

# Effect of prucalopride on symptoms of chronic constipation

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## Key Messages

- This study shows that 12 weeks of treatment with prucalopride 2 mg once daily is associated with significant improvements, compared with placebo, in common constipation symptoms in women in whom previous laxative treatment had failed to provide adequate relief.
- Prucalopride is a selective 5-HT<sub>4</sub> receptor agonist with gastrointestinal prokinetic activities. The aim of this research was to use integrated data from the prucalopride 2 mg and placebo arms of the prucalopride phase III trials to assess the effects of prucalopride on changes in specific symptoms of constipation in female patients with chronic constipation who had self-reported inadequate relief from previous treatment with laxatives.
- Symptom response was measured using the Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaire.
- Data from 936 women with chronic constipation were included in this analysis. After 12 weeks of treatment, statistically significantly greater improvements were seen in the prucalopride 2 mg group compared with the placebo group in overall PAC-SYM score, abdominal symptoms score, stool symptoms score and rectal symptoms score. When symptoms were analysed individually, large effect sizes (>0.8) were seen on bloating and incomplete bowel movements.

## Abstract

**Background** Prucalopride is a 5-HT<sub>4</sub> receptor agonist with gastrointestinal prokinetic activities. This inte-

grated analysis of data from three 12-week, double-blind trials evaluated the effect of prucalopride 2 mg q.d. on common constipation symptoms in women in whom laxatives had failed to provide adequate relief. The effect of prucalopride on bowel function was outside the scope of the analysis and has been described elsewhere. **Methods** Women with self-reported inadequate relief from laxatives and included in the prucalopride 2 mg or placebo arm of the trials were selected for analysis. Symptom severity was determined with the Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaire. Observed changes from baseline in individual item scores were also evaluated by calculating Cohen's D effect sizes using baseline standard deviation (SD) (>0.2–0.5, >0.5–0.8 and >0.8 for small, moderate and large effects, respectively). **Key Results** Data were analyzed

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Part of the results of the study has previously been presented at the British Society of Gastroenterology Annual General Meeting, 14–17 March 2011 (same analysis but in a slightly different study population): Kerstens R, Vandeplassche L, Dubois D, Wouters L. Response of chronic constipation symptoms to prucalopride treatment and relationship with patient satisfaction. *Gut* 2011; 60 (Suppl. 1): A159.

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for 936 women. The proportion of women with a PAC-SYM severity score  $>2$  at baseline was 50.0% for abdominal symptoms, 71.4% for stool symptoms, and 15.5% for rectal symptoms. Excluding the women without presence of a symptom at baseline from the effect size calculations showed that prucalopride 2 mg had a large effect ( $>0.8$ ) on all PAC-SYM items, including abdominal pain, abdominal discomfort, bloating, straining, and painful bowel movements. For abdominal symptoms and stool symptoms, effect sizes with prucalopride 2 mg were 1.3–2.3 times larger than those with placebo. **Conclusions & Inferences** Prucalopride 2 mg q.d. for 12 weeks alleviates common constipation symptoms in women in whom laxatives had failed to provide adequate relief.

**Keywords** abdominal discomfort, bloating, chronic constipation, PAC-SYM, painful bowel movements, prucalopride.

## INTRODUCTION

Constipation is a common, often chronic, gastrointestinal problem.<sup>1,2</sup> Several working groups, including the Rome Foundation,<sup>3</sup> have recognized that functional constipation is a heterogeneous gastrointestinal problem, with a diversity of symptoms including straining, bloating, abdominal pain, hard or lumpy stools, and a feeling of incomplete evacuation,<sup>4–6</sup> in addition to a decreased frequency of stools.<sup>3,7–9</sup> Studies have shown that bothersome symptoms associated with constipation negatively impact patients' quality of life, and that the degree of symptom severity negatively correlates with perceived quality of life.<sup>10–12</sup>

Prucalopride is a selective, high-affinity agonist of the 5-HT<sub>4</sub> receptor with gastrointestinal prokinetic activities. Data from three identical, double-blind phase III trials in men and women with chronic constipation previously showed that once-daily treatment with prucalopride for 12 weeks improved bowel function, overall symptom scores, and patient satisfaction with bowel function and treatment.<sup>13–15</sup> The results of these trials formed the basis for marketing authorization of prucalopride (RESOLOR®) in the European Union (EU) for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. The recommended dose is 2 mg once daily. In elderly women ( $>65$  years), the recommended dose is 1 mg once daily (with an increase to 2 mg once daily, if needed).<sup>16</sup>

The aim of the present integrated analysis was to evaluate and present the effects of prucalopride 2 mg,

the recommended daily dose, on changes in constipation symptoms in women in the phase III trials in whom laxatives had failed to provide adequate relief (the population for which prucalopride is indicated in the EU). Integrated data on bowel function in the phase III trials were outside the scope of the present analysis and have been described elsewhere.<sup>17</sup>

## MATERIALS AND METHODS

This integrated analysis used the raw data from three multicenter, double-blind, randomized, placebo-controlled, parallel-group trials. To date, these three pivotal trials used for registration have been the only published trials of prucalopride with a treatment duration of 12 weeks and using the recommended dose regimen of 2 mg once daily in mainly Caucasian patients (<http://www.clinicaltrials.gov/>). To our knowledge, no other clinical trials of prucalopride in a Caucasian population with chronic constipation have been fully published by independent parties.

The study design and methodology for the trials have been described elsewhere in detail,<sup>13–15</sup> and are briefly summarized below. The protocols were approved by independent Institutional Review Boards/independent Ethics Committees, and the trials were conducted in compliance with the Declaration of Helsinki, Good Clinical Practice, and local laws and regulations. Patients provided written informed consent before the first trial-related procedure. The trials are registered on ClinicalTrials.gov (NCT00488137, NCT00483886 and NCT00485940).

## Data source

Each original trial enrolled men and women  $\geq 18$  years of age with chronic constipation. Patients were selected based on modified Rome II criteria for functional constipation, i.e., they had to have on average  $\leq 2$  spontaneous (non-laxative induced) complete (resulting in a sensation of complete evacuation) bowel movements per week and one or more of the following, for a minimum of 6 months before trial entry: hard/very hard stools, straining during defecation, or a sensation of incomplete evacuation, with at least a quarter of bowel movements.<sup>18</sup> Patients could not participate if their constipation was attributable to a secondary identified cause.

In each trial, following a 2-week drug-free run-in period, patients were randomized to double-blind treatment with placebo or prucalopride 2 or 4 mg once daily, for 12 weeks. Patients who did not have a bowel movement for three consecutive days were allowed to take bisacodyl (Dulcolax®, Boehringer Ingelheim, Ingelheim, Germany) or to use an enema. All patients entering the trials were asked whether they had used dietary measures, bulk-forming agents and/or other laxatives in the previous 6 months and, if so, whether they would rate the overall therapeutic effect of these measure(s) as 'adequate' or 'inadequate'.

In the analysis presented here, only female patients who reported 'inadequate' relief from laxatives at trial entry and who received placebo or prucalopride at the recommended dose of 2 mg once daily, were included. Male patients and female patients who received prucalopride 4 mg were excluded from this analysis, because they do not reflect the target population and the recommended dose of prucalopride according to EU prescribing information.<sup>16</sup>

## PAC-SYM questionnaire

In each original trial, patients were asked to complete the Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaire at baseline and at weeks 2, 4, 8 and 12.

PAC-SYM is a 12-item, self-administered questionnaire used to measure severity of symptoms over the past 2 weeks in patients with constipation.<sup>19</sup> The questionnaire was developed based on literature review and patient interviews. Initial psychometric testing was performed in 216 constipated patients at nine centers in the United States, showing internal consistency, reproducibility, validity, and responsiveness to changes over time.<sup>19</sup> PAC-SYM items are rated on a 5-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe) and grouped into three subscales related to abdominal symptoms (bloating, discomfort, pain, and cramps), stool symptoms (incomplete bowel movement, false alarm, straining, too hard, and too small), and rectal symptoms (painful bowel movement, burning, and bleeding or tearing). The total score and subscale scores are computed by taking the mean of item responses (score range 0–4). A reduction in score reflects an improvement in symptoms.

## Statistical analysis

Statistical analysis was performed with Statistical Analysis System (SAS) software, version 9.2 (SAS Institute Inc., Cary, NC, USA). The PAC-SYM analyses comprised all female patients who reported that laxatives had failed to provide adequate relief, took at least one dose of trial medication (placebo or prucalopride 2 mg), and had any postbaseline data.

The PAC-SYM total score and subscale scores were computed based on non-missing item responses. If more than 50% of items in the total scale/subscale were missing, the score for the total scale/subscale was set to 'missing'. Rates of response to treatment were assessed by the percentage of patients with an improvement from baseline of  $\geq 1$  in their PAC-SYM total score or subscale score, which is considered clinically meaningful.<sup>19,20</sup>

Changes from baseline in the individual PAC-SYM item scores were also evaluated. To compare the effects on the 12 items and to evaluate the size, the changes from baseline were standardized as 'effect size' (Cohen's D),<sup>21</sup> defined as the change from baseline related to the variability observed at baseline: the mean change in item score from baseline divided by the standard deviation (SD) of the baseline value. Calculated effect sizes can be interpreted using thresholds of  $>0.2$ – $0.5$ ,  $>0.5$ – $0.8$ , and  $>0.8$  for small, moderate, and large effects, respectively.<sup>21</sup>

The Cochran-Mantel-Haenszel test, controlling for trial, was used to test differences between groups in binary endpoints (response rates). For continuous data, analysis of covariance was used (including factors for treatment, baseline value and trial) to evaluate differences between treatment groups.

All reported *p*-values are two-sided. All tests were performed with a 5% level of significance.

## RESULTS

Patient disposition (the number of patients who were randomized, received the intended study treatment, and were analyzed), demographics and constipation characteristics at screening (i.e., prior to run-in) for women in whom laxatives had failed to provide adequate relief have been described elsewhere.<sup>17</sup> In brief, the population

of women in whom laxatives had failed to provide adequate relief comprised 936 patients, 458 of whom were treated with prucalopride 2 mg and 478 of whom received placebo. Approximately 90% of patients in the prucalopride 2 mg and placebo groups completed the trials. The main reason for early trial discontinuation was the occurrence of adverse events (placebo: 3.8% and prucalopride 2 mg: 5.5%). The early discontinuations were primarily caused by nausea, diarrhea, abdominal pain, and headache.<sup>17</sup>

Demographics and constipation characteristics at screening were similar for the prucalopride 2 mg and placebo groups (Table 1). At trial entry, the most commonly reported constipation-related complaints were (in order of decreasing frequency): infrequent defecation, abdominal bloating, abdominal pain, sense of incomplete evacuation, straining, and hard stools.<sup>17</sup>

**Table 1** Demographics and constipation characteristics at screening in women in whom laxatives had failed to provide adequate relief – integrated analysis of three identical double-blind phase III trials

Parameter	Placebo (N = 478)	Prucalopride 2 mg (N = 458)
Race, n (%)		
Black	19 (4.0)	27 (5.9)
Caucasian	442 (92.5)	418 (91.3)
Hispanic	8 (1.7)	7 (1.5)
Oriental	4 (0.8)	4 (0.9)
Other	5 (1.0)	2 (0.4)
Age (years)		
Mean (SE)	45.4 (0.62)	44.5 (0.65)
Median (range)	44 (18–81)	44 (17–95)
Height (cm)		
Mean (SE)	164.2 (0.33)	163.7 (0.34)
Median (range)	165 (125–191)	164 (132–188)
Weight (kg)		
Mean (SE)	66.5 (0.59)	67.2 (0.62)
Median (range)	64 (42–131)	65 (40–141)
Reported duration of constipation (years)		
Mean (SE)	20.8 (0.69)	19.6 (0.70)
Range	0.5–69	0.5–63
Reported main complaints,* n (%)		
Infrequent defecation	134 (28.0)	143 (31.2)
Abdominal bloating	127 (26.6)	114 (24.9)
Abdominal pain	77 (16.1)	77 (16.8)
Feeling not completely empty	71 (14.9)	59 (12.9)
Straining	43 (9.0)	41 (9.0)
Hard stools	26 (5.4)	24 (5.2)
Reported use of laxatives in the previous 6 months, n (%)		
Dietary	327 (68.4)	341 (74.5)
Bulk-forming	313 (65.5)	301 (65.7)
Other laxatives	421 (88.1)	403 (88.0)

Data were used with permission of Tack *et al.*<sup>17</sup>

N, number of patients; n, number of patients with observation; SE, standard error.

\*Main complaints are presented in order of decreasing frequency. Patients could report more than one complaint.

**Table 2** Mean change from baseline in PAC-SYM total score and subscale scores in women in whom laxatives had failed to provide adequate relief – integrated analysis of three identical double-blind phase III trials

	Placebo			Prucalopride 2 mg		
	N	Mean (SD)	Change from Baseline <sup>‡</sup> Mean (SD)	N	Mean (SD)	Change from Baseline <sup>‡</sup> Mean (SD)
<b>Total</b>						
Baseline	475	2.07 (0.664)		458	2.10 (0.677)	
Week 4	475	1.73 (0.745)	−0.34 (0.690)	449	1.41 (0.745)	−0.69* (0.716)
Week 12	475	1.70 (0.781)	−0.36 (0.783)	450	1.40 (0.771)	−0.70* (0.771)
<b>Abdominal symptoms</b>						
Baseline	475	2.11 (0.831)		457	2.13 (0.862)	
Week 4	475	1.76 (0.964)	−0.34 (0.894)	449	1.39 (0.915)	−0.74* (0.901)
Week 12	475	1.72 (0.987)	−0.38 (0.979)	450	1.40 (0.998)	−0.73* (0.981)
<b>Stool symptoms</b>						
Baseline	474	2.56 (0.836)		458	2.58 (0.851)	
Week 4	475	2.20 (0.907)	−0.36 (0.912)	449	1.80 (0.888)	−0.78* (0.921)
Week 12	475	2.17 (0.924)	−0.39 (0.997)	450	1.80 (0.920)	−0.78* (0.987)
<b>Rectal symptoms</b>						
Baseline	475	1.18 (0.929)		456	1.25 (0.945)	
Week 4	474	0.89 (0.874)	−0.30 (0.843)	449	0.79 (0.852)	−0.46 <sup>†</sup> (0.854)
Week 12	474	0.88 (0.903)	−0.30 (0.896)	450	0.72 (0.805)	−0.52* (0.924)

N, number of patients; SD, standard deviation; PAC-SYM, Patient Assessment of Constipation Symptoms; PAC-SYM evaluation: absent = 0; mild = 1; moderate = 2; severe = 3; very severe = 4.

\* $p < 0.001$ , <sup>†</sup> $p < 0.05$  for comparison vs placebo.

<sup>‡</sup>Reduction in score (i.e., negative number) reflects improvement in symptoms.

**Table 3** Percentage of patients with an improvement from baseline of  $\geq 1$  in PAC-SYM total score and subscale scores for women in whom laxatives had failed to provide adequate relief – integrated analysis of three identical double-blind phase III trials

	Placebo		Prucalopride 2 mg	
	N	%	N	%
<b>Total (12 items)</b>				
Week 4	472	15.9	449	34.3*
Week 12	472	20.8	450	34.9*
<b>Abdominal symptoms (four items)</b>				
Week 4	472	26.9	448	41.3*
Week 12	472	26.9	449	43.4*
<b>Stool symptoms (five items)</b>				
Week 4	471	24.4	449	41.6*
Week 12	471	27.2	450	42.9*
<b>Rectal symptoms (three items)</b>				
Week 4	471	22.9	447	31.3 <sup>†</sup>
Week 12	471	23.4	448	31.7 <sup>†</sup>

N, number of patients; PAC-SYM, Patient Assessment of Constipation Symptoms.

\* $p < 0.001$ , <sup>†</sup> $p < 0.01$  for comparison vs placebo.

### PAC-SYM total score

The mean PAC-SYM total score at baseline was 2.10 in the prucalopride 2 mg group and 2.07 in the placebo group (Table 2). Overall, 51.7% of patients had a PAC-SYM total severity score  $>2$ , indicating a higher than moderate symptom severity overall.

The mean reduction (improvement) in PAC-SYM total score at week 4 and week 12 vs baseline was greater with prucalopride 2 mg than with placebo

(Table 2). At week 12, the mean reduction from baseline was 0.70 in the prucalopride 2 mg group compared with 0.36 in the placebo group.

The percentage of patients with a clinically meaningful improvement of  $\geq 1$  at week 4 and week 12 compared with baseline was also greater with prucalopride 2 mg than with placebo (Table 3). At week 12, this percentage was 34.9% in the prucalopride 2 mg group compared with 20.8% in the placebo group ( $p < 0.001$ ).

### PAC-SYM subscale scores

The mean PAC-SYM subscale scores at baseline were comparable for the prucalopride 2 mg group and the placebo group on each subscale (Table 2). Overall, the proportion of patients with a PAC-SYM severity score  $>2$  at baseline was 50.0% for abdominal symptoms, 71.4% for stool symptoms, and 15.5% for rectal symptoms.

The mean reduction (improvement) from baseline at week 4 and week 12 was greater with prucalopride 2 mg than with placebo for each subscale score (Table 2). At week 12, the mean reduction from baseline in the abdominal symptoms score was 0.73 in the prucalopride 2 mg group compared with 0.38 in the placebo group. A similar magnitude of improvement was observed for the stool symptoms score. The mean reduction in rectal symptoms score was smaller than the mean reduction in abdominal and stool

symptoms scores, but was still greater in the prucalopride 2 mg group than in the placebo group.

The percentage of patients with a clinically meaningful improvement vs baseline of  $\geq 1$  in PAC-SYM subscale scores was also greater with prucalopride 2 mg than with placebo (Table 3). In line with the results on the mean changes from baseline at week 4 and week 12, the proportion of patients with an improvement of  $\geq 1$  was smaller for the rectal symptoms score than for the abdominal and stool symptoms scores, but was still greater with prucalopride 2 mg than with placebo at both week 4 and week 12.

**PAC-SYM individual item scores**

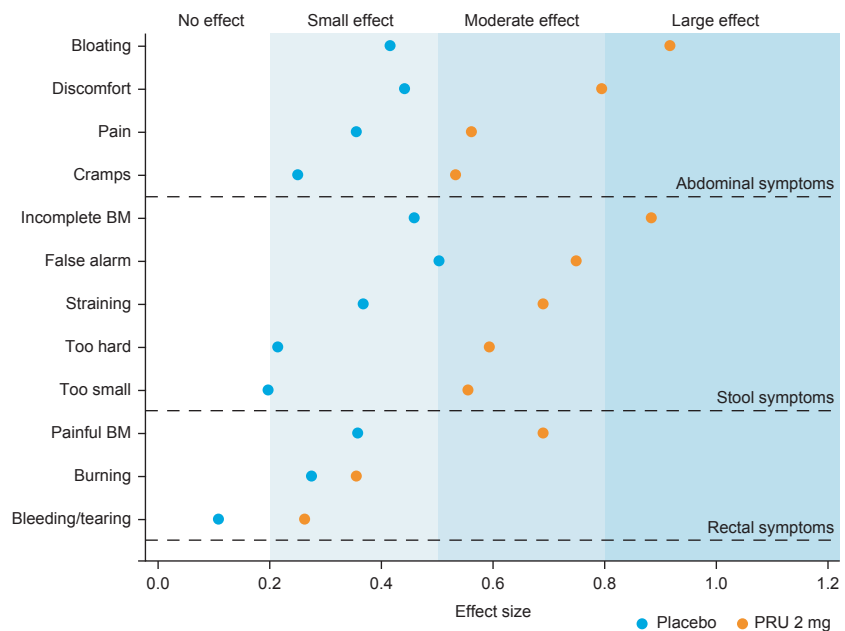
When evaluating effect sizes, prucalopride 2 mg had a large effect ( $>0.8$ ) on bloating and incomplete bowel movements, and a moderate effect ( $>0.5-0.8$ ) on almost all other items, including abdominal pain, abdominal discomfort, and painful bowel movements (Fig. 1 and Table S1). Prucalopride 2 mg had a small effect ( $>0.2-0.5$ ) on rectal burning and rectal bleeding/tearing. In the placebo group, all effect sizes were small or absent.

When computing the effect sizes excluding women with no baseline symptoms, a similar pattern of results was observed for abdominal symptoms and stool symptoms. For rectal symptoms, the largest effect with prucalopride 2 mg was on painful bowel movements (effect size 1.15, compared with 0.80 with placebo; Table S2 and Fig. S1).

**DISCUSSION**

The results of this integrated analysis of three double-blind phase III trials show that treatment with prucalopride 2 mg once daily for 12 weeks is superior to placebo in alleviating common symptoms of chronic constipation, including abdominal pain, abdominal discomfort, bloating, cramps, straining, and painful bowel movements, in women in whom laxatives have failed to provide adequate relief. The improvements in PAC-SYM overall score as observed in this female population are similar to those reported previously for the all-patient population of the trials, comprising both men and women with chronic constipation who had or had not obtained self-perceived adequate relief from previous laxative therapy.<sup>13-15</sup>

Overall, our findings indicate that the therapeutic effects of prucalopride at the recommended dose of 2 mg once daily are not limited to measurable bowel movements, as demonstrated in the individual phase III trials and an integrated analysis of these trials with focus on bowel function,<sup>13-15,17</sup> but influence a range of symptoms measured by the PAC-SYM questionnaire. More prucalopride-treated patients than placebo-treated patients experienced a clinically meaningful improvement of  $\geq 1$ <sup>19,20</sup> in PAC-SYM total score and PAC-SYM subscale scores. This is noteworthy, because the patient population for the phase III trials used for this integrated analysis was heterogeneous and selected on the basis of their bowel function at trial entry and not on the basis of associated



**Figure 1** PAC-SYM effect sizes at week 12 in women in whom laxatives had failed to provide adequate relief – integrated analysis of three identical double-blind phase III trials – including women without presence of a symptom at baseline. BM, bowel movement; PRU, prucalopride.

symptoms measured with the PAC-SYM questionnaire.<sup>13–15</sup>

Unlike previous observations in a population-based sample,<sup>4</sup> the most common constipation-related complaint reported at trial entry was infrequent defecation. This is likely due to the inclusion of more patients in the severe spectrum of chronic constipation, who present with very few bowel movements after failing previous therapies. The small effect size observed with prucalopride on symptoms like rectal bleeding/tearing and rectal burning when including all patients is due to the large proportion of patients (more than 50%) who did not have these symptoms at baseline. As such, a large group of patients with a zero baseline severity level was included, which largely contributed to the small effect size for these symptoms.

Health regulatory authorities in different parts of the world, such as the U.S. Food and Drug Administration, recognize the usefulness of patient-reported outcome instruments in clinical trials when ‘measuring a concept best known by the patient or best measured from the patient’s perspective’.<sup>22</sup> As such, patient-reported symptom severity can provide a more complete picture of treatment benefit in conditions such as chronic constipation in which patients are the primary source of information regarding symptom changes, in addition to bowel movement frequency. The PAC-SYM questionnaire was developed to capture the full symptom impact of chronic constipation from the patient’s perspective.

A limitation of this integrated analysis relates to the selection of the patient population. The results were analyzed in a population of women in the trials who rated the overall therapeutic effect of dietary measures, bulk-forming agents and/or other laxatives in the previous 6 months as ‘inadequate’ and who received placebo or prucalopride at the recommended dose of 2 mg once daily. These women comprised 71.0% (936/1318) of the total population in the pivotal trials. In addition, patients were eligible for inclusion in the trials if they met modified Rome II criteria for functional constipation. However, due to the currently accepted international definitions of functional digestive disorders, the edges between functional constipation and irritable bowel syndrome with constipation (IBS-C) are rather blurred. Although the Rome criteria present the two entities as mutu-

ally exclusive, the distinction remains largely artificial and we cannot exclude that some patients with symptoms resembling IBS-C may also have been included in the trials.

Based on the integrated analysis presented here, it can be concluded that prucalopride 2 mg once daily, taken for 12 weeks, effectively alleviates common abdominal and stool-related symptoms of chronic constipation in women in whom laxatives have failed to provide adequate relief.

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## CONFLICTS OF INTEREST

Jan Tack has acted as an advisor to Addex, Almirall, AstraZeneca, Danone, Ironwood, Menarini, Novartis, Sanofi-Aventis, Shire-Movetis, SK Life Sciences, Takeda, Theravance, Tranzyme Pharma, XenoPort and Zeria, and has undertaken speaking engagements for Abbott, Alfa Wasserman, Almirall, AstraZeneca, Janssen, Menarini, Novartis, Nycomed, Shire-Movetis, and Takeda. Vincenzo Stanghellini is a member of the advisory board and/or speaker for Alfa Wassermann, Almirall, Aptalis Pharma, Italchimici, Janssen, Norgine, Nycomed, Shire-Movetis, Valeas, and receives scientific support from Aptalis Pharma, CM&D Pharma, Italchimici, Sofar, and Valeas. Dominique Dubois is a paid consultant for Shire. Lieve Vandeplasseche and René Kerstens owned stock in Shire and, at the time the study was conducted, were employees of Shire-Movetis, Turnhout, Belgium. Alain Joseph is an employee of Shire based in Nyon, Switzerland. RESOLOR is a CTM registered trademark of Shire.

## AUTHOR CONTRIBUTION

JT was investigator for trial PRU-INT-6 (ClinicalTrials.gov number NCT00488137); LV and RK contributed to the conception and the design of the integrated analysis; RK performed the statistical analyses; all authors participated in the interpretation of the data and contributed to draft, review and/or revision of the manuscript; all authors read and approved the final manuscript.

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## SUPPORTING INFORMATION

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

**Figure S1.** PAC-SYM effect sizes at week 12 in women in whom laxatives had failed to provide adequate relief – integrated analysis of three identical double-blind phase III trials – excluding women without presence of a symptom at baseline. BM, bowel movement; PAC-SYM, Patient Assessment of Constipation Symptoms; PRU, prucalopride. Effect sizes were derived excluding patients without the presence of a particular symptom at baseline (i.e., PAC-SYM score 0 and no improvement possible).

**Table S1.** PAC-SYM effect sizes in women in whom laxatives had failed to provide adequate relief – integrated analysis of three identical double-blind phase III trials – including women without presence of a symptom at baseline.

**Table S2.** PAC-SYM effect sizes in women in whom laxatives had failed to provide adequate relief – integrated analysis of three identical double-blind phase III trials – excluding women without presence of a symptom at baseline.