Gastroenterology 2014;147:1285–1295

Prucalopride Is No More Effective Than Placebo for Children With Functional Constipation

Suzanne M. Mugie,[1] Bartosz Korczowski,[2] Piroska Bodi,[3] Alexandra Green,[4] René Kerstens,[5] Jannie Ausma,[5] Magnus Ruth,[5] Amy Levine,[6] and Marc A. Benninga[1]

[1]Division of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital/Academic Medical Center, Amsterdam, The Netherlands; [2]Pediatric Department, Medical College, University of Rzeszów, Rzeszów, Poland; [3]Department of Paediatrics, Pándy Kálmán Hospital, Gyula, Hungary; [4]Shire, Basingstoke, UK; [5]Shire-Movetis NV, Turnhout, Belgium; and [6]Shire, Wayne, Pennsylvania

See editorial on page 1214.

BACKGROUND & AIMS: Prucalopride is a selective, high-affinity agonist of the 5-hydroxytryptamine (serotonin) receptor 4 that enhances motility in the gastrointestinal tract. We performed a multicenter, randomized, placebo-controlled, double-blind, phase 3 trial to evaluate the efficacy and safety of prucalopride in children (6 months to 18 years old) with functional constipation. **METHODS:** Children with functional constipation, based on the Rome III criteria, were given prucalopride (children ≤50 kg were given a 0.04 mg/kg oral solution; children >50 kg were given a 2-mg tablet) or placebo once daily for 8 weeks. The primary efficacy end point was the proportion of children with toileting skills who had a mean of ≥3 spontaneous bowel movements/week and ≤1 episode of fecal incontinence/2 weeks, from study weeks 5–8 (responders). Adverse events, clinical laboratory values, and electrocardiograms were monitored. **RESULTS:** Efficacy and safety were assessed in 213 children (106 prucalopride, 107 placebo). Twenty-five percent were younger than 4 years old, 50% were 4–11 years old, and 25% were 12–18 years old; 55.4% were girls. At screening, 62.3% of patients in the prucalopride group and 55.1% in the placebo group had a history of fecal incontinence; 60.4% and 55.1% in the prucalopride and placebo groups, respectively, had a mean of ≤1 spontaneous bowel movements/week. The proportion of responders was similar between groups (prucalopride, 17.0% and placebo, 17.8%). There were no statistically significant differences in the primary efficacy end point when patients were stratified by sex, age group, or country. The incidence of treatment-emergent adverse events was similar in the prucalopride (69.8%) and placebo (60.7%) groups. **CONCLUSIONS:** Prucalopride, although generally well tolerated, was not more effective than placebo in children with functional constipation. ClinicalTrials.gov Number: NCT01330381.

Keywords: TEAEs; 5-HT$_4$ Receptor; Pediatric; Clinical Trial.

Childhood constipation is a common problem, with an estimated worldwide prevalence of 0.7%−29.6%.[1] In most children, constipation is characterized by infrequent painful defecation, large stools, fecal incontinence (FI), and abdominal pain.[2,3] Chronic constipation is associated with impaired health-related quality of life (HRQoL),[4,5] with many children needing long-term treatment. Despite treatment, up to 25% of children continue to have constipation beyond puberty.[6] The treatment of functional constipation in children comprises education, behavioral modification, and oral laxatives. Despite the widely accepted use of laxatives, clinical evidence of their efficacy and safety in children is limited.[7] The 5-HT$_4$ agonist cisapride was shown to be effective in the treatment of children with constipation;[8] however, cisapride has now been withdrawn from use because of cardiovascular safety concerns.

Prucalopride (Resolor; Shire-Movetis NV, Turnhout, Belgium) a dihydrobenzofurancarboxamide derivative, is a selective, high-affinity 5-HT$_4$ receptor agonist with gastrointestinal prokinetic properties.[9,10] Prucalopride is approved in the EU for the symptomatic treatment of chronic constipation in women for whom laxatives fail to provide adequate relief. Prucalopride stimulates colonic motility by increasing high-amplitude propagated contractions, and accelerates colonic transit in healthy volunteers and adult patients with constipation.[11–13] Several randomized, double-blind, placebo-controlled, phase 3 trials in adults have demonstrated that prucalopride is well tolerated and effective in increasing stool frequency, reducing constipation-related symptoms, and improving HRQoL.[14–19] Its high affinity and selectivity for 5-HT$_4$ receptors differentiates prucalopride from previous-generation compounds, such as cisapride and tegaserod, and minimizes the potential for target-unrelated side effects.[20,21]

To date, one open-label pilot study has investigated the effect of prucalopride in children.[22] After 8 weeks of treatment, constipation-related symptoms improved in 55% of patients, including an increase in bowel movement (BM) frequency and a reduction in FI. Prucalopride

Abbreviations used in this paper: **5-HT$_4$, 5-hydroxytryptamine (serotonin) receptor 4; AE, adverse event; BM, bowel movement; ECG, electrocardiogram; FI, fecal incontinence; HRQoL, health-related quality of life; PedsQL, Pediatric Quality of Life Inventory Generic Core Scales Version 4.0; PEG, polyethylene glycol; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.**

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2014.09.005

was well tolerated and no relevant changes in vital parameters or electrocardiogram (ECG) recordings were observed.

The aim of this trial was to determine the efficacy, safety, and tolerability of prucalopride compared with placebo for the treatment of functional constipation in children.

Methods

Study Design

A multicenter, randomized phase 3 trial was conducted from April 2011 to March 2013 at 33 centers in Europe (ClinicalTrials.gov: NCT01330381). The trial comprised an 8-week double-blind, placebo-controlled period and a 16-week, open-label, active-controlled period (Figure 1).

The study was conducted in accordance with the International Conference on Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki, and applicable local ethical and legal requirements. The protocol was reviewed and approved by the ethical committees of all participating centers. Written informed consent was obtained and signed by each child's legal guardian and by the investigator before the initiation of any study procedures. Assent was obtained for children aged >6 years. All authors had access to the study data and reviewed and approved the final manuscript.

Study Population

Children aged between 6 months and 18 years with a confirmed diagnosis of functional constipation based on the Rome III criteria were eligible for inclusion.[23] Functional constipation was defined as <3 spontaneous bowel movements (SBMs)/week with at least 1 of the following during the previous month (for patients aged <4 years) or 2 months (for patients aged ≥4 years): ≥1 episode of FI/week (after the acquisition of toileting skills); retentive posturing or excessive volitional stool retention; painful or hard BMs; large-diameter stools; or a large fecal mass in the rectum. A BM was considered spontaneous when neither an oral laxative nor an enema had been used in the preceding 24 hours. After screening, eligible patients entered a run-in period that comprised 1 week of control measurements for the documentation of constipation symptoms, followed by fecal disimpaction with an oral laxative (eg, polyethylene glycol [PEG] 3350 for 1–3 days) or an enema (sodium dioctylsulfosuccinate and sorbitol), if required. The success of disimpaction was evaluated by questioning the patient and/or their legal guardian(s) regarding BMs.

In cases in which a laxative or other prohibited medication was used at screening, this medication was stopped and the run-in period extended by 1 week to allow for washout. Prohibited medications are listed in the Supplementary Materials.

The following exclusion criteria were applied: underlying cause of defecation disorder (eg, Hirschsprung's disease, spina bifida occulta, cystic fibrosis, or gastrointestinal malformations); significant developmental delays associated with musculoskeletal or neurologic conditions affecting the gastrointestinal tract; constipation secondary to endocrine, metabolic, neurologic, organic, autoimmune disorders, surgery, or drugs; clinically significant cardiac, vascular, liver, pulmonary, or psychiatric disorders; severe renal insufficiency; human immunodeficiency virus; acquired immunodeficiency syndrome; hepatitis B; hepatitis C; or clinically significant abnormalities of hematology, urinalysis, or blood biochemistry at screening. Patients with known lactose intolerance for whom it was expected that low doses of lactose could lead to diarrhea, or those who were known to have an allergy to one of the investigational drugs or its excipients, were also excluded. Patients who were breast-fed during the study or who used any investigational drug within the 30 days preceding screening were also excluded.

The children were not to change their lifestyle or diet. This instruction was given to the children and/or their legal guardian(s), and included no changes to exercise levels or fiber intake. If applicable, legal guardians of children aged ≥4 years were instructed to continue with toilet training (defined as at least three 5-minute visits to the toilet in a silent relaxed atmosphere after each meal) during the study.

Randomization and Dosing

Participants were randomized 1:1 to placebo or prucalopride. Randomization was organized using a central interactive web-based, voice-response system, which applied a minimization algorithm and generated a medication number to ensure blinding. Randomization was stratified by country and

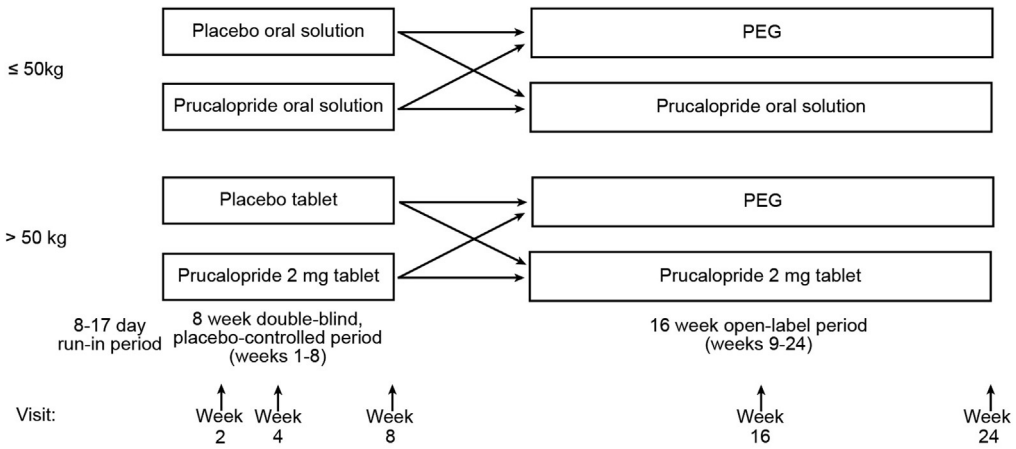

Figure 1. Study design.

age (≥6 months to <4 years; ≥4 to <12 years; and ≥12 to <18 years). It was planned to enroll a minimum of 30% of the total number of patients from either sex, and at least 15% of the total from each age group.

During the 8-week double-blind period (Figure 1), children weighing ≤50 kg received prucalopride or placebo 0.04 mg/kg body weight, once daily (prucalopride succinate oral solution equivalent to 0.4 mg/mL prucalopride). After 4 weeks, the dose could be increased to 0.06 mg/kg or decreased to 0.02 mg/kg, based on treatment response and the presence of safety/tolerability concerns, respectively. Children who underwent dose adjustment remained on that dose for the remainder of the double-blind period. Patients weighing >50 kg received either placebo or a 2-mg prucalopride tablet once daily with no dose adjustments. Irrespective of body mass, the maximum dose per intake was 2 mg prucalopride or placebo. The preferred daily dosing schedule was 1–3 hours before evening meals. Patients and investigators were blinded to treatment allocation; placebo was identical in taste and appearance to prucalopride. Patients visited the study center at weeks 2, 4, and 8 for efficacy and safety assessments.

To evaluate long-term safety and tolerability, patients who completed the 8-week double-blind period and wished to continue treatment were re-randomized 1:1 to receive, without a washout period, 16 weeks of open-label treatment with prucalopride or PEG 4000. Randomization was stratified by preceding treatment, country, and age group. For children randomized to prucalopride, dosing was set by body mass as measured at the start of the double-blind period. No dose adjustments were permitted during the open-label period. Patients assigned to PEG 4000 received 4–20 g once daily before the evening meal based on their age (≥6 months to <1 year: 4 g; ≥1 to <4 years: 8 g; ≥4 to <8 years: 12 g; ≥8 to <18 years: 20 g). Patients visited the study center at weeks 16 and 24 for assessment of safety, and patient's global assessment of constipation severity, and treatment convenience and efficacy.

Concomitant Medication

Laxatives and agents that influence bowel habits were not permitted during the run-in or study periods. If the patient did not have a BM for ≥3 consecutive days, they could take 5 mg bisacodyl or 7.5 mg/mL sodium picosulfate droplets (1 droplet per 5 kg body mass) for rescue purposes. If the standard dose was insufficient, an increase was allowed after discussion with the investigator. If the patient had no BMs, an enema (eg, sodium dioctylsulfosuccinate and sorbitol) or oral agent (eg, PEG 3350) could be administered to remove the impaction.

Efficacy End Points

Response was defined as a mean SBM frequency of ≥3/week and a mean FI frequency of ≤1/2 weeks during weeks 5–8 of the double-blind period. FI was taken into account only after the acquisition of toileting skills.

Secondary end points assessed during the double-blind period included SBM frequency, FI frequency, retentive posturing or excessive volitional stool retention, pain during defecation, stool consistency, abdominal pain, use of rescue medication, and HRQoL. During the open-label period, efficacy was assessed by global assessment of constipation severity, treatment convenience, and efficacy. Safety and tolerability were assessed throughout.

Efficacy Assessments

E-diary. From the start of the run-in period through to the end of the double-blind period, patients and/or their legal guardian(s) recorded in daily e-diaries the timing of BMs, stool consistency (using the Bristol Stool Scale), presence of painful defecation (6-point scale), passing of a large-diameter stool, number of FI episodes, presence of abdominal pain (using the Wong–Baker Faces Pain Rating Scale),[24] and presence of retentive posturing or excessive volitional stool retention. Date and time of study drug intake, rescue medication use, and toilet training were also recorded.

Global assessment. At screening, baseline, and weeks 2, 4, 8, 16, and 24, the severity of constipation during the previous 2 weeks (0 = absent, 4 = very severe) and global evaluation of treatment efficacy were assessed (0 = not at all effective, 4 = extremely effective). At week 24 or discontinuation, treatment convenience was evaluated (−2 = not at all convenient/very difficult, 2 = very convenient/very easy).

Questionnaires. HRQoL was evaluated at the end of the run-in period and at weeks 8 and 24, or on discontinuation using the Pediatric Quality of Life Inventory Generic Core Scales Version 4.0 (PedsQL) and the PedsQL gastrointestinal symptoms module.[25–30]

Safety and tolerability assessments. Blood pressure, pulse rate, and temperature were recorded at screening, and at weeks 0, 8, and 24. ECGs were taken at these visits to measure RR, PR, QRS, and QT intervals, as well as heart rate. Physical examinations, including pregnancy testing for girls who were of childbearing potential, were performed at screening and weeks 0, 8, and 24. Weight and height were recorded at all visits except the second screening visit; Tanner stages were recorded at weeks 0 and 24. Blood samples for biochemistry/hematology and a urine sample for urinalysis were taken at screening and at weeks 8 and 24. All adverse events were recorded. Safety was monitored by an independent monitoring board.

Statistical Analysis

It was calculated that 97 patients per treatment group would be sufficient to detect a difference of ≥20% in response rate between prucalopride and placebo with a 5% level of significance and a power of 80%. To take into account the possibility of discontinuations or insufficient e-diary data, the sample size was set at 105 patients in each group. After approximately 70 children had completed the double-blind period, a formal interim analysis was performed and evaluated by an independent data safety monitoring board to decide whether a general dose adjustment was required for the open-label period.

The primary efficacy analysis was performed on the intent-to-treat population, which included all patients who were randomized and used the investigational product at least once. The per-protocol set was used for sensitivity analysis, and was a subpopulation of the intent-to-treat population, excluding patients who stopped treatment with the investigational product before day 37, or who had a protocol violation that had the potential to affect efficacy and/or safety.

For inferential statistics on binary data, the Cochran–Mantel–Haenszel test (controlled for stratification factors

[country and age group]) was used to test for differences between treatments. For inferential statistics on continuous parameters, treatment comparisons were performed using an analysis of covariance model, including treatment, country, and age group as factors and baseline score as a covariate. Time-to-event data were analyzed descriptively using a Kaplan–Meier curve. For inferential statistics, the log-rank test (controlled for country and age group) was used.

The safety analysis was performed on the safety set, which comprised all patients who were randomized and used the investigational product at least once. For each safety parameter, the last nonmissing value collected before the first dose of investigational product was used as baseline.

Results

Enrollment

Of the 304 screened patients, 89 were excluded before randomization (Figure 2). Therefore, 215 patients were randomized, 107 to the prucalopride group and 108 to the placebo group. Two patients withdrew consent before investigational product dosing and, as a result, the safety population comprised 213 children (prucalopride: 106; placebo: 107). The per-protocol set excluded 12 patients who stopped treatment with the investigational product before day 37, and 43 who had a protocol violation that had the potential to affect efficacy and/or safety.

The majority (91.6%) of patients completed the double-blind period (prucalopride: 89.7%; placebo 93.5%). The most common reason for withdrawal was withdrawn consent (Figure 2). Overall, 197 patients entered the open-label period; 98 were re-randomized to prucalopride and 99 to PEG. The discontinuation rate in the PEG group was 18.2%, compared with 10.2% in the prucalopride group.

Demographics and Baseline Characteristics

Slightly more girls (55.4%) than boys (44.6%) were randomized; this was similar in both groups (Table 1). Mean (SD) age was 8.3 (4.54) years in the prucalopride group and 8.2 (4.69) years in the placebo group. Approximately 25% of patients were aged <4 years, 50% were ≥4 to <12 years, and 25% were ≥12 to <18 years.

Baseline disease characteristics were well balanced across treatment groups. Patients had a mean duration of constipation of 4.4 years in the prucalopride group and 4.2

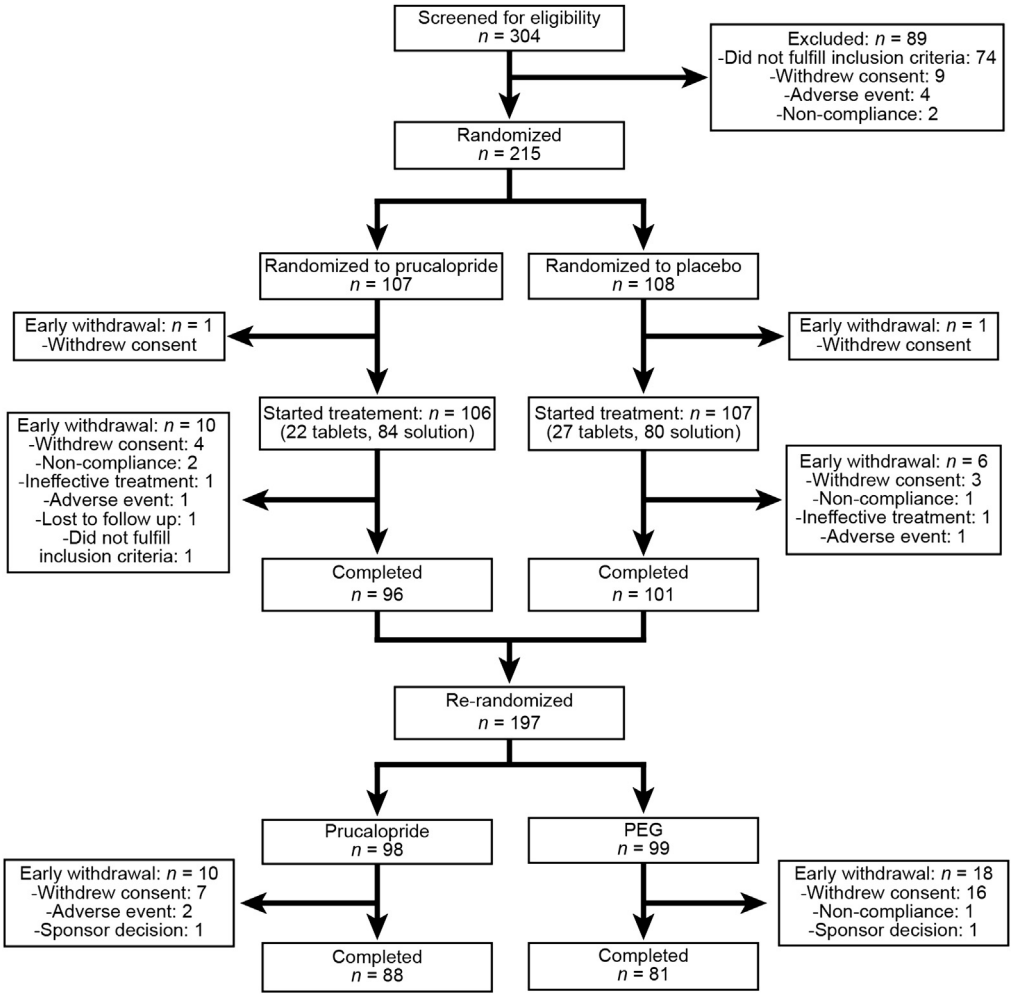

Figure 2. Study flow and disposition of patients.

Table 1. Patient Demographics and Baseline Characteristics (Safety Analysis Set)

	Prucalopride			Placebo		
	Tablet (n = 22)	Solution (n = 84)	Total (n = 106)	Tablet (n = 27)	Solution (n = 80)	Total (n = 107)
Age, *y*, mean (SD)	14.9 (1.95)	6.6 (3.26)	8.3 (4.54)	14.7 (2.26)	6.1 (2.98)	8.2 (4.69)
Age group, n (%)						
<4 y	0	27 (32.1)	27 (25.5)	0	26 (32.5)	26 (24.3)
≥4 to <12 y	1 (4.5)	51 (60.7)	52 (49.1)	2 (7.4)	52 (65.0)	54 (50.5)
≥12 to <18 y	21 (95.5)	6 (7.1)	27 (25.5)	25 (92.6)	2 (2.5)	27 (25.2)
BMI, kg/m^2, mean (SD)	23.8 (5.86)	16.0 (2.08)	17.6 (4.51)	22.5 (2.69)	16.0 (2.62)	17.6 (3.87)
Sex, n (%)						
Female	17 (77.3)	43 (51.2)	60 (56.6)	16 (59.3)	42 (52.5)	58 (54.2)
Male	5 (22.7)	41 (48.8)	46 (43.4)	11 (40.7)	38 (47.5)	49 (45.8)
Race, n (%)						
White	20 (90.9)	81 (96.4)[a]	101 (95.3)[a]	27 (100.0)	75 (93.8)	102 (95.3)
Black	2 (9.1)	1 (1.2)	3 (2.8)	0	3 (3.8)	3 (2.8)
Not allowed to ask	0	2 (2.4)	2 (1.9)	0	2 (2.5)	2 (1.9)
Country, n (%)						
Hungary	6 (27.3)	33 (39.3)	39 (36.8)	5 (18.5)	30 (37.5)	35 (32.7)
Netherlands	11 (50.0)	14 (16.7)	25 (23.6)	16 (59.3)	10 (12.5)	26 (24.3)
Poland	2 (9.1)	21 (25.0)	23 (21.7)	1 (3.7)	22 (27.5)	23 (21.5)
United Kingdom	2 (9.1)	8 (9.5)	10 (9.4)	1 (3.7)	9 (11.3)	10 (9.3)
Belgium	1 (4.5)	3 (3.6)	4 (3.8)	2 (7.4)	2 (2.5)	4 (3.7)
Germany	0	1 (1.2)	1 (0.9)	2 (7.4)	4 (5.0)	6 (5.6)
France	0	2 (2.4)	2 (1.9)	0	2 (2.5)	2 (1.9)
Italy	0	2 (2.4)	2 (1.9)	0	1 (1.3)	1 (0.9)
Duration of symptoms, *y*, mean (SD)	8.4 (5.46)	3.4 (3.13)	4.4 (4.23)	7.0 (5.56)	3.2 (2.63)	4.2 (3.93)
SBMs/week, mean (SD)	0.7 (0.73)	0.9 (0.91)	0.8 (0.87)	1.0 (1.00)	1.1 (1.04)	1.1 (1.03)
FI episodes/2 weeks, mean (SD)	7.1 (15.18)	21.4 (40.50)	18.0 (36.58)	7.6 (15.19)	28.8 (80.10)	22.7 (68.50)
Severity of constipation, n (%)						
Mild	1 (4.5)	1 (1.2)	2 (1.9)	1 (3.7)	3 (3.8)	4 (3.7)
Moderate	3 (13.6)	14 (16.7)	17 (16.0)	9 (33.3)	7 (8.8)	16 (15.0)
Severe	9 (40.9)	40 (47.6)	49 (46.2)	8 (29.6)	33 (41.3)	41 (38.3)
Very severe	9 (40.9)	29 (34.5)	38 (35.8)	9 (33.3)	37 (46.3)	46 (43.0)

BMI, body mass index.
[a]Includes 1 patient who identified as white/Asian mixed race.

years in the placebo group. The majority of patients in each group had ≤1 SBM/week (prucalopride: 60.4%; placebo: 55.1%) at baseline. The presence of FI was similar in both groups (prucalopride: 62.3%; placebo: 55.1%). The majority of children (81.7%) had severe or very severe constipation, a history of excessive volitional stool retention (61.0%), painful or hard BMs (85.9%), a large fecal mass in the rectum (79.7%), large-diameter stools (79.3%), and rectal fecal impaction (64.8%). More than half of all patients (63.4%) had never had toilet training.

Study Medication

In total, 68% of patients receiving prucalopride solution (57 of 84) and 75% of patients receiving placebo solution (60 of 80) increased their dose to 0.06 mg/kg, and 1 patient in each group decreased their dose to 0.02 mg/kg after 4 weeks. Concomitant medication use was balanced across the treatment periods (double-blind: 66.7% of patients; open-label: 65.5%). The most commonly used medications in the double-blind and open-label periods were paracetamol (30.0% and 21.3%, respectively) and ibuprofen (9.4% and 6.1%, respectively). Based on e-diary data, compliance was 93.2% in the prucalopride group and 90.5% in the placebo group in the double-blind phase. In the open-label period, compliance was 96.6% in the prucalopride group and 95.4% in the PEG group.

Efficacy—Double-Blind Period

Primary efficacy end point. A similar proportion of patients in the prucalopride (17.0%) and placebo (17.8%) groups met the primary responder definition (mean of ≥3 SBMs/week and ≤1 FI episode/2 weeks during weeks 5–8; $P = .90$; Figure 3). No differences in the primary efficacy end point were found when comparing prucalopride (tablet 13.6%; solution 17.9%) and placebo (tablet 18.5%; solution 17.5%) formulations.

Results from the sensitivity analysis on the per-protocol set were consistent with the intent-to-treat population ($P = .78$). Subgroup analyses of the primary end point by country, dose group, and sex did not reveal any significant differences (data not shown). The prucalopride group had a higher proportion of responders than the placebo

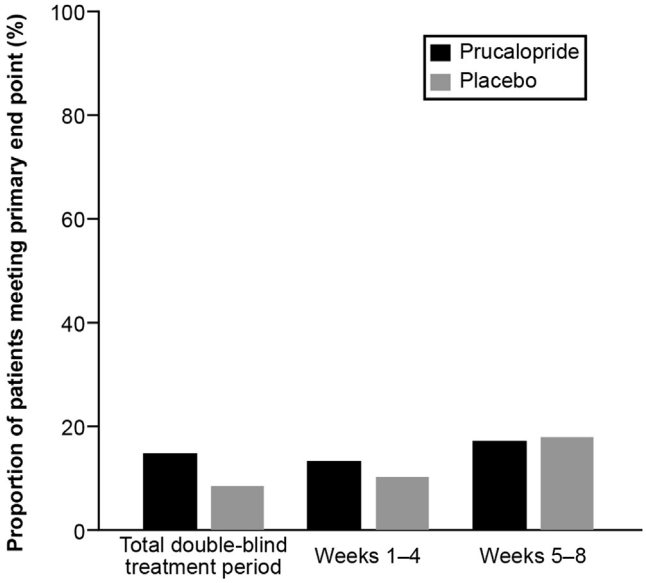

Figure 3. Primary efficacy end point data (intent-to-treat population).

group during the total 8-week double-blind period (prucalopride 14.3%; placebo 8.4%; Figure 3) and weeks 1–4 (prucalopride 13.3%; placebo 10.3%); however, the difference between treatment groups was not statistically significant for either analysis period ($P = .06$ and $P = .21$, respectively).

Analysis of the primary end point by age showed that the proportion of patients who met the primary responder definition was numerically higher in the prucalopride group than the placebo group in patients aged ≥12 to <18 years (prucalopride: 18.5%; placebo: 14.8%; $P = .38$), but not in those aged <4 years (prucalopride: 11.1%; placebo: 15.4%; $P = .73$) or ≥4 to <12 years (prucalopride: 19.2%; placebo: 20.4%; $P = .88$).

Additional subgroup analyses were performed post hoc and showed that there was no significant difference in response rate in patients who had a history of withholding behavior or retentive posturing (prucalopride: 17.7%; placebo: 11.8%; $P = .40$), or who had no such history (prucalopride: 16.3%; placebo: 28.2%; $P = .58$). The data were also analyzed by the presence of FI at baseline. There was no significant difference in the primary end point regardless of whether FI was (prucalopride: 19.2%; placebo: 24.6%; $P = .34$) or was not present at baseline (prucalopride: 12.1%; placebo: 7.1%; $P = .28$).

Secondary efficacy end points. There was no significant difference between groups in improvement from baseline to the double-blind period in the number of SBMs or FI episodes, pain during defecation, abdominal pain, or the use of rescue medication (Table 2). There was significant improvement in stool consistency in the prucalopride group compared with the placebo group ($P = .02$; Table 2). A larger proportion of patients in the prucalopride group than the placebo group had an improvement of 1 point in Bristol Stool Scale score (32.6% vs 21.8%, $P = .09$). Median time to first SBM was 67 hours for prucalopride and 100 hours for placebo ($P = .38$). Overall, a similar proportion of patients in the prucalopride (29.2%) and placebo (35.5%) groups had a mean of ≥3 SBM/week during weeks 5–8. An identical proportion of patients (43.0% in both groups) experienced ≤1 episode of FI/2 weeks during weeks 5–8. Post-hoc analyses showed that, in weeks 5–8, the mean abdominal pain score was significantly lower in patients with ≥3 SBM/week than in those with <3 SBM/week (0.72 vs 1.10; $P = .02$). This difference was more pronounced in patients in the prucalopride group (0.37 vs 1.06; $P = .02$) than the placebo group (0.97 vs 1.15; $P = .30$).

At the end of the double-blind period, the proportions of patients rating their constipation severity as severe or very severe were similar in the prucalopride (43.7%) and placebo (48.6%) groups, compared with 82.1% and 81.3% at baseline, respectively. There was no significant difference in severity ratings between treatment groups at baseline ($P = .27$) or at the end of the double-blind period ($P = .16$). More patients in the prucalopride than the placebo group considered their treatment to be quite effective to extremely effective (36.9% vs 23.3%) at the end of the double-blind

Table 2. Secondary End Point Data at Baseline and Changes From Baseline to Double-Blind Period[a] (Intention-to-Treat Population)

	Prucalopride (n = 106)	Placebo (n = 107)	*P* value[b]
No. of SBMs/week			
Mean at baseline (SD)	0.8 (0.87)	1.1 (1.03)	
Mean change from baseline (SD)	+1.5 (2.35)	+1.0 (1.78)	.16
No. of FI episodes/2 weeks			
Mean at baseline (SD)	18.0 (36.58)	22.7 (68.50)	
Mean change from baseline (SD)	−8.7 (36.85)	−13.9 (64.91)	.59
Stool consistency[c] (1–7)			
Mean at baseline (SD)	3.2 (1.42)	3.4 (1.54)	
Mean change from baseline (SD)	+0.6 (1.41)	+0.1 (1.17)	.02
Mean level of defecation pain (0–5)			
Baseline (SD)	2.0 (1.53)	2.1 (1.47)	
Mean change from baseline (SD)	−0.6 (1.36)	−0.4 (1.19)	.06
Mean level of abdominal pain (0–5)			
Baseline (SD)	1.1 (1.25)	1.3 (1.33)	
Mean change from baseline (SD)	−0.2 (0.76)	−0.3 (0.94)	.89
Mean no. of days rescue medication used			
Baseline (SD)	1.5 (1.28)	1.6 (1.48)	
Mean change from baseline (SD)	−0.3 (1.20)	−0.4 (1.36)	.87

[a]Change from baseline value to mean value across weeks 1–8.
[b]*P* values calculated from analysis of covariance model.
[c]7-Point Bristol Stool Scale for children.

period, but the difference in effectiveness ratings was not significant ($P = .47$).

Overall improvements in PedsQL score from baseline to week 8 were similar in the prucalopride (child-report: +3.9 [SD 13.8]; parent-report: +6.5 [SD 13.9]) and placebo groups (child-report: +2.7 [SD 12.4]; parent-report: +4.1 [SD 14.2]). PedsQL subscale results showed no consistent changes (data not shown). There was no significant difference between the prucalopride and placebo groups in any of the PedsQL GI module symptom items (data not shown).

Efficacy—Open-Label Period

At the end of the open-label period, 40.2% of patients taking prucalopride rated their constipation as severe to very severe compared with 28.0% of patients taking PEG ($P = .0003$); 39.2% of patients taking prucalopride rated their treatment as quite effective to extremely effective compared with 67.7% of patients taking PEG ($P < .0001$). The proportion of patients considering their treatment to be quite or very convenient at the end of the open-label period was 82.4% among those taking prucalopride and 76.7% among those taking PEG ($P = .30$).

At week 16 of the open-label period, mean (SD) scores on the child-report PedsQL were 81.4 (16.1), 74.8 (14.3), 76.3 (15.4), and 75.8 (17.2) for the prucalopride–prucalopride, prucalopride–PEG, placebo–prucalopride, and placebo–PEG treatment sequences, respectively. Mean (SD) scores on the parent-reported questionnaire were 79.7 (18.7), 78.6 (18.8), 80.5 (16.8), and 80.3 (16.6), respectively. Analysis of the changes from baseline to the end of week 16 showed no differences between prucalopride, placebo, and PEG in child or parent reports (data not shown).

Safety—Double-Blind Period

During the double-blind period, treatment-emergent adverse events (TEAEs) were reported by 69.8% of patients in the prucalopride group (tablet: 81.8%; solution: 66.7%) and 60.7% of patients in the placebo group (Table 3). The prucalopride group (21.7%) had a higher proportion of patients with a TEAE on day 1 than the placebo group (3.7%). The most common (>10% overall) TEAE in either group on day 1 was headache (prucalopride: 13.2%; placebo: 0.9%). After day 1, TEAEs were reported by

Table 3. Most Frequent (>5%) Treatment-Emergent Adverse Events (TEAEs) and All Serious Treatment-Emergent Adverse Events (Safety Analysis Set)

	Double-blind period		Open-label period	
	Prucalopride (n = 106)	Placebo (n = 107)	Prucalopride (n = 98)	PEG (n = 99)
TEAEs, n (%)				
≥1 TEAE	74 (69.8)	65 (60.7)	63 (64.3)	61 (61.6)
Headache	17 (16.0)	9 (8.4)	3 (3.1)	7 (7.1)
Pyrexia	15 (14.2)	3 (2.8)	5 (5.1)	7 (7.1)
Abdominal pain	14 (13.2)	13 (12.1)	9 (9.2)	12 (12.1)
Vomiting	15 (14.2)	5 (4.7)	10 (10.2)	5 (5.1)
Nausea	10 (9.4)	6 (5.6)	4 (4.1)	1 (1.0)
Viral infection	6 (5.7)	5 (4.7)	4 (4.1)	4 (4.0)
Cough	6 (5.7)	2 (1.9)	4 (4.1)	6 (6.1)
Diarrhea	6 (5.7)	6 (5.6)	3 (3.1)	12 (12.1)
Nasopharyngitis	3 (2.8)	2 (1.9)	6 (6.1)	5 (5.1)
Pharyngitis	3 (2.8)	6 (5.6)	5 (5.1)	4 (4.0)
Bronchitis	2 (1.9)	7 (6.5)	5 (5.1)	3 (3.0)
Upper respiratory tract infection	2 (1.9)	5 (4.7)	5 (5.1)	5 (5.1)
Constipation	2 (1.9)	3 (2.8)	8 (8.2)	2 (2.0)
Serious TEAEs, n (%)				
≥1 serious TEAE	5 (4.7)	2 (1.9)	4 (4.1)	1 (1.0)
Abdominal pain	1 (0.9)	1 (0.9)	0	1 (1.0)
Constipation	0	1 (0.9)	2 (2.0)	0
Vomiting	1 (0.9)	0	1 (1.0)	0
Diarrhea	1 (0.9)	0	0	0
Nausea	1 (0.9)	0	0	0
Appendicitis	1 (0.9)	0	0	0
Pneumonia	1 (0.9)	0	0	0
Dizziness	1 (0.9)	0	0	0
Syncope	1 (0.9)	0	0	0
Anxiety	1 (0.9)	0	0	0
Viral infection	0	0	1 (1.0)	0
Contusion	0	0	1 (1.0)	0
Proctalgia	0	0	0	1 (1.0)
Anorectal discomfort	0	1 (0.9)	0	0

a similar proportion of patients in the prucalopride (62.3%) and placebo (57.9%) groups.

Five patients receiving prucalopride reported a total of 9 serious TEAEs, and 2 patients receiving placebo reported a total of 3 serious TEAEs (Table 3). Five of the 12 serious TEAEs were considered by the investigator to be related to the investigational product; for all 5, treatment with the investigational product continued, in 4 cases after drug interruptions. No fatal TEAEs occurred. Two patients (1 in each treatment group) permanently discontinued treatment because of a TEAE.

Changes in clinical chemistry, hematology, and urinalysis parameters were minimal and similar in both treatment groups. None of the TEAEs related to clinical laboratory abnormalities was considered serious, and none led to treatment discontinuation. Changes over time in physical examination results and vital signs were comparable across the treatment groups. The majority of patients were in Tanner stage I and all pregnancy test results were negative. The TEAEs related to vital sign abnormalities were nonserious, mild to moderate in severity, and did not result in treatment discontinuation.

Mean ECG changes from baseline to final on-treatment assessment are summarized in Table 4. The proportion of patients who experienced changes from normal at baseline to abnormal at the final on-treatment assessment was minimal and similar in the prucalopride and placebo groups for pulse rate, PR interval, and QRS interval. No patients had a change in QT interval corrected according to Bazett's formula or QT interval corrected according to Fridericia's formula from $\leq$450 milliseconds at baseline to >480 milliseconds at the final on-treatment assessment. One patient in the prucalopride group had an ECG-related TEAE (increased heart rate), which was nonserious, mild, and was not considered clinically relevant. No clinically significant QT prolongation was observed.

Safety—Open-Label Period

During the open-label period, the prucalopride and PEG groups had a similar proportion of patients with a TEAE (64.3% vs 61.6%, respectively; Table 3). The most common (>10% overall) TEAEs in either group were vomiting (prucalopride: 10.2%; PEG: 5.1%), diarrhea (prucalopride: 3.1%; PEG: 12.1%), and abdominal pain (prucalopride: 9.2%; PEG: 12.1%). Five patients (4 in the prucalopride group and 1 in the PEG group) experienced serious TEAEs; all were considered to be unrelated to treatment (Table 3). Two children (both in the prucalopride group) permanently discontinued treatment because of a TEAE.

Consistent with the double-blind period, changes in clinical chemistry, hematology, and urinalysis parameters were minimal and similar in both treatment groups. Two patients in the PEG group had an ECG-related TEAE (first-degree atrioventricular block and QT prolongation). There were no other ECG-related TEAEs in this period. Both ECG-related events were nonserious, mild, and not considered clinically relevant.

Discussion

This multicenter, placebo-controlled, double-blind trial used a carefully chosen primary end point to evaluate the efficacy of prucalopride in children fulfilling the Rome III criteria for functional constipation. In contrast to adults with constipation, the majority of children have infrequent defecation accompanied by FI as a result of rectal fecal impaction; therefore, effective treatment should lead not only to an increase in defecation frequency but also to a decrease in FI. For this reason, response in this study was defined using SBMs and FI episodes. After 8 weeks, no significant difference was found in the proportion of responders after treatment with prucalopride (17.0%) or placebo (17.8%). In addition, subgroup analyses of the primary end point by country, dose, sex, and history of retentive posturing did not reveal any meaningful trends.

The difference in efficacy of prucalopride between adults and children suggests that childhood constipation differs considerably from constipation in adults.[31] This may be reflected in the finding in the current study that the proportion of patients who met the primary end point was higher in the prucalopride group than the placebo group in adolescents ($\geq$12 to <18 years), but not in younger children. It is known that in a majority of children, functional constipation is caused by the voluntary withholding of feces due to fear of painful defecation. In contrast, voluntary withholding is not a contributing factor in the onset or maintenance of constipation in adults.[31] In the current

Table 4. Electrocardiogram (ECG) Changes From Baseline to Final On-Treatment Assessment (Safety Analysis Set)

	Double-blind period		Open-label period	
ECG parameter, mean (SD)	Prucalopride (n = 91)	Placebo (n = 102)	Prucalopride (n = 87)	PEG (n = 86)
Pulse rate, *beats/min*	−3.3 (12.80)	+0.4 (14.28)	−3.8 (15.45)	−1.5 (14.29)
PR interval, *ms*	−1.1 (13.60)	+2.1 (21.77)	−4.4 (14.31)	+0.5 (13.10)
QRS interval, *ms*	+0.3 (8.07)	+0.5 (8.92)	+1.4 (9.27)	−0.1 (9.69)
QT interval,[a] *ms*	+0.5 (20.42)	+1.1 (22.52)	+6.7 (25.92)	+4.4 (23.56)
QTcB interval,[a] *ms*	−6.1 (25.94)	+2.8 (24.37)	−0.3 (29.30)	+3.7 (22.95)
QTcF interval,[a] *ms*	−3.5 (20.17)	+2.1 (18.49)	+2.3 (22.73)	+4.1 (19.11)

QTcB, QT interval corrected according to Bazett's formula; QTcF, QT interval corrected according to Fridericia's formula.
[a]Calculations based on 90 patients in the double-blind period (prucalopride) and 85 patients in the open-label period (PEG).

study, 61% of participants had a history of excessive volitional stool retention, which may have contributed to the low response rates. Previous research has suggested that prucalopride might accelerate gastrointestinal transit in constipated patients without rectal evacuation disorder.[12]

Similar to a placebo-controlled study of prucalopride in adults with constipation,[14] 29% of the pediatric patients receiving prucalopride in the present study had a mean of ≥3 SBMs/week after 8 weeks; however, the proportion of patients with ≥3 SBMs/week in the placebo group was 36%, compared with only 12% in the adult study. It is unclear why there is a discrepancy in the placebo response between children and adults.[14,18] Behaviour modification, including toilet training and positive parental reinforcement, may be significant factors in explaining the high placebo response rate in children.[32] In the current study, toilet training in combination with keeping an e-diary, the high level of expectancy of children and their parents participating in this study, and the frequent contacts between the doctors and patients, might have contributed to the outcomes in the placebo group.[33]

In the current study, outcomes during the open-label period were based on patients' subjective assessment. HRQoL results during this period were similar between prucalopride and PEG groups. Of note, more early withdrawals occurred in the PEG group than the placebo group (18.2% vs 10.2%), and the most frequent reason was withdrawn consent (16.2% vs 7.1%). This might reflect patients who did not tolerate PEG, or who had been unsuccessfully treated with PEG before inclusion in the current study and thus did not complete the open-label period if they were randomized to the PEG group.

Comparison of this study with others is difficult because of the lack of high-quality trials of treatments for pediatric constipation. One study of PEG 3350 vs placebo in children with constipation demonstrated that the mean number of complete BMs/week was significantly higher with PEG than with placebo (3.12 vs 1.45; $P < .001$).[34] However, this study did not include FI or the proportion of patients with ≥3 SBM/week in the primary end point so the results are difficult to compare with the present study. A 2-week, multicenter, placebo-controlled trial of PEG 3350 in children with chronic constipation reported that 77%, 74%, and 73% of children in the 0.2 g/kg (n = 26), 0.4 g/kg (n = 27), and 0.8 g/kg (n = 26) PEG groups, respectively, and 42% in the placebo group (n = 24) were successfully treated (>3 BMs in week 2; $P < .04$).[32] However, the proportion of patients with >3 BMs and no FI in week 2 was 31% for 0.2 g/kg, 26% for 0.4 g/kg, and 31% for 0.8 g/kg, and 8% for placebo ($P = .2$). This suggests that the difference in treatment response between this and the current study might be driven by the inclusion of FI in the primary end point.

A third study in 100 children with constipation comparing PEG 3350 with lactulose over 8 weeks and using a primary end point (BMs and FI) similar to that in the current study, showed success rates of 56% and 29%, respectively,[35] which are much higher than those seen in the current study, despite both studies being performed in tertiary centers. However, the duration and severity of constipation at baseline is not provided in the PEG/lactulose study. Additionally, the success rate was lower and not significantly different (33% and 14% for PEG and lactulose, respectively) in children who had been treated for constipation >1 year before enrollment, suggesting that the overall study population could have had less severe disease than the population in the current study. This is supported by the finding that >80% of patients in the current study reported that their constipation was severe or very severe at baseline, and >50% had ≤1 SBM/week. This suggests that they may have had very severe (intractable) disease that could have been less responsive to therapy.

In accordance with earlier trials in adults and children,[14,18,22,36] prucalopride was generally well tolerated. The incidence of TEAEs was comparable among the treatment groups, except for headache, pyrexia, vomiting, and abdominal pain, which were more common with prucalopride. These differences probably reflect the serotonergic (headache) and enterokinetic (gastrointestinal adverse events) properties of prucalopride. Most adverse events were mild to moderate in severity. There were no clinically relevant changes over time in laboratory parameters, vital signs, or ECG parameters. During the open-label continuation, good safety and tolerability profiles were maintained to 16 weeks. This is in accordance with a follow-up study in adults, which evaluated patients receiving prucalopride for up to 18 months.

The strengths of this study were the international composition of the study population, large patient sample (including a range of age groups), placebo-controlled design, use of the Rome III criteria, and well-defined primary end point, which permits firm conclusions to be drawn regarding the effectiveness of prucalopride and placebo in children with constipation. A potential limitation was that the study was conducted in secondary and tertiary care centers, thus reflecting a more severely affected patient population. This precludes the application of the results to the general population of children with constipation.

In conclusion, current guidelines for the treatment of constipation in children recommend a combination of education, behavioral therapy, and laxative use; however, well-designed, placebo-controlled trials that support efficacy of pharmacologic agents in pediatric patients are limited. This large, multicenter, placebo-controlled trial showed that prucalopride, although generally well tolerated, was not more effective than placebo in pediatric patients with constipation. This is in contrast to its efficacy in adults, and is supportive of a need for more effective drugs to treat childhood constipation.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.09.005.

References

1. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best Pract Res Clin Gastroenterol 2011;25:3–18.

2. Gijsbers CF, Kneepkens CM, Schweizer JJ, et al. Recurrent abdominal pain in 200 children: somatic causes and diagnostic criteria. Acta Paediatr 2011; 100:e208–e214.
3. Gijsbers CF, Kneepkens CM, Vergouwe Y, et al. Occult constipation: faecal retention as a cause of recurrent abdominal pain in children. Eur J Pediatr 2014; 173:781–785.
4. Youssef NN, Langseder AL, Verga BJ, et al. Chronic childhood constipation is associated with impaired quality of life: a case-controlled study. J Pediatr Gastroenterol Nutr 2005;41:56–60.
5. Bongers ME, Benninga MA, Maurice-Stam H, et al. Health-related quality of life in young adults with symptoms of constipation continuing from childhood into adulthood. Health Qual Life Outcomes 2009;7:20.
6. Bongers ME, van Wijk MP, Reitsma JB, et al. Long-term prognosis for childhood constipation: clinical outcomes in adulthood. Pediatrics 2010;126:e156–e162.
7. Pijpers MA, Tabbers MM, Benninga MA, et al. Currently recommended treatments of childhood constipation are not evidence based: a systematic literature review on the effect of laxative treatment and dietary measures. Arch Dis Child 2009;94:117–131.
8. Nurko S, Garcia-Aranda JA, Worona LB, et al. Cisapride for the treatment of constipation in children: a double-blind study. J Pediatr 2000;136:35–40.
9. Briejer MR, Bosmans JP, Van Daele P, et al. The *in vitro* pharmacological profile of prucalopride, a novel enterokinetic compound. Eur J Pharmacol 2001;423:71–83.
10. Briejer MR, Prins NH, Schuurkes JA. Effects of the enterokinetic prucalopride (R093877) on colonic motility in fasted dogs. Neurogastroenterol Motil 2001;13:465–472.
11. Bouras EP, Camilleri M, Burton DD, et al. Selective stimulation of colonic transit by the benzofuran 5HT4 agonist, prucalopride, in healthy humans. Gut 1999; 44:682–686.
12. Bouras EP, Camilleri M, Burton DD, et al. Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. Gastroenterology 2001;120:354–360.
13. De Schryver AM, Andriesse GI, Samsom M, et al. The effects of the specific 5HT(4) receptor agonist, prucalopride, on colonic motility in healthy volunteers. Aliment Pharmacol Ther 2002;16:603–612.
14. Camilleri M, Kerstens R, Rykx A, et al. A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med 2008;358:2344–2354.
15. Emmanuel AV, Roy AJ, Nicholls TJ, et al. Prucalopride, a systemic enterokinetic, for the treatment of constipation. Aliment Pharmacol Ther 2002;16:1347–1356.
16. Coremans G, Kerstens R, De Pauw M, et al. Prucalopride is effective in patients with severe chronic constipation in whom laxatives fail to provide adequate relief. Results of a double-blind, placebo-controlled clinical trial. Digestion 2003;67:82–89.
17. Quigley EM, Vandeplassche L, Kerstens R, et al. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation—a 12-week, randomized, double-blind, placebo-controlled study. Aliment Pharmacol Ther 2009;29:315–328.
18. Tack J, van Outryve M, Beyens G, et al. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. Gut 2009;58:357–365.
19. Muller-Lissner S, Rykx A, Kerstens R, et al. A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation. Neurogastroenterol Motil 2010;22:991–998.
20. Tack J, Camilleri M, Chang L, et al. Systematic review: cardiovascular safety profile of 5-HT(4) agonists developed for gastrointestinal disorders. Aliment Pharmacol Ther 2012;35:745–767.
21. De Maeyer JH, Lefebvre RA, Schuurkes JA. 5-HT4 receptor agonists: similar but not the same. Neurogastroenterol Motil 2008;20:99–112.
22. Winter HS, Di Lorenzo C, Benninga MA, et al. Oral prucalopride in children with functional constipation. J Pediatr Gastroenterol Nutr 2013;57:197–203.
23. Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006;130:1527–1537.
24. Wong DL, Baker CM. Pain in children: comparison of assessment scales. Pediatr Nurs 1988;14:9–17.
25. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39:800–812.
26. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care 1999;37:126–139.
27. Varni JW, Limbers CA. The PedsQL 4.0 Generic Core Scales Young Adult Version: feasibility, reliability and validity in a university student population. J Health Psychol 2009;14:611–622.
28. Varni JW, Seid M, Knight TS, et al. The PedsQL 4.0 Generic Core Scales: sensitivity, responsiveness, and impact on clinical decision-making. J Behav Med 2002;25: 175–193.
29. Chan KS, Mangione-Smith R, Burwinkle TM, et al. The PedsQL: reliability and validity of the short-form generic core scales and Asthma Module. Med Care 2005; 43:256–265.
30. Hartman EE, Pawaskar M, Williams V, et al. Psychometric Properties of the PedsQL Generic Core Scales for Children With Functional Constipation in the Netherlands. J Pediatr Gastroenterol Nutr 2014 Aug 7. [Epub ahead of print].
31. Solzi G, Di Lorenzo C. Are constipated children different from constipated adults? Dig Dis 1999;17:308–315.
32. Nurko S, Youssef NN, Sabri M, et al. PEG3350 in the treatment of childhood constipation: a multicenter, double-blinded, placebo-controlled trial. J Pediatr 2008; 153:254–261.
33. Benninga MA, Mayer EA. The power of placebo in pediatric functional gastrointestinal disease. Gastroenterology 2009;137:1207–1210.
34. Thomson MA, Jenkins HR, Bisset WM, et al. Polyethylene glycol 3350 plus electrolytes for chronic constipation in children: a double blind, placebo controlled, crossover study. Arch Dis Child 2007;92:996–1000.

35. Voskuijl W, de Lorijn F, Verwijs W, et al. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. Gut 2004;53:1590–1594.
36. Camilleri M, Van Outryve MJ, Beyens G, et al. Clinical trial: the efficacy of open-label prucalopride treatment in patients with chronic constipation—follow-up of patients from the pivotal studies. Aliment Pharmacol Ther 2010; 32:1113–1123.

Received April 24, 2014. Accepted September 1, 2014.

Reprint requests
Address requests for reprints to: Suzanne M. Mugie, MD, Department of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital/ Academic Medical Center, Meibergdreef 9, Room C2-312, 1105 AZ Amsterdam, Netherlands. e-mail: s.m.mugie@amc.nl; fax: +31-20-5669478.

Acknowledgments
The authors would like to thank the following investigators who, together with their site personnel, enrolled patients into the study. Belgium: G. Veereman-Wauter, I. Paquot, M. Scaillon, E. Sokal; France: F. Gottrand; Germany: S. Koletsko, A. Krahl; Hungary: J. Biro, F. Fekete, L. Karsza, E. Stunya, E. Szakos, C. Szekely, E. Tomsits, G. Toth; Italy: A. Staiano; Netherlands: M. Groeneweg, O. Norbruis, N. van den Berg; Poland: E. Happyn, B. Iwanczak, J. Kierkus, H. Szajewska; UK: N., Croft, R., Heuschkel, A., Fagmeni, B., Odeka, N., Thapar.

Catherine Hill of PharmaGenesis London was funded by Shire to provide editorial assistance for this manuscript.

Conflicts of interest
These authors disclose the following: Alexandra Green and Amy Levine are employees of Shire. Rene Kerstens, Jannie Ausma, and Magnus Ruth are former employees of Shire-Movetis. Marc A. Benninga is a consultant for AstraZeneca, Danone, Shire, Sucampo, and Zeria. The remaining authors disclose no conflicts.

Funding
This study was sponsored by Shire Development LLC.

List of Prohibited Medications

Medication prohibited throughout the trial: opiates (eg, codeine), antacids containing calcium carbonate or aluminum hydroxide, magnesium-containing drugs, β-blockers, calcium supplements, clonidine, non–potassium-sparing diuretics, ganglionic blockers, muscle blockers (D-tubocurarine, succinylcholine), phenytoin, 5-HT_3 antagonists, loperamide, sucralfate and antispasmodics (eg, dicyclomine).

Medication allowed under certain conditions: nonsteroidal anti-inflammatory drugs (occasional use of oral paracetamol is allowed); antibiotics (allowed for a restricted period of time); iron preparations (allowed during open-label phase); anticholinergic drugs (occasional use of second-generation oral antihistamines, such as desloratidine for allergic rhinitis or urticaria, allowed); and sympathomimetics (inhalated sympathomimetics allowed).

Medication allowed if the patient had been on a stable dose for at least 4 weeks before screening and the same regimen will be used throughout the trial period: antidepressants, attention deficit—hyperactivity disorder medication, inhaled sympathomimetics, and calcium channel blockers.