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Efficacy and safety of prucalopride in patients with renal dysfunction: a *post hoc* analysis of phase 3 and 4 clinical trials in chronic idiopathic constipation

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Introduction

- Chronic idiopathic constipation (CIC) has an estimated global prevalence of 14% in individuals ≥ 15 years old.[1,2]
- Prucalopride, a US Food and Drug Administration-approved selective serotonin type 4 receptor agonist, is indicated for the treatment of CIC in adults (2 mg once daily).[3] It has been shown to improve colonic motility and the number of complete spontaneous bowel movements (CSBMs) in patients with CIC in an integrated summary of efficacy in six phase 3 and 4 clinical trials.[4]
- Renal excretion is the main route of prucalopride elimination; on average, 84.2% and 13.3% of the administered dose is recovered in the urine and feces, respectively, of healthy individuals.[3,5]
  - A phase 1 study demonstrated significant reductions in renal clearance of prucalopride in participants without constipation who had severe renal impairment compared with those who had normal renal function.[6]
  - A reduced oral dosing regimen (1 mg once daily) is thus recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min).[3]
- However, no studies to date have investigated the efficacy and safety of prucalopride in patients with CIC and impaired renal function.

Objective

- The aim of this analysis was to evaluate the effect of mildly or moderately impaired renal function on the efficacy and safety of prucalopride in adults with CIC.

Methods

Study design and patients

- This *post hoc* analysis used pooled data from six phase 3 and 4 multicenter, double-blind, randomized, placebo-controlled trials of prucalopride (2 mg once daily for 12 weeks) in adults with CIC (ClinicalTrials.gov identifiers: NCT01147926,[7] NCT01424228,[8] NCT01116206,[9] NCT00483886,[10] NCT00485940[11] and NCT00488137[12]).
- Patients were included if they had one or more of the following for ≥ 6 months: ≤ 2 CSBMs per week, hard or very hard stools, a sensation of incomplete evacuation, or straining during defecation in at least 25% of bowel movements.[7-12]
- Exclusion criteria included: drug-induced constipation; constipation secondary to causes such as endocrine, metabolic and neurological disorders or surgery; and a history of clinically significant cancer or cardiac, vascular, hepatic, pulmonary, endocrine, metabolic, neurological or psychiatric disorders.[7-12]
  - Additionally, patients with severely impaired renal function (serum creatinine > 180 µmol/L) were excluded from these trials.[7-12]
- Patients were stratified by estimated glomerular filtration rate (eGFR) into three renal function subgroups (normal function, ≥ 90 mL/min/1.73 m²; mild impairment, 60 to < 90 mL/min/1.73 m²; and moderate impairment, 30 to < 60 mL/min/1.73 m²).

Efficacy and safety endpoints

- The prespecified primary endpoint was the proportion of patients with a mean frequency of ≥ 3 CSBMs per week over 12 weeks.
- Secondary efficacy outcomes were analyzed over 12 weeks of treatment and included: change in CSBM frequency; stool characteristics; time to first CSBM; rescue medication use; Patient Assessment of Constipation Symptoms (PAC-SYM) and Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire scores; and global severity of constipation and efficacy of treatment scores.
- Safety data were also analyzed over the 12-week treatment period.
  - Cardiovascular events of interest (angina pectoris, angina unstable, cerebrovascular accident, ischemic stroke, myocardial infarction and myocardial ischemia) were assessed.

Statistical analyses

- The primary efficacy endpoint for prucalopride- compared with placebo-treated patients was assessed using the χ^2 test.
- The change in CSBM frequency was assessed using the Cochran–Mantel–Haenszel test, and time to first CSBM was evaluated using a proportional hazards regression model (both analyses controlled for clinical trial number, sex, country and number of complete bowel movements per week at baseline [0 or > 0]).
- Safety data were evaluated descriptively.

Results

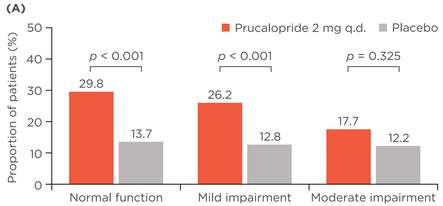
Patient demographics and characteristics

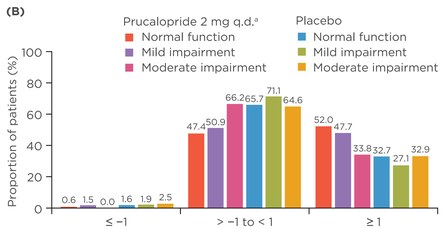
- Overall, 2474 patients were included in this analysis (mean age, 47.4 years; 75.9% female).
  - Of these patients, 1444 (58.4%) had normal renal function, 869 (35.1%) had mild renal impairment and 161 (6.5%) had moderate renal impairment (**Table 1**).

Efficacy endpoints

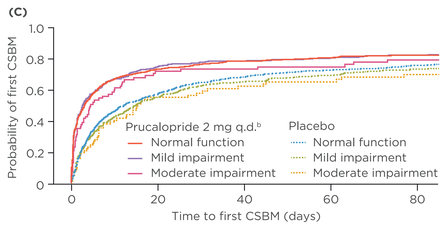
- Within each eGFR subgroup, a greater proportion of patients treated with prucalopride achieved a mean frequency of ≥ 3 CSBMs per week over 12 weeks compared with placebo (normal function, 29.8% vs 13.7%, $p < 0.001$; mild impairment, 26.2% vs 12.8%, $p < 0.001$; and moderate impairment, 17.7% vs 12.2%, $p = 0.325$; **Figure 1A**).
- Significantly more prucalopride- than placebo-treated patients had an increase from baseline to week 12 in CSBM frequency per week across renal function subgroups, except for patients with moderate impairment (**Figure 1B**).

Figure 1. Proportion of prucalopride- and placebo-treated patients with a mean frequency of ≥ 3 CSBMs per week over 12 weeks of treatment (A), proportion who exhibited a change from baseline to week 12 in CSBM frequency per week (B), and time to first CSBM after the first dose of prucalopride or placebo (C), stratified by renal function.





[a]Prucalopride versus placebo: normal function, $p < 0.001$; mild impairment, $p < 0.001$; moderate impairment, $p = 0.572$.



[b]Prucalopride versus placebo: normal function, $p < 0.001$; mild impairment, $p < 0.001$; moderate impairment, $p = 0.043$.
CSBM, complete spontaneous bowel movement; q.d., once daily.

This *post hoc* analysis of clinical trial data found that the efficacy and safety profiles of prucalopride were similar in adult patients with chronic idiopathic constipation with normal or mildly impaired renal function.

Conclusions

- **This pooled *post hoc* analysis found that a significantly greater proportion of patients treated with prucalopride than placebo over 12 weeks achieved a mean frequency of ≥ 3 CSBMs per week among those with normal or mildly impaired renal function.**
  - **No significant differences were observed between the prucalopride and placebo groups among patients with moderately impaired renal function.**
- **Similar improvements in prucalopride-treated patients with normal or mildly impaired renal function were also observed for several secondary efficacy endpoints compared with placebo-treated patients.**
- **There was no clear relationship between the incidence of TEAEs and renal function in patients receiving prucalopride.**

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- Additionally, prucalopride-treated patients had a significantly shorter time to first CSBM than placebo-treated patients across all renal function subgroups (**Figure 1C**).
- At week 12, greater improvements in other secondary efficacy outcomes were generally also observed with prucalopride than with placebo across renal function subgroups (data not shown).

Safety endpoints

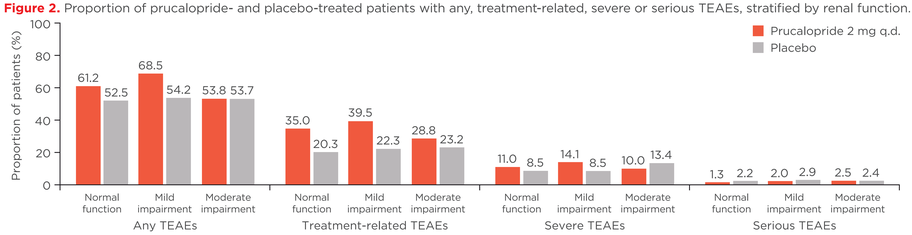
- The proportions of patients with any treatment-emergent adverse events (TEAEs) were higher with prucalopride than placebo in the normal function and mild impairment subgroups, but were similar in the moderate impairment subgroup (**Figure 2**).
- The proportions of prucalopride-treated patients with treatment-related TEAEs were higher in those with normal function or mild impairment than in those with moderate impairment (**Figure 2**).
  - An increase in the proportion of patients with treatment-related TEAEs was observed with prucalopride versus placebo.
- The proportions of prucalopride-treated patients with severe TEAEs were highest in those with mild impairment and lowest in those with moderate impairment.
  - There was no clear difference in the proportion of patients with serious or severe TEAEs between the prucalopride and placebo groups.
- Cardiovascular events of interest were not observed in prucalopride-treated patients with normal or moderately impaired function and occurred in < 1% of patients with mild impairment (data not shown).

Table 1. Patient demographics and baseline characteristics stratified by renal function.

	Prucalopride 2 mg q.d. (n = 1233)			Placebo (n = 1241)		
	Normal function (n = 722, 58.6%)	Mild impairment (n = 432, 35.0%)	Moderate impairment (n = 79, 6.4%)	Normal function (n = 722, 58.2%)	Mild impairment (n = 437, 35.2%)	Moderate impairment (n = 82, 6.6%)
Age, years, mean (SD)	42.4 (13.2)	52.4 (15.7)	66.6 (15.2)	42.6 (12.8)	51.7 (15.4)	66.8 (12.6)
Sex, n (%)						
Female	544 (75.3)	336 (77.8)	56 (70.9)	539 (74.7)	345 (78.9)	58 (70.7)
Male	178 (24.7)	96 (22.2)	23 (29.1)	183 (25.3)	92 (21.1)	24 (29.3)
SBMs per week,[a] n (%)						
0	214 (29.6)	134 (31.0)	35 (44.3)	185 (25.6)	151 (34.6)	23 (28.0)
> 0 to ≤ 1	244 (33.8)	132 (30.6)	21 (26.6)	238 (33.0)	128 (29.3)	26 (31.7)
> 1 to ≤ 3	257 (35.6)	154 (35.6)	22 (27.8)	290 (40.2)	148 (33.9)	31 (37.8)
> 3	7 (1.0)	12 (2.8)	1 (1.3)	9 (1.2)	10 (2.3)	2 (2.4)
Hard stools, n (%)	66 (9.1)	48 (11.1)	8 (10.1)	68 (9.4)	42 (9.6)	8 (9.8)
Previous use of laxatives, n (%)						
Yes	500 (69.3)	312 (72.2)	59 (74.7)	493 (68.3)	308 (70.5)	62 (75.6)
No	222 (30.7)	120 (27.8)	20 (25.3)	229 (31.7)	129 (29.5)	20 (24.4)
Duration of constipation, years						
Mean (SD)	15.3 (13.4)	17.2 (15.6)	21.8 (19.5)	15.5 (13.6)	17.1 (14.6)	22.1 (18.6)
n (%)						
< 1	17 (2.4)	15 (3.5)	1 (1.3)	29 (4.0)	13 (3.0)	0 (0.0)
1 to < 5	175 (24.2)	85 (19.7)	12 (15.2)	158 (21.9)	75 (17.2)	19 (23.2)
5 to < 10	92 (12.7)	54 (12.5)	11 (13.9)	97 (13.4)	75 (17.2)	6 (7.3)
10 to < 15	109 (15.1)	77 (17.8)	16 (20.3)	104 (14.4)	56 (12.8)	10 (12.2)
15 to < 20	59 (8.2)	38 (8.8)	3 (3.8)	62 (8.6)	31 (7.1)	4 (4.9)
≥ 20	244 (33.8)	154 (35.6)	35 (44.3)	247 (34.2)	177 (40.5)	42 (51.2)
Missing	26 (3.6)	9 (2.1)	1 (1.3)	25 (3.5)	10 (2.3)	1 (1.2)
Overall therapeutic effect of laxatives or bulk-forming agents, n (%)						
Adequate	109 (15.1)	73 (16.9)	15 (19.0)	107 (14.8)	78 (17.8)	6 (7.3)
Inadequate	514 (71.2)	326 (75.5)	61 (77.2)	517 (71.6)	314 (71.9)	70 (85.4)
Not applicable	24 (3.3)	10 (2.3)	0 (0.0)	22 (3.0)	14 (3.2)	1 (1.2)
Missing	75 (10.4)	23 (5.3)	3 (3.8)	76 (10.5)	31 (7.1)	5 (6.1)

[a]Number of SBMs per week was measured during the 6-month period before clinical trial initiation.
q.d., once daily; SBM, spontaneous bowel movement; SD, standard deviation.

Figure 2. Proportion of prucalopride- and placebo-treated patients with any, treatment-related, severe or serious TEAEs, stratified by renal function.



q.d., once daily; TEAE, treatment-emergent adverse event.

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