo.

At week 4, 42% of patients receiving 1 mg prucalopride, 24% of patients receiving 2 mg prucalopride, and 39% of patients receiving 4 mg prucalopride rated their treatment as either 'quite a bit effective' or 'extremely effective' compared with only 16% of patients receiving placebo ($P < 0.001$ for 1 mg prucalopride *vs* placebo, $P < 0.05$ for both 2 and 4 mg prucalopride *vs* placebo; data not shown).

Safety: AEs

The incidence of treatment-emergent AEs in prucalopride-treated patients was similar to the incidence in patients randomized to placebo (48.7%, 38.7%, and 47.5% for prucalopride 1, 2, and 4 mg, respectively *vs* 44.4% for placebo). The most frequently reported AEs were headache and GI events Table 3, which occurred most frequently on the first days of treatment.

Most of the AEs were considered by the investigators to be mild or moderate. The incidences of severe AEs were similar between treatment groups (3.9%, 6.7%, 6.3%, and 6.9% for 1, 2, and 4 mg prucalopride and placebo, respectively). Only a few AEs were considered to be related to the study medication, with a slightly higher incidence of abdominal pain, diarrhea, and headache at least possibly related to prucalopride treatment. One patient in the placebo group died during the study from a myocardial infarction. Overall, only three patients experienced a serious AE (SAE): one patient in the placebo group ('arrhythmia' and 'myocardial infarction' considered not related to the study drug; the patient died); one patient taking 1 mg prucalopride ('mild drug abuse' considered doubtfully related and accidentally reported as an SAE); and one patient treated with 4 mg prucalopride ('fracture of the left forearm' reported as moderate and not related to study medication). Few patients discontinued study medication due to AEs (2.6%, 5.3%, and 8.8% for prucalopride 1, 2, and 4 mg respectively *vs* 4.2% for placebo). Most of the AEs leading to discontinuation of study medication were gastro-intestinal disorders.

Table 3 Treatment-emergent AEs reported by at least 5% of patients in any treatment group at any time during treatment or within 5 days of the end of treatment

WHO preferred terms	Placebo (n = 72)	Prucalopride 1 mg (n = 76)	Prucalopride 2 mg (n = 75)	Prucalopride 4 mg (n = 80)
Total % of patients with an AE	44.4	48.7	38.7	47.5
Abdominal pain, %	5.6	9.2	4.0	11.3
Diarrhea, %	0	6.6	1.3	6.3
Nausea, %	2.8	5.3	1.3	5.0
Back pain, %	2.8	2.6	5.3	3.8
Headache, %	4.2	6.6	5.3	8.8
Dizziness, %	1.4	0	0	5.0

Safety: clinical laboratory safety

There were no clinically relevant changes in hematology, clinical chemistry, or urinalysis variables over time or between treatments.

Safety: cardiovascular safety

There were no clinically relevant changes in vital signs or in any of the ECG variables, including corrected QT interval (QTcF), in any treatment group. There were also no statistically significant differences in QTcF change from baseline between groups (Table S1).

The incidence of abnormalities in HR, PR interval and QRS width was low and comparable between treatment groups. There were no differences in the incidence of prolonged QTcF intervals between prucalopride and placebo.

Changes in QTcF interval from normal to prolonged or vice versa were similar in all groups. Two patients in the placebo group had an increase in QTcF of >60 msec during treatment compared with one in the 1 mg, none in the 2 mg and three in the 4 mg prucalopride group (two of these three patients had very low baseline values [<350 msec]).

DISCUSSION

This multicenter, randomized, placebo-controlled 4-week study shows that prucalopride has beneficial effects on BMs, symptoms associated with constipation, and QoL in elderly patients with chronic constipation. For achieving the primary endpoint (proportion of patients having on average ≥3 SCBMs per week), prucalopride was significantly better than placebo at the highest dose (4 mg once daily) after 1 week of treatment, but this effect was not observed at lower doses of prucalopride, or at any other time point. Although disappointing, the primary endpoint in this study was considered an ambitious target for this group of patients. However, for the secondary efficacy endpoint (the proportion of patients with an average increase of ≥1 SCBMs per week above baseline) prucalopride showed significant benefits over placebo ($P \leq 0.05$) at all doses after the first week of treatment, and in the group receiving 1 mg prucalopride at week 4. Notably, this secondary efficacy endpoint was the criterion on which the FDA approved the less selective 5-HT_4 agonist, tegaserod, for constipation. We also found that patients treated with prucalopride achieved a significantly greater and clinically relevant increase from baseline in the frequency of SCBM than patients receiving placebo. The effect of prucalopride on BMs was greater in the first week of treatment than in subsequent weeks (Fig. 2). Similar findings were obtained with tegaserod.[28] This may represent an initial emptying of retained stools from the colon rather than a loss of effect of the prokinetic action of the drugs.

In previous studies with prucalopride, it has been shown that the majority of responders over 4 weeks of treatment are still responders after 12 weeks.[22] Therefore, the effect seen here over 4 weeks of prucalopride treatment, in the 1 mg group, can be predictive for the effect in the longer term.

Patients receiving prucalopride reported greater satisfaction with their BMs and improved constipation symptoms. Moreover, the improvements in the PAC-QOL satisfaction score are particularly significant to the patient, as this elderly patient group has lower mean baseline scores (2.69) than those reported for a younger cohort (score of 3.12; mean age, 43.9 years).[24] The importance of these patient perceptions are not always fully appreciated by many of the treating physicians, who may often be more concerned with the patients' stool frequency.[29] However, especially in this elderly patient group, perceived effectiveness of treatment and relief of constipation symptoms beyond just BM frequency are particularly relevant to address.

Of particular interest in this study was the finding that, in this elderly patient group, there appears to be at least similar efficacy of prucalopride at 1 mg once daily compared with the recommended adult dose of 2 mg once daily. Therefore, it may not be necessary to give doses higher than 1 mg to the majority of elderly patients. The reason for the sensitivity of these elderly patients to this low dose may be due to slower elimination of the drug, as unpublished studies have suggested that the area under the concentration–time curve for prucalopride in elderly patients is approximately 25% higher than in younger individuals.[30]

The disadvantages of and reason for dissatisfaction with other laxatives include the sudden need to defecate leading to incontinence, due to reduced mobility of some older patients, particularly with stimulant laxatives. In addition, lactulose and macrogol can cause bloating,[31,32] which is a symptom that the older population finds particularly bothersome.[33] Hence, there is a need for alternative treatments.

Other prokinetic drugs have proven their therapeutic value in different motility disorders and have been well accepted by prescribing physicians and treated patients. However, they have poor selectivity for 5-HT_4 receptors at the concentrations reached after normal therapeutic doses,[34] resulting in a higher risk of safety issues. Prucalopride is the first highly selective 5-HT_4 agonist, with an affinity for 5-HT_4 receptors approximately 150 times higher than for any other receptor.[35] Hence, it is expected that prucalopride will have an enhanced safety profile with at least similar efficacy as the other prokinetic drugs. It has been shown that prucalopride does not lead to CYP3A4 induction; therefore, drug interactions with prucalopride are not expected. This is of particular interest in the elderly population where drug interactions are always of major concern.

Adverse events observed with prucalopride were mostly mild and included headache and GI disturbances, the latter being expected and due to the pharmacological action of prucalopride. It is worth noting that most AEs were reported during the first days of treatment. After this period, the incidences of AEs in the prucalopride groups were similar to that in the placebo group. There was no evidence of adverse effects on the electrical activity of the heart with prucalopride. After 4 weeks of treatment, no differences in QTcF change from baseline were observed between placebo and prucalopride treatment groups. Changes in QTcF from normal to prolonged were comparable between prucalopride-treated groups and placebo.

CONCLUSIONS

We conclude that prucalopride, in the dose-range tested (1–4 mg once daily), has beneficial effects on BMs, symptoms associated with constipation, and QoL, and is safe and well-tolerated in elderly patients with chronic constipation.

ACKNOWLEDGMENTS

Medical writing support was provided by Jude Douglass and Emma Mast and funded by Movetis NV.

FINANCIAL DISCLOSURES

The study was funded by the Janssen Research Foundation. Stefan Müller-Lissner is currently a medical consultant for AstraZeneca, Axcan, Boehringer International, Movetis and Mundipharma. Potential investigator conflicts of interest were not disclosed to study participants as these regulations were not in place at the time of study conduct. An Rykx, Rene Kerstens, and Lieve Vandeplassche are employees of Movetis NV, which now owns the product.

Employees at Janssen were involved in study design and analysis of data. Employees at Movetis were involved in the analysis and interpretation of data. All authors have participated fully in the development of the manuscript. Lieve Vandeplassche was involved in the study design, An Rykx and Rene Kerstens were involved in the data analysis, interpretation and figure design, Stefan Müller-Lissner was involved in data review and interpretation. All authors reviewed drafts and made extensive comments, and all approved the final draft of the manuscript.

CLINICAL TRIAL REGISTRATION

This clinical trial is registered at http://www.clinicaltrials.gov/ct2/show/NCT00487422?term=prucalopride&rank=9 [Identifier: NCT00487422].

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Effect of prucalopride on quality of life, symptoms and severity of constipation assessments. (A) Proportion of patients with improvement from baseline of ≥1 in PAC-QOL satisfaction subscale score and PAC-SYM stool symptom score [intent-to-treat (ITT) population] at Week 4, $^*P \leq 0.05$ *vs* placebo. (B) Changes from baseline in patients' global assessment of the severity of constipation (ITT population) at Week 4 (mean ± SE). $^*P \leq 0.05$ *vs* placebo. (Constipation severity scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe; decreases in severity score are shown here as improvement).

Table S1. Effect of treatment on heart rate and corrected QT interval by Fridericia (QTcF).

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