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Clinical trial: the efficacy of open-label prucalopride treatment in patients with chronic constipation – follow-up of patients from the pivotal studies

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SUMMARY

Background
Prucalopride is approved in Europe for symptomatic treatment of chronic constipation in women with inadequate relief from laxatives.

Aim
To evaluate efficacy of prucalopride during long-term treatment of patients with chronic constipation.

Methods
Patients from three pivotal double-blind, placebo-controlled, 12-week studies with prucalopride could continue treatment in open-label studies up to 24 months. Efficacy was evaluated every 3 months using the Patient Assessment of Constipation-Quality of Life (PAC-QOL) satisfaction scale. Laxative use and reasons for study discontinuation were recorded.

Results
Eighty-six percent of patients who completed the pivotal studies continued prucalopride treatment in the open-label studies (n = 1455, 90% female). Improvement in average PAC-QOL satisfaction score observed after 12-week, double-blind prucalopride was maintained during open-label treatment for up to 18 months; in each 3 month period, 40–50% of patients did not use any laxatives. Most frequent adverse events (AEs) resulting in discontinuation were gastrointestinal events (3.3%) and headache (1.0%). Only 10% of patients who had normalized bowel function on prucalopride at the end of pivotal trials discontinued due to insufficient response during open-label treatment.

Conclusion
Satisfaction with bowel function is maintained for up to 18 months of treatment with prucalopride. Gastrointestinal events and headache cause discontinuation of prucalopride treatment in ~5% of patients (ClinicalTrials.gov identifiers: NCT01070615 and NCT00987844).

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INTRODUCTION

It is estimated that approximately 80 million people worldwide experience constipation [Intercontinental Marketing Services (IMS) Health data], which is often the result of a chronic gastrointestinal motility disorder. It affects up to one in five people in western countries and has a negative impact on patients' perceived quality of life.[1–4] Although constipation is commonly defined as infrequent stools, patients report other symptoms, including hard or lumpy stools, straining, bloating, abdominal discomfort, abdominal distention and a feeling of incomplete evacuation after a bowel movement.[5] Epidemiological surveys document the persistent nature of constipation and the high frequency of associated gastrointestinal symptoms.[6, 7] In a survey performed in the United States in 2004, nearly 50% of patients with constipation were not completely satisfied with over-the-counter or prescription medications (primarily laxatives) available on the market.[7] The dissatisfaction mainly arose from lack of efficacy.[7] An internet survey among 774 patients with chronic constipation in seven European countries during the first quarter of 2009 showed that one in three patients is not taking any medication, and that only 27% of patients are satisfied with current treatment options.[8]

High-amplitude propagated contractions (HAPCs, also called propagated sequences) in the colon cause mass movements through the colon, particularly in the proximal region;[9] HAPCs occur on average six times per day, especially soon after awakening and during the first 30 min after meals.[10] HAPCs are followed by an urge to defecate.[11] Patients with chronic constipation have a significantly lower number of HAPCs compared with controls[12, 13] and often have prolonged transit in the proximal colon.[14] A logical approach to treat chronic constipation is to reproduce normal colonic functions, including the stimulation of HAPCs and colonic transit.

Prucalopride is a selective, high-affinity serotonin (5-HT_4) receptor agonist, recently authorized by the European Medicines Agency for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. The approved doses are 1 mg once daily for elderly patients and 2 mg once daily for adults. Prucalopride is the first representative of a new chemical class (dihydrobenzofurancarboxamide compounds) with strong gastrointestinal prokinetic activity.[15]

In vitro studies using isolated tissues from the rat, guinea pig and dog gastrointestinal tract showed that prucalopride stimulates contractile activity. *In vivo* studies in conscious fasted dogs showed that prucalopride induced colonic giant migrating contractions (the term used to describe HAPCs in dogs).[16, 17] In humans, prucalopride stimulated HAPCs[18] and accelerated colonic transit in healthy volunteers[19] and patients with constipation.[20]

In three identical double-blind, placebo-controlled pivotal Phase III studies, treatment of patients with chronic constipation with prucalopride at daily doses of 2 mg or 4 mg for 12 weeks resulted in a significant increase in the proportion of patients with ≥3 spontaneous complete bowel movements (SCBMs) per week and a clinically relevant increase of ≥1 SCBM per week relative to baseline. Patient satisfaction with treatment and bowel function [as measured with the satisfaction subscale of the Patient Assessment of Constipation-Quality of Life (PAC-QOL) Questionnaire] also improved with both the 2-mg and 4-mg dose. For all efficacy parameters, the 2-mg dose provided comparable efficacy to the 4-mg dose. Over 80% of patients included in the three double-blind studies reported that they had not obtained adequate relief of constipation with previous laxative therapy.[21–24]

Patients who completed the three double-blind studies were invited to continue prucalopride treatment in two open-label, long-term follow-up studies with similar design. This report pools data from the two open-label, long-term studies related to the satisfaction with treatment and bowel movements, the patterns of prucalopride and laxative use, and the reasons for discontinuation of prucalopride treatment during the open-label studies.

MATERIALS AND METHODS

All patients who completed the three double-blind, 12-week pivotal Phase III studies (study IDs PRU-INT-6,[23] PRU-USA-11,[21] PRU-USA-13[22]) were invited to continue prucalopride treatment in one of two open-label, Phase III, multicentre, long-term follow-up studies (study IDs PRU-INT-10 and PRU-USA-22; see Figure 1). When patients were recruited at the start of the double-blind study, they had chronic constipation, defined as having two or fewer SCBMs per week, accompanied by straining or a sensation of incomplete evacuation, or hard stools. Eligible male and nonpregnant, nonbreastfeeding female out-patients, at least 18 years of age, were invited to continue treatment with prucalopride for up to 24 or 36 months in the PRU-INT-10 and PRU-USA-22 studies, respectively. The two studies were conducted between June 1998 and November 2000. In November 2000, both studies were stopped to allow for data collection and analysis to start. All patients who were still in the study at that time point were discontinued. The protocols and amendments were reviewed and approved by

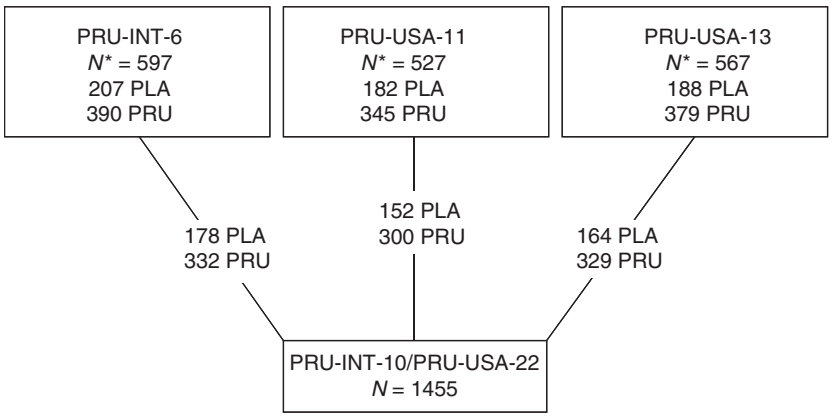


Figure 1 | Patient disposition. Number of patients enrolled from previous double-blind prucalopride studies. *N** = Number of patients who completed the double-blind study and who were eligible to participate in the open-label study. PLA, placebo; PRU, prucalopride.

an Independent Ethics Committee. The studies were conducted in accordance with the applicable local requirements, the principles of the Declaration of Helsinki, and the Good Clinical Practice guidelines of the International Conference on Harmonisation. Written informed consent was obtained from each patient prior to study entry. The PRU-INT-10 and PRU-USA-22 studies are registered with ClinicalTrials.gov (ClinicalTrials.gov Identifiers: NCT01070615; NCT00987844).

Prucalopride was originally developed by Johnson & Johnson (J & J). After phase III, toxicology questions on a preliminary data package required J & J to perform additional toxicology experiments, and J & J chose to prioritize other parts of their Research & Development portfolio. In 2006, Movetis resumed the drug development programme. The toxicology packages were completed, discussed with the Competent Authorities of the European Medicines Agency, and in October 2009, prucalopride was authorized by the European Medicines Agency, confirming resolution of toxicology problems.

Prucalopride dosing in open-label studies

In the PRU-INT-10 follow-up study, patients started with 2-mg prucalopride tablets for seven consecutive days and were then allowed to determine the dose (0 mg, 2 mg or 4 mg once daily), based on efficacy/tolerability (adverse events) of the treatment during a period of up to 24 months. In the PRU-USA-22 follow-up study, 1-mg prucalopride tablets were provided and treatment was self-titrated by the patients to obtain the desired response (up to a maximum 4 mg once daily) for up to 36 months. Dosage interruptions were allowed and the time of medication intake once per day was at the patients' own discretion. Patients were encouraged not to use laxatives or enemas, or other medicines that might interfere with their bowel functions. In the PRU-INT-10 study, a specific rescue rule was specified, allowing patients to use a laxative (preferably bisacodyl 5-mg tablets) prescribed by the investigator, or an enema if the patient did not have a bowel movement for three or more consecutive days. Study visits were scheduled every 3 months and at discontinuation.

Efficacy analysis

At each study visit, patients were asked to complete the five-item satisfaction subscale of the PAC-QOL (see Table 1). The PAC-QOL is a self-administered questionnaire, developed and validated as a constipation-specific assessment tool for use in clinical studies.[25] The PAC-QOL satisfaction subscale contains five items: fewer bowel movements than you would like, satisfied with how often you have a bowel movement, satisfied with the regularity of your bowel movements, satisfied with the time it takes for food to pass through the intestines, satisfied with your treatment. Each item in this subscale is rated on a 5-point

Table 1 | Patient Assessment of Constipation-Quality of Life satisfaction scale

Item
1) Fewer bowel movements than you would like
2) Satisfied with how often you have a bowel movement
3) Satisfied with the regularity of your bowel movements
4) Satisfied with the time it takes for food to pass through the intestines
5) Satisfied with your treatment
Likert Score (0–4)
Score 4 indicating not at all/none of the time satisfied
Score 3 indicating a little bit/a little bit of the time satisfied
Score 2 indicating moderately/some of the time satisfied
Score 1 indicating quite a bit/most of the time satisfied
Score 0 indicating extremely/all of the time satisfied

scale, from 0 to 4 with higher scores reflecting a lower satisfaction (or more discomfort).

The total PAC-QOL instrument is composed of 28 items grouped into four subscales related to dissatisfaction (5 items), physical discomfort (4 items), psychosocial discomfort (8 items), and worries and concerns (11 items). The overall scale and all subscale scores range from 0 to 4, with lower scores indicating better health-related quality of life. Validation studies in the United States, Europe, Canada and Australia have demonstrated that the PAC-QOL is internally consistent, reproducible, valid, and responsive to improvements over time.[25] The additional evaluation of the psychometric properties of the PAC-QOL in the prucalopride pivotal trials population further confirmed its internal consistency, reliability, validity and responsiveness to measure the impact of chronic constipation symptoms on health-related quality of life.[26]

To evaluate exposure to prucalopride and laxatives, patients were asked to record in a daily diary the time of prucalopride intake, the number of tablets taken, and the use of laxatives and/or enemas.

Reasons for study discontinuation

Reasons for study discontinuation were recorded in the Case Report Form (CRF) and could include one of the following categories: death, adverse event (specified), insufficient response, patient asymptomatic/cured, ineligible to continue the study, lost to follow-up, withdrew consent, noncompliant and other (including administrative closure of trial).

Statistical analysis

Statistical analyses were performed with Statistical Analysis System (SAS) software, version 9.1 (SAS Institute Inc., Cary, NC, USA). All patients with treatment information were included in the efficacy analysis. All tests were interpreted at the 5% significance level (two-sided).

For the calculation of change from baseline, the patient's baseline value prior to commencing treatment in the preceding double-blind study was used.

The total score of the PAC-QOL satisfaction subscale was defined as the sum of all nonmissing items, divided by the number of nonmissing items. It was set to missing when more than two items were missing. Descriptive statistics on the total PAC-QOL satisfaction subscale score were calculated per visit (mean, and 95%-confidence limits). Also, a frequency tabulation presenting the number of patients with an improvement in total PAC-QOL satisfaction subscale score of at least one relative to baseline was calculated per visit.

For week 4 and week 12 of the double-blind period, each prucalopride group (2 and 4 mg respectively) is compared with placebo using a *t*-test. Primary focus is on the statistical test at week 12. No formal correction for multiple testing is undertaken.

For month 18 of the open-label period, the within-patient change relative to baseline was evaluated using a paired *t*-test. Changes in PAC-QOL satisfaction scores of at least one point were considered clinically relevant improvements.[26]

Laxative use was summarized by the average number of days with laxative use per 91 days (3 months), and a subgroup analysis was performed on the PAQ-QOL data for patients who did use laxatives at least once and those who did not use any laxatives.

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (MedDRA version 11.0; MedDRA MSSO, Chantilly, VA, USA).

Reasons for study discontinuation were analysed in 3-month intervals with special attention to discontinuation due to adverse events and insufficient response. Study discontinuation due to insufficient response was also analysed by response/nonresponse in the preceding double-blind pivotal studies, based on a responder definition of an average of ≥3 SCBMs per week after the 12-week double-blind prucalopride treatment. This reflects normalization of bowel function, and was the primary endpoint of the double-blind pivotal studies.

RESULTS

Patient population and prucalopride intake

Of the 1691 patients who completed the 12-week double-blind pivotal studies (treatment with placebo, prucalopride 2 mg or prucalopride 4 mg), 1455 (86.0%) patients continued prucalopride treatment in 1 of the 2 open-label studies (Figure 1), with 34.0% patients having received placebo and 66.0% of patients having received prucalopride 2 mg or 4 mg during the double-blind studies. A majority of patients were Caucasian (91.6%) and female (90.2%), and the mean age was 46.7 years (range: 18–86 years). At the start of the double-blind studies, the median duration of constipation of these patients was 15 years, with 30.5% having a history of constipation of more than 20 years.

The median study duration in the open label studies was 450 days (14.8 months, range: 1–1034 days). Twelve months of study data are available for 788 (54.2%) patients, 18 months of study data for 516 (35.5%)

Table 2 | Patient disposition

Time point	Patients participating in open-label study	
	N	%
Month 0–3	1455	100
Month 3–6	1157	79.5
Month 6–9	1018	70.0
Month 9–12	901	61.9
Month 12–15	788	54.2
Month 15–18	655	45.0
Month 18–21	516	35.5
Month 21–24	368	25.3
>Month 24	216	14.8

patients, and ≥24 months of study data for 216 (14.8%) patients (Table 2). The median number of days with prucalopride exposure in the open-label studies was 308 days (10 months). In addition, 961 (66%) patients had been previously treated with prucalopride during 3 months in the double-blind studies. Therefore, the calculated total exposure to prucalopride was 1464 patient-years. During open-label treatment, 30.2% of patients used prucalopride 2 mg most of the time and 52.3% used prucalopride 4 mg most of the time.

Efficacy

Mean PAC-QOL satisfaction scores measured at the end of the double-blind studies and during the open-label studies are shown in Table 3. Mean satisfaction scores at the start of the pivotal studies indicated a high level of

Table 3 | Evolution of PAC-QOL satisfaction throughout double-blind and open-label studies

	Randomization group in pivotal study *N* = 1977*								
	Placebo			Prucalopride 2 mg			Prucalopride 4 mg		
	N with data	Mean	95% CI	*N* with data	Mean	95% CI	*N* with data	Mean	95% CI
Baseline	636	3.30	3.25; 3.36	639	3.29	3.23; 3.34	636	3.27	3.21; 3.32
Week 4	597	3.01	2.92; 3.09	581	2.36†	2.27; 2.46	567	2.31†	2.21; 2.40
Week 12	553	2.93	2.84; 3.02	553	2.40†	2.30; 2.50	517	2.34†	2.24; 2.45

	Continuation with long-term prucalopride treatment *N* = 1455*			
		Prucalopride		
		N with data	Mean	95% CI
Month 3	Placebo patients switch to prucalopride in open-label study	1322	1.95	1.89; 2.02
Month 6		1076	1.81	1.74; 1.87
Month 9		915	1.74	1.67; 1.81
Month 12		780	1.69	1.62; 1.77
Month 15		681	1.68	1.60; 1.76
Month 18		509	1.67‡	1.58; 1.76

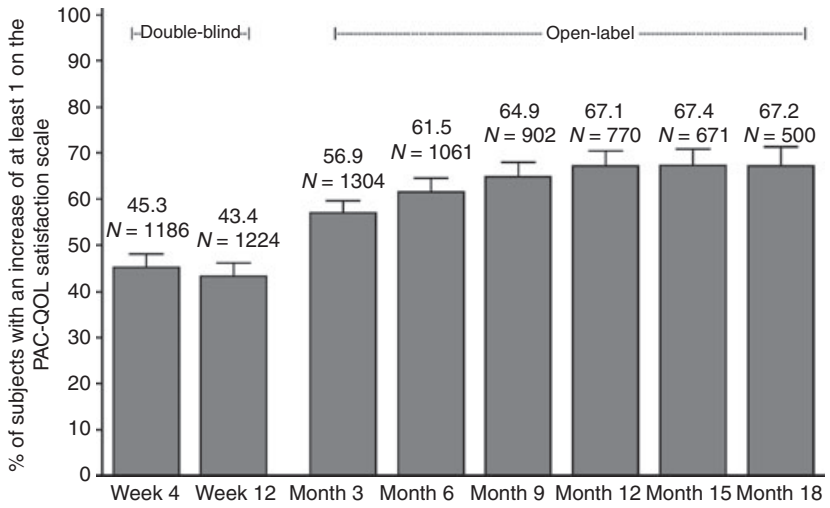
PAC-QOL items are scored on a five-point scale from 0 to 4, with lower values indicating improvement/more satisfaction.

CI, confidence interval.

* Of the 1977 patients included in the three double-blind pivotal studies, 1691 patients completed the studies and 1455 continued prucalopride treatment in the two open-label studies.

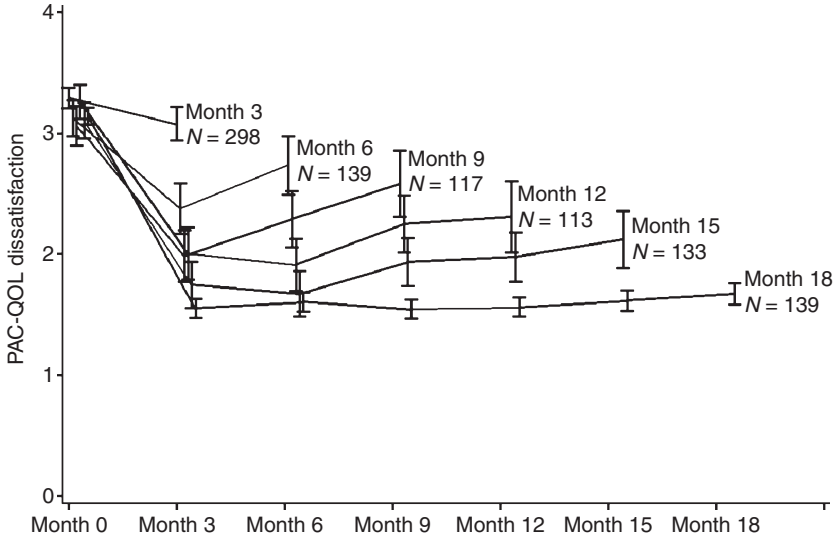
† $P < 0.001$ vs. placebo (unpaired *t*-test).

‡ $P < 0.001$ vs. double-blind baseline (paired *t*-test).



Error bars show the 95% confidence limit

Figure 2 | Improvement on the PAC-QOL satisfaction scale over time for prucalopride patients rolling over into open-label. *N* (%, provided above *N*) of prucalopride-treated patients with improvement of ≥1 point on PAC-QOL satisfaction score over time.



Error bars show the 95% confidence limit. *N* refers to the number of dropouts per timepoint.

Figure 3 | Patient Assessment of Constipation-Quality of Life dissatisfaction over time for dropouts. Month 0 reflects satisfaction score at baseline before the entry into the randomized controlled study.

dissatisfaction (3.27 to 3.30 on a scale of 0 to 4 in all randomization groups). During double-blind treatment, average satisfaction scores significantly improved with prucalopride to 2.40 and 2.34 on prucalopride 2 mg and 4 mg respectively, compared with 2.93 on placebo after 12 weeks of treatment. Continued measurements of the satisfaction during the subsequent open-label studies showed that this average improvement was maintained from month 3 onwards, at least up to 18 months of prucalopride treatment. For patients who received placebo during the pivotal studies, a similar improvement of satisfaction was observed during the first 3 months of treatment with prucalopride in the open-label studies and values also remained stable from month 3 onwards. Evaluating satisfaction by the proportion of patients with a clinically relevant improvement of ≥1 point gives proportions of satisfied patients between 43.4% and 67.4% of patients over the 18-month period (Figure 2).

The mean satisfaction scores for patients who discontinued the open-label studies over time are shown in Figure 3. On average, patients who discontinued had a worsening of satisfaction at the time of drop out. Patients who discontinued at month 3 had on average a worse satisfaction with bowel movements and treatment than patients who discontinued later (Figure 3).

Impact of laxative use on satisfaction with bowel function

Laxative use was permitted during the open-label studies, with a limit to the permitted rescue medication specified in one of the two studies. Analysis over time, in 3-month intervals, showed that 40.8–50% of patients had not used

Table 4 | Patient Assessment of Constipation-Quality of Life satisfaction according to laxative use

Time point	*N*	Patients without laxative use		Patients with laxative use	
		n (% of *N*)	Satisfaction score, mean (95% CI)	*n* (% of *N*)	Satisfaction score, mean (95% CI)
Baseline (Month −3)	1431	455 (31.8)	2.98 (2.90; 3.07)	976 (68.2)	3.26 (3.21; 3.31)
Month 3	1321	539 (40.8)	1.46 (1.37; 1.55)	782 (59.2)	2.29 (2.21; 2.37)
Month 6	1070	448 (41.9)	1.37 (1.28; 1.46)	622 (58.1)	2.12 (2.03; 2.21)
Month 9	909	409 (45.0)	1.32 (1.23;1.41)	500 (55.0)	2.08 (1.99; 2.17)
Month 12	775	366 (47.2)	1.29 (1.19; 1.38)	409 (52.8)	2.05 (1.95; 2.15)
Month 15	676	338 (50.0)	1.28 (1.18; 1.38)	338 (50.0)	2.07 (1.96; 2.18)
Month 18	505	249 (49.3)	1.38 (1.25;1.50)	256 (50.7)	1.95 (1.83; 2.07)

CI, confidence interval.

0 or ≥1 laxative dose or enema used within time interval.

Baseline = run-in of the preceding double-blind study (Month −3).

N refers to the number of patients with PAC-QOL and laxative data at each time point.

any laxative (Table 4). Satisfaction scores improved significantly from baseline in both groups of patients who used or did not use laxatives. Patients who used laxatives were on average less satisfied (i.e. had higher satisfaction scale scores) than patients who did not use laxatives.

Reasons for study discontinuation

In total, 647 (44.5%) patients discontinued at administrative closure of the trial (Table 5). The next most frequent reasons for discontinuation were insufficient response (20.1%), withdrawal of consent (14.0%) and adverse events (8.0%). Furthermore, 6.9% of patients were lost to follow-up and 4.1% of patients discontinued for other reasons (ineligible to continue, noncompliance, patient asymptomatic/cured).

Analysis of the reasons for study discontinuation over time showed that during the first 9 months of open-label treatment, the most frequent reasons for study discontin-

Table 5 | Reasons for study discontinuation

Time point, month	Patients who discontinued at each time point, *n* (%)*	Reason for study discontinuation, *n*					
		Discontinued at trial closure	Insufficient response	Withdrew consent	Adverse events	Lost to follow-up	Other†
3	298 (20.5)	6	150	61	58	13	10
6	139 (9.6)	8	57	29	19	19	7
9	117 (8.0)	9	31	35	17	16	9
12	113 (7.8)	26	30	23	8	16	10
15	133 (9.5)	67	14	25	7	9	11
18	139 (9.5)	93	5	18	4	11	6
21	148 (10.1)	104	4	12	4	11	4
24–36	152 (10.4)	123	1	1	0	3	1
Total, *n* (%)		647 (44.5)	292 (20.1)	204 (14.0)	117 (8.0)	101 (6.9)	60 (4.1)

* Planned durations of the PRU-INT-10 and PRU-USA-22 studies were 24 months and 36 months, respectively. Thirty-four patients completed the PRU-INT-10 study at the time of trial closure; none of the patients in the PRU-USA-22 study had completed the study at trial closure.

† Category 'Other' includes analysis cut-off (1 patient), ineligible to continue (10 patients), noncompliance (34 patients), and patient asymptomatic/cured (15 patients).

uation were insufficient response, withdrawal of consent and adverse events. At month 12 and later, the main reason for study discontinuation was administrative trial closure. Half of the 409 patients who discontinued the study because of insufficient response or adverse events dropped out during the first 3 months of open-label treatment (51.4% and 49.6% respectively; Table 5). Study discontinuation due to insufficient response was also evaluated by response/nonresponse on the primary efficacy endpoint, i.e. ≥3 SCBMs per week over 12 weeks, in the preceding pivotal trial. Of the 961 patients who were treated with prucalopride in the double blind studies, 198 discontinued open-label prucalopride treatment because of insufficient response. Of these 198 patients, 172 (86.9%) turned out to be nonresponders in the preceding pivotal study. Of the 252 patients who were responders in the preceding pivotal studies, only 10.3% (n = 26) discontinued treatment because of insufficient response in the open-label studies.

Of the 961 patients who received prucalopride in the double-blind pivotal studies, 24 (2.5%) discontinued within 3 months of open-label treatment because of adverse events. Of the 494 patients who received placebo in the double-blind studies, 34 (6.9%) discontinued during the first 3 months of open-label treatment because of adverse events. The most frequent adverse events resulting in study discontinuation during these first 3 months were abdominal pain, diarrhoea, nausea and headache, accounting for 74.1% of the cases of withdrawal because of adverse effects (43 out of 58). Most of these events (30 out of the 43) occurred in patients previously treated with placebo, and in 16 of these 30 prucalopride-naïve patients, the adverse event started on day 1 or 2 of prucalopride treatment. The frequency of discontinuation due to adverse events after month 3 was lower, varying between 0.6% and 1.7% in the different 3-month time intervals (Table 6).

DISCUSSION

Prucalopride treatment relieves symptoms of chronic constipation by targeting the underlying impaired colonic motility; prucalopride is not a disease-modifying or curing drug.[27] As constipation is a chronic disease, patients may require treatment for a long period of time. Hence, it is relevant to assess the performance of the drug in open-label studies that followed three identical 12-week double-blind pivotal clinical studies, all of which demonstrated significant efficacy of prucalopride.[21–23]

Table 6 | Most frequent adverse events resulting in study discontinuation

Time point	*N* with data	Total number of patients who discontinued due to adverse events at each time point (% of *N*)*	Most frequent adverse events resulting in discontinuation, *n* (% of *N*)			
			Headache	Nausea	Abdominal pain	Diarrhoea
Month 3	1455	58 (4.0)	13 (0.9)	9 (0.7)	11 (0.8)	10 (0.7)
Randomization group in the preceding double-blind study	PRU: 961 PLA: 494	PRU: 24 PLA: 34	PRU: 5 PLA: 8 (3 with onset on day 1–2)	PRU: 3 PLA: 6 (3 with onset on day 1–2)	PRU: 3 PLA: 8 (5 with onset on day 1–2)	PRU: 2 PLA: 8 (5 with onset on day 1–2)
Month 6	1157	19 (1.6)	1 (0.1)	2 (0.2)	3 (0.3)	2 (0.2)
Month 9	1018	17 (1.7)	0	1 (0.1)	1 (0.1)	3 (0.3)
Month 12	901	8 (0.9)	0	1 (0.1)	3 (0.3)	0
Month 15	788	7 (0.9)	0	0	0	0
Month 18	655	4 (0.6)	0	0	0	1 (0.2)
Month 21	516	4 (0.8)	0	0	0	1 (0.2)
Month 24–36	368	0	0	0	0	0
Total	1455	117 (8.0)	14 (1.0)	13 (0.9)	18 (1.2)	17 (1.2)

Fifteen patients discontinued the study because of pregnancy, as per protocol; all other adverse events resulted in study discontinuation in <0.5% of patients.

* Each patient is only counted once; patients can discontinue because of more than one adverse event.

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A high percentage of patients treated with prucalopride during the double-blind phase (86%) chose to continue prucalopride use in the open-label phase, and the median duration of time the patients participated in the open-label phase was 14.8 months, suggesting that patients are satisfied with prucalopride treatment. Dosing was not maintained as rigorously as in the double-blind studies, as dosage interruptions were allowed, and patients were free to switch doses. Mean treatment duration was 10 months and 30.2% and 52.3% used prucalopride 2 mg (recommended therapeutic dose) and 4 mg respectively, most of the time. Prucalopride 2 mg is the recommenced therapeutic dose, as three double-blind pivotal studies clearly showed that prucalopride 4 mg does not have increased efficacy over the 2-mg dose.[21–23]

Ninety percent of patients who participated in the two open-label studies were female, consistent with the estimated prevalence ratio of 1.01–3.37 females to 1 male, and the known probability of women with constipation to seek healthcare being twice the probability of men.[5–7, 28–31] This explains the relative under-representation of male patients in these clinical studies.

The PAC-QOL satisfaction score, which measures satisfaction with bowel functioning and treatment, was used as primary efficacy endpoint in these two studies. The PAC-QOL questionnaire is composed of four subscales related to dissatisfaction (5 items), physical discomfort (4 items), psychosocial discomfort (8 items) and worries and concerns (11 items). The overall score and all subscale scores range from 0 to 4, with higher scores indicating worse health-related quality of life. Validation studies in the United States, Europe, Canada and Australia have demonstrated that the PAC-QOL is internally consistent, reproducible, valid and responsive to improvement over time.[25] For the overall PAC-QOL score, patients reporting marked to very severe constipation reported mean scores that were 0.52 to 0.66 points higher than patients reporting mild-to-moderate severity, suggesting that 0.5 is already a valid threshold for defining a clinically meaningful difference. In these studies, an improvement of one point was considered clinically meaningful, demonstrating that the analysis was conservative. The psychometric properties of the PAC-QOL were further evaluated in the prucalopride pivotal trials population, which confirmed its responsiveness to measure the impact of chronic constipation symptoms on health-related quality of life.[26] The results presented in this manuscript show that in patients with a long history of constipation and high mean PAC-QOL satisfaction scores (reflecting poor satisfaction) at baseline of the preceding double-blind studies, improvements over placebo that had been observed after 4 and 12 weeks of double-blind treatment were maintained for up to 18 months.

Although laxative use was permitted during this study, at each 3 months interval, 40–50% of patients did not use laxatives in addition to prucalopride treatment. The PAC-QOL satisfaction scores were lower (indicating greater satisfaction) in patients who did not use laxatives in addition to prucalopride treatment. This suggests that the improvements in patient satisfaction with bowel movement and treatment are attributable to prucalopride use, and not to laxative use. An alternative explanation is that the group that did not have a satisfactory response to 2 or 4 mg prucalopride also did not respond to laxative/enema treatment provided as rescue. It remains unclear whether the patients who did not respond to prucalopride or prucalopride and bisacodyl/enemas may have improved with alternative approaches, such as the addition of more effective osmotic agents or secretagogues.

Early trial closure was the most frequent reason for study discontinuation. Insufficient response and adverse events were the reason for discontinuation of prucalopride treatment in 20.1% and 8.0% of patients respectively.

The higher frequency of discontinuation due to adverse events observed during the first 3 months is explained by gastrointestinal-related adverse events and headache in the first days of prucalopride treatment in those patients who had received placebo during the preceding double-blind studies. As known from other studies with prucalopride, these adverse events are generally transient and disappear with continued prucalopride use.[21–23] Majority of patients who discontinued open-label prucalopride treatment for insufficient response turned out to have been nonresponders on the primary efficacy parameter in the double-blind studies, i.e. they had on average <3 SCBMs per week after 12 weeks of double-blind treatment. Only 10.3% of patients who experienced normalization of bowel movements during the 12 weeks of double-blind treatment discontinued prucalopride treatment because of insufficient response during the open-label studies.

We believe, the major strength of this study is that it reports on approximately 1464 patient-years equivalent in the double-blind and open-label phases of treatment and therefore the observations have some value in predicting the likely effectiveness (not just efficacy) in clinical practice. On the other hand, the main limitation is the open-label design, the lack of comparison with placebo and the lack of documentation of the SCBMs dur-

ing the long-term studies. However, efficacy was assessed based on a validated patient-reported outcome, the PAC-QOL satisfaction scale, that focuses on the degree of dissatisfaction with bowel dysfunction and treatment. The results obtained using this satisfaction scale are complemented by the commitment of patients to the treatment, as shown by the long duration of self-administration of the treatment. In addition, the relatively small number of discontinuations for lack of efficacy corroborates the conclusion that prucalopride results in satisfaction with bowel function as shown by the PAC-QOL satisfaction scores. As in all long-term trials, there was enrichment over time of patients who respond well to treatment. However, there was no loss of efficacy over time, as the majority of patients dropping out due to insufficient response were already nonresponders in the previous 12-week, double-blind studies. Patients who did respond to prucalopride treatment in the pivotal studies remained responders over time.

In conclusion, the results of the two long-term, open-label studies show that the improvements in patient satisfaction with bowel movements and treatment, as observed after 4 and 12 weeks of double-blind treatment, are maintained for at least 18 months. Forty to fifty percent of patients do not need laxatives in addition to prucalopride treatment to maintain satisfactory control of chronic constipation, based on an experience of approximately 1464 patient-years exposure to prucalopride. Gastrointestinal-related adverse events and headache may result in discontinuation of prucalopride treatment, but these events occur predominantly during the first days of treatment. This experience also provides practitioners with valuable guidance on the decision to initiate and continue use of this medication in practice. Thus, patients who do not respond to prucalopride treatment during a first trial of 3 months will probably not respond afterwards, and patients that do respond will remain satisfied with bowel movements and treatment for several months following the success achieved in the first 3 months.

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