Prucalopride for the Treatment of Chronic Idiopathic Constipation

FDA Advisory Committee Meeting Briefing Document

Gastrointestinal Drugs Advisory Committee

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LIST OF ABBREVIATIONS

$5\text{-}HT_x$	5-hydroxytryptamine type X
ADR	adverse drug reaction
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ANCOVA	analysis of covariance
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero extrapolated to infinity
BID	twice daily
BMI	body mass index
CBM	complete bowel movement
CI	confidence interval
CIC	chronic idiopathic constipation
Cl_{CR}	creatinine clearance
Cl_{renal}	renal clearance
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CPRD	Clinical Practice Research Datalink
CSBM	complete spontaneous bowel movement
CYP	cytochrome P450
DBPC	double-blind placebo-controlled
ECG	electrocardiogram
EU	European Union
FDA	Food and Drug Administration
GePaRD	German Pharmacoepidemiological Research Database
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HAPC	high amplitude propagating contraction
hERG	Human Ether-à-go-go Related Gene
HR	heart rate

IBS-C	constipation-predominant irritable bowel syndrome
I_{Kr}	rapidly activating delayed rectifier potassium channel
IRD	incidence rate differences
IRR	incidence rate ratio
ISD	Information Services Division
ITT	intent-to-treat
LOCF	last observation carried forward
MACE	major adverse cardiovascular events
mITT	modified intent-to-treat
NDA	New Drug Application
PAC-QOL	patient assessment of constipation – quality of life
PAC-SYM	patient assessment of constipation – symptoms
PD	pharmacodynamic(s)
PEG	polyethylene glycol
PK	pharmacokinetic(s)
PLA	placebo
PRU	prucalopride
PSUR	periodic safety update report
PT	Preferred Term
PYE	patient-years of experience
QD	once daily
QTcB	QT interval corrected for heart rate according to Bazett's formula, ie, QTcB=QT(ms) x (HR(beats/min)/60)1/2
QTcF	QT interval corrected for heart rate according to Fridericia's formula, ie, QTcB=QT(ms) x (HR(beats/min)/60)1/3
QTcSS	study-specific QT corrected QT interval
SAE	serious adverse event
SBM	spontaneous bowel movement
SD	standard deviation
SNR	Swedish National Registers

SOC	System Organ Class
$t_{1/2}$	half-life
THIN	The Health Improvement Network
TQT	Thorough QT
UK	United Kingdom
US	United States

1. EXECUTIVE SUMMARY

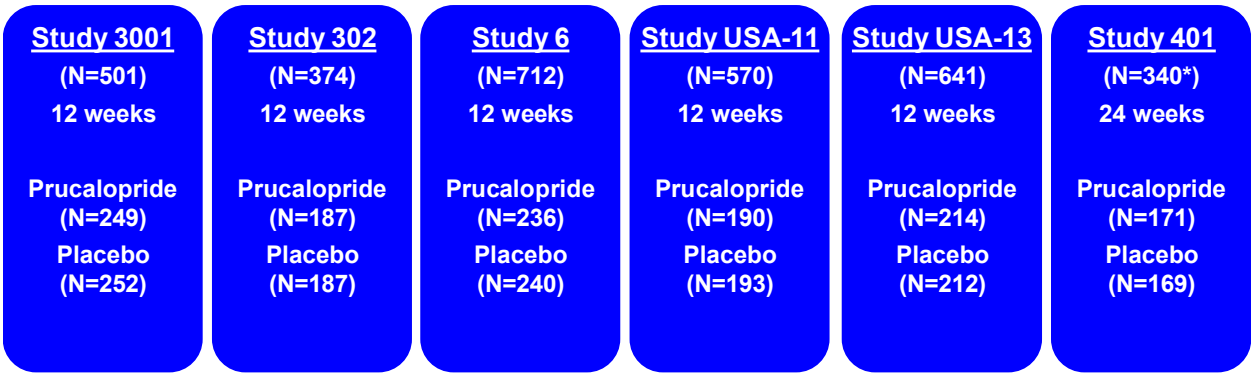
Prucalopride is a highly selective 5-hydroxytryptamine type 4 (5-HT_4) receptor agonist developed by Shire Pharmaceuticals that stimulates colonic motility to provide effective relief to patients with chronic idiopathic constipation (CIC). Prucalopride has high-affinity for the 5-HT_4 receptors and strong prokinetic activity. Prucalopride exerts its effect in CIC by increasing the number and amplitude of high amplitude propagating contractions (HAPCs), ie, the peristaltic contractions moving the contents of the colon forward, whereas osmotic laxatives and prosecretory products use alternative mechanisms of action.

Compared to other 5-HT_4 agonists, prucalopride is unique due to its high selectivity for the 5-HT_4 receptors. In vitro affinity for other receptors was only detected at concentrations of prucalopride exceeding its 5-HT_4 receptor affinity by ≥150-fold. A comprehensive nonclinical safety pharmacology and toxicology program confirmed the selectivity of prucalopride and demonstrated none of the off-target interactions of previously approved nonselective 5-HT_4 agonists.

Prucalopride is marketed in 59 countries worldwide including the European Union (EU) since 2009, as well as Australia, Canada, China, South Korea, and Switzerland. As of October 2017, there are over 280,000 patient years of experience supporting the safety of prucalopride. Importantly, the safety profile of prucalopride has remained consistent since its launch, and no postmarketing adverse drug reactions (ADRs) have been added to product labeling.

Shire communicated with the Food and Drug Administration (FDA) regarding efficacy and safety plans for the prucalopride New Drug Application (NDA) submission. A total of 76 clinical studies were conducted to examine the efficacy and safety of prucalopride in CIC, including 46 Phase 1 studies, 14 Phase 2 studies, and 16 Phase 3/4 studies. As shown in Figure 1, the primary evidence of efficacy in CIC comes from 6 randomized controlled studies lasting ≥12 weeks: PRU-CRC-3001 (referred to hereafter as Study 3001), SPD555-302 (referred to hereafter as Study 302), PRU-INT-6 (referred to hereafter as Study 6), PRU-USA-11 (referred to hereafter as Study USA-11), PRU-USA-13 (referred to hereafter as Study USA-13), and SPD555-401 (referred to hereafter as Study 401). Studies 3001 and 302 were listed as "pivotal" within the NDA submission because they were the most recent; however, all 6 studies are considered to be supportive of prucalopride effectiveness. The primary evidence of safety comes from these 6 studies as well as 10 additional randomized, double-blind, placebo-controlled (DBPC) studies of ≥4 weeks duration in CIC. Studies 6, USA-11, and USA-13 continued as long-term open-label extension Study USA-22.

Figure 1: Overview of Prucalopride Randomized Double-blind Placebo-controlled Efficacy Studies ≥12 Weeks



*ITT Population omitting 21 patients due to potential unblinding, and 3 patients who received no treatment

Note: Studies 3001, 302, and 401 excluded 4 mg dose arm due to lack of incremental efficacy compared to 2 mg dose

1.1 Unmet Need

Chronic idiopathic constipation, defined as constipation in which the underlying cause is unknown (ie, not caused by another disease or a medicine), is a common and often debilitating medical problem. Chronic idiopathic constipation is characterized by symptoms including straining during defecation, lumpy or hard stools, sensation of incomplete evacuation, and fewer than 3 defecations per week. Additionally, patients with CIC often feel bloated and have abdominal pain. The multiple effects of CIC can have a similar impact on health-related quality of life as other chronic conditions such as musculoskeletal diseases and diabetes (Belsey et al., 2010). Additionally, CIC can lead to increased risk for serious complications and has been associated with comorbidities such as fecal impaction, diverticular disease, and rectal prolapse (Talley et al., 2009). Chronic constipation is the most prevalent gastrointestinal condition presented to primary care physicians or subspecialty physicians and surgeons globally. The prevalence of chronic constipation is 10.0% – 14.9% in the USA (Camilleri et al., 2017;Suares and Ford, 2011).

An estimated 35 million adults have CIC in the United States (US) (Suares and Ford, 2011). Chronic idiopathic constipation is more prevalent in women, non-Whites, and elderly patients. Chronic idiopathic constipation is associated with lower socioeconomic status, low fiber diet, and lack of exercise (Bosshard et al., 2004;Higgins and Johanson, 2004;Peppas et al., 2008;Suares and Ford, 2011).

The goal of treatment of CIC is to improve symptoms and increase the frequency of bowel movements. While all increases in bowel movements are considered meaningful, objective evaluations have relied upon the number of complete spontaneous bowel movements (CSBM) to determine clinically meaningful improvements, where a CSBM is defined as a bowel movement that is initiated without a laxative and results in a feeling of complete evacuation. Patients with CIC typically have fewer than 1 CSBM per week.

Treatment interventions for CIC range from lifestyle modifications to prescription therapies; however, there continues to be high patient dissatisfaction with available therapies. Treatment for CIC typically begins with diet changes (increase in dietary fiber), increasing fluid intake, and exercise. Patients then progress to over-the-counter osmotic laxatives (ie, polyethylene glycol [PEG]), bulking agents, stool softeners, or stimulants, all of which have limited effectiveness. Current prescription therapies for CIC – lubiprostone, linaclotide, and plecanatide – function via increasing colonic secretions (ie, prosecretory) but do not have a direct effect on colonic peristalsis. These therapies can be effective in some patients, however, due to the similar mechanism of action of these prosecretory agents, patients who do not respond have no alternative treatment options.

Tegaserod (marketed as ZELNORM™) is a first generation non-selective 5-HT_4 agonist that was previously approved for women with constipation-predominant irritable bowel syndrome (IBS-C) but was later withdrawn from the market. Tegaserod was reported to have rare occurrences of serious cardiovascular ischemic events, unstable angina, heart attack, and stroke.

There is an unmet medical need for a treatment for CIC that promotes effective bowel movements using a mechanism of action that can increase colonic peristalsis to improve the symptoms of CIC and health-related quality of life.

1.2 Mechanism of Action

Prucalopride effectively stimulates or enhances propulsive motor patterns in the large intestine due to a high affinity for 5-HT_4 receptors in gastrointestinal (GI) tissues. Affinity of prucalopride for other receptors is present only at concentrations that exceed its 5-HT_4 receptor affinity by at least 150 times. Prucalopride is therefore differentiated from other 5-HT_4 receptor agonists such as tegaserod and cisapride, whose affinity for other receptors/channels such as 5-$HT_{1,2}$ (tegaserod) and the 5-HT_2 and human Ether à-go-go Related Gene (hERG) channel (cisapride) is in the same range as their affinity for the 5-HT_4 receptor.

Upon first exposure, a slight and transient increase in heart rate (HR) was observed after prucalopride treatment in anesthetized pigs and in healthy subjects. In healthy subjects, HR increases of 5-8 bpm were observed at 3 hours [C_{max}], and HR returned to baseline at steady state. No other relevant effects were seen on cardiovascular or cardiac electrophysiological parameters in nonclinical species at concentrations of at least 50 times the therapeutic plasma concentrations in humans. In addition, prucalopride had no effect on coronary artery contraction or platelet aggregation at concentrations exceeding those seen with the therapeutic dose of 2 mg once daily (QD).

1.3 Clinical Pharmacology

The pharmacokinetics (PK) and pharmacodynamics (PD) of prucalopride have been extensively studied. A summary of key findings is as follows:

- Prucalopride had low plasma protein binding, with mean values ranging from 28.9% to 33.3%.

- After intravenous (IV) administration, distribution of prucalopride was rapid and extensive.
- The half-life ($t_{1/2}$) of prucalopride was in the order of 1 day and was independent of dose.
- Prucalopride was primarily excreted in urine (63.6%), with the most prominent metabolite accounting for approximately 6% of the dose excreted in urine and feces.
- The absolute oral bioavailability of prucalopride exceeded 90%.
- The single-dose and steady-state PK of prucalopride were dose-proportional, and the plasma concentrations after repeated oral doses up to 20 mg QD were predictable from single-dose data. Dose-titration did not affect the steady-state kinetics of the target dose.
- Renal clearance (Cl_{renal}) and apparent total clearance were dependent on renal status: in subjects with mild renal impairment, the reduced clearance did not translate to clinically relevant changes in the plasma PK profile; in subjects with moderate and severe renal impairment, area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$) was 1.5- and 2.3-fold higher, and $t_{1/2}$ was prolonged by about 40% and 50%, respectively. In all stages of renal disease, no or only minor effects were found on C_{max}.
- In healthy elderly subjects, steady-state plasma concentrations of prucalopride 1 mg QD were on average 28% higher than in healthy young subjects, and $t_{1/2}$ after single and repeated dosing in healthy elderly was slightly longer than the in young subjects.
- Sparse blood sampling in Phase 2 and 3 studies in patients with CIC indicated that prucalopride plasma concentrations in these patients were on the same order as in healthy subjects.
- Population PK modeling based on data from PK studies in healthy subjects and Phase 2 and 3 studies with sparse sampling in subjects with CIC showed that creatinine clearance (CL_{CR}) had a statistically significant and clinically relevant effect on the apparent total clearance of prucalopride, but none of the other covariates tested (age, body mass index [BMI], dose, body weight, sex, race, study, and elderly) had an effect when CL_{CR} was included in the model.
- Findings from PD studies indicated that prucalopride decreased total colonic transit times (Bouras et al., 2001) and increased colonic motility (De Schryver et al., 2002;Miner et al., 2016) in both healthy subjects and patients with CIC.
- An integrated analysis of 3 randomized, placebo-controlled, Phase 2 dose-finding studies in 280 patients with CIC showed a clear correlation between constipation symptom severity and increased colonic transit time, and that improvements in CIC response correlated with decreased colonic transit time (Emmanuel et al., 2014).

1.4 Efficacy

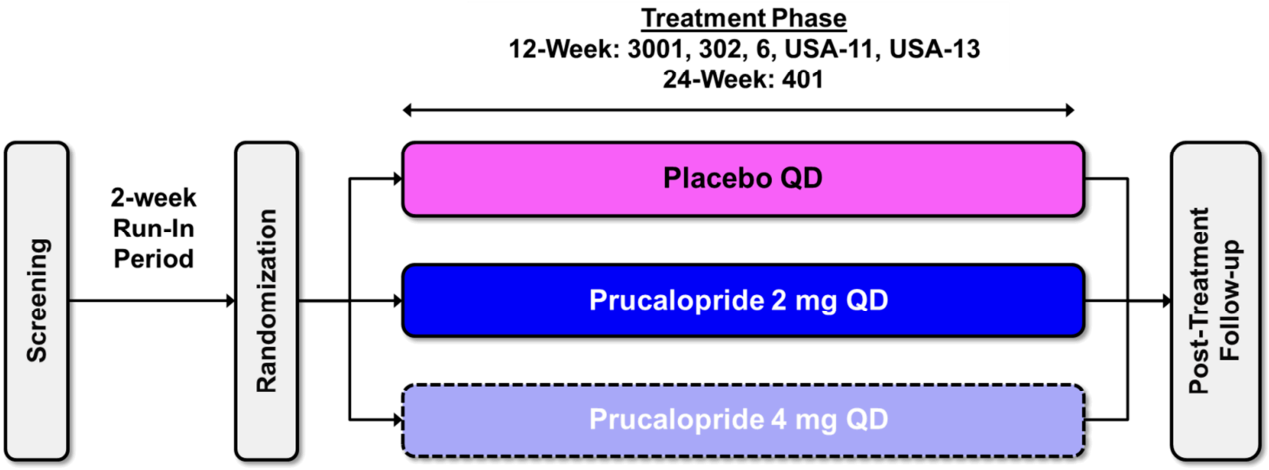
The evidence of efficacy of prucalopride comes from 6 randomized DBPC studies of ≥12 weeks duration in patients with confirmed CIC.

All 6 studies had a similar design (Figure 2), beginning with a 2-week observational period to establish baseline constipation characteristics, followed by randomization to placebo or

prucalopride for a 12-week treatment period (24 weeks in Study 401). Follow-up visits were conducted 7 days following the last dose of study drug.

Prucalopride 2 mg and 4 mg were included in the initial studies; however, the 4 mg dose was omitted from the later studies due to lack of increased efficacy compared to the 2 mg dose. In Studies 302 and 401, patients ≥65 years of age started at a dose of 1 mg prucalopride QD, with the option to increase to 2 mg QD. If the dose was increased to 2 mg QD, the patient remained on this dose for the duration of the study. Since the majority of patients who initially started on prucalopride 1 mg increased to 2 mg during the study, the efficacy results for these studies were combined into a single group identified as 2 mg*.

Figure 2: Design of Prucalopride Randomized Double-blind Placebo-controlled Studies ≥12 Weeks



Note: Studies 6, USA-11, and USA-13 included 4 mg dose arm. Studies 302 and 401 included a 1 mg starting dose for elderly patients ≥65 years old.

Patients were selected for the studies based on modified ROME Foundation diagnostic criteria for functional constipation. The modification was that patients had to have <3 CSBMs per week and at least 2 of the following for at least 25% of the time, and symptoms must have occurred at least 6 months prior to diagnosis and should have been present during the last 3 months:

- Straining during defecations
- Lumpy or hard stools
- Sensation of incomplete evacuation
- Sensation of anorectal obstruction/blockage
- Manual maneuvers to facilitate defecations (e.g., digital evacuation, support of pelvic floor)

Exclusion criteria for the studies included:

1. Constipation caused by secondary causes, drug-induced or after surgery
2. Organic disorders of the large bowel (megacolon/megarectum, pseudo-obstruction)
3. Severe and clinically uncontrolled cardiovascular, liver, or lung disease, neurologic or psychiatric disorders, cancer or acquired immune deficiency syndrome (AIDS), and other GI or endocrine disorders
4. Clinically significant laboratory abnormalities
5. Impaired renal function (creatine clearance <30/≤50 mL/min)

The primary efficacy endpoint in all studies was the proportion of patients with ≥3 CSBMs per week over the 12-week treatment period. A CSBM is defined as a bowel movement that is initiated without a laxative (last laxative was taken >24 hours before the bowel movement) and results in a feeling of complete evacuation. A spontaneous bowel movement (SBM) is defined as

any bowel movement that is initiated without a laxative, and a bowel movement is any bowel movement and can be initiated by a laxative.

Additionally, for the NDA submission the FDA requested that another efficacy endpoint be analyzed with the data from the clinical studies (post hoc) to demonstrate persistence of the effect. This endpoint was defined as the proportion of patients with ≥3 CSBMs per week and an increase from baseline of ≥1 CSBM per week, for ≥9 out of 12 weeks including ≥3 out of the last 4 weeks of treatment, which was referred to as Alternative Endpoint A.

Protocol prespecified secondary endpoints included the proportion of patients with an increase of ≥1 CSBM per week, time to first CSBM, and endpoints derived from 2 patient assessments of constipation questionnaires: a symptom questionnaire (Patient Assessment of Constipation – Symptoms [PAC-SYM]) and a disease-specific quality of life questionnaire (Patient Assessment of Constipation – Quality of Life [PAC-QOL]).

1.4.1 Efficacy Results

Overall, demographics varied across the studies but were balanced within each study (Table 1). In the 2 US studies, USA-11 and USA-13, enrolled patients had a mean age of 46 to 49 years, respectively. Consistent with the US patient population with CIC, the majority of patients from these 2 studies were female and White.

The remaining 4 studies enrolled only patients outside of the US. In Study 3001, conducted primarily in China and South Korea, the mean age was approximately 42 years, and the majority of patients were female. Study 302, a study in male patients conducted in Europe, enrolled patients with a mean age of approximately 58 years. Studies 6 and 401 enrolled patients with a mean age of 43 to 49 years, and most patients were White and female.

Baseline disease characteristics were similar between treatment arms within each of the 6 studies (Table 2). The mean duration of constipation varied somewhat across the studies and ranged from 9 to 23 years. At baseline, patients reported an average of 0.3-0.5 CSBMs per week.

Table 1: Overview of Patient Demographics in Randomized Double-Blind Placebo-Controlled Studies ≥ 12 Weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	**PRU 2 mg N=249**	**PLA N=181**	**PRU 2 mg* N=177**	**PLA N=240**	**PRU 2 mg N=238**	**PLA N=209**	**PRU 2 mg N=207**	**PLA N=212**	**PRU 2 mg N=214**	**PLA N=180**	**PRU 2 mg* N=181**
Age, years, mean (SE)	41.8 (12.88[a])	41.4 (12.92[a])	58.6 (16.46)	58.8 (17.44)	43.7 (0.99)	42.7 (0.98)	48.9 (0.9)	48.2 (0.98)	46.2 (0.89)	48.6 (0.97)	48.3 (16.25[a])	49.4 (15.78[a])
≥ 65, n (%)	0	0	71 (39.23)	79 (44.63)	24 (10.0)	27 (11.3)	31 (14.8)	27 (13.0)	23 (10.8)	34 (15.9)	31 (17.2)	35 (19.3)
Female, n (%)	223 (88.5)	227 (91.2)	0	0	222 (92.5)	213 (89.5)	183 (87.6)	188 (90.8)	189 (89.2)	181 (84.6)	153 (85.0)	155 (85.6)
Race, n (%)												
White	19 (7.5)	12 (4.8)	174 (96.1)	172 (97.2)	226 (94.2)	223 (93.7)	182 (87.1)	188 (90.8)	197 (92.9)	183 (85.5)	169 (93.9)	168 (92.8)
Asian	231 (91.7)	232 (93.2)	1 (0.6)	0	2 (0.8)	5 (2.1)	2 (1.0)	1 (0.5)	0	3 (1.4)	1 (0.6)	0
Region, n (%)												
US	0	0	0	0	0	0	209 (100)	207 (100)	212 (100)	214 (100)	0	0
Outside of US	252 (100)	249 (100)	181 (100)	177 (100)	240 (100)	238 (100)	0	0	0	0	180 (100)	181 (100)

PLA=placebo; PRU=prucalopride

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

[a] Data shown for SD in Study 3001 and Study 401

Table 2: Overview of Baseline Disease Characteristics in Randomized Double-Blind Placebo-Controlled Studies ≥ 12 Weeks

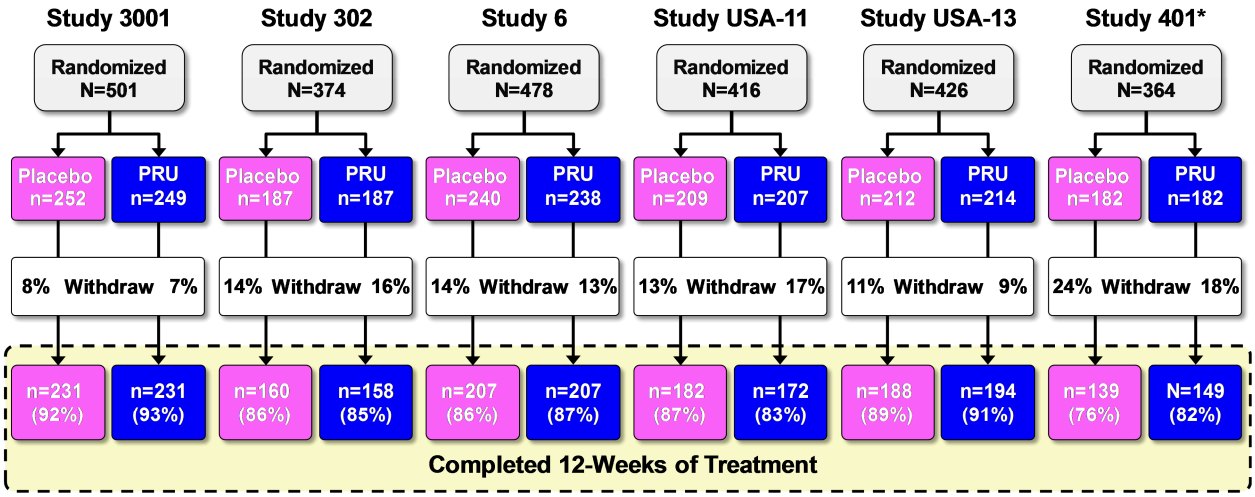
	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	**PRU 2 mg N=249**	**PLA N=181**	**PRU 2 mg* N=177**	**PLA N=240**	**PRU 2 mg N=238**	**PLA N=209**	**PRU 2 mg N=207**	**PLA N=212**	**PRU 2 mg N=214**	**PLA N=180**	**PRU 2 mg* N=181**
History of Constipation, Mean (SD) years	12.8 (9.97)	12.9 (9.75)	9.4 (11.46)	9.3 (12.13)	18.5 (0.9)	15.9 (0.97)	21.6 (1.19)	21.1 (1.10)	21.4 (1.06)	22.7 (1.08)	13.7 (13.33)	15.7 (15.77)
Baseline CSBMs/week, Mean	0.3	0.3	0.4	0.5	0.4	0.4	0.4	0.5	0.4	0.4	0.4	0.4
Frequency of SBMs/week, n (%)												
0	57 (22.6)	57 (22.9)	14 (7.7)	22 (12.4)	99 (41.3)	86 (36.1)	79 (37.8)	77 (37.2)	85 (40.1)	96 (44.9)	97 (57.4)	107 (62.6)
>0 - ≤1	63 (25.0)	73 (29.3)	48 (26.5)	56 (30.5)	84 (35.0)	78 (32.8)	78 (37.3)	79 (38.2)	65 (30.7)	73 (34.1)	41 (24.3)	34 (19.9)
>1 - ≤-3	132 (52.4)	119 (47.8)	107 (59.1)	93 (52.5)	57 (23.8)	74 (31.1)	52 (24.9)	51 (24.6)	62 (29.2)	45 (21.0)	31 (17.2)	30 (16.6)

PLA=placebo; PRU=prucalopride

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Patient disposition is shown in Figure 3. Overall, most of the studies had a similar disposition over the first 12 weeks, with a similar percentage of patients withdrawing from each arm in each study. The majority (83-93%) of randomized patients across all 6 studies completed the treatment period. The primary reasons for withdrawal were due to withdrawn consent and adverse event (AE).

Figure 3: Patient Disposition in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

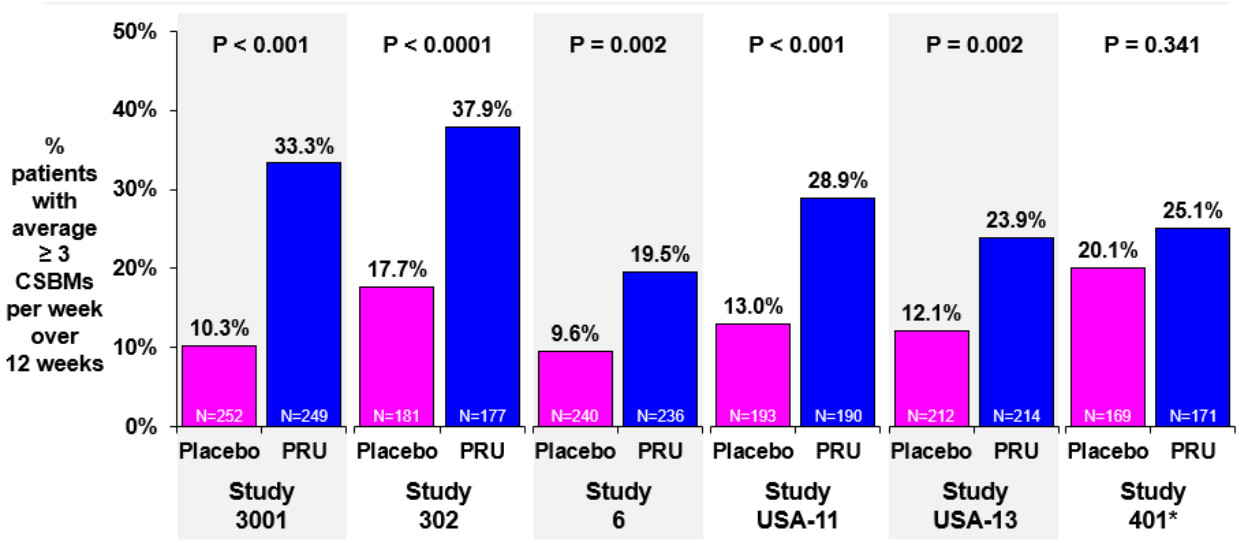


PRU=prucalopride
*Week 12 data presented

Five of the 6 studies met the primary endpoint, showing a higher proportion of patients treated with prucalopride achieving ≥3 CSBMs per week over the 12-week treatment period (Figure 4). The absolute treatment effect between the arms was statistically significant in Studies 3001, 302, 6, USA-11, and USA-13 ($p < 0.01$).

In Study 401, the primary endpoint did not reach statistical significance. An extensive investigation into the results of Study 401 failed to determine a clear rationale for the inconsistent results, including investigations of the placebo rate, which was higher than in the other 5 studies and what has been reported in the literature. Given that Study 401 was the only 24-week study, the data were analyzed at Week 12, showing similar results to those at Week 24. Additional evaluations of potential differences in baseline demographics, disease characteristics, and use of rescue medication also failed to explain the results. More details on the investigation into the results of Study 401 are found in Section 6.4.2. Since Study 401 failed to meet the primary endpoint, the secondary and exploratory endpoint results are only detailed in Section 6.5.

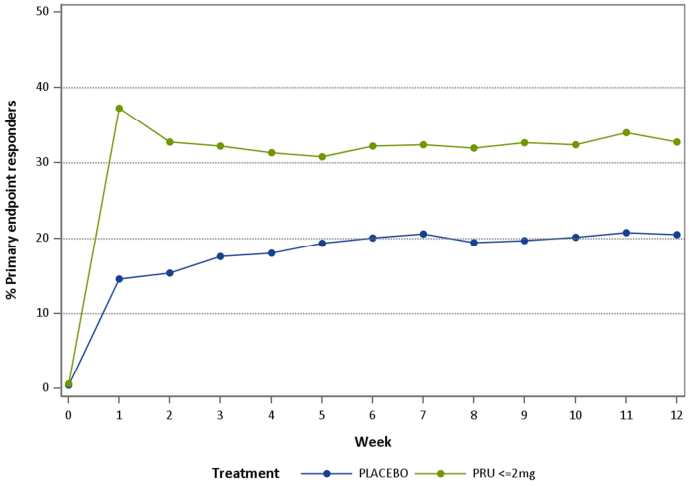
Figure 4: Primary Endpoint – Proportion of Patients Achieving ≥3 CSBMs/Week over Weeks 1-12 in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks



CSBM=complete spontaneous bowel movement; PRU=prucalopride
*Week 12 data presented

Importantly, the effects of prucalopride on CSBMs/week occurred quickly and persisted. In the 5 positive efficacy studies with prucalopride, the response was attained within the first week and maintained over the entire treatment period (Figure 5).

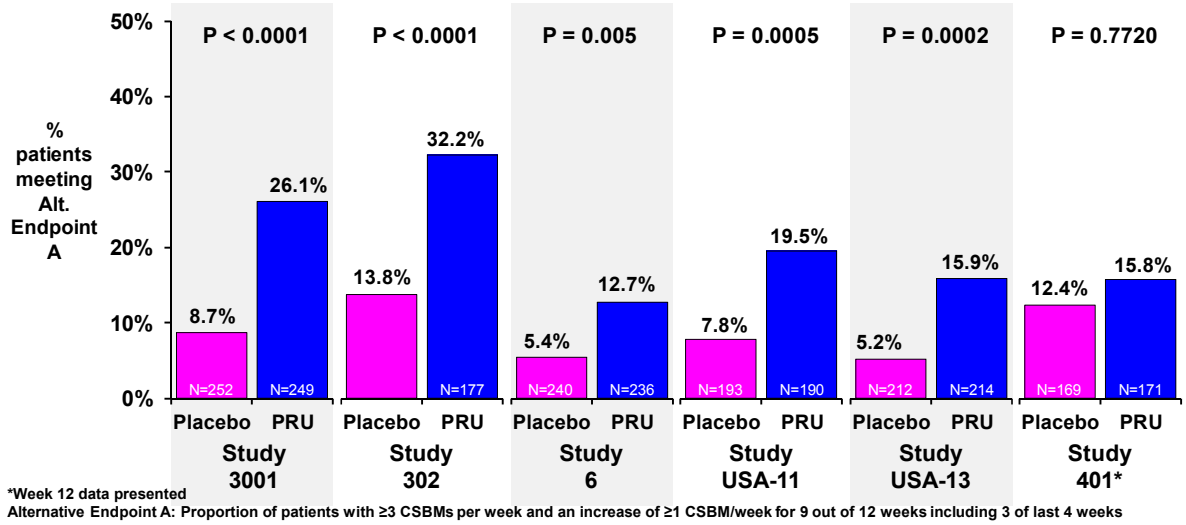
Figure 5: Primary Endpoint Over Time in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks



CSBM=complete spontaneous bowel movement

At the request of the FDA, a post hoc analysis was conducted using a more rigorous definition of the response to show a persistent effect (Alternative Endpoint A): the proportion of patients with an average weekly frequency of ≥3 CSBMs/week and an increase of ≥1 CSBM/week for ≥9 out of the 12 weeks including 3 of the last 4 weeks. Similar to the original primary endpoint, the treatment effect between arms was statistically significant (p=0.0001) in favor of prucalopride in 5 of the 6 studies (Figure 6). These results support the robustness of the prespecified primary endpoint results.

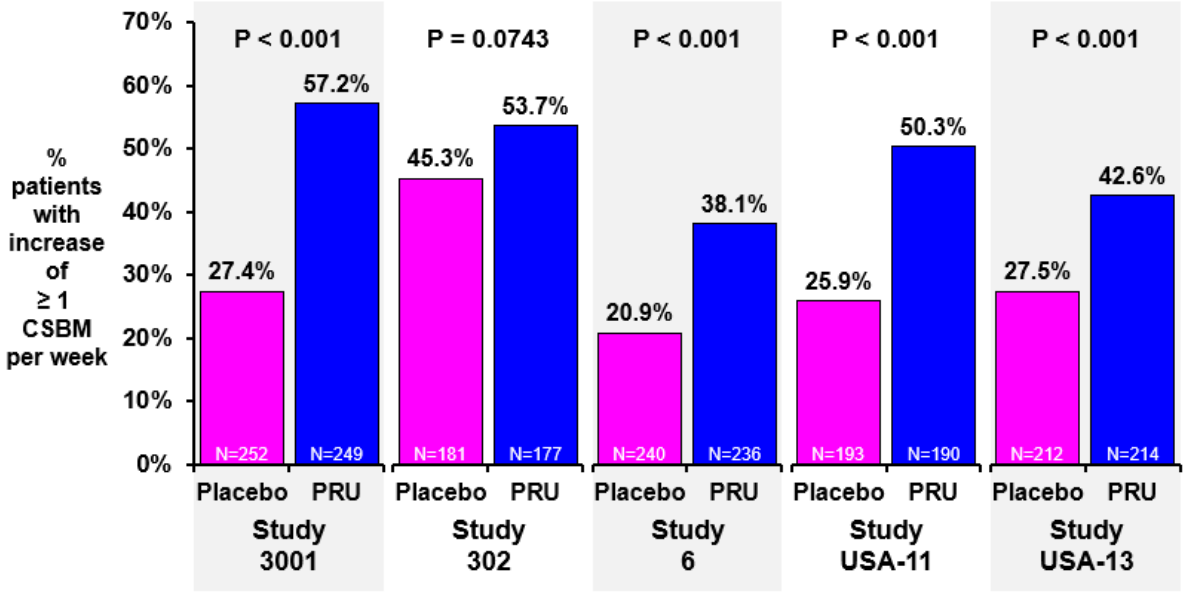
Figure 6: Alternative Endpoint A - Proportion of Patients with an Average of ≥3 CSBMs/Week and an Increase of ≥1 CSBM/Week for ≥9 out of the 12 Weeks Including 3 of the Last 4 Weeks in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks



CSBM=complete spontaneous bowel movement; PRU=prucalopride
*Week 12 data presented

On the secondary endpoint assessing the proportion of patients with an average increase of ≥1 CSBMs/week, a higher proportion of patients on prucalopride reported an average increase of ≥1 CSBMs per week from baseline over the 12-week treatment period in Studies 3001, 6, USA-11, and USA-13 ($p < 0.001$; Figure 7). Study 302 showed a numerical improvement that did not reach statistical significance ($p = 0.074$).

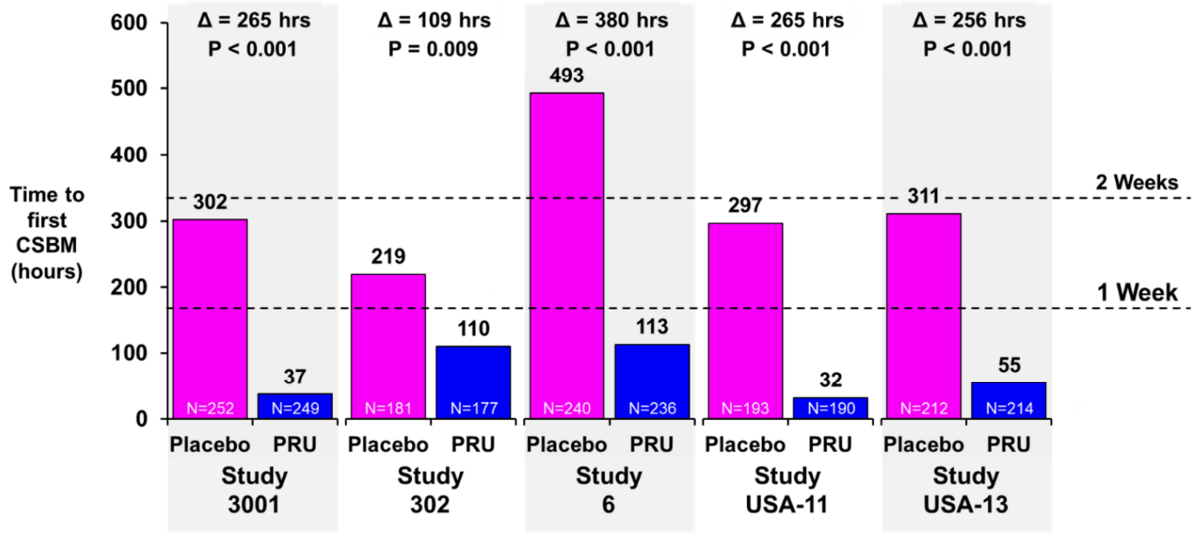
Figure 7: Proportion of Patients with an Average Increase of ≥1 CSBMs/week in Studies 3001, 302, 6, USA-11, and USA-13



CSBM=complete spontaneous bowel movement; PRU=prucalopride

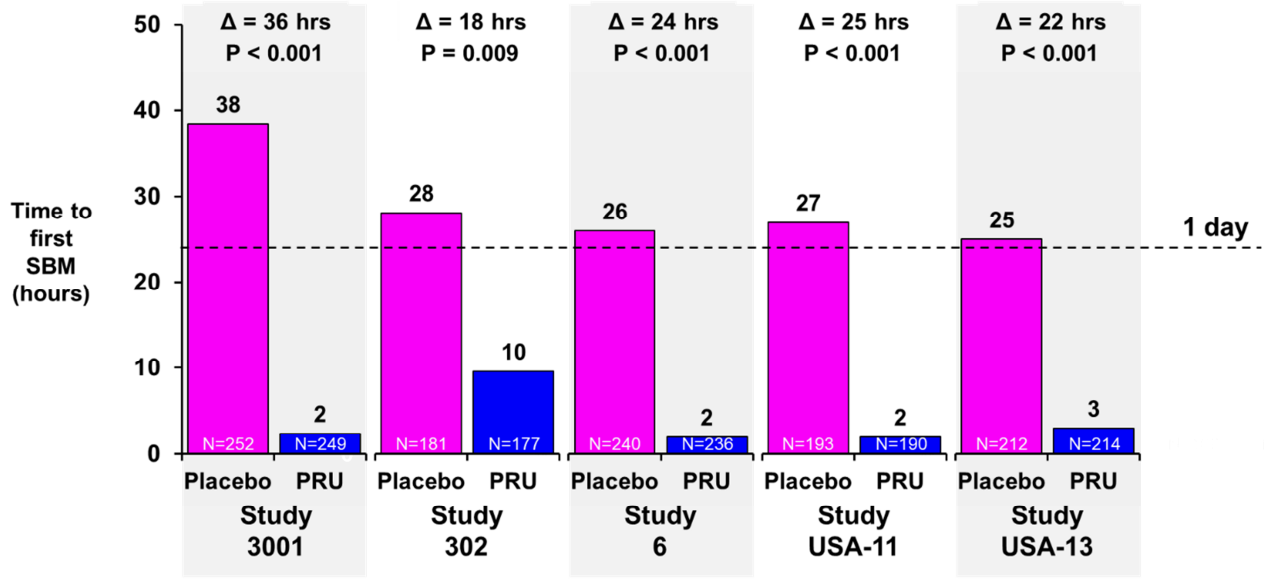
As shown in Figure 8, prucalopride also provided a statistically significant reduction in the time to first CSBM compared with the placebo group across all 5 studies ($p < 0.01$). The average difference between treatment groups ranged from 109 to 380 hours, meaning that the first CSBM occurred 4 to 16 days faster with prucalopride. A post hoc analysis of time to first SBM showed that patients reported having their first SBM within 2-10 hours after initiation of prucalopride (Figure 9).

Figure 8: Time to First CSBM in in Studies 3001, 302, 6, USA-11, and USA-13



CSBM=complete spontaneous bowel movement; PRU=prucalopride

Figure 9: Time to First SBM in Studies 3001, 302, 6, USA-11, and USA-13

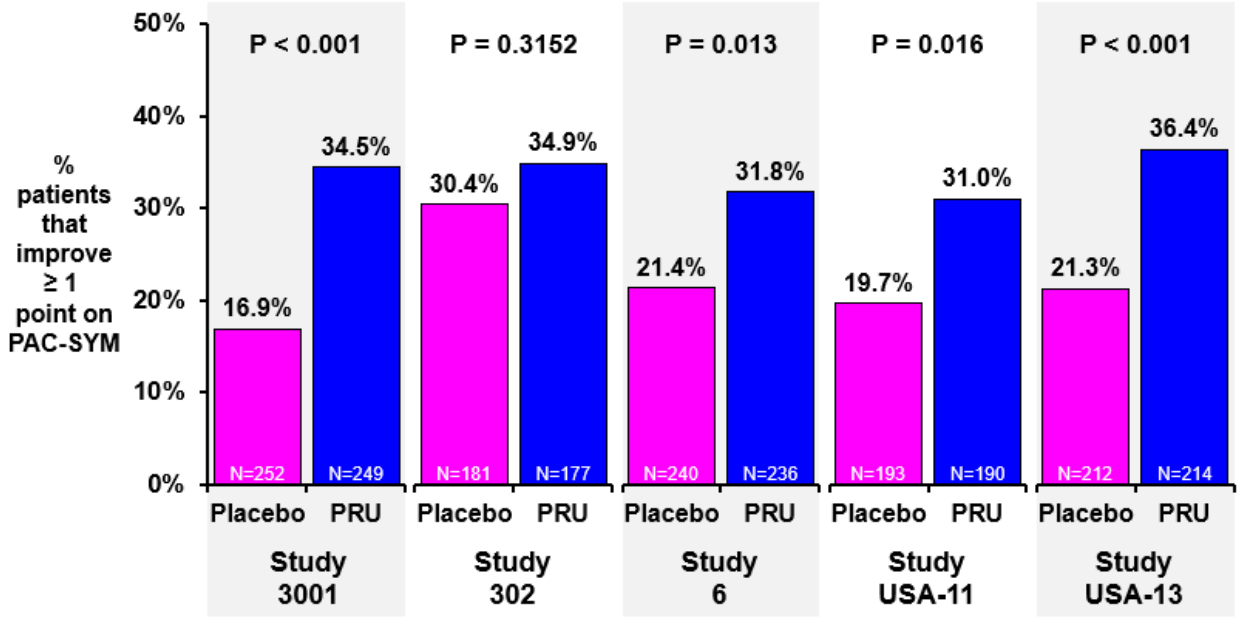


CSBM=complete spontaneous bowel movement; PRU=prucalopride

The PAC-SYM and PAC-QOL were self-administered questionnaires used to measure symptoms and quality of life, respectively, and were assessed at baseline, Week 2, Week 4, and Week 12. The PAC-SYM measures the severity of constipation-related symptoms, and the PAC-QOL measures quality of life in patients with constipation, both using a 5-point Likert scale, where a 1-point change represents a clinically meaningful change (Dubois et al., 2010;Frank et al., 1999). As shown in Figure 10, 4 of the 5 studies showed a greater proportion of patients with an improvement of ≥1 point from baseline at the end of treatment (Week 12) in the total PAC-SYM score in the prucalopride group compared with placebo. The PAC-SYM results were not statistically significant in Study 302.

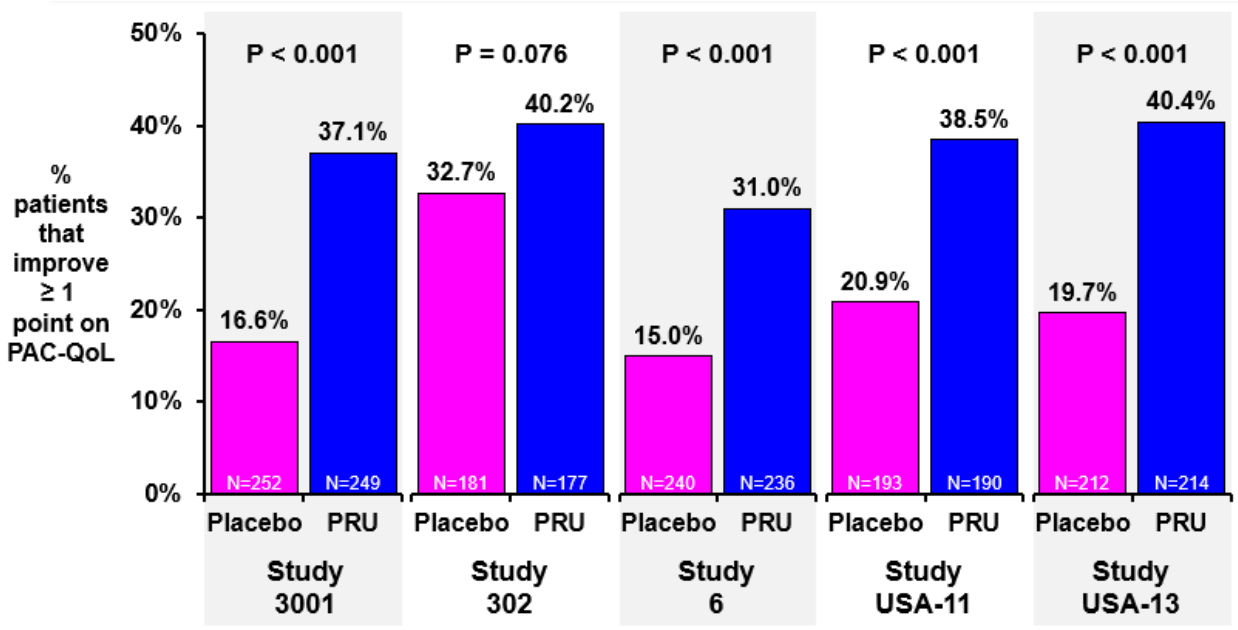
Similarly, the proportion of patients with an improvement of ≥1 point in total score on the PAC-QOL was statistically significantly higher in the prucalopride group compared with placebo in all studies except for Study 302, which did not reach statistical significance (Figure 11).

Figure 10: Proportion of Patients with ≥1 Point Improvement on the PAC-SYM in Studies 3001, 302, 6, USA-11, and USA-13



PAC-SYM= patient assessment of constipation – symptoms; PRU=prucalopride

Figure 11: Proportion of Patients with ≥1 Point Improvement on the PAC-QOL in Studies 3001, 302, 6, USA-11, and USA-13



PAC – QoL=patient assessment of constipation – quality of life; PRU=prucalopride

1.4.2 Efficacy Conclusions

Overall, the efficacy findings were consistent across studies (Figure 12) and baseline demographic characteristics (Figure 13). As shown by the prespecified primary endpoint, a higher proportion of prucalopride treated patients met the primary endpoint compared to placebo, regardless of geographic location. Similar results are obtained when evaluating Alternative Endpoint A. Further subgroup analyses showed that the treatment difference (i.e. effect size) was similar in each of the subgroups by age, sex, race, region or BMI.

Figure 12: Forest Plot of Primary Efficacy Endpoint Results in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

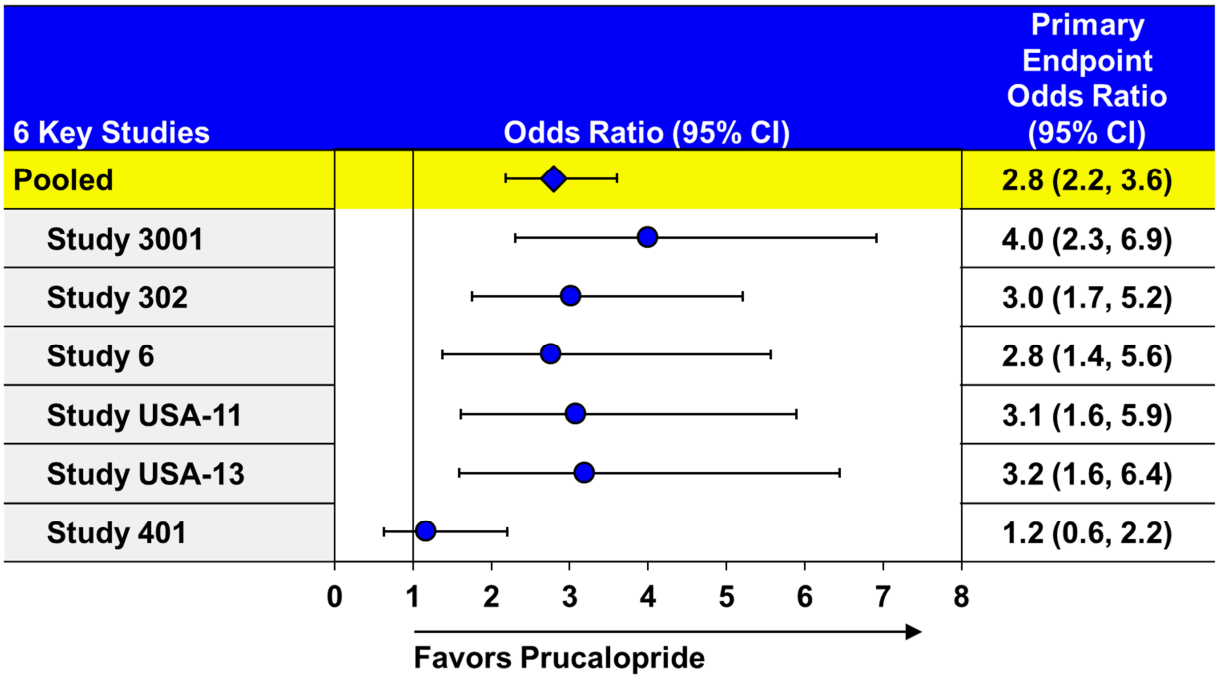
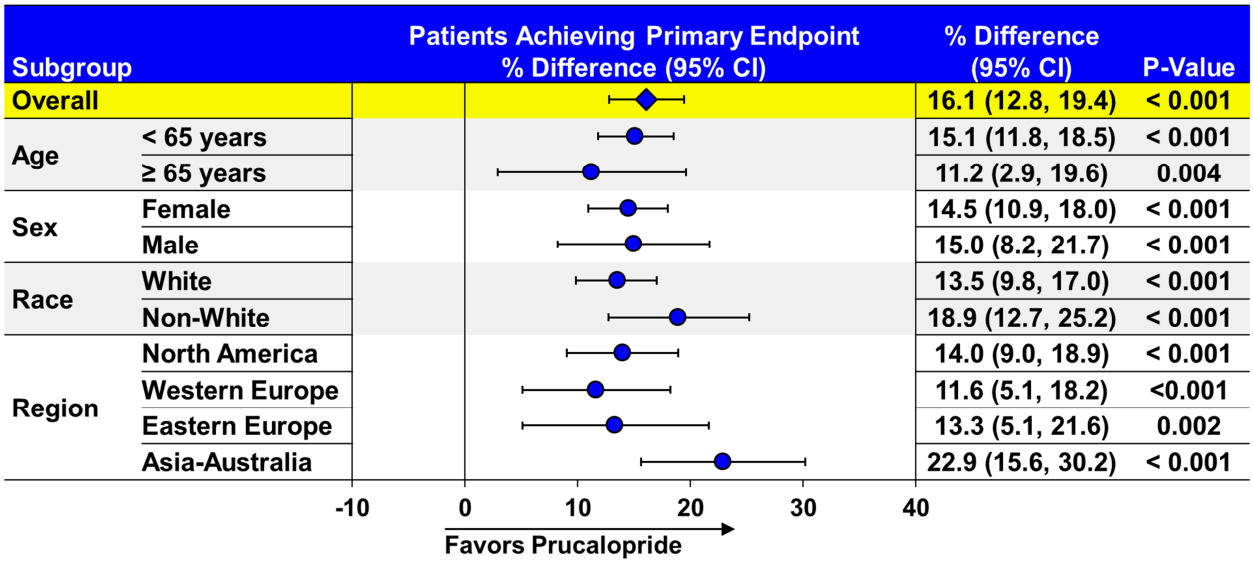


Figure 13: Forest Plot of Primary Efficacy Endpoint Results in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks by Baseline Demographic Characteristics



1.5 Safety

Prucalopride has a favorable safety profile supported by a robust non-clinical and clinical program and more than 8 years of post-marketing experience.

The clinical evidence for safety derives from 16 randomized, double-blind, placebo-controlled studies in adult patients with CIC. This pool of Phase 2, 3, and 4 studies (Pooled Randomized DBPC) is comprised of all studies that were ≥4 weeks in duration in patients with CIC and includes the 6 efficacy studies with a duration of 12 or 24 weeks.

A total of 5,278 patients with CIC are included in the Pooled Randomized DBPC safety analyses (Table 3). Of these, 1,973 patients were on placebo and 3,295 were treated with at least 1 dose of prucalopride (10 patients were randomized but not treated). As previously discussed, many of these studies included a 4 mg dose that is not the dose to be marketed. The focus of the safety assessment is on the recommended doses for prucalopride of 2 mg and 1 mg for patients with severe renal impairment (glomerular filtration rate less than 30 mL/min/1.73 m^2). In the Pooled Randomized DBPC, 330 patients started with the 1 mg dose, and 1,516 patients received the 2 mg* dose.

Table 3: Summary of Exposure in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks Safety Analysis

		Prucalopride				
	Placebo N=1973	**Total N=3305**	**0.5 mg N=110**	**1 mg N=330**	**2 mg* N=1516**	**4 mg N=1349**
Mean days exposure (SD)	72 (36)	64 (36)	27 (6)	40 (29)	79 (38)	56 (29)
Patient exposure						
At least 28 days	1816 (92.0%)	2786 (84.3%)	79 (71.8%)	252 (76.4%)	1363 (89.9%)	1092 (80.9%)
At least 90 days	292 (14.8%)	363 (11.0%)	0	17 (5.2%)	250 (16.5%)	96 (7.1%)

Note: Randomized DBPC=16 Phase 2-4 studies ≥4 weeks duration in chronic idiopathic constipation

* Includes all patients titrated from prucalopride 1 mg to 2 mg.

In addition, in open label extension studies, a substantial number of subjects were exposed to prucalopride for more at least a year (N = 1052; Table 4).

Table 4: Summary of Exposure in Pooled Randomized Open-label Studies ≥4 Weeks Safety Analysis

	Prucalopride
Any patient dosed	2759
At least 90 days	2151
At least 180 days	1710
At least 360 days	1052

Additional prucalopride exposure data come from Phase 1 studies (939 subjects exposed to prucalopride), open-label studies (2,795 patients treated with prucalopride), and a pharmacoepidemiology study, Study 802 (5,717 patients exposed to prucalopride). The total estimated post-marketing exposure through October 2017 is >280,000 person years of exposure.

1.5.1 Safety in Randomized Double-blind Placebo-controlled Studies

From the Pooled Randomized DBPC, more patients on prucalopride 2 mg* reported an AE compared with placebo (Table 5). Specifically, 53.6% of patients on placebo reported an AE compared to 55.8% and 62.4% on prucalopride 1 mg and 2 mg*, respectively. The majority of AEs were mild to moderate, and approximately 15% were reported as severe. More severe AEs and AEs leading to discontinuation occurred among patients on prucalopride compared with placebo. However, there was no difference in the rate of serious adverse events (SAEs) or events with fatal outcome among treatment groups.

Table 5: Overview of Adverse Events in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks Safety Analysis

	Placebo N=1973	Prucalopride		
		Total N=3305	1 mg N=330	2 mg* N=1516
Any AE	1058 (53.6%)	2146 (64.9)	184 (55.8%)	946 (62.4%)
Any severe AE	208 (10.5%)	1238 (37.5)	48 (14.5%)	193 (12.7%)
Any serious AE	38 (1.9%)	66 (2.0)	9 (2.7%)	27 (1.8%)
Any AE leading to discontinuation	58 (2.9%)	220 (6.7)	17 (5.2%)	81 (5.3%)
Events with fatal outcome	1 (<1%)	2 (<1)	1 (<1%)	1 (<1%)

Note: Randomized DBPC=16 Phase 2-4 studies ≥4 weeks duration in chronic idiopathic constipation
*Includes all patients titrated from prucalopride 1 mg to 2 mg.

There were 4 AEs reported with an incidence of >5%: headache, nausea, diarrhea, and abdominal pain. These 4 AEs occurred at a higher rate in patients on prucalopride than placebo and were consistently reported among the 16 randomized controlled studies (Table 6). The majority of these AEs were mild or moderate in severity. There was a low incidence of severe AEs, with only 2-3% of patients reporting a severe headache, nausea, diarrhea, or abdominal pain over the entire course for each of the controlled studies.

Table 6: Commonly Reported (>5%) Adverse Events in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks

	Placebo N=1973	Prucalopride		
		Total N=3305	**1 mg** N=330	**2 mg*** N=1516
Any AE	1058 (53.6%)	2146 (64.9)	184 (55.8%)	964 (62.4%)
Headache	186 (9.4%)	642 (19.4)	44 (13.3%)	265 (17.5%)
Nausea	126 (6.4%)	509 (15.4)	32 (9.7%)	206 (13.6%)
Diarrhea	72 (3.6%)	396 (12.0)	27 (8.2%)	179 (11.8%)
Abdominal pain	153 (7.8%)	321 (9.7)	22 (6.7%)	151 (10.0%)

Note: Randomized DBPC=16 Phase 2-4 studies ≥4 weeks duration in chronic idiopathic constipation

* Includes all patients titrated from prucalopride 1 mg to 2 mg.

Almost all AEs occurred early and resolved within a few days. A large proportion of the most common AEs began on the first day of treatment with prucalopride. When excluding events that began on day 1 of dosing, incidences in the total prucalopride group were 3.0-15.6% lower than when including these events. Events were also generally transient, with few (≤6%) lasting more than 5 days (Table 7).

Table 7: Adverse Events Persisting >5 Days in Pooled Randomized Double-Blind Placebo-Controlled Studies ≥4 Weeks

	Placebo N=1973	Prucalopride	
		1 mg N=330	2 mg* N=1516
Headache	88 (4.5%)	12 (3.6%)	93 (6.1%)
Nausea	50 (2.5%)	11 (3.3%)	95 (6.3%)
Diarrhea	10 (<1%)	5 (1.5%)	42 (2.8%)
Abdominal pain	58 (2.9%)	6 (1.8%)	64 (4.2%)

Note: Randomized DBPC=16 Phase 2-4 studies ≥4 weeks duration in chronic idiopathic constipation
*Includes all patients titrated from prucalopride 1 mg to 2 mg.

From the 16 studies, there was a similar rate of SAEs between prucalopride and placebo (Table 8). Most SAEs occurred in ≤2 patients, with only 3 SAEs reported in ≥3 patients: abdominal pain, vaginal hemorrhage, and hysterectomy.

Table 8: Serious Adverse Events Occurring in ≥3 Patients in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks

	Placebo N=1973	**Prucalopride**	
		1 mg N=330	**2 mg*** N=1516
Any SAE	2%	3%	2%
Abdominal pain	3 (<1%)	0	3 (<1%)
Vaginal hemorrhage	1 (<1%)	0	2 (<1%)
Hysterectomy	3 (<1%)	1 (<1%)	0

Note: Randomized DBPC=16 Phase 2-4 studies ≥4 weeks duration in chronic idiopathic constipation

* Includes all patients titrated from prucalopride 1 mg to 2 mg.

There were 3 AEs that led to discontinuation in ≥1% of patients treated with prucalopride: headache, diarrhea, and nausea (Table 9). The overall rate of AEs leading to discontinuation was low, with a pattern consistent with the most common AEs.

Table 9: Adverse Events Leading to Discontinuation (≥1%) in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks

	Placebo N=1973	Prucalopride	
		1 mg N=330	2 mg* N=1516
Any AE leading to discontinuation	58 (2.9%)	17 (5.2%)	81 (5.3%)
Headache	9 (<1%)	5 (1.5%)	22 (1.5%)
Nausea	9 (<1%)	4 (1.2%)	20 (1.3%)
Diarrhea	2 (<1%)	5 (1.5%)	22 (1.5%)

Note: Randomized DBPC=16 Phase 2-4 studies ≥4 weeks duration in chronic idiopathic constipation

* Includes all patients titrated from prucalopride 1 mg to 2 mg.

A similar incidence of events with fatal outcome (deaths) was observed between treatment groups within the CIC clinical program for prucalopride (Table 10 and Table 11). There were 8 reported events with fatal outcome from all Phase 2 to 4 studies, including the Pooled Randomized DBPC as well as the open-label extensions of Studies 6, USA-11, and USA-13. Three patients died during the Pooled Randomized DBPC: 2 on prucalopride and 1 on placebo. Five events with fatal outcome occurred during open-label extensions, where all patients were treated with prucalopride. All 8 events were assessed by the respective investigator as not related to prucalopride, and this was corroborated by the Shire medical safety physician. Six of the events were reported in elderly patients ≥70 years of age. Full narratives of these events are found in Appendix 11.1.

Table 10: Events with Fatal Outcome Across Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks

Age/Sex	Cause of Death	Dose	Studies	Duration of Treatment	Causality Assessment
83 / M	Lobar pneumonia	1 mg	Randomized DBPC	11 days	Not related
86 / F	Bronchitis	2 mg	Randomized DBPC	31 days	Not related
89 / M	MI	Placebo	Randomized DBPC	7 days	Not related

MI=myocardial infarction

Note: Randomized DBPC=16 Phase 2-4 studies ≥4 weeks duration in chronic idiopathic constipation. Open-label extensions were included in the analysis of deaths.

Table 11: Events with Fatal Outcome in Open Label Extensions of Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks

Age/Sex	Cause of Death	Dose	Studies	Duration of Treatment	Causality Assessment
81 / M	MI	2 mg	Open-label	67 days after discontinuation	Not related
89 / F	Pneumonia	2 mg	Open-label	218 days	Not related
56 / M	MI	2 mg	Open-label	48 days	Not related
70 / M	Suicide	2 mg	Open-label	29 days after discontinuation	Not related
40 / F	Suicide	4 mg	Open-label	52 days after discontinuation	Not related

MI=myocardial infarction

Note: Randomized DBPC=16 Phase 2-4 studies ≥4 weeks duration in chronic idiopathic constipation. Open-label extensions were included in the analysis of deaths.

1.5.2 Cardiovascular Safety Assessment

Due to concerns regarding possible cardiovascular risk in patients treated with non-selective 5-HT_4 agonist products, Shire conducted extensive proactive and retrospective analyses on cardiovascular and major adverse cardiovascular events (MACE) risk. All investigations have been unable to demonstrate increased cardiovascular risk.

The investigations of MACE come from 6 different sources:

- Extensive set of in vitro and in vivo nonclinical studies
- Five clinical studies with intense cardiovascular monitoring including a thorough QT (TQT) study
- Comprehensive evaluation of cardiovascular AEs as well as AEs that might suggest cardiovascular events in the Pooled Randomized DBPC studies and open-label safety extensions
- Independent, blinded expert adjudication of MACE or preferred terms that might suggest potential MACE in the Pooled Randomized DBPC studies and open-label safety extensions
- A retrospective observational study comparing prucalopride to matched controls treated with PEG (Study 802)
- Pharmacovigilance monitoring from over 8 years of post-marketing experience

Nonclinical and clinical evidence together support the conclusion that an increased cardiovascular risk could not be established in the treatment of patients with CIC with prucalopride.

1.5.2.1 In Vitro and In Vivo Nonclinical Cardiovascular Testing

As part of the safety pharmacology and toxicology programs, a comprehensive set of nonclinical cardiovascular studies were completed for prucalopride in a variety of in vitro and in vivo models at concentrations covering and exceeding therapeutic dose in humans.

Prucalopride demonstrated a wide safety margin, with physiologically significant effects on electrophysiological and cardiovascular parameters observed only at supratherapeutic concentrations that were considered clinically irrelevant.

These investigations included studies to exclude all potential 5-HT_4 and non-5-HT_4 receptor-mediated cardiovascular pharmacology that have been observed with cisapride and tegaserod.

The in vitro and in vivo nonclinical cardiovascular studies included:

- Electrophysiological studies in the hERG channel (human) and in guinea pig ventricular myocytes
- Electrophysiological studies in isolated rabbit and dog Purkinje fibers, in isolated guinea pig papillary muscle, and in the isolated Langendorff rabbit heart (Hondeghem model)
- Platelet aggregation studies in human blood samples
- Contractility assessment in isolated coronary arteries (dog, pig, and human)
- Chronotropic and inotropic effects in piglet and human atrial myocardium
- Cardiovascular assessments in anesthetized guinea pigs, dogs, and juvenile pigs, and in conscious dogs
- Torsade de pointes and arrhythmogenicity assessment in anesthetized rabbits (Carlsson model)
- Cardiovascular assessments in repeated dose toxicity studies in rats and dogs

In nonclinical animal models, no relevant effects were seen on cardiovascular or cardiac electrophysiological parameters at concentrations of at least 50 times the therapeutic plasma concentrations in humans. Importantly, there was no effect of prucalopride on the hERG channel at concentrations up to 50 times the therapeutic concentration. There were no effects of prucalopride on other ion channels or proarrhythmia tendencies observed at concentrations up to 500 times the therapeutic dose.

In an in vitro study of human platelet aggregation, prucalopride (up to 200 nM; 10 times greater the therapeutic plasma concentrations) did not cause a statistically significant increase in platelet aggregation responses to a range of physiologically relevant platelet activators. In addition, at concentrations up to 10 µM (500 times the therapeutic plasma concentrations), there were no effects on contraction in porcine, canine, or human isolated left anterior descending coronary arteries, further demonstrating that prucalopride has no significant affinity or selectivity for 5-HT_{2A} and 5-HT_{1B} receptors.

1.5.2.2 Studies with Intense Cardiovascular Monitoring (Thorough QT and Phase 1 Cardiovascular Monitoring)

A TQT study was conducted using a positive control (moxifloxacin), and cardiovascular monitoring was included in several Phase 1 studies in healthy subjects. For both the therapeutic prucalopride dose of 2 mg and the supratherapeutic dose of 10 mg, the mean differences in time-matched study-specific QT corrected QT interval (QTcSS) change from baseline between prucalopride and placebo were all <5 msec, and the upper limit of the confidence interval (CI) for the difference in time-matched QTcSS change from baseline between prucalopride and placebo was below the non-inferiority margin of 10 msec at all time points, confirming the absence of any clinically relevant effect of prucalopride on cardiac repolarization. Assay sensitivity was confirmed with the positive control, moxifloxacin, in which the lower limit for the difference from placebo was ≥5 msec for all time points measured except for the 1-hour time point ($t_{1/2}$ of moxifloxacin is 12 to 24 hours).

1.5.2.3 Events from Randomized Double-Blind Placebo-Controlled Studies and Open-Label Extensions with QT Prolongation, Arrhythmia, and Ischemia

The reported cardiovascular AEs within the Pooled Randomized DBPC database from all 16 studies were infrequent and similar among all treatment arms (Table 12). There were few events across all doses, with no indication of a difference between groups. Data from the open-label extension studies were similar to the Pooled Randomized DBPC studies.

Table 12: Incidence of QT Prolongation, Arrhythmia, and Ischemic Events in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks

		Prucalopride		Open-Label
QT Prolongation, Ventricular Arrhythmia, and Syncope	**Placebo N=1973**	**2 mg* N=1516**	**Total** N=3305**	**Total N=2759**
Any AE	11 (0.6%)	6 (0.4%)	22 (0.7%)	32 (1.2%)
Any severe AE	2 (0.1%)	0	2 (0.1)	3 (0.1%)
Any SAE	2 (0.1%)	1 (0.1%)	1 (0.03%)	5 (0.2%)
Any AE leading to discontinuation	0	0	4 (0.1%)	3 (0.1%)
Events with Fatal Outcome	0	0	0	0
Cardiovascular and Cerebrovascular Ischemic Events				
Any AE	5 (0.3%)	6 (0.4%)	9 (0.3%)	23 (0.8%)
Any severe AE	2 (0.1%)	0	0	11 (0.4%)
Any SAE	3 (0.2%)	2 (0.1%)	3 (0.1%)	15 (0.5%)
Any AE leading to discontinuation	2 (0.1%)	1 (0.1%)	1 (0.03%)	2 (0.1%)
Events with Fatal Outcome	1 (0.1%)	0	0	2 (0.1%)

Note: Pooled Randomized DBPC=16 Phase 2-4 studies ≥4 weeks duration in chronic idiopathic constipation

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

**Total column includes all prucalopride doses: 0.5, 1, 2, and 4 mg

Source: Table 51, Table 53, Table 55 ISS

1.5.2.4 Independent Blinded Adjudication for MACE of the Randomized Double-Blind Placebo-Controlled Studies

An independent panel of experts (Adjudication Committee) established prespecified selection criteria used to screen the entire clinical dataset for possible MACE. This panel triaged, reviewed and adjudicated all identified cases of possible MACE, as well as unstable angina requiring hospitalization (extended MACE), and either confirmed or refuted the events using strict, prespecified criteria.

Overall, the independent adjudication committee concluded that there was no evidence suggesting excess cardiovascular risk for MACE with prucalopride.

Four patients met the criteria for MACE in the Pooled Randomized DBPC: 2 patients on placebo and 2 on prucalopride. These numbers result in an incidence rate of 5.2 patients per 1000 patient-years exposure in the placebo group compared to 3.5 patients per 1000 patient-years for prucalopride (Table 13). With the extended MACE definition including unstable angina requiring hospitalization, 2 additional cases were identified in patients treated with prucalopride, making the incidence rate 7.1 per 1000 patient-years for prucalopride. Regardless of MACE definition, the rates were low and similar to placebo.

Table 13: Independent Adjudication of MACE in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks

		Prucalopride	
Safety Dataset (Dosed in Randomized Double-blind Placebo-controlled Studies)	**Placebo (N=2019)**	**2 mg* (N=1545)**	**Total** (N=3366)**
MACE	2 (0.10%)	1 (0.07%)	2 (0.06%)
Cardiovascular events with fatal outcome	1 (0.05%)	0	0
Nonfatal MI	0	0	1 (0.03%)
Nonfatal stroke	1 (0.05%)	1 (0.07%)	1 (0.03%)
MACE rate/1000 PYE	5.2	3.1	3.5
Extended MACE (with unstable angina requiring hospitalization)	0.10%	0.06%	0.12%
Extended MACE rate/1000 PYE	5.2	3.1	7.1

MACE=major adverse cardiovascular event; MI=myocardial infarction, PYE=patient years of exposure

Note: Pooled Randomized DBPC=16 Phase 2-4 studies ≥4 weeks duration in chronic idiopathic constipation.

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

**Total column includes all prucalopride doses: 0.5, 1, 2, and 4 mg

Expanding the MACE definition to include unstable angina requiring hospitalization also supported the conclusion that the rate of cardiovascular events was similar to placebo (Table 14).

Table 14: Independent Adjudication of Extended MACE (with Unstable Angina Requiring Hospitalization) in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks

		Prucalopride	
Safety Dataset (Dosed in Randomized Double-blind Placebo-controlled Studies)	**Placebo (N=2019)**	**2 mg* (N=1545)**	**Total** (N=3366)**
Extended MACE (with unstable angina)	2 (0.10%)	1 (0.06%)	4 (0.12%)
Extended MACE rate/1000 PYE	5.2	3.1	7.1

MACE=major adverse cardiovascular event

Note: Pooled Randomized DBPC=16 Phase 2-4 studies ≥4 weeks duration in chronic idiopathic constipation.

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

**Total column includes all prucalopride doses: 0.5, 1, 2, and 4 mg

The independent panel of experts also adjudicated open-label data from the randomized DBPC studies, further supporting the conclusion that there are no signs suggestive of cardiovascular risk with prucalopride.

1.5.2.5 Pharmacoepidemiology Study 802 (EUPAS9200)

In agreement with FDA, Shire sponsored a pharmacoepidemiology study (Study 802) to further support cardiovascular safety. Overall, the pooled incidence rate ratio (IRR) estimate did not show evidence of an overall increased risk of MACE in patients using prucalopride compared with PEG for constipation.

The primary objective of Study 802 was to estimate the adjusted IRR and 95% CI for MACE in adult new users of prucalopride compared with adult new users of PEG. In this study, MACE included hospitalization for acute myocardial infarction or stroke and in-hospital cardiovascular events with fatal outcome. Patients were identified using electronic medical records, administrative claims, or national health-data registers. MACE outcomes in the United Kingdom (UK) were validated using additional clinical data, as available, and adjudicated by a committee of 3 clinicians. Cases included in Sweden were identified using previously validated algorithms.

Standardized incidence rates and IRRs of MACE comparing the 2 drugs were derived using propensity scores for each data source separately and after pooling aggregate data from the data sources. A sensitivity analysis was conducted to assess the impact of including out-of-hospital coronary heart disease and cerebrovascular events with fatal outcome in the MACE endpoint. A bias analysis was conducted to determine the potential impact of unmeasured confounding.

The pooled analyses included 35,087 patients treated with prucalopride (n=5,715) or PEG (n=29,372). The average total duration of use was 175 days for prucalopride and 82 days for PEG. In all data sources, >90% of participants were women, and the proportion of patients aged ≥55 years was 21%-34% for UK data sources and 53% in Sweden. Pooled standardized incidence rate per 1,000 person-years (95% CI) of MACE was 6.57 (3.90-10.39) for patients initiating prucalopride; 10.30 (7.03-14.19) for PEG (Table 15). The pooled adjusted IRR for MACE was 0.64 (95% CI, 0.36, 1.13). Results were robust to the alternative definition of MACE that included out-of-hospital cardiovascular events with fatal outcome and bias analyses of unmeasured confounding.

Table 15: MACE Risk Assessment from Study 802

	Prucalopride (N=5717)	**PEG (N=2938)**
MACE rate/1000 PYE (95% CI)	6.57 (3.90, 10.39)	10.30 (7.03, 14.19)
Adjusted IRR (95% CI)	0.64 (0.36, 1.13)	

1.6 Conclusions

Prucalopride is a next-generation selective 5-HT_4 agonist that has been shown to be safe and effective in adults with CIC in the US and around the world. With its different mechanism of action from available prescription medicines for CIC, prucalopride can provide relief to adult patients who have been unable to achieve ≥3 CSBMs per week with other therapies. Due to its high selectivity, prucalopride has not demonstrated an increased risk for cardiac side effects. The AEs that were identified in the program result in an acceptable benefit-risk profile and this is further supported by more than 280,000 patient years of experience from 59 countries.

Across the clinical studies, efficacy evidence demonstrated that prucalopride increases CSBMs in patients with CIC. Five of 6 efficacy studies demonstrated statistical significance for the primary endpoint and FDA requested Alternative Endpoint A; the sixth study showed a non-significant increase compared to placebo. Prucalopride showed numerical or statistically significant results across a variety of secondary and post hoc efficacy endpoints. These benefits are also supported by the results from 2 patient-reported assessments of constipation. Importantly, the response rate on the primary efficacy endpoint was similar in both US and non-US populations.

The clinical safety profile has remained consistent since launch in 2009. Shire's Global Drug Safety performs continuous safety monitoring and signal detection for prucalopride based on all available sources of published and post-marketing data. Through October 2017, 5072 post-marketing AEs were reported in patients receiving prucalopride. The majority of events were non-serious, and the assessments do not establish any increased cardiovascular risk with prucalopride. The safety profile of prucalopride has been well characterized with no new Adverse Drug Reactions added in the core data sheet or the EU label since first launch.

In summary, prucalopride consistently demonstrated a favorable safety profile. The most common side effects were headache, nausea, diarrhea, and abdominal pain, and most events were mild or moderate in severity. These AEs occurred in the first few days of treatment and were transient in nature. Systematic and comprehensive investigation from the extensive clinical program, more than 8 years of postmarketing experience, and an observational study were unable to detect an increase in cardiovascular risk in patients treated with prucalopride.

In conclusion, prucalopride demonstrated efficacy over placebo and has proven to be safe and well tolerated after rigorous evaluation of clinical studies and extensive real-world experience.

2. BACKGROUND ON CHRONIC IDIOPATHIC CONSTIPATION

Summary

- Chronic idiopathic constipation is constipation that is not caused by another disease or medicine and results in <3 CSBMs per week.
- Chronic idiopathic constipation can be characterized by infrequent defecation, straining, lumpy or hard stools, sensation of incomplete evacuation, and abdominal pain.
- Symptoms of CIC can be severe and impact health-related quality of life.
- The goal of treatment for CIC is to restore normal bowel function, which typically means increasing CSBMs and related symptoms.
- Treatment for CIC ranges from lifestyle modifications, over-the-counter medications, and prescription medications.
- The currently available prescription medications are prosecretory agents that all work through a similar mechanism of action to increase colonic secretions.
- Despite available treatment options, there continues to be high patient dissatisfaction with results and an overall unmet need for additional treatment options for CIC.

2.1 Overview of Chronic Idiopathic Constipation

Chronic idiopathic constipation, or constipation that is not caused by another disease or a medicine, is a common and often debilitating medical problem. Several working groups (World Gastroenterology Organization, American Gastroenterological Association, American College of Gastroenterology, and the Rome Foundation working group) have recognized that CIC is a condition that comprises multiple symptoms, including infrequent defecation, straining, lumpy or hard stools, sensation of incomplete evacuation, and abdominal symptoms.

Symptoms of CIC can be severe and significantly affect daily functioning. In addition to infrequent and hard stools, patients experience bloating, abdominal pain, and feeling like they have to go to the bathroom when they cannot. Several types of primary chronic constipation, which show substantial overlap, have been described, including normal-transit constipation, rectal evacuation disorders, and slow-transit constipation (Camilleri et al., 2017). Patients with chronic constipation differ significantly from healthy subjects in the number and duration of mass movements, as well as the circadian pattern of bowel motility (Bassotti et al., 1988). In some cases, CIC can lead to serious complications and has been associated with comorbidities such as fecal impaction, diverticular disease, and rectal prolapse (Talley et al., 2009). Furthermore, CIC has a demonstrated impact on health-related quality of life and is associated with a substantial economic burden (Dennison et al., 2005;Peery et al., 2015). Health-related quality of life scores for patients with CIC are comparable to those in patients with chronic musculoskeletal conditions and diabetes (Belsey et al., 2010), and heart disease and depression in

women (Wald et al., 2007). Diagnosis of primary chronic constipation involves a multistep process initiated by the exclusion of 'alarm' features (for example, unintentional weight loss or rectal bleeding) that might indicate organic diseases (Camilleri et al., 2017).

Chronic constipation is the most prevalent gastrointestinal condition presented to primary care physicians or subspecialty physicians and surgeons globally. The prevalence of chronic constipation is 10.0% – 14.9% in the US (Camilleri et al., 2017;Suares and Ford, 2011). Chronic idiopathic constipation is more prevalent in women, non-Whites, and elderly patients and has been associated with lower socioeconomic status, low fiber diet, and lack of exercise (Bosshard et al., 2004;Higgins and Johanson, 2004;Peppas et al., 2008;Suares and Ford, 2011).

Gastrointestinal diseases are a source of substantial morbidity, mortality, and cost in the US (Nguyen et al., 2018;Peery et al., 2015;Peery et al., 2012), and the number of inpatient discharges for constipation and associated costs has significantly increased between 1997 and 2010 (Sethi et al., 2014).

2.1.1 Clinical Diagnosis

The Rome criteria (Table 16) are used to define constipation, which is now considered a continuous spectrum with IBS-C.

Table 16: Rome II/III Criteria Adults

Diagnostic criteria for functional constipation in adults[a]:

1. Must include 2 or more of the following:
   - Straining during at least 25% of defecations
   - Lumpy or hard stools in at least 25% of defecations
   - Sensation of incomplete evacuation for at least 25% of defecations
   - Sensation of anorectal obstruction/blockage for at least 25% of defecations
   - Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of pelvic floor)
   - Fewer than 3 defecations per week.
2. Loose stools are not/rarely[b] present without the use of laxatives.
3. Insufficient criteria for irritable bowel syndrome.

a Criteria fulfilled for at least 3 months in the preceding 12 months (Rome II) or at least 3 months with symptom onset at least 6 months prior to diagnosis (Rome III).

b Not present according to Rome II, rarely present according to Rome III.

Source: Drossman et al., (2006);Drossman et al., (2000)

2.1.2 Types of Bowel Movements

- Complete spontaneous bowel movement (CSBM): a bowel movement that is initiated without a laxative and results in a feeling of complete evacuation.
- Spontaneous bowel movement (SBM): a bowel movement that is initiated without a laxative.
- Bowel movement: any bowel movement and can be initiated by a laxative.

2.1.3 Goal of Treatment

The goal of treatment for CIC is to increase CSBMs, which is associated with a reduction in symptoms and an improvement in health-related quality of life.

2.2 Treatment for Chronic Idiopathic Constipation

2.2.1 Non-prescription Treatment

Dietary and lifestyle changes, such as increased dietary fiber intake, water consumption, and physical exercise, are recommended as initial treatment for constipation. If dietary and lifestyle modifications are not sufficiently effective to improve constipation symptoms, most treatment guidelines recommend dietary fiber or fiber supplements (20-30 g/day) before considering laxative therapies or physiological testing (Bharucha et al., 2013;Ford et al., 2014). Osmotic laxatives such as PEG are often considered the next logical choice for patients who do not benefit from fiber intake, followed by stimulant laxatives. Patients who have exhausted all non-prescription treatment options move on to prescription prosecretory agents.

2.2.2 Prosecretory Agents

The only approved, available prescription products for CIC in the US are prosecretory agents. In general, prosecretory agents work by promoting fluid secretion into the GI tract. Three products are approved in the US: lubiprostone, linaclotide, and plecanatide.

Lubiprostone (marketed as AMITIZA; Sucampo Pharmaceuticals Inc.) is a locally acting selective chloride channel activator promoting fluid secretion into the intestinal lumen. In a 4-week, randomized, controlled study in patients with CIC, lubiprostone was superior to placebo in increasing stool frequency, improving stool consistency, reducing straining, and improving overall constipation-related symptoms (Barish et al., 2010;Johanson et al., 2008;Johanson and Ueno, 2007). Lubiprostone is currently approved in the US for the treatment of CIC in adults, IBS-C in adult women, and opioid-induced constipation in adults with chronic non-cancer pain.

Linaclotide (marketed as LINZESS; Ironwood Pharmaceuticals Inc. and Forest Pharmaceuticals Inc.) is a guanylate cyclase C agonist that binds to the guanylate receptor in the gut, thereby increasing fluid in the bowel. In a 12-week, randomized, controlled study, linaclotide proved more effective compared with placebo at increasing stool frequency and improving stool consistency, straining, and overall constipation-related symptoms (Lembo et al., 2011). Linaclotide is currently approved in the US for the treatment of CIC and IBS-C in adults.

Plecanatide (marketed as TRULANCE; Synergy Pharmaceuticals Inc.) is also a guanylate cyclase C agonist. Results from recent Phase 3 studies demonstrated that plecanatide was more effective than placebo in patients with CIC (Miner et al., 2017;Nualart et al., 2016). Plecanatide was recently approved in the US (January 2017) for the treatment of CIC.

2.2.3 Prokinetic Agents

Prokinetic agents work by stimulating gut motility via 5-HT_4 agonism (Bouras et al., 2001;Prather et al., 2000). Tegaserod (ZELNORM) is a non-selective 5-HT_4 agonist that was approved in the US in 2002 for the treatment of IBS-C and CIC. Tegaserod was later voluntarily withdrawn from the US market in 2007 and is only available for patients without any other therapeutic options via a Limited Access Program.

2.3 Patient Medical Need

For many patients, constipation is a chronic condition associated with decreased health-related quality of life (Dennison et al., 2005;Peery et al., 2015). Chronic idiopathic constipation is difficult to treat, and there is a high rate of treatment dissatisfaction (Johanson and Kralstein, 2007;Muller-Lissner et al., 2013). There remains an unmet need for effective therapies that increase the frequency of bowel movements, while relying on a different mechanism of action than currently available prosecretory agents (Camilleri et al., 2017).

3. PRODUCT DESCRIPTION

3.1 Proposed Indication

The proposed indication for prucalopride is for the treatment of CIC in adults. The proposed dose is 2 mg QD, and 1 mg QD for patients with severe renal impairment (glomerular filtration rate less than 30 mL/min/1.73 m^2).

3.2 Dosing Regimen

Three dose-response studies (PRU-INT-1, PRU-INT-2, and PRU-USA-3), supported the testing of 2 mg and 4 mg QD in the initial Phase 3 studies (Studies 6, USA-11, and USA-13). Results of these studies showed that the 4 mg QD prucalopride dose provided no significant benefit over the 2 mg QD dose. Therefore, a dose of 2 mg QD is considered appropriate for the treatment of CIC in adult patients. Only the 2 mg QD dose was investigated in Studies 3001 and 302.

The 1 mg dose is the recommended dose in patients with severe renal impairment (glomerular filtration rate less than 30 mL/min/1.73 m^2).

3.3 Mechanism of Action

Prucalopride is a next-generation highly selective and high-affinity 5-HT_4 agonist that stimulates colonic peristalsis. Prucalopride has shown prokinetic effects in both dogs and humans.

Prucalopride effectively stimulates or enhances propulsive motor patterns in the large intestine due to a high affinity for 5-HT_4 receptors in GI tissues. Affinity for other receptors is present only at concentrations that exceed its 5-HT_4 receptor affinity by at least 150 times. This differentiates prucalopride from other 5-HT_4 receptor agonists such as tegaserod and cisapride, whose affinity for other receptors/channels such as 5-$HT_{1,2}$ (tegaserod) and the 5-HT_2 and hERG channel (cisapride) is in the same range as their affinity for the 5-HT_4 receptor.

3.3.1 Selective vs. Non-selective 5-HT_4 Agonists

It is important to highlight the distinction between prucalopride and non-selective 5-HT_4 agonists such as tegaserod and cisapride. Due to their relatively low selectivity for the 5-HT_4 receptor, first generation 5-HT_4 agonists interact with other receptors in a concentration range relevant for their interaction with the 5-HT_4 receptors.

Although the etiology or mechanism underlying the potential for rare occurrences of serious cardiovascular ischemic events associated with tegaserod is unclear, it has been suggested that it is related to the non-selectivity of its affinity for other 5-HT receptors (5-HT_1 and 5-HT_2) in addition to 5-HT_4.

Cisapride, marketed as PREPULSID, was approved for the treatment of gastroesophageal reflux disease (GERD) in 1993 but was voluntarily withdrawn from the US market in 2000 due to cardiovascular toxicity concern and is only available for patients without any other therapeutic options via a Limited Access Program. It is now clearly established that the cardiac effects of cisapride are unrelated to its 5-HT_4 receptor agonism and attributable to its affinity for the hERG

channel. This affinity of cisapride for the hERG channel is within the range of 1-5 times human plasma levels, or a concentration ratio ≤5 between its 5-HT_4 receptor-mediated effects and its inhibitory effect on the rapidly activating delayed rectifier potassium channel (I_{Kr}) (Drolet et al., 1998;Mohammad et al., 1997;Potet et al., 2001).

In contrast to tegaserod and cisapride, prucalopride has been shown to have high receptor specificity for 5-HT_4 with an affinity in nanomolar range (pK_i=8.7; K_i=2.5-8 nM; half maximal effective concentration [EC_{50}]=5 nM), and in vitro affinity for other receptors was only detected at concentrations exceeding its 5-HT_4 receptor affinity by at least 150-fold. Figure 14 shows the results of competitive receptor-ligand binding studies using agonist (green and black circles) and antagonist (red and white circles) radioligands. These data show the high selectivity of prucalopride for the 5-HT_4 receptor compared to 5-HT_{2A}, 5-HT_{1B}, and hERG, while the affinity of tegaserod for the 5-HT_4 receptor is in the same range as its affinity for the 5-HT_{2A} and 5-HT_{1B} receptors (Table 17).

Figure 14: 5-HT$_4$ Receptor Selectivity of Prucalopride Compared to Tegaserod

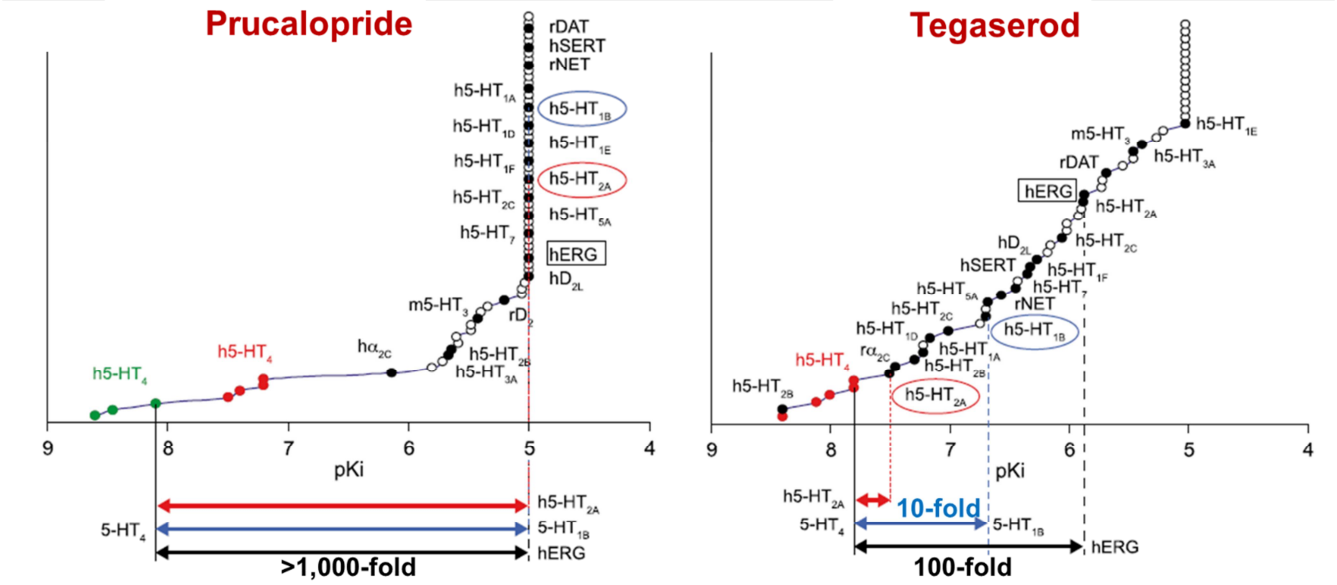


Table 17: Affinity of Prucalopride and Tegaserod for 5-HT_4, 5-HT_{2A}, and 5-HT_{1B} Receptors

Assay (pKi values)	Prucalopride	Tegaserod
5-HT_4	8.7	8.4
5-HT_{2A}	5	7.5
5-HT_{1B}	5	7.2-8.1

The substantial safety margins for prucalopride over effects on the hERG channel contrast with those for cisapride. As shown in Figure 15 and Table 18, the affinity of cisapride for 5-HT_{2A} and hERG channel is in the same range as its affinity for the 5‑HT_4 receptor. In contrast, prucalopride does not have hERG blockade in the therapeutic range; the hERG half maximal inhibitory concentration (IC_{50}) of prucalopride is 22 µM, which is over 1,100-fold the therapeutic plasma concentration, and the affinity of prucalopride for the 5-HT_4 receptor is over 4,000-fold its affinity for the hERG channel (Table 18).

Figure 15: 5-HT4 Receptor Selectivity of Prucalopride Compared to Cisapride

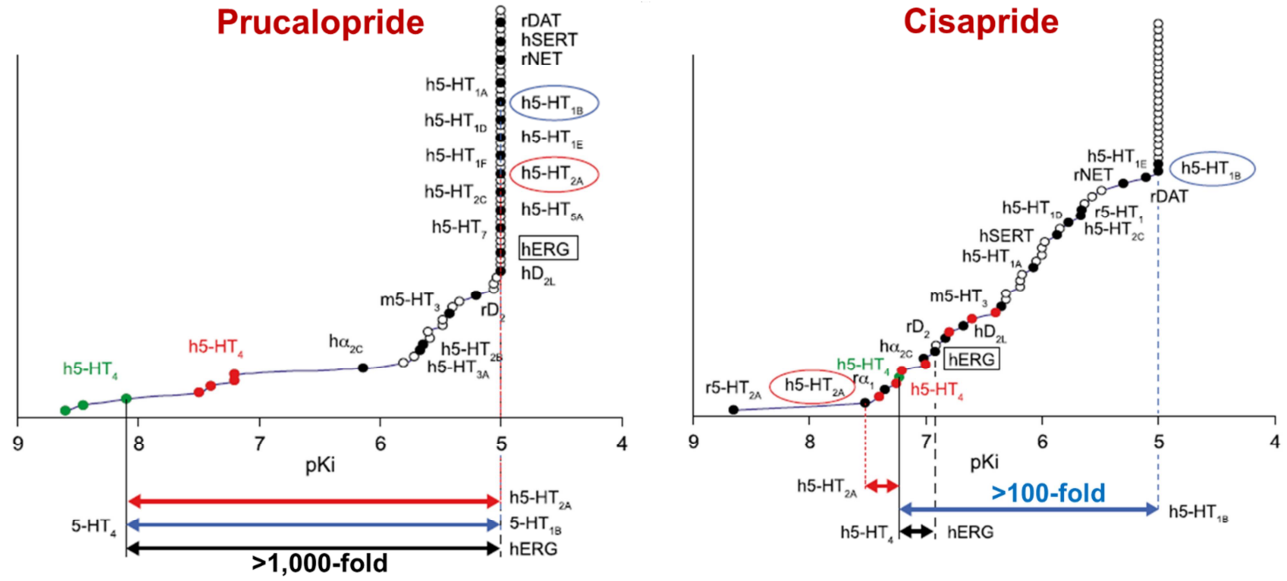


Table 18: Affinity of Prucalopride, Tegaserod, and Cisapride for 5-HT_4 and hERG Channel Receptors

Assay (IC_{50} values)	Prucalopride	Tegaserod	Cisapride
5-HT_4 (EC_{50} nM)	5	5	13
hERG (IC_{50} nM)	22,000	13,000	44
5-HT_4/hERG Ratio	4,400x	2,600x	3x

EC_{50}= half maximal effective concentration; IC_{50}= half maximal inhibitory concentration

In conclusion, non-5-HT_4 receptor-mediated pharmacology has been implicated in the etiology of cardiovascular AEs for the withdrawn first-generation 5-HT_4 receptor agonists, cisapride and tegaserod. Prucalopride is a highly selective 5-HT_4 receptor agonist; its in vitro affinity for the 5-HT_4 receptor is at least 150-fold greater than its affinity for other receptors and ion channels, and it demonstrates none of the off-target mediated cardiovascular interactions that have been observed with cisapride and tegaserod.

4. REGULATORY AND DEVELOPMENT HISTORY

4.1 Regulatory Milestones

Prucalopride was originally developed by Johnson & Johnson Pharmaceutical Research and Development. In 2006, the rights in the EU and Switzerland were out-licensed to Movetis NV. On 15 Oct 2009, centralized European approval for prucalopride was obtained. In October 2010, Shire acquired Movetis NV and continued the development and marketing of prucalopride. In January 2012, Shire obtained the rights to develop and market prucalopride in the US.

Between 2012 and 2014, Shire and FDA discussed the efficacy and safety plans for the NDA submission in several meetings. As a result of these meetings, agreement was reached on:

- the need for a platelet aggregation and coronary artery contractility study
- the design of the pharmacoepidemiology study, Study 802, to address the Agency's concern with regards to cardiovascular safety
- the efficacy requirements for the NDA submission for the treatment of CIC in adults

The sponsor is also completing its requirements for the pediatric study plan.

4.2 Clinical Development Program

The proposed indication for prucalopride is supported by the efficacy results from 6 studies that are regarded as equally important. All 6 studies were randomized, double-blind, placebo-controlled studies that evaluated efficacy and safety of prucalopride in patients with CIC. Five of the 6 studies (Studies 3001, 302, 6, USA-11 and USA-13) were 12-weeks in duration; Study 401 was 24 weeks.

The primary endpoint in all 6 studies was the proportion of patients with an average of ≥3 CSBMs/week over 12 weeks of treatment and 24 weeks of treatment in Study 401. Table 19 shows more details of these studies.

Table 19: Phase 3/4 Efficacy and Safety Studies in Chronic Idiopathic Constipation

Study Number	Title	Number of Patients Randomized and Treated	Primary Efficacy Endpoint
3001	A randomized DBPC study to evaluate the efficacy and safety of prucalopride tablets in patients with chronic constipation	501	The proportion of patients with an average of ≥ 3 CSBMs/week over the 12-week treatment period
302	A randomized DBPC study to evaluate the efficacy, quality of life, safety and tolerability of prucalopride in male patients with chronic constipation	370	The proportion of patients with an average of ≥ 3 CSBMs/week over the 12-week treatment period
6	A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of prucalopride tablets in patients with chronic constipation	716	The proportion of patients with an average of ≥ 3 CSBMs/week over the 12-week treatment period
USA-11	A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of prucalopride tablets in patients with chronic constipation	620	The proportion of patients with an average of ≥ 3 CSBMs/week over the 12-week treatment period
USA-13	A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of prucalopride tablets in patients with chronic constipation	641	The proportion of patients with an average of ≥ 3 CSBMs/week over the 12-week treatment period
401	A randomized, double-blind, placebo-controlled study to evaluate the efficacy, quality of life, safety and tolerability of long-term treatment (24 weeks) with prucalopride in patients aged ≥ 18 years with chronic constipation	361	The proportion of patients who had an average of ≥ 3 CSBM/week over the 24-week treatment period

CSBM=complete spontaneous bowel movement; DBPC=double-blind placebo-controlled
Source: Module 5.3.5.1, 302, 3001, 6, USA-11, USA-13, 401

4.3 Global Regulatory Approvals

Prucalopride was approved for use in Europe in 2009, Canada in 2011, and Israel in 2014. In total, prucalopride is currently marketed in 59 countries with over 280,000 patient years of experience supporting its efficacy and safety.

5. CLINICAL PHARMACOLOGY

Summary

- The absolute oral bioavailability of prucalopride exceeds 90%, with peak plasma concentrations attained 2-3 hours after intake, unaffected by food intake.
- The single-dose and steady-state PK of prucalopride were dose-proportional, and the plasma concentrations after repeated oral doses up to 20 mg QD were predictable from single dose data.
- Prucalopride stimulates high-amplitude colonic peristalsis and decreases colonic transit time.
- Subjects with mild renal impairment did not show clinically relevant changes in the prucalopride plasma PK profile; subjects with moderate and severe renal impairment had higher $AUC_{0-\infty}$ and $t_{1/2}$. Patients with severe renal impairment (glomerular filtration rate less than 30 mL/min/1.73 m^2) should be dosed at 1 mg.
- No clinically relevant drug interactions of prucalopride on other drugs were detected, nor were there clinically relevant effects from other drugs on the disposition of prucalopride.

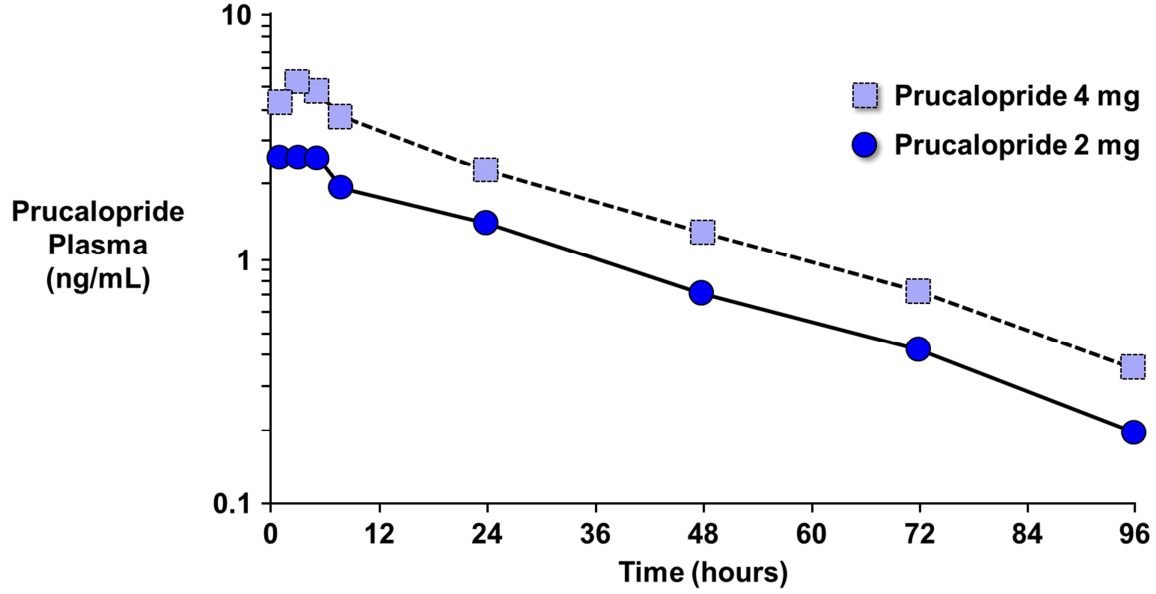
5.1 Pharmacokinetics

The PK profile of prucalopride has been extensively studied in vitro and in vivo.

The absorption, metabolism, and excretion of prucalopride were studied in an open-label study in healthy male subjects. After single-dose administration of ^{14}C-prucalopride and 10 days of complete urine and fecal collections, almost all of the dose was recovered, with 84.2% in urine and 13.3% in feces. Unchanged drug made up 92-94% of the total radioactivity in plasma.

The absolute oral bioavailability of prucalopride exceeds 90%. Peak plasma concentrations were generally attained in 2 to 3 hours after intake, and food did not affect the rate or extent of absorption. The mean $t_{1/2}$ is approximately 1 day, and steady-state was virtually attained in 3 days with repeated dosing. The accumulation ratio averaged 1.9-2.3 after QD dosing and 3.1-3.7 after twice daily (BID) dosing. At 2 mg QD, steady-state plasma concentrations fluctuated between 2.5 and 7 ng/mL. The single-dose and steady-state PK of prucalopride were dose-proportional, and the plasma concentrations after repeated oral doses up to 20 mg QD were predictable from single dose data. The time course of the mean plasma concentrations of prucalopride after the single dose is shown in Figure 16.

Figure 16: Time Course of the Mean Prucalopride Plasma Concentration After Single Oral Doses of 2 mg and 4 mg as a Tablet, Each to 15 Healthy Subjects



The results from sparse blood sampling in Phase 2 and 3 studies demonstrated that prucalopride plasma concentrations in patients with CIC were of the same order as in healthy subjects. Average plasma concentrations increased dose-proportionally, and no undue accumulation occurred during prolonged treatment.

5.1.1 Pharmacokinetics in Renal Impairment

In subjects with varying degrees of renal impairment, Cl_{renal} and apparent total clearance were dependent on the renal status of the subjects. In subjects with mild renal impairment, the reduced clearance did not translate to clinically relevant changes in the plasma PK profile. In subjects with moderate and severe renal impairment, $AUC_{0-\infty}$ was 1.5- and 2.3-fold higher, and $t_{1/2}$ was prolonged by about 40 and 50%, respectively

A population analysis of combined Phase 1, 2, and 3 data demonstrated that age does not affect the apparent plasma clearance of prucalopride, but that prucalopride clearance is correlated with Cl_{CR} as a measure of renal function. The somewhat higher plasma steady-state concentrations observed in elderly subjects can be explained by their diminished renal function.

5.1.2 Population Pharmacokinetics

An integrated population analysis of single and repeated dose data from PK studies in healthy subjects and Phase 2 and 3 studies with sparse sampling in patients with CIC was performed. The Cl_{CR} in adults had a statistically significant and clinically relevant effect on the apparent total clearance of prucalopride, but none of the other covariates tested (age, BMI, dose, body weight, sex, race, and study) had an effect when Cl_{CR} was included in the model.

5.2 Drug-Drug Interactions

In vitro studies in human liver microsomes indicated that a clinically relevant inhibition of the metabolism of co-medicated drugs is not expected at therapeutic concentrations of prucalopride. Nevertheless, several PK interaction studies in healthy subjects were conducted.

Prucalopride had no effect on the single-dose PK and PD (prothrombin times) of warfarin. Despite a minor decrease (approximately 10%) in the steady-state plasma concentrations, no clinically relevant effect was shown on the PK of digoxin. Prucalopride slightly increased the rate of absorption of alcohol but did not affect its C_{max} or overall extent of absorption, and there was no effect on the psychomotor performance under alcohol. Prucalopride did not affect the plasma concentrations of paroxetine. With co-treatment of prucalopride and erythromycin for 1 week, there was an increase in the exposure of erythromycin of about 28%, which was not considered clinically relevant.

In view of the high Cl_{renal} of prucalopride, the absence of appreciable first-pass metabolism, and the results of in vitro studies indicating that metabolism is not a major route of elimination for prucalopride, it is unlikely that inhibition of drug-metabolizing enzymes will lead to increased plasma concentrations of prucalopride. Formal PK interaction studies in healthy subjects were performed, and neither cimetidine nor probenecid had any influence on the steady-state PK parameters of prucalopride. Steady-state plasma concentrations of paroxetine, an inhibitor of CYP2D6, had no effect on the steady-state concentrations of prucalopride. With co-treatment with ketoconazole, prucalopride plasma concentrations were increased by approximately 40% (likely caused by ketoconazole's inhibition of P-glycoprotein and breast cancer resistance protein transporters), whereas erythromycin, another potent inhibitor of CYP3A4, did not affect the steady-state PK of prucalopride.

Phase 3 studies demonstrated that twice the recommended therapeutic dose (and thus an increase of 100% of the plasma concentrations) is still safe and well tolerated. *In vitro*, supra-therapeutic concentrations (10 μM) of the azole antimycotics ketoconazole, itraconazole and hydroxyitraconazole showed no inhibitory effect on the biotransformation of prucalopride. Finally, prucalopride did not have an effect on the PK of oral contraceptives (ethinylestradiol and norethisterone).

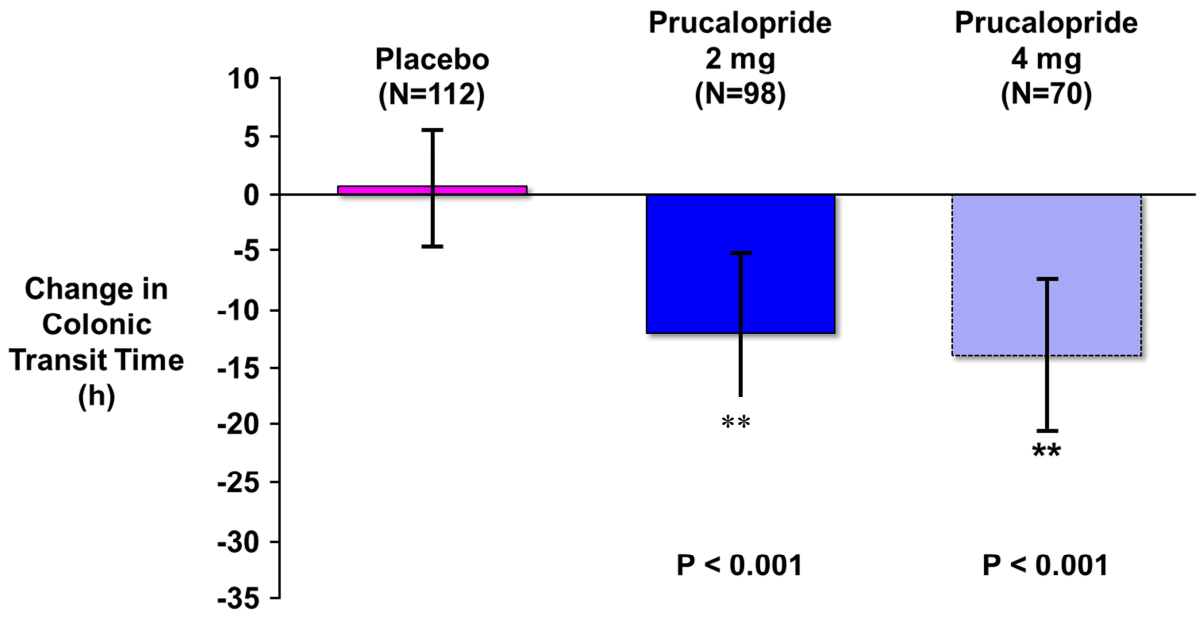
5.3 Pharmacodynamics

Five PD studies were conducted in healthy subjects, and 6 studies were conducted in patients with CIC.

Prucalopride decreased total colonic transit times in both healthy subjects and patients with CIC. Prucalopride had greater effects on the colonic transit times than on gastric emptying or transit through the small intestine (Bouras et al., 2001). Studies using a multiple sensor manometry catheter showed that prucalopride increased the number and amplitude of HAPCs, i.e., the peristaltic contractions moving the contents of the colon forward, in both healthy subjects and patients with CIC (Miner et al., 2016).

Additionally, an integrated analysis of 3 randomized, placebo-controlled, Phase 2 dose-finding studies in 280 patients with CIC (Studies PRU-INT-1, PRU-INT-2, and PRU-USA-3) showed that treatment with prucalopride 2 or 4 mg QD reduced colonic transit time by 12.0 hours and 13.9 hours, respectively (Figure 17). A clear correlation was found between constipation symptom severity and increased colonic transit time as well as between response and decreased colonic transit time (Emmanuel et al., 2014).

Figure 17: Change in Colonic Transit Time from Before Treatment to the end of Treatment with Placebo, Prucalopride 2 mg, or Prucalopride 4 mg



** p <0.001 versus baseline; 2-sample t-test
Data are shown as mean ± 95% confidence interval
Source: Emmanuel et al., (2014)

5.4 Dose Selection

The initial dose recommendation of 2 mg QD for adult subjects was based primarily on a Phase 2 dose-response study (PRU-USA-3) as well as 2 other dose-ranging studies (PRU-INT-1 and PRU-INT-2), and that dose was further supported by the overall results from the Phase 3 studies. Study PRU-USA-3 showed a clear dose-related increase in the proportion of patients achieving ≥ 3 CSBMs/week, with 2 mg and 4 mg showing statistically significant improvements. Across all 3 dose-response studies, prucalopride was well-tolerated, and therefore both doses were further evaluated in the initial Phase 3 studies (Studies 6, USA-11, and USA-13), which ultimately showed that the 4 mg QD dose provided no significant benefit over the 2 mg QD dose. Accordingly, a dose of 2 mg QD was evaluated in Studies 3001, 302, and 401 and is the recommended dose for marketing.

6. CLINICAL EFFICACY

Summary

- The evidence of efficacy of prucalopride comes from 6 randomized, double-blind, placebo-controlled studies of ≥12 weeks duration in patients with confirmed CIC: Studies 3001, 302, 6, USA-11, USA-13, and 401.
- The primary efficacy endpoint, the proportion of patients with ≥3 CSBMs/week over 12 weeks (or 24 weeks in Study 401) of treatment, was statistically significant in 5 of 6 studies: 3001, 302, 6, USA-11, and USA-13.
- Results for the analysis of Alternative Endpoint A, the proportion of patients with an average weekly frequency of ≥3 CSBMs/week and an increase of ≥1 CSBM/week for ≥9 out of the 12 weeks including 3 of the last 4 weeks, were consistent with the primary endpoint.
- Prucalopride consistently showed numerically and/or statistically significantly better results compared with placebo on the primary endpoint and a variety of secondary efficacy endpoints, including the proportion of patients with an average increase of ≥1 CSBM, the increase in average number of CSBMs, the time to first CSBM, and improvement in PAC-SYM and PAC-QOL scores.
- Patients from within and outside of the US were compared to assess the generalizability of the results, and no differences were found between the subgroups.
- Overall, prucalopride increased the frequency of bowel movements and improved symptoms and health-related quality of life in patients with CIC.

6.1 Clinical Study Design

Evidence of efficacy of prucalopride comes from 6 randomized, double-blind, placebo-controlled studies of ≥ 12 weeks in patients with confirmed CIC.

All 6 studies used a similar design to evaluate the effects of prucalopride in adults with CIC (Figure 18). Studies 6, USA-11, and USA-13 included 2 mg and 4 mg doses of prucalopride; however, the 4 mg dose did not provide significant benefit over the 2 mg QD dose and was not included in Studies 3001 and 302. Data for the 4 mg dose are found in Appendix 11.2.

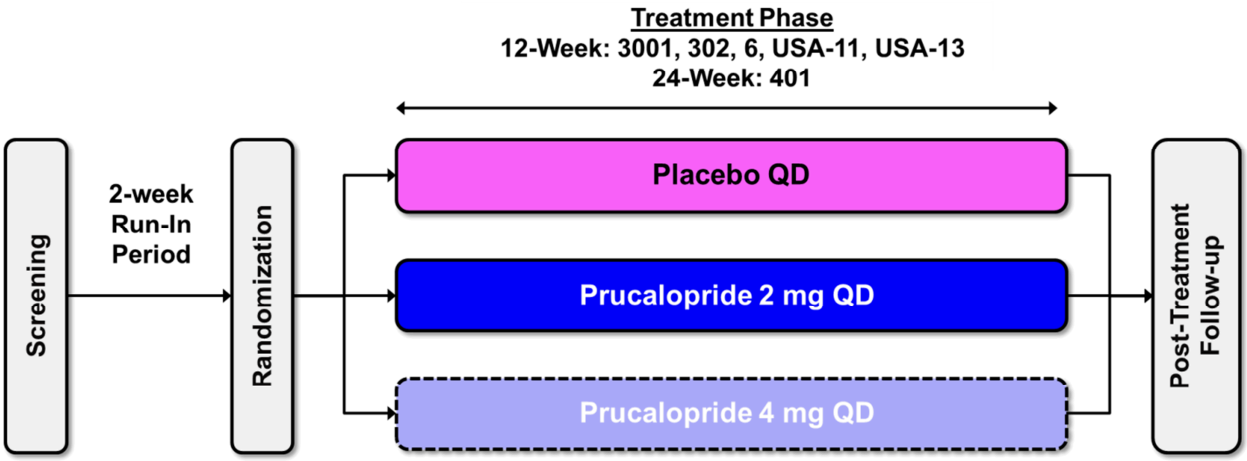
Elderly patients (i.e. ≥65 years of age) started at a dose of 1 mg prucalopride QD in Studies 302 and 401. In case of insufficient response, defined as an average of <3 CSBM/week during the preceding 2 weeks of treatment at the Week 2 or Week 4 Visit, the investigator increased the patient's daily dose to 2 mg QD. Once the dose was increased to 2 mg QD, the patient remained on this dose for the duration of the study. Since the majority of patients who initially started on prucalopride 1 mg had their dose increased to 2 mg during the study, the efficacy results for these studies were combined into a single prucalopride 2 mg* group.

Patients were randomized to prucalopride 2 mg or placebo (1:1) in Studies 3001, 302, and 401 and to prucalopride 2 mg or 4 mg or placebo (1:1:1) in Studies 6, USA-11, and USA-13.

The studies began with a 2-week run-in period (2-4 weeks in Study 401) during which patients' bowel habits were documented and the existence of constipation was confirmed. At the start of this period, all existing laxative medications were withdrawn, and patients were instructed not to change their diet or lifestyle during the study.

During the treatment period, patients were treated with prucalopride or placebo for 12 weeks (24 weeks in Study 401) and were instructed to take their study medication before breakfast. Patients recorded study drug and rescue medication dosing information and information related to BMs in a daily diary throughout the study. Patients were permitted to take a laxative (bisacodyl) as rescue medication throughout the study (including the run-in period) only if they had not had a bowel movement for 3 or more consecutive days, and an enema could only be used after unsuccessful use of bisacodyl.

Figure 18: Design of Prucalopride Randomized Double-blind Placebo-controlled Studies ≥12 Weeks



Note: Studies 6, USA-11, and USA-13 included 4 mg dose arm. Studies 302 and 401 included a 1 mg starting dose for elderly patients ≥65 years old.

6.1.1 Inclusion and Exclusion Criteria

All 6 studies included adults (≥18 years) with a history of CIC, defined as the occurrence of ≤2 SBMs and at least 2 of the following criteria for at least 25% of the time for the preceding 3 months with onset at least 6 months before the screening visit:

- Straining during defecation
- Very hard (little balls) and/or hard stools
- Sensation of incomplete evacuation
- Sensation of anorectal obstruction or blockade
- A need for digital manipulation to facilitate evacuation

The above criteria were only applicable for SBMs, i.e., not preceded within a period of 24 hours by the intake of a laxative agent or by the use of an enema.

Patients were excluded from the studies if they had constipation that was thought to be drug-induced or due to secondary causes.

A full list of inclusion and exclusion criteria is found in Appendix 11.3.

6.1.2 Endpoints

The primary endpoint for all 6 studies was the proportion of patients achieving an average of ≥3 CSBMs per week over the entire 12-week (24-week in Study 401) treatment period. In all studies, CSBMs were defined as bowel movements that were not initiated by other means, leaving patients with the feeling of complete evacuation. Any bowel movements achieved through the use of rescue medication (bisacodyl) did not count toward the ≥ 3 CSBMs for the primary endpoint.

Secondary Endpoints

Secondary efficacy endpoints included the time to first CSBM, proportion of patients achieving an average of ≥1 CSBM per week over the 12-week treatment period, increase in CSBM frequency over the 12-week treatment period, number of CSBMs over the 12-week treatment period, and PAC-SYM and PAC-QOL scales.

The PAC-SYM is a self-administered questionnaire that measures the severity of constipation-related symptoms (Frank et al., 1999). The PAC-SYM contains 12 items within the following 3 subscales: stool symptoms (5 items), abdominal symptoms (4 items), and rectal symptoms (3 items). Each item is rated on a 5-point Likert scale, with 0=absent, 1=mild, 2=moderate, 3=severe, and 4=very severe. All items are given equal weight, and the total score is calculated as the mean of answered questions. A 1-point improvement in PAC-SYM total score is considered clinically meaningful (Frank et al., 1999;Yiannakou et al., 2017). The PAC-SYM instrument is found in Appendix 11.4.

The PAC-QOL is a questionnaire for the evaluation of disease-specific quality of life in patients with constipation over the past 2 weeks (Marquis et al., 2005). The PAC-QOL contains 28 items within the following 4 subscales: physical discomfort (4 items), psychosocial discomfort (8 items), worries and concerns (11 items), and satisfaction (5 items). Each item is rated on a 5-point Likert scale, with 0=not at all/none of the time, 1=a little bit/a little bit of the time, 2=moderately/some of the time, 3=quite a bit/most of the time, and 4=extremely/all of the time. All items are given equal weight, and the total score is calculated as the mean of answered questions. If more than 50% of items are missing from a subscale, the subscale score and the PAC-QOL total score are set to missing. A 1-point improvement in the total score is considered clinically meaningful (Dubois et al., 2010). The PAC-QOL instrument is found in Appendix 11.4.

Additional Endpoints

At the request of the FDA, Shire also analyzed the proportion of patients with ≥3 CSBMs/week and an increase of ≥1 CSBM/week for ≥9 out of the 12 weeks including 3 of the last 4 weeks. This rigorous endpoint has been used as the primary endpoint for other recently completed constipation studies to show persistence of effect. This endpoint is referred to as Alternative Endpoint A.

Additional exploratory analyses examined the time to first SBM, which represents a clinically meaningful outcome for patients with CIC.

6.1.3 Statistical Analyses

The analysis of efficacy was performed on the intent-to-treat (ITT) Population unless otherwise specified.

Primary Endpoint:

The primary endpoint, the proportion of patients with an average weekly frequency of ≥3 CSBMs/week (i.e. a responder) over the 12-week (24-week in Study 401) treatment period in the prucalopride group compared to placebo, was analyzed using a Cochran-Mantel-Haenszel (CMH) test for general association, controlling for the randomization stratification factors.

In all 6 studies except Study 401, imputation of missing diary days after the last day of treatment was only performed for patients who had at least 7 diary days after week 1. The data (i.e., times of BMs, times of laxative intakes, consistency, straining and incomplete evacuation information per BM) from the last 7 diary days were carried forward (i.e., copied as 7-day blocks) up to day 84 (12 weeks) (i.e., LOCF methodology). Week 1 data were to be excluded for this imputation, as preceding studies showed a relatively higher number of bowel movements in the first week of treatment, which could result in an unrealistically high response rate over 12 weeks when used for this imputation. The patients who dropped-out before day 14 were considered non-responders.

For study 401, a similar approach was used (14-day data were copied forward) for patients with at least 28 diary days and carried forward up to 168 days (24 weeks). Patients who dropped-out before day 28 were considered non-responders.

To assess the robustness of the primary analysis results, the following sensitivity analyses were performed to evaluate the impact of the imputation method for missing data:

- No imputation
- Multiple Imputation – on-treatment imputed data: To impute the weekly number of SBMs per week, if a patient had fewer than 4 evaluable days in a week, the number of SBMs for that week was set to missing and imputed using multiple imputation (on-treatment) methodology. The estimate for missing number of SBMs was based on the treatment group of the patient.
- Multiple Imputation – placebo imputed data: To impute the weekly number of SBMs per week, if a patient had fewer than 4 evaluable days in a week, the number of SBMs for that week was set to missing and imputed using placebo multiple imputation. The estimate for the missing weekly frequencies was based on data of the placebo group. In other words, for a patient on prucalopride, data from the placebo group were used to impute the weekly number of SBMs.
- Complete Case Analysis: An analysis on a subset of the (modified) intent-to-treat (mITT) population that excluded patients whose status at study termination was early withdrawal or whose duration of treatment in the study was less than 81 days.

6.2 Demographic and Baseline Characteristics

Overall, demographics varied across the 6 studies but were well balanced within each study (Table 20). The mean age of patients in the 6 studies ranged from 41-59 years old, with 4 studies

including patients ≥65 years old. The 2 studies conducted in the US, Studies USA-11 and USA-13, enrolled patients with a mean age of 46-49 years old and included patients ≥65 years old. Aside from Study 3001, which primarily enrolled Asian patients, and Study 302, which enrolled only males, the majority of patients were female and White, consistent with the US patient population with CIC.

The baseline disease characteristics were comparable between placebo and prucalopride arms in each study and were generally comparable between studies (Table 21). The mean duration of constipation ranged from 9-23 years, with patients in Study 302 having the shortest duration and patients in Studies USA-11 and USA-13 having the longest.

Overall, the use of previous constipation treatment was comparable between studies. None of the observed differences in baseline disease characteristics or prior medication use were judged to be of any clinical significance.

Table 20: Patient Demographics* in Randomized Double-blind Placebo-controlled Studies ≥12 weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=238	PLA N=209	PRU 2 mg N=207	PLA N=212	PRU 2 mg N=214	PLA N=180	PRU 2 mg* N=181
Age, years												
Mean (SE)	41.8 (12.9[a])	41.4 (12.9[a])	58.6 (16.5)	58.8 (17.4)	43.7 (1.0)	42.7 (1.0)	48.9 (0.9)	48.2 (1.0)	46.2 (0.9)	48.6 (1.0)	48.3 (16.3)	49.4 (15.8)
Median (min, max)	43 (18; 65)	43 (18; 65)	62 (20; 89)	62 (18; 91)	43 (18, 80)	40 (17, 83)	48 (18, 81)	48 (20, 83)	45 (18, 82)	46.5 (20, 95)	49.0 (18, 91)	50 (18, 80)
Age category, n (%)												
< 18	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0	1 (0.4)	0	0	0	0	0 (0.00)	0 (0.00)
[18,40]	107 (42.5)	115 (46.2)	34 (18.3)	33 (17.9)	107 (44.6)	122 (51.3)	60 (28.7)	62 (30.0)	70 (33.0)	56 (26.2)	61 (33.9)	52 (28.7)
[41,64]	144 (57.1)	133 (53.4)	81 (43.6)	71 (38.6)	109 (45.4)	88 (37.0)	118 (56.5)	118 (57.0)	119 (56.1)	124 (57.9)	88 (48.9)	94 (51.9)
≥ 65	1 (0.4)	1 (0.4)	71 (38.2)	80 (43.5)	24 (10.0)	27 (11.3)	31 (14.8)	27 (13.0)	23 (10.8)	34 (15.9)	31 (17.22)	35 (19.3)
Sex, n (%)												
Female	223 (88.5)	227 (91.2)	0	0	222 (92.5)	213 (89.5)	183 (87.6)	188 (90.8)	189 (89.2)	181 (84.6)	153 (85.0)	155 (85.6)
Male	29 (11.5)	22 (8.8)	181 (100.0)	177 (100.0)	18 (7.5)	25 (10.5)	26 (12.4)	19 (9.2)	23 (10.8)	33 (15.4)	27 (15.0)	26 (14.4)
Weight, kg												
Mean (SE)	59.1 (10.3[a])	59.2 (10.0[a])	83.4 (1.0)	82.7 (1.0)	66.7 (0.8)	68.8 (0.9)	68.4 (1.0)	69.3 (1.0)	70.7 (1.0)	71.1 (1.0)	68.64 (1.0)	70.7 (1.1)
Height, cm												
Mean (SE)	162.7 (7.3[a])	161.7 (6.4[a])	175.6 (0.5)	175.0 (0.5)	165.1 (0.5)	165.8 (0.5)	164.7 (0.6)	164.7 (0.6)	165.3 (0.6)	165.2 (0.6)	166.6 (0.6)	166.2 (0.6)
Race, n (%)												
White	19 (7.5)	12 (4.8)	174 (96.1)	172 (97.2)	226 (94.2)	223 (93.7)	182 (87.1)	188 (90.8)	197 (92.9)	183 (85.5)	169 (93.9)	168 (92.8)
Black	0	0	3 (1.7)	5 (2.8)	2 (0.8)	3 (1.3)	18 (8.6)	13 (6.3)	9 (4.2)	24 (11.2)	0	1 (0.6)
Hispanic					2 (0.8)	0	4 (1.9)	5 (2.4)	5 (2.4)	3 (1.4)		
Asian	231 (91.7)	232 (93.2)	1 (0.6)	0	2 (0.8)	5 (2.1)	2 (1.0)	1 (0.5)	0	3 (1.4)	1 (0.6)	0
Other	2 (0.8)	5 (2.0)	3 (1.7)	0	8 (3.3)	7 (2.9)	3 (1.4)	0	1 (0.5)	1 (0.5)	1 (0.6)	3 (1.7)
Region												
US	0	0	0	0	0	0	100	100	100	100	0	0
Outside of US	100	100	100	100	100	100	0	0	0	0	100	100

* ITT population for Studies 3001, 302, 6, USA-11 and 13, and Safety Population for Study 401

[a] Standard deviation (SD) is shown for Study 3001

BMI=body mass index; max=maximum; min=minimum; N=number of patients in treatment group; n=number of patients with characteristic; PLA=placebo; PRU=prucalopride; SE=standard error

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Source: Module 5.3.5.1, PRU-INT-6, Section 14, Display SUB.7; PRU-USA-11, Section 14, Display SUB.7; PRU-USA-13, Section 14, Display SUB.7

Table 21: Baseline Disease Characteristics in Randomized Double-blind Placebo-controlled Studies ≥12 weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=238	PLA N=209	PRU 2 mg N=207	PLA N=212	PRU 2 mg N=214	PLA N=180	PRU 2 mg* N=181
History of constipation, years												
Mean (SD)	12.8 (10.0)	12.9 (9.7)	9.4 (11.5)	9.3 (12.1)	18.5 (0.9)	15.9 (1.0)	21.6 (1.2)	21.1 (1.10)	21.4 (1.1)	22.7 (1.1)	13.7 (13.3)	15.7 (15.8)
Median (Min; Max)	10.0 (0.5; 45.5)	10.0 (0.7; 60.0)	5.0 (0.5; 57.0)	5.0 (0.5; 65.0)	18 (1; 68)	10 (1; 70)	20 (1; 77)	20 (1; 78)	20 (1; 71)	20 (1; 63)	10 (0.5; 60.0)	10 (0.6; 66.0)
< 1	7 (2.8)	1 (0.4)	14 (7.6)	11 (6.0)	8 (3.3)	9 (3.8)	5 (2.4)	4 (1.9)	3 (1.4)	2 (0.9)	5 (3.5)	6 (4.1)
1-< 10	96 (38.1)	88 (35.3)	106 (57.6)	110 (59.8)	66 (27.5)	83 (34.9)	59 (28.2)	51 (24.6)	54 (25.5)	52 (24.3)	66 (45.8)	63 (43.5)
10-< 20	73 (29.0)	90 (36.1)	38 (20.5)	39 (21.2)	51 (21.3)	69 (29.0)	37 (17.7)	47 (22.7)	42 (19.8)	41 (19.2)	31 (21.5)	27 (18.6)
20-< 30	50 (19.8)	46 (18.5)	14 (7.6)	13 (7.1)	63 (26.3)	36 (15.1)	40 (19.1)	40 (19.3)	46 (21.7)	40 (18.7)	16 (11.1)	17 (11.7)
30-< 40	18 (7.1)	17 (6.8)	5 (2.7)	2 (1.1)	25 (10.4)	18 (7.6)	30 (14.4)	32 (15.5)	33 (15.6)	38 (17.8)	16 (11.1)	14 (9.7)
40-< 50	8 (3.2)	6 (2.4)	1 (0.5)	4 (2.2)	17 (7.1)	12 (5.0)	21 (10.0)	18 (8.7)	22 (10.4)	24 (11.2)	6 (4.2)	10 (6.9)
≥ 50	0 (0.0)	1 (0.4)	6 (3.3)	5 (2.7)	10 (4.2)	11 (4.6)	17 (8.1)	15 (7.2)	12 (5.7)	17 (7.9)	4 (2.8)	8 (5.5)
Main complaint, n (%)												
Infrequent defecation	45 (17.9)	55 (22.1)	42 (23.2)	29 (16.5)	59 (24.6)	57 (23.9)	71 (34.0)	86 (41.5)	61 (28.8)	66 (30.8)	43 (23.9)	45 (24.9)
Abdominal bloating	53 (21.0)	50 (20.1)	22 (12.2)	14 (8.0)	64 (26.7)	73 (30.7)	45 (21.5)	30 (14.5)	58 (27.4)	53 (24.8)	25 (13.9)	25 (13.8)
Abdominal pain	12 (4.8)	15 (6.0)	19 (10.5)	18 (10.2)	61 (25.4)	58 (24.4)	19 (9.1)	18 (8.7)	19 (9.0)	27 (12.6)	35 (19.4)	28 (15.5)
Feeling not completely empty	35 (13.9)	33 (13.3)	33 (18.2)	54 (30.7)	29 (12.1)	26 (10.9)	38 (18.2)	30 (14.5)	30 (14.2)	29 (13.6)	46 (25.6)	43 (23.8)
Straining	58 (23.0)	47 (18.9)	44 (24.3)	38 (21.6)	17 (7.1)	18 (7.6)	24 (11.5)	28 (13.5)	30 (14.2)	22 (10.3)	16 (8.9)	26 (14.4)
Hard stools	49 (19.4)	49 (19.7)	21 (11.6)	23 (13.1)	10 (4.2)	6 (2.5)	12 (5.7)	15 (7.2)	14 (6.6)	17 (7.9)	15 (8.3)	14 (7.7)
Previous use of diet adjustments as constipation treatment, n (%)												
Yes	147 (58.3)	126 (50.6)	108 (59.7)	120 (67.8)	140 (58.3)	154 (64.7)	137 (65.6)	150 (72.5)	144 (67.9)	139 (65.0)	NA[a]	NA
No	105 (41.7)	123 (49.4)	73 (40.3)	57 (32.2)	100 (41.7)	84 (35.3)	72 (34.4)	57 (27.5)	68 (32.1)	75 (35.0)	NA	NA
Previous use of laxatives, n (%)												
Yes	177 (70.2)	183 (73.5)	110 (60.8)	113 (63.8)	198 (82.5)	191 (80.3)	183 (87.6)	185 (89.4)	189 (89.2)	189 (88.3)	NA	NA
No	75 (29.8)	66 (26.5)	71 (39.2)	64 (36.2)	42 (17.5)	47 (19.7)	26 (12.4)	22 (10.6)	23 (10.8)	25 (11.7)	NA	NA
Previous use of bulk-forming laxatives, n (%)												
Yes	177 (70.2)	183 (73.5)	110 (60.8)	113 (63.8)	141 (58.8)	143 (60.1)	138 (66.0)	136 (65.7)	122 (57.5)	123 (57.5)	NA	NA
No	75 (29.8)	66 (26.5)	71 (39.2)	64 (36.2)	99 (41.3)	95 (39.9)	71 (34.0)	71 (34.3)	90 (42.5)	91 (42.5)	NA	NA
Number of SBMs/Week during the last 6 months n (%)												
0	57 (22.6)	57 (22.9)	14 (7.7)	22 (12.4)	99 (41.3)	86 (36.1)	79 (37.8)	77 (37.2)	85 (40.1)	96 (44.9)	97 (57.4)	107 (62.6)
> 0 - ≤ 1	63 (25.0)	73 (29.3)	48 (26.5)	54 (30.5)	84 (35.0)	78 (32.8)	78 (37.3)	79 (38.2)	65 (30.7)	73 (34.1)	41 (24.3)	34 (19.9)

Table 21: Baseline Disease Characteristics in Randomized Double-blind Placebo-controlled Studies ≥12 weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=238	PLA N=209	PRU 2 mg N=207	PLA N=212	PRU 2 mg N=214	PLA N=180	PRU 2 mg* N=181
> 1 - ≤ 3	132 (52.4)	119 (47.8)	107 (59.1)	93 (52.5)	51 (21.3)	65 (27.3)	49 (23.4)	50 (24.2)	60 (28.3)	43 (20.1)	29 (16.1)	28 (15.5)
> 3	0	0	12 (6.6)	8 (4.5)	6 (2.5)	9 (3.8)	3 (1.4)	1 (0.5)	2 (0.9)	2 (0.9)	2 (1.2)	2 (1.2)

Note: ITT population for Studies 3001, 302, 6, USA-11 and 13, and Safety Population for Study 401

[a.] Data not collected in Study 401

BM=bowel movement; max=maximum; min=minimum; N= number of patients in treatment group; n=number of patients with characteristic; PLA=placebo; PRU=prucalopride; SBM=spontaneous bowel movement SD=standard deviation

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Source: Module 5.3.5.1, PRU-INT-6, Section 14, Display SUB.9; PRU-USA-11, Section 14, Display SUB.9; PRU-USA-13, Section 14, Display SUB.9

6.3 Patient Disposition

As shown in Table 22, most of the studies had a similar disposition over the first 12 weeks, with a similar percentage of patients withdrawing in each arm from each study. The higher discontinuation rate in Study 401 is likely due to the longer duration of the study (24 weeks) in comparison with the other studies (12 weeks). The main reasons for withdrawal in most studies were withdrawal of consent and the occurrence of AEs. The proportion of patients withdrawing was similar in the prucalopride and placebo groups.

Table 22: Patient Disposition in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=252	PRU 2 mg* N=249	PLA N=240	PRU 2 mg N=238	PLA N=209	PRU 2 mg N=207	PLA N=212	PRU 2 mg N=214	PLA N=182	PRU 2 mg* N=182
Completed (Week 12)	231 (91.7)	231 (92.8)	160 (85.6)	158 (84.5)	207 (86.3)	207 (87.0)	182 (87.1)	172 (83.1)	188 (88.7)	194 (90.7)	137 (75.3)	149 (81.9)
Completed (Week 24)	-	-	-	-	-	-	-	-	-	-	126 (69.2)	135 (74.2)
Withdrawn	21 (8.3)	18 (7.2)	27 (14.4)	29 (15.5)	33 (13.8)	31 (13.0)	27 (12.9)	35 (16.9)	24 (11.3)	20 (9.3)	56 (30.8)	47 (25.8)
Withdrawal of consent	8 (3.2)	3 (1.2)	9 (4.8)	10 (5.3)	5 (2.1)	5 (2.1)	7 (3.3)	3 (1.4)	5 (2.4)	4 (1.9)	27 (14.8)	11 (6.0)
AE	3 (1.2)	8 (3.2)	7 (3.7)	6 (3.2)	16 (6.7)	15 (6.3)	4 (1.9)	18 (8.7)	5 (2.4)	8 (3.7)	10 (5.5)	14 (7.7)
Noncompliance	0	1 (0.4)	5 (2.7)	4 (2.1)	1 (0.4)	0	4 (1.9)	4 (1.9)	1 (0.5)	4 (1.9)	2 (1.1)	0
Lost to follow-up	2 (0.8)	3 (1.2)	0	2 (1.1)	1 (0.4)	3 (1.3)	3 (1.4)	3 (1.4)	2 (0.9)	3 (1.4)	0	0
Lack of efficacy [a]	6 (2.4)	0	0	0	7 (2.9)	3 (1.3)	5 (2.4)	2 (1.0)	3 (1.4)	1 (0.5)	0	0
Other	0	1 (0.4)	3 (1.6)	5 (2.7)	2 (0.8)	4 (1.7)	4 (1.9)	2 (1.0)	5 (2.4)	0	6 (3.3)	8 (4.4)
Ineligible to continue	0	0	0	0	1 (0.4)	1 (0.4)	0	3 (1.4)	3 (1.4)	0	0	0
Sponsor's decision	0	0	0	1 (0.5)	0	0	0	0	0	0	9 (4.9)	12 (6.6)
Did not fulfill inclusion/exclusion criteria	0	0	3 (1.6)	1 (0.5)	0	0	0	0	0	0	2 (1.1)	2 (1.1)
Protocol violation	2 (0.8)	2 (0.8)	0	0	0	0	0	0	0	0	0	0

AE=adverse event; ITT=intent-to-treat; N=number of patients in treatment group; n=number of patients who completed/withdrew; PLA=placebo; PRU=prucalopride

[a] Labeled insufficient response in these studies.

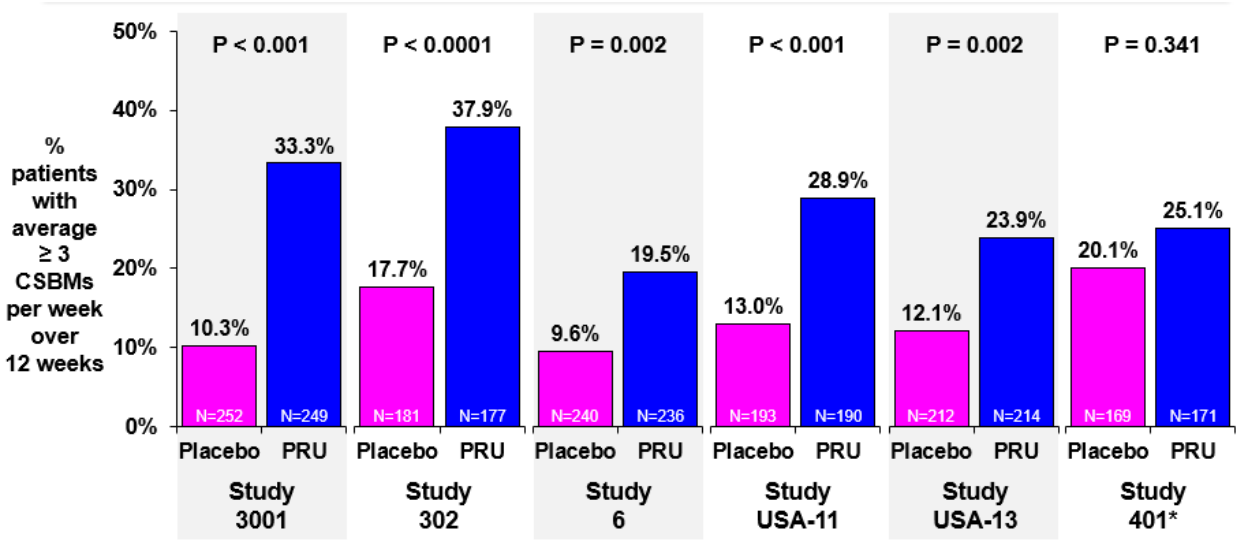
*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Source: Module 5.3.5.1, PRU-INT-6, Section 14, Display SUB.4; PRU-USA-11, Section 14, Display SUB.4; PRU-USA-13, Section 14, Display SUB.4

6.4 Primary Endpoint Results: Proportion of Patients with an Average of ≥3 CSBMs/week Over 12 Weeks of Treatment

Five of the 6 studies met the primary endpoint, showing that the proportion of patients with an average of ≥3 CSBMs/week over Weeks 1-12 was statistically significantly higher in the prucalopride group compared with the placebo group ($p < 0.01$ Figure 19 and Table 23). As discussed in Section 1.2, the primary endpoint did not reach statistical significance in Study 401, and an extensive investigation (see Section 6.4.2 for more details) failed to determine a clear rationale for these results.

Figure 19: Primary Endpoint – Proportion of Patients with an Average of ≥3 CSBMs/week over Weeks 1-12 in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks



*Week 12 data presented

PRU=prucalopride; CSBM=complete spontaneous bowel movement

Source: Module 5.3.5.1, PRU-CRC-3001, Section 5.2, Table 14, SPD555-302, Section 14, Table EFF.1, PRU-INT-6, Section 11.3.1.1, Table 11.3-1, PRU-USA-11, Section 11.3.1.1, Table 11.3-1, Study PRU-USA-13, Section 11.3.1.1, Table 11.3-1, and Study SPD555-401, Section 9.2.1, Table 8

Table 23: Proportion of Patients with an Average of ≥3 CSBMs/week in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=236	PLA N=193	PRU 2 mg N=190	PLA N=212	PRU 2 mg N=214	PLA N=169	PRU 2 mg* N=171
Week 1-12, n (%)	26 (10.3)	83 (33.3)	32 (17.7)	67 (37.9)	23 (9.6)	46 (19.5)	25 (13.0)	55 (28.9)	25 (12.1)	50 (23.9)	34 (20.1)	43 (25.1)
p-value		< 0.001 [a]		< 0.0001 [b]		0.002 [a]		< 0.001 [a]		0.002 [a]		0.341 [b]
Week 1-24, n (%)											35 (20.7)	43 (25.1)
p-value												0.367 [b]

PLA=placebo; PRU=prucalopride; CSBM=complete spontaneous bowel movement

[a] p-value based on a CMH test controlling for country/investigator

[b] p-value based on a CMH test controlling for country, sex, and the average number of CBMs during the run-in period

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Source: Module 5.3.5.1, PRU-INT-6, Section 14, Display EFF.1; PRU-USA-11, Section 14, Display EFF.1; PRU-USA-13, Section 14, Display EFF.1; SPD555-401, Section 14,Table EFF.1

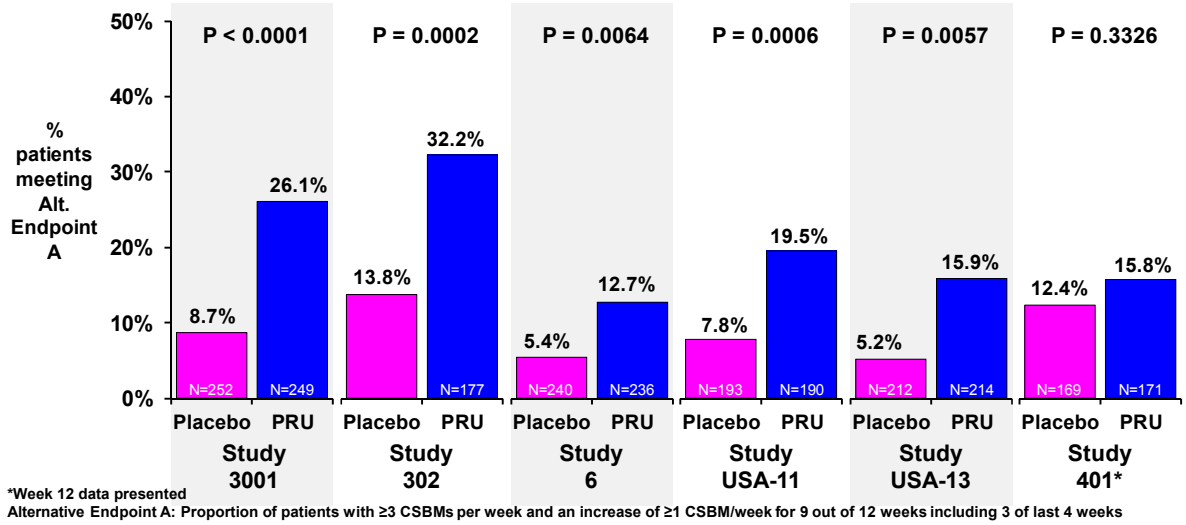
6.4.1 Alternative Endpoint A: Proportion of Patients with an Average of ≥3 CSBMs/week and ≥1 CSBM/week for ≥9/12 Weeks including 3/4 of the Last Weeks of Treatment

Alternative Endpoint A, i.e., the proportion of patients with an average weekly frequency of ≥3 CSBMs/week and an increase of ≥1 CSBM/week for ≥9 out of the 12 weeks including 3 of the last 4 weeks, was analyzed post hoc using several different statistical (CMH and logistic regression) and imputation methods. All of these analyses yielded very similar results.

The results for Alternative Endpoint A were similar to the primary endpoint results, with a statistically significant treatment effect between arms in all studies except for Study 401 (Figure 20 and Table 24).

In Study 401, the response in the prucalopride group was numerically but not statistically significantly higher compared with the placebo group at Week 12 and Week 24 (p=0.5528 and p=0.3735, respectively).

Figure 20: Alternative Endpoint A – Proportion of Patients with ≥3 CSBMs/week and an Increase of ≥1 CSBM/week for ≥9 out of the 12 Weeks Including 3 of the Last 4 Weeks in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks



*Week 12 data presented
PRU=prucalopride; CSBM=complete spontaneous bowel movement
Source: Module 5.3.5.1, Display EFF x2.12 (SPD555-302) and Display EFF x2.12 (PRU-CRC-3001)

Table 24: Proportion of Patients with an Average of ≥3 CSBMs/week and an Increase of ≥1 CSBM/week for ≥9 out of the 12 Weeks (18 out of 24 weeks for Study 401) Including 3 of the Last 4 Weeks in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks (Alternative Endpoint A)

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=236	PLA N=193	PRU 2 mg N=190	PLA N=212	PRU 2 mg N=214	PLA N=169	PRU 2 mg* N=171
n (%)	22 (8.7)	65 (26.1)	25 (13.8)	57 (32.2)	13 (5.4)	30 (12.7)	15 (7.8)	37 (19.5)	11 (5.2)	34 (15.9)	22 (13.0)	29 (17.0)
Weeks 1-12												
Diff. in proportion		0.174		0.184		0.073		0.117		0.107		0.022
95% CI		0.109, 0.238		0.099, 0.269		0.022, 0.124		0.049, 0.185		0.050, 0.164		-0.055, 0.098
p-value [a]		< 0.0001		< 0.0001		0.0050		0.0005		0.0002		0.6295
Weeks 1-24												
Diff. in proportion												0.039
95% CI												-0.036, 0.115
p-value [a]												0.3735

CI=confidence interval; CMH=Cochrane Mantel Haenszel; Diff.=difference; PLA=placebo; PRU=prucalopride; CSBM=complete spontaneous bowel movement

[a] p-value based on a CMH test for general association controlling for (pooled) country (Study 6, Study 401)/center (Study USA-11, Study USA-13), sex (Study 401), and number of CBMs/week at baseline (Study 401)

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Source: Module 5.3.5.3, Display EFF x2.13 (PRU-INT-6), Display EFF x2.13 (PRU-USA-11), Display EFF x2.13 (PRU-USA-13), and Display EFF x2.13 (SPD555-401)

6.4.2 Study 401 Investigation

Shire conducted an extensive investigation into the results of Study 401 in an attempt to understand the inconsistent finding with the results from the other DBPC studies lasting 12 weeks in CIC. The design of Study 401 was comparable to that of the other studies. No noteworthy differences in demographic data, baseline disease characteristics, and use of rescue medications were observed between Study 401 and the other studies.

In the prucalopride 2 mg* treatment group of Study 401, 18% of patients prematurely discontinued by Week 12, and 26% prematurely discontinued by Week 24. This is consistent with the other DBPC studies, in which the proportion ranged from 7.2-16.8% over 12-weeks. In the placebo group, 25% of patients prematurely discontinued by Week 12, and 31% prematurely discontinued by Week 24. This is a higher proportion compared with the other DBPC studies, in which the proportion ranged from 8.3-13.8% over 12 weeks. Specifically, the proportion of patients who withdrew consent was 3-5 times higher in Study 401 (10.1%) compared to the other DBPC studies (range: 2.1-3.6%).

The impact of discontinuations on the study results was explored in sensitivity analyses. A complete case analysis, per-protocol analysis, and multiple imputation and logistic regression showed results that were consistent with the primary efficacy analysis, i.e. there was no statistically significant effect of prucalopride.

6.5 Secondary Endpoint Results

6.5.1 Proportion of Patients with an Average Increase of ≥1 CSBM/Week

In 4 of the 6 studies (Studies 3001, 6, USA-11, and USA-13), the proportion of patients with an average increase of ≥1 CSBM/week over the 12-week treatment period was statistically significantly higher in the prucalopride 2 mg group compared with the placebo group ($p < 0.001$; Table 25). Study 302 showed a numerical improvement in the prucalopride 2 mg* group compared with placebo, but this difference did not reach statistical significance ($p=0.07$). In Study 401, the proportion of patients with an average increase of ≥1 CSBM/week over 12 weeks was higher in the prucalopride 2 mg* group (49.1%) compared with the placebo group (40.2%) and nearly statistically significant ($p=0.051$). Over the entire 24-week treatment period, the proportion of patients with an average increase of ≥1 CSBM/week was not statistically significantly different between the treatment groups. The number of CSBMs/week returned to baseline following discontinuation of prucalopride.

Table 25: Proportion of Patients with an Average Increase of ≥1 CSBMs/week in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=236	PLA N=193	PRU 2 mg N=190	PLA N=212	PRU 2 mg N=214	PLA N=169	PRU 2 mg* N=171
Week 1-12, n (%)	68 (27.4)	139 (57.2)	82 (45.3)	95 (53.7)	49 (20.9)	86 (38.1)	49 (25.9)	89 (50.3)	57 (27.5)	89 (42.6)	68 (40.2)	84 (49.1)
p-value		< 0.001[a]		0.0743[b]		< 0.001[a]		< 0.001[a]		0.001[a]		0.051[b]
Week 1-24, n (%)											71 (42.0)	82 (48.0)
p-value												0.179[b]

CBM=complete bowel movement; CMH=Cochrane-Mantel-Haenszel; PLA=placebo; PRU=prucalopride; CSBM=complete spontaneous bowel movement

[a] p-value based on a CMH test controlling for country/investigator

[b] p-value based on a CMH test controlling for country, sex, and the average number of CBMs during the run-in period

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Source: Module 5.3.5.1, PRU-INT-6, Section 14, Display EFF.4; PRU-USA-11, Section 14, Display EFF.4; PRU-USA-13, Section 14, Display EFF.4; SPD555-401, Table EFF.13

Source: Module 5.3.5.1, PRU-CRC-3001, Section 5.2, Table 19 and SPD555-302, Section 14, Table EFF.14

6.5.2 Time to First CSBM and SBM

Across all 6 studies, the time to first CSBM was statistically significantly shorter in the prucalopride 2 mg* group compared with the placebo group ($p < 0.01$; Table 26). The time to first SBM was also statistically significantly shorter in the prucalopride 2 mg* group compared with the placebo group in all 6 studies ($p < 0.001$). The typical patient on prucalopride experienced his/her first SBM within 2-3 hours following initiation of treatment.

Table 26: Time to First Bowel Movement in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=169	PLA N=171	PRU 2 mg N=190	PLA N=212	PRU 2 mg N=214	PLA N=169	PRU 2 mg* N=171
	Median (95% CI)											
Time to first CSBM (hours)												
Since Day 1	301.92 (216.48; 482.16)	37.44 (24.24; 73.44)	218.92 (143.93; 291.43)	110.27 (70.8; 172.77)	493 (362, 646)	113 (57.75, 174)	297 (220, 484)	32.50 (13.83; 53)	311 (214; 425)	54.83 (29.35; 97.08)	359.67 (179.6, 461.42)	100.83 (74, 170.75)
p-value [a]		< 0.001[a]		0.0090[b]		< 0.001		< 0.001		< 0.001		0.007
Time to first SBM (hours)												
Since Day 1	38.4 (32.16; 48.72)	2.4 (1.92; 3.12)	28.07 (25.83; 33)	9.58 (8.08; 20.9)	26.53 (24.25, 32.25)	2.25 (1.92, 3.08)	27.50 (25.25, 36)	2.00 (1.50, 2.50)	24.92 (14.83; 28.50)	3.00 (2.33; 4.25)	29.82 (25.95, 38.5)	7.75 (3.87, 15.33)
p-value [a]		< 0.001[a]		< 0.0001[b]		< 0.001		< 0.001		< 0.001		< 0.001

CI=confidence interval; PLA=placebo; PRU=prucalopride; CSBM=complete spontaneous bowel movement; SBM=spontaneous bowel movement

[a] p-value based on a log-rank test

[b] p-value based on a stratified log-rank test containing country and the average number of CBMs/week during the run-in period as stratification factors

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Source: Module 5.3.5.1, PRU-INT-6 CSR, Section 14, Table EFF.10; PRU-USA-11 CSR, Section 14, Table EFF.10; PRU-USA-13 CSR, Section 14, Table EFF.10; SPD555-401, Section 14, Table EFF.47

Source: Module 5.3.5.1, PRU-CRC-3001, Section 5.4.4, Table 21 and SPD555-302, Section 14, Table EFF.38, Table EFF.39

6.5.3 Average Number of CSBMs

In all 6 studies, the average number of CSBMs per week over the 12-week treatment period was statistically significantly higher in the prucalopride treatment groups compared with placebo ($p < 0.05$; Table 27). The number of SBMs and all bowel movements per week was also higher in the prucalopride treatment groups compared with placebo in all 6 studies.

Table 27: Average Number of Bowel Movements in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=236	PLA N=193	PRU 2 mg N=190	PLA N=212	PRU 2 mg N=214	PLA N=169	PRU 2 mg* N=171
	Mean Actual Value (Mean Change)											
Average number of CSBMs per week												
BL/RI[b]	0.3 (NA)	0.3 (NA)	0.5 (NA)	0.4 (NA)	0.4 (NA)	0.4 (NA)	0.4 (NA)	0.5 (NA)	0.4 (NA)	0.4 (NA)	0.4 (NA)	0.4 (NA)
Week 1-12	1.1 (0.8)	2.4 (2.1)	1.8 (1.3)	2.6 (2.2)	1.0 (0.5)	1.6 (1.2)	1.3 (0.8)	2.3 (1.9)	1.2 (0.8)	1.9 (1.5)	1.6 (1.2)	2.0 (1.6)
p-value[a]		< 0.001[a]		0.0001[b]		< 0.001		< 0.001		< 0.001		0.024
Week 1-24											1.7 (1.3)	2.1 (1.7)
p-value [a]												0.029
Average number of SBMs per week												
BL/RI[b]	1.0 (NA)	1.1 (NA)	3.4 (NA)	3.3 (NA)	3.6 (NA)	4.0 (NA)	3.0 (NA)	3.5 (NA)	3.3 (NA)	3.7 (NA)	2.6 (NA)	2.6 (NA)
Week 1-12	2.5 (1.4)	4.7 (3.7)	4.6 (1.2)	6.1 (2.8)	4.4 (0.7)	6.2 (2.4)	4.0 (1.0)	6.6 (3.2)	4.2 (0.9)	6.0 (2.3)	3.8 (1.2)	4.6 (2.1)
p-value[a]		< 0.001[a]		NA		< 0.001		< 0.001		< 0.001		0.013
Week 1-24											3.8 (1.2)	4.5 (2.0)
p-value [a]												0.001
Average number of BMs per week												
BL/RI[b]	2.2 (NA)	2.2 (NA)	4.4 (NA)	4.1 (NA)	5.6 (NA)	5.4 (NA)	5.2 (NA)	5.7 (NA)	5.1 (NA)	5.6 (NA)	3.7 (NA)	3.8 (NA)
Week 1-12	3.3 (1.1)	5.2 (2.9)	5.2 (0.8)	6.4 (2.3)	6.1 (0.4)	7.1 (1.8)	6.0 (0.8)	7.7 (2.0)	5.8 (0.7)	7.4 (1.8)	4.5 (0.9)	5.2 (1.5)
p-value[a]		< 0.001[a]		NA		< 0.001		< 0.001		< 0.001		< 0.001
Week 1-24											4.5 (0.8)	5.1 (1.4)
p-value [a]												0.002

Table 27: Average Number of Bowel Movements in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=236	PLA N=193	PRU 2 mg N=190	PLA N=212	PRU 2 mg N=214	PLA N=169	PRU 2 mg* N=171
	Mean Actual Value (Mean Change)											

ANCOVA=analysis of covariance; BL=baseline; BM=bowel movement; CBM=complete bowel movement; NA=not applicable; PLA=placebo; PRU=prucalopride; RI=run-in; SBM=spontaneous bowel movement; CSBM=complete spontaneous bowel movement

[a] p-value based on an ANCOVA model with factors treatment, baseline value, and country/region for PRU-INT-6, PRU-USA-11, and PRU-USA-13 and average number of CBMs during the run-in period, country, and sex for Study 401

[b] BL/RI was calculated to assess the number of CSBMs during the run-in period to evaluate if patients could be randomized (≤ 2 CSBMs during run in=yes)

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Source: Module 5.3.5.1, PRU-INT-6, Section 14, Display EFF.7; PRU-USA-11, Section 14, Display EFF.7; PRU-USA-13, Section 14, Display EFF.7, SPD555-401, Section 14, Table EFF.19, Table EFF.18, Table EFF.21

Source: Source: Module 5.3.5.1, PRU-CRC-3001, Attachment 3.5.1 and SPD555-302, Section 14, Table EFF.18, Table EFF.19, Table EFF.21

6.5.4 Use of Rescue Medication (Bisacodyl)

Pooling the results across studies, patients receiving prucalopride required less rescue medication (bisacodyl) use per week (Figure 21). Use of bisacodyl dropped to approximately half of what it was during the run-in phase. Importantly, the efficacy findings with prucalopride do not appear to be influenced by the use of bisacodyl as rescue medication. Changes in bisacodyl and laxative rescue medication use in the BDPC studies are shown in Table 28.

Figure 21: Rescue Medication (Bisacodyl) Use Across Pooled Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

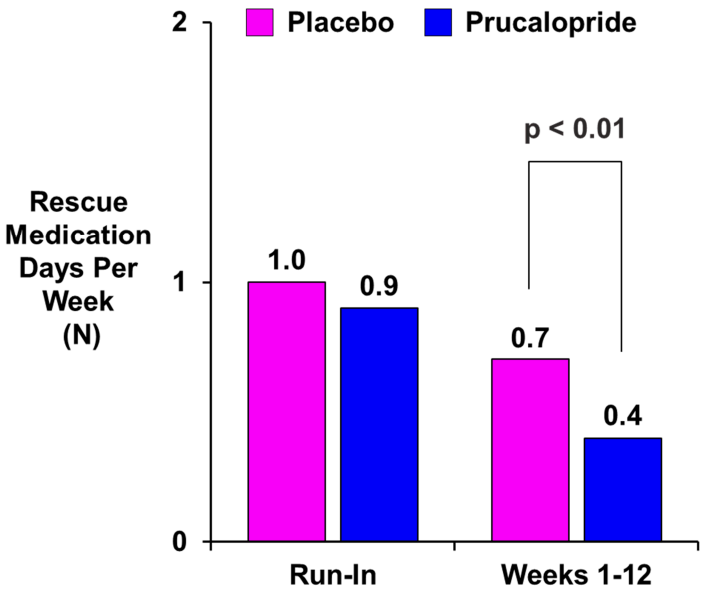


Table 28: Changes in Rescue Medication Use – Average Number of Rescue Medication (Bisacodyl) Tablets Taken per Week in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=236	PLA N=193	PRU 2 mg N=190	PLA N=212	PRU 2 mg N=214	PLA N=169	PRU 2 mg* N=171
Mean Actual Value (Mean Change)												
Overall Score												
BL/RI	1.6	1.7	1.71	1.54	2.3	1.8	2.2	1.9	1.8	2.1	1.87	1.79
FoTA Week 12	1.3 (-0.3)	0.6 (-1.0)	0.96 (-0.72)	0.56 (-0.96)	2.1 (-0.2)	1.1 (-0.8)	2.0 (0.0)	0.9 (-1.1)	1.7 (-0.1)	1.4 (-0.7)	1.06 (-0.64)	0.88 (-0.94)
FoTA Week 24											1.00 (-0.68)	0.84 (-0.97)

BL=baseline; FoTA=final on-treatment assessment; PLA=placebo; PRU=prucalopride; RI=run-in

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

6.5.5 Patient Assessment of Constipation – Symptoms (PAC-SYM)

The average PAC-SYM total score at baseline was similar for the prucalopride and placebo groups in all 6 studies. In Studies 3001, 6, USA-11, and USA-13, the mean improvement in PAC-SYM total score was statistically significantly higher in the prucalopride group compared with the placebo group ($p < 0.01$; Table 29). The results of the PAC-SYM were not statistically significant in Studies 302 ($p=0.0623$) and 401 ($p=0.532$).

In the 4 studies with statistically significant results, the proportion of patients with an improvement of ≥1 point in total PAC-SYM score from baseline (i.e., a change that is considered clinically relevant (Frank et al., 1999;Yiannakou et al., 2017) at the final on-treatment assessment was also statistically significantly higher in the prucalopride group compared with the placebo group. The results of ≥1 point improvement in total PAC-SYM were not statistically significant in Studies 302 ($p=0.3152$) and 401 ($p=0.035$) (Table 30).

Figure 22 shows that the PAC-SYM total score improved with increasing number of CSBMs/week across the 12-week treatment period, and Figure 23 shows that responders on the primary efficacy endpoint had better overall PAC-SYM scores.

Table 29: Patient Assessment of Constipation – Symptoms (PAC-SYM) in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=236	PLA N=193	PRU 2 mg N=190	PLA N=212	PRU 2 mg N=214	PLA N=169	PRU 2 mg* N=171
Mean Actual Value (Mean Change)												
Overall Score												
BL/RI	1.5 (NA)	1.5 (NA)	1.8 (NA)	1.8 (NA)	2.1 (NA)	2.1 (NA)	2.0 (NA)	1.9 (NA)	2.0 (NA)	2.0 (NA)	2.0 (NA)	1.8 (NA)
FoTA Week 12	1.2 (-0.4)	0.8 (-0.7)	1.2 (-0.6)	1.1 (-0.8)	1.7 (-0.3)	1.5 (-0.6)	1.6 (-0.4)	1.3 (-0.6)	1.6 (-0.4)	1.3 (-0.8)	1.2 (-0.7)	1.2 (-0.7)
p-value[a]		< 0.001[a]		0.0623[b]		< 0.001		0.004		< 0.001		0.530
FoTA Week 24											1.3 (-0.7)	1.3 (-0.6)
p-value[a]												0.532
Stool Symptom Score												
BL/RI	1.5 (NA)	1.5 (NA)	2.3 (NA)	2.4 (NA)	2.5 (NA)	2.6 (NA)	2.5 (NA)	2.4 (NA)	2.5 (NA)	2.6 (NA)	2.4 (NA)	2.3 (NA)
FoTA Week 12	1.7 (-0.5)	1.2 (-1.0)	1.6 (-0.7)	1.4 (-1.0)	2.1 (-0.4)	1.9 (-0.7)	2.0 (-0.5)	1.8 (-0.6)	2.1 (-0.4)	1.8 (-1.8)	1.6 (-0.8)	1.6 (-0.7)
p-value[a]		< 0.001[a]		0.0373[b]		< 0.001		0.028		< 0.001		0.704
FoTA Week 24											1.6 (-0.8)	1.7 (-0.6)
p-value[a]												0.493
Abdominal Symptom Score												
BL/RI	1.1 (NA)	1.2 (NA)	1.5 (NA)	1.7 (NA)	2.1 (NA)	2.2 (NA)	2.0 (NA)	1.9 (NA)	2.0 (NA)	2.0 (NA)	2.0 (NA)	1.7 (NA)
FoTA Week 12	0.9 (-0.3)	0.6 (-0.6)	1.0 (-0.6)	1.0 (-0.7)	1.8 (-0.3)	1.6 (-0.6)	1.6 (-0.4)	1.2 (-0.7)	1.5 (-0.5)	1.2 (-0.8)	1.2 (-0.8)	1.0 (-0.7)
p-value[a]		< 0.001[a]		0.4661[b]		0.015		< 0.001		< 0.001		0.180
FoTA Week 24											1.3 (-0.7)	1.2 (-0.6)
p-value[a]												0.956
Rectal Symptom Score												
BL/RI	0.9 (NA)	1.0 (NA)	1.1 (NA)	1.2 (NA)	1.3 (NA)	1.3 (NA)	1.0 (NA)	1.2 (NA)	1.1 (NA)	1.2 (NA)	1.3 (NA)	1.3 (NA)
FoTA Week 12	0.7 (-0.3)	0.4 (-0.5)	0.7 (-0.4)	0.6 (-0.6)	1.0 (-0.3)	0.9 (-0.4)	0.7 (-0.3)	0.7 (-0.5)	0.8 (-0.3)	0.6 (-0.6)	0.7 (-0.6)	0.7 (-0.6)
p-value[a]		< 0.001[a]		0.1247[b]		0.126		0.701		0.002		0.719
FoTA Week 24											0.7 (-0.6)	0.8 (-0.5)
p-value[a]												0.204

BL=baseline; CBM=complete bowel movement; FoTA=final on-treatment assessment; NA=not applicable; PAC-SYM=patient assessment of constipation – symptoms; PLA=placebo; PRU=prucalopride; RI=run-in

[a] p-value based on an ANCOVA model with factors treatment, baseline value, and country/region for Studies 6, USA-11, and USA-13 and average number of CBMs during the run-in period, country, and sex for Study 401

Table 29: Patient Assessment of Constipation – Symptoms (PAC-SYM) in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Note 1: Numbers were rounded.

Note 2: Week 12 is the FoTA for Studies 6, USA-11, and USA-13; for Study 401, Week 24 is the FoTA.

Source: Module 5.3.5.1, PRU-CRC-3001, Section 5.4.10, Table 25, SPD555-302, Section 14, Table PAC.1; PRU-INT-6, Section 14, Display EFF.16; PRU-USA-11, Section 14, Display EFF.16 PRU-USA-13, Section 14, Display EFF.16; SPD555-401, Section 14, Table PAC.1

Table 30: Proportion of Patients with ≥1 Point Improvement on the Patient Assessment of Constipation – Symptoms (PAC-SYM) in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=236	PLA N=193	PRU 2 mg N=190	PLA N=212	PRU 2 mg N=214	PLA N=169	PRU 2 mg* N=171
	Mean Actual Value (Mean Change)											
Overall Score												
FoTA Week 12	42 (16.9)	86 (34.5)	52 (30.4)	59 (34.9)	51 (21.4)	74 (31.8)	37 (19.7)	57 (31.0)	45 (21.3)	76 (36.4)	55 (39.6)	47 (32.4)
p-value[a]		< 0.001[a]		0.3152[b]		0.013[c]		0.016[c]		< 0.001[c]		0.217[d]
FoTA Week 24											67 (40.1)	50 (29.9)
p-value[a]												0.035[d]
Stool Symptom Score												
FoTA Week 12	74 (29.7)	125 (50.2)	62 (36.3)	90 (53.3)	57 (24.1)	96 (41.4)	59 (31.4)	72 (39.1)	65 (30.8)	87 (41.6)	61 (43.9)	54 (37.2)
p-value[a]		< 0.001[a]		0.0005 [b]		< 0.001[c]		0.111[c]		0.016[c]		0.630
FoTA Week 24											81 (48.5)	60 (35.9)
p-value[a]												0.024[d]
Abdominal Symptom Score												
FoTA Week 12	45 (18.1)	72 (28.9)	60 (35.1)	66 (39.1)	65 (27.3)	88 (37.8)	45 (23.9)	78 (42.4)	68 (32.2)	98 (47.1)	57 (41.3)	55 (37.9)
p-value[a]		0.003[a]		0.4874 [b]		0.016[c]		< 0.001[c]		0.001[c]		0.832[d]
FoTA Week 24											69 (41.3)	56 (33.3)
p-value[a]												0.185[d]
Rectal Symptom Score												
FoTA Week 12	54 (21.7)	71 (28.5)	50 (29.2)	59 (34.9)	52 (21.9)	69 (29.7)	43 (23.1)	52 (28.3)	40 (19.0)	68 (32.7)	51 (36.7)	53 (36.6)
p-value[a]		0.080[a]		0.2759 [b]		0.060[c]		0.269[c]		0.001[c]		0.804[d]
FoTA Week 24											62 (37.1)	50 (29.9)
p-value[a]												0.219[d]

CBM=complete bowel movement; CMH=Cochrane-Mantel-Haenszel; FoTA=final on-treatment assessment; ITT=intent-to-treat; PAC-SYM=patient assessment of constipation – symptoms; PLA=placebo; PRU=prucalopride

[a] p-value based on a CMH test controlling for country/region, and baseline severity (SBM< 1 vs SBM≥ 1)

[b] p-value based on a CMH test controlling for the average number of CBMs per week during the run-in period and ....country.

[c] p-value based on a CMH test controlled for country/investigator

[d] p-value based on a CMH test controlling for country, sex, and the average number of CBMs during the run-in period

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

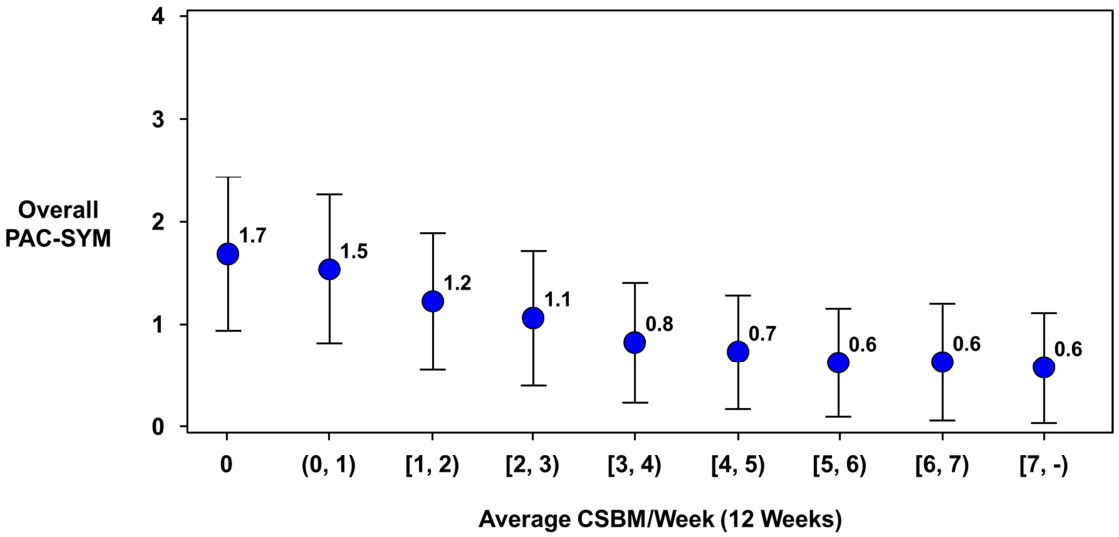
Note: Week 12 is the FoTA for Studies 6, USA-11, and USA-13; for Study 401, Week 24 is the FoTA.

Source: Module 5.3.5.1, PRU-CRC-3001, Section 5.4.11, Table 26 and SPD555-302, Section 14, Table PAC.2; Module 5.3.5.1, PRU-INT-6 CSR, Section 14, Table EFF.16A;

Table 30: Proportion of Patients with ≥1 Point Improvement on the Patient Assessment of Constipation – Symptoms (PAC-SYM) in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

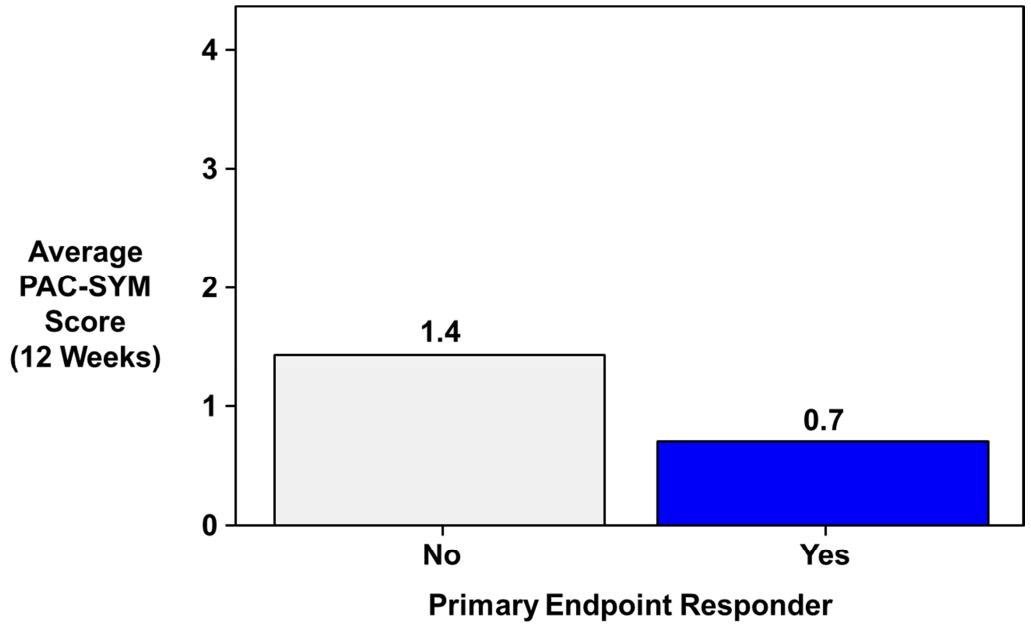
PRU-USA-11 CSR, Section 14, Table EFF.16A; PRU-USA-13 CSR, Section 14, Table EFF.16A; SPD555-401, Section 14, Table PAC.2

Figure 22: Overall PAC-SYM Score by Average Number of CSBMs/Week Over 12 Weeks in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks



CSBM=complete spontaneous bowel movement; PAC-SYM= patient assessment of constipation – symptoms

Figure 23: Overall PAC-SYM Score by Primary Endpoint Responder Status in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks



CSBM=complete spontaneous bowel movement; PAC-SYM= patient assessment of constipation – symptoms

6.5.6 Patient Assessment of Constipation – Quality of Life (PAC-QOL)

The average PAC-QOL score at baseline was similar for the prucalopride and placebo groups in all 6 studies. In all 6 studies, the mean improvement in PAC-QOL total score was statistically significantly higher in the prucalopride group compared with the placebo group at Week 12 (Table 31).

The proportion of patients with an improvement of ≥1 point in total PAC-QOL score from baseline (i.e., a change that is considered clinically relevant (Dubois et al., 2010) at the final on-treatment assessment was statistically significantly higher in the prucalopride group compared with the placebo group in Studies 3001, 6, USA-11, and USA-13. The results of ≥1 point improvement in total PAC-QOL were not statistically significant in Studies 302 (p=0.076) and 401 (p=0.862) (Table 32).

Figure 24 shows that the PAC-QOL total score improved with increasing number of CSBMs/week across the 12-week treatment period, and Figure 25 shows that responders on the primary efficacy endpoint had better overall PAC-QOL scores.

Table 31: Patient Assessment of Constipation – Quality of Life (PAC-QOL) in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

	Study 3001		Study 302		PRU-INT-6		PRU-USA-11		PRU-USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=236	PLA N=193	PRU 2 mg N=190	PLA N=212	PRU 2 mg N=214	PLA N=169	PRU 2 mg* N=171
	Mean Actual Value (Mean Change)											
Overall Score												
BL/RI	1.9 (NA)	1.8 (NA)	1.9 (NA)	2.0 (NA)	2.1 (NA)	2.0 (NA)	2.2 (NA)	2.2 (NA)	2.1 (NA)	2.2 (NA)	2.3 (NA)	2.1 (NA)
FoTA Week 12	1.5 (-0.4)	1.1 (-0.8)	1.3 (-0.6)	1.2 (-0.8)	1.7 (-0.3)	1.4 (-0.6)	1.8 (-0.5)	1.4 (-0.8)	1.7 (-0.4)	1.4 (-0.8)	1.5 (-0.7)	1.3 (-0.8)
p-value[a]		< 0.001 [a]		0.0158 [b]		< 0.001		< 0.001		< 0.001		0.042
FoTA Week 24											1.5 (-0.7)	1.4 (-0.7)
p-value[a]												0.770
Satisfaction Subscore												
BL/RI	3.0 (NA)	3.0 (NA)	2.9 (NA)	3.1 (NA)	3.2 (NA)	3.1 (NA)	3.3 (NA)	3.4 (NA)	3.4 (NA)	3.4 (NA)	3.1 (NA)	3.0 (NA)
FoTA	2.8 (-0.2)	2.1 (-0.9)	2.3 (-0.7)	1.9 (-1.2)	2.9 (-0.3)	2.4 (-0.7)	3.0 (-0.3)	2.5 (-0.9)	3.1 (-0.4)	2.5 (-0.9)	2.3 (-0.8)	2.1 (-0.9)
p-value[a]		< 0.001 [a]		0.0009 [b]		< 0.001		< 0.001		< 0.001		0.032
FoTA Week 24											2.4 (-0.7)	2.2 (-0.9)
p-value[a]												0.081
Physical Discomfort Subscore												
BL/RI	1.7 (NA)	1.7 (NA)	2.0 (NA)	2.1 (NA)	2.4 (NA)	2.4 (NA)	2.6 (NA)	2.4 (NA)	2.4 (NA)	2.5 (NA)	2.5 (NA)	2.2 (NA)
FoTA	1.3 (-0.4)	0.9 (-0.8)	1.3 (-0.7)	1.2 (-0.9)	1.9 (-0.5)	1.6 (-0.8)	2.0 (-0.6)	1.5 (-0.9)	1.9 (-0.5)	1.5 (-1.0)	1.6 (-0.9)	1.4 (-0.8)
p-value[a]		< 0.001 [a]		0.1132 [b]		< 0.001		< 0.001		< 0.001		0.107
FoTA Week 24											1.6 (-0.9)	1.5 (-0.7)
p-value[a]												0.910
Psychosocial Discomfort Subscore												
BL/RI	1.3 (NA)	1.2 (NA)	1.2 (NA)	1.4 (NA)	1.3 (NA)	1.2 (NA)	1.4 (NA)	1.2 (NA)	1.1 (NA)	1.3 (NA)	1.7 (NA)	1.5 (NA)
FoTA	0.9 (-0.4)	0.6 (-0.6)	0.8 (-0.4)	0.8 (-0.6)	1.0 (-0.3)	0.8 (-0.4)	1.0 (-0.4)	0.7 (-0.6)	0.8 (-0.3)	0.7 (-0.5)	1.0 (-0.7)	0.8 (-0.7)
p-value[a]		< 0.001 [a]		0.0747 [b]		0.040		< 0.001		0.065		0.170
FoTA Week 24											1.0 (-0.7)	1.0 (-0.5)
p-value[a]												0.543
Worries and Concerns Subscore												
BL/RI	2.0 (NA)	1.8 (NA)	1.9 (NA)	1.9 (NA)	2.0 (NA)	2.0 (NA)	2.2 (NA)	2.2 (NA)	2.1 (NA)	2.2 (NA)	2.2 (NA)	2.1 (NA)
FoTA	1.5 (-0.5)	1.1 (-0.8)	1.3 (-0.6)	1.2 (-0.7)	1.6 (-0.4)	1.3 (-0.7)	1.7 (-0.5)	1.3 (-0.9)	1.6 (-0.5)	1.3 (-0.9)	1.5 (-0.7)	1.3 (-0.8)
p-value[a]		< 0.001 [a]		0.0616 [b]		< 0.001		< 0.001		< 0.001		0.045
FoTA Week 24											1.5 (-0.7)	1.4 (-0.7)
p-value[a]												0.745

BL= baseline; FoTA=final on-treatment assessment; NA=not applicable; PAC-QOL=patient assessment of constipation – quality of life; PLA=placebo; PRU=prucalopride

a p-value based on an ANCOVA model with factors treatment, baseline value, and country/region for Studies INT-6, USA-11, and USA-13 and average number of CBMs during the run-in period, country, and sex for Study 401

Table 31: Patient Assessment of Constipation – Quality of Life (PAC-QOL) in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

Note 1: Numbers were rounded.

Note 2: Week 12 is the FoTA for Studies 6, USA-11, and USA-13; for Study 401, Week 24 is the FoTA.

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Source: Module 5.3.5.1, PRU-CRC-3001, Section 5.5..1, Table 26, SPD555-302, Section 14, Table QOL.1; PRU-INT-6, Section 14, Display QOL.1; PRU-USA-11, Section 14, Display QOL.1; PRU-USA-13, Section 14, Display QOL.1; SPD555-401, Section 14, Table QOL.1

Table 32: Proportion of Patients with ≥1 Point Improvement on the Patient Assessment of Constipation – Quality of Life (PAC-QOL) in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	PLA N=252	PRU 2 mg N=249	PLA N=181	PRU 2 mg* N=177	PLA N=240	PRU 2 mg N=236	PLA N=193	PRU 2 mg N=190	PLA N=212	PRU 2 mg N=214	PLA N=169	PRU 2 mg* N=171
Mean Actual Value (Mean Change)												
Overall Score												
FoTA Week 12	41 (16.6)	92 (37.1)	56 (32.7)	68 (40.2)	35 (15.0)	72 (31.0)	38 (20.9)	70 (38.5)	41 (19.7)	84 (40.4)	52 (37.1)	56 (38.9)
p-value[a]		<0.001[a]		0.0755[b]		<0.001[a]		<0.001[a]		<0.001[a]		0.862[b]
FoTA Week 24											62 (37.8)	57 (33.9)
p-value[a]												0.759[b]
Satisfaction Subscore												
FoTA Week 12	55 (22.3)	117 (47.2)	66 (38.8)	89 (52.7)	47 (20.1)	101 (43.5)	42 (23.3)	81 (44.5)	48 (23.5)	90 (43.5)	56 (40.0)	70 (49.6)
p-value[a]		<0.001[a]		0.0035[b]		<0.001[a]		<0.001[a]		<0.001[a]		0.163[b]
FoTA Week 24											60 (36.8)	74 (44.0)
p-value[a]												0.252[b]
Physical Discomfort Subscore												
FoTA Week 12	67 (27.1)	110 (44.4)	67 (39.2)	85 (50.3)	67 (28.5)	112 (48.3)	59 (32.4)	87 (48.1)	74 (35.6)	105 (50.5)	64 (45.7)	64 (44.8)
p-value[a]		<0.001[a]		0.0249 [b]		<0.001[a]		<0.001[a]		0.001[a]		0.820[b]
FoTA Week 24											85 (51.8)	67 (39.9)
p-value[a]												0.127[b]
Psychosocial Discomfort Subscore												
FoTA Week 12	56 (22.7)	71 (28.6)	42 (24.6)	51 (30.2)	40 (17.2)	54 (23.3)	36 (19.8)	41 (22.5)	38 (18.4)	55 (26.4)	53 (38.4)	53 (36.8)
p-value[a]		0.143 [a]		0.1234[b]		<0.001[a]		<0.001[a]		0.043[a]		0.980[b]
FoTA Week 24											56 (34.1)	49 (29.2)
p-value[a]												0.623[b]
Worries and Concerns Subscore												
FoTA Week 12	60 (24.3)	93 (37.5)	50 (29.2)	63 (37.3)	52 (22.3)	83 (35.8)	47 (25.8)	78 (42.9)	49 (23.6)	94 (45.2)	50 (36.2)	57 (39.6)
p-value[a]		0.002 [a]		0.0637[b]		<0.001[a]		<0.001[a]		<0.001[a]		0.772[b]
FoTA Week 24											62 (37.8)	58 (34.5)
p-value[a]												0.828[b]

CBM=complete bowel movement; CMH=Cochran-Mantel-Haenszel; FoTA=final on-treatment assessment; PAC-QOL=patient assessment of constipation – quality of life; PLA=placebo; PRU=prucalopride

[a] p-value based on a CMH controlling for country/region, and baseline severity (SBM<1 vs SBM≥1)

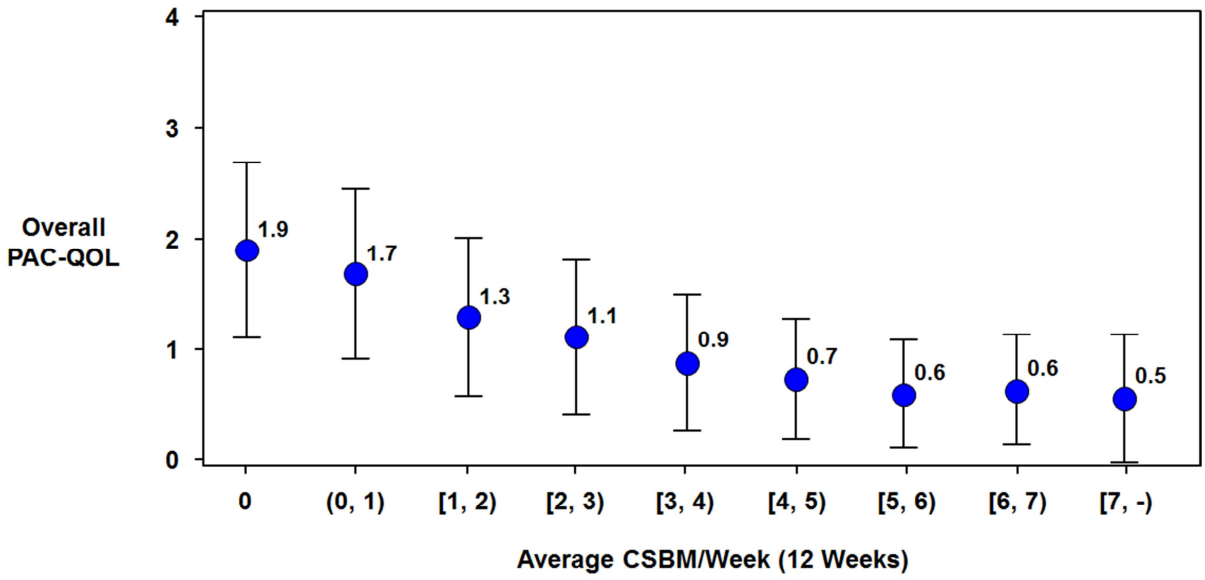
Table 32: Proportion of Patients with ≥1 Point Improvement on the Patient Assessment of Constipation – Quality of Life (PAC-QOL) in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks

[b] p-value based on a CMH test controlling for the average number of CBMs per week during the run-in period and country.

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

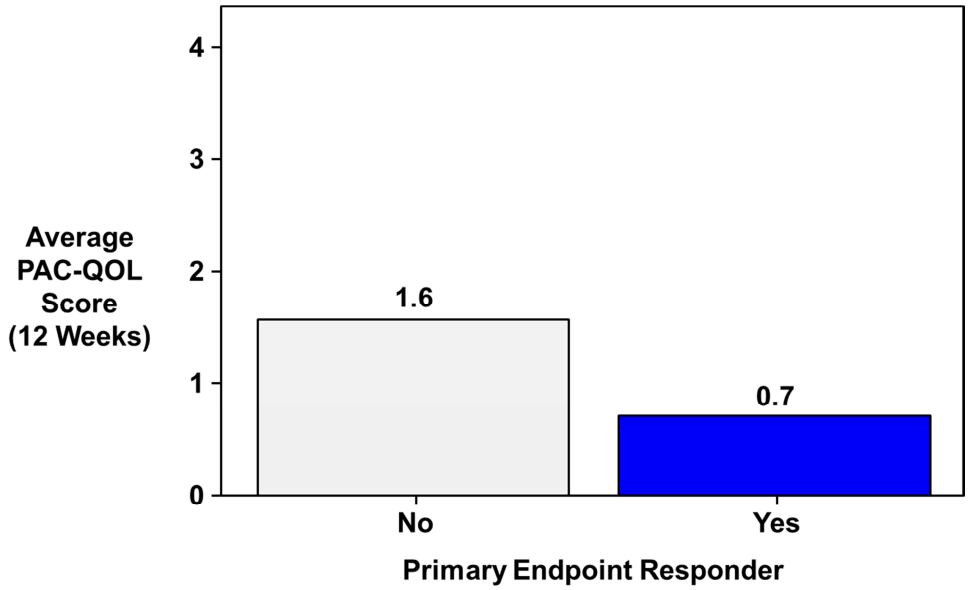
Source: Module 5.3.5.1, PRU-CRC-3001, Section 5.5.2, Table 28 and SPD555-302, Section 14, Table QOL.2; PRU-INT-6, Section 14, Display QOL.1A; PRU-USA-11, Section 14, Display QOL.1A; PRU-USA-13, Section 14, Display QOL.1A; SPD555-401, Section 14, Table QOL.2

Figure 24: Overall PAC-QOL Score by Average Number of CSBMs/Week Over 12 Weeks in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks



CSBM=complete spontaneous bowel movement; PAC-QOL= patient assessment of constipation – quality of life

Figure 25: Overall PAC-QOL Score by Primary Endpoint Responder Status in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks



CSBM=complete spontaneous bowel movement; PAC-QOL= patient assessment of constipation – quality of life

6.6 Subgroup Analyses

6.6.1 Subgroup Analysis by Age

Overall, the proportion of patients meeting the primary efficacy endpoint, ≥3 CSBMs per week over the 12-week treatment period, was consistent across age groups and statistically significantly higher in the prucalopride 2 mg* treatment group compared with placebo in both patients aged <65 years (27.8% and 12.7%, respectively) and patients aged ≥65 years (28.1% and 16.9%, respectively) (p <0.001 and p=0.004, respectively; Table 33).

Table 33: Proportion of Patients with an Average of ≥ 3 CSBMs per Week Over 12 Weeks by Age in Phase 3/4 Efficacy and Safety Studies in Chronic Constipation

	Patients Aged < 65 years		Patients Aged ≥ 65 years		Difference in Proportion p-value [a]	
	PLA N=1069	PRU 2 mg* N=1041	PLA N=178	PRU 2 mg* N=196	Patients Aged < 65 years	Patients Aged ≥ 65 years
	n (%)				(95% CI)	
Weeks 1-12	135 (12.6)	289 (27.8)	30 (16.9)	55 (28.1)	0.151 (0.118; 0.185)	0.112 (0.029; 0.196)
p-value					< 0.001	0.004

CI=confidence interval; CMH=Cochran-Mantel-Haenszel; PLA=placebo; PRU=prucalopride

[a] p-value based on a CMH test, performed on the proportion of patients with an average weekly frequency of ≥ 3 CSBMs/week over Week 1-12 in the placebo and prucalopride treatment groups controlling for stratification factors study, sex, country, and number of CBMs/week (0 or > 0) at baseline

*Includes all patients titrated from prucalopride 1 mg to 2 mg

Source: Table EFF.B.04.2

6.6.2 Subgroup Analysis by Sex

Overall, the proportion of patients with ≥3 CSBMs per week over the 12-week treatment period was consistent across sexes and statistically significantly higher in the prucalopride 2 mg* treatment group compared with placebo in both the male (31.6% and 16.7%, respectively) and female subgroups (26.6% and 12.1%, respectively; p <0.001 for both comparisons; Table 34). The difference in response rate in the prucalopride 2 mg* treatment group compared with the placebo group was similar for the male (15.0%) and female (14.5%) subgroups.

Table 34: Proportion of Patients with an Average of ≥3 CSBMs per Week Over 12 Weeks by Sex in Phase 3/4 Efficacy and Safety Studies in Chronic Constipation

	Female		Male		Difference in Proportion p-value [a]	
	PLA N=947	PRU 2 mg* N=940	PLA N=300	PR 2 mg* N=297	Female	Male
	n (%)				95% CI	
Weeks 1-12	115 (12.1)	250 (26.6)	50 (16.7)	94 (31.6)	0.145 (0.109; 0.180)	0.150 (0.082; 0.217)
p-value					< 0.001	< 0.001

CI=confidence interval; CMH=Cochran-Mantel-Haenszel; PLA=placebo; PRU=prucalopride

[a] p-value based on a CMH test, performed on the proportion of patients with an average weekly frequency of ≥ 3 CSBMs/week over Week 1-12 in the placebo and prucalopride treatment groups controlling for stratification factors study, sex, country, and number of CBMs/week (0 or > 0) at baseline

*Includes all patients titrated from prucalopride 1 mg to 2 mg

Source: Table EFF.B.04.1

6.6.3 Subgroup Analysis by Race

Overall, the proportion of patients with ≥3 CSBMs per week over the 12-week treatment period was consistent across White and non-White patients and statistically significantly higher in the prucalopride 2 mg* treatment group compared with placebo in both White (27.6% and 14.1%, respectively) and non-White patients (29.4% and 10.5%, respectively; p <0.001 for both races; Table 35).

Table 35: Proportion of Patients with an Average of ≥3 CSBMs per Week Over 12 Weeks by Race in Phase 3/4 Efficacy and Safety Studies in Chronic Constipation

	White Patients		Non-White Patients		Difference in Proportion p-value [a]	
	PLA N=951	PRU 2 mg* N=925	PLA N=287	PRU 2 mg* N=303	White Patients	Non-White Patients
	n (%)				95% CI	
Weeks 1-12	134 (14.1)	255 (27.6)	30 (10.5)	89 (29.4)	0.135 (0.098; 0.1701)	0.189 (0.127; 0.252)
p-value					< 0.001	< 0.001

CI=confidence interval; CMH=Cochran-Mantel-Haenszel; PLA=placebo; PRU=prucalopride

[a] p-value based on a CMH test, performed on the proportion of patients with an average weekly frequency of ≥ 3 CSBMs/week over Week 1-12 in the placebo and prucalopride treatment groups controlling for stratification factors study, sex, country, and number of CBMs/week (0 or > 0) at baseline

*Includes all patients titrated from prucalopride 1 mg to 2 mg

Source: Table EFF.B.04.3

6.6.4 Subgroup Analysis by Region

The primary endpoint was also analyzed as a comparison of North America vs Western Europe, Eastern Europe, and Asia as well as the US vs outside of the US.

In the analyses comparing North America vs Western Europe, Eastern Europe, and Asia, the proportion of patients with ≥3 CSBMs per week over the 12-week treatment period was statistically significantly higher in the prucalopride 2 mg* treatment group compared with placebo in patients across all 4 regions (Table 36).

While the proportion of responders in the prucalopride 2 mg* group was similar for North American and Western European patients and higher for Eastern European and Asian patients, the difference in proportion (i.e., effect size) was similar across all regions.

Table 36: Proportion of Patients with an Average of ≥3 CSBMs per Week Over 12 Weeks by Region in Phase 3/4 Efficacy and Safety Studies in Chronic Constipation

	North America		Western Europe		Difference in Proportion	
	PLA N=471	PRU 2 mg* N=472	PLA N=245	PRU 2 mg* N=243	North America	Western Europe
	n (%)				95% CI	
Weeks 1-12	58 (12.3)	124 (26.3)	27 (11.0)	55 (22.6)	0.140 (0.090; 0.189)	0.116 (0.051; 0.182)
p-value [a]					<0.001	<0.001

	North America		Eastern Europe		Difference in Proportion	
	PLA N=471	PRU 2 mg* N=472	PLA N=228	PRU 2 mg* N=224	North America	Eastern Europe
	n (%)				95% CI	
Weeks 1-12	58 (12.3)	124 (26.3)	50 (21.9)	79 (35.3)	0.140 (0.090; 0.189)	0.133 (0.051; 0.216)
p-value [a]					< 0.001	0.002

	North America		Asia		Difference in Proportion	
	PLA N=471	PRU 2 mg* N=472	PLA N=245	PRU 2 mg* N=243	North America	Asia
	n (%)				95% CI	
Weeks 1-12	58 (12.3)	124 (26.3)	25 (10.8)	78 (33.8)	0.140 (0.090; 0.189)	0.229 (0.156; 0.302)
p-value [a]					<0.001	<0.001

CI=confidence interval; CMH=Cochran-Mantel-Haenszel; PLA=placebo; PRU=prucalopride

[a] p-value based on a CMH test, performed on the proportion of patients with an average weekly frequency of ≥3 CSBMs/week over Week 1-12 in the placebo and prucalopride treatment groups controlling for stratification factors study, sex, country, and number of CBMs/week (0 or >0) at baseline

*Includes all patients titrated from prucalopride 1 mg to -2 mg

Source: Table EFF.B.04.4

For the analysis of US vs non-US, the response rate (percentage of patients with a mean frequency of ≥3 CSBMs/week over the 12-weeks) with prucalopride was improved over placebo to a similar extent in both US and non-US populations, with a therapeutic gain of 13.6% and 15.0%, respectively (Table 37 and Figure 26). The value of the therapeutic gain in the US is included within the 95% CI of the non-US population, and the same is true for the therapeutic gain in the non-US population, indicating therapeutic gain is comparable between US and non-US populations.

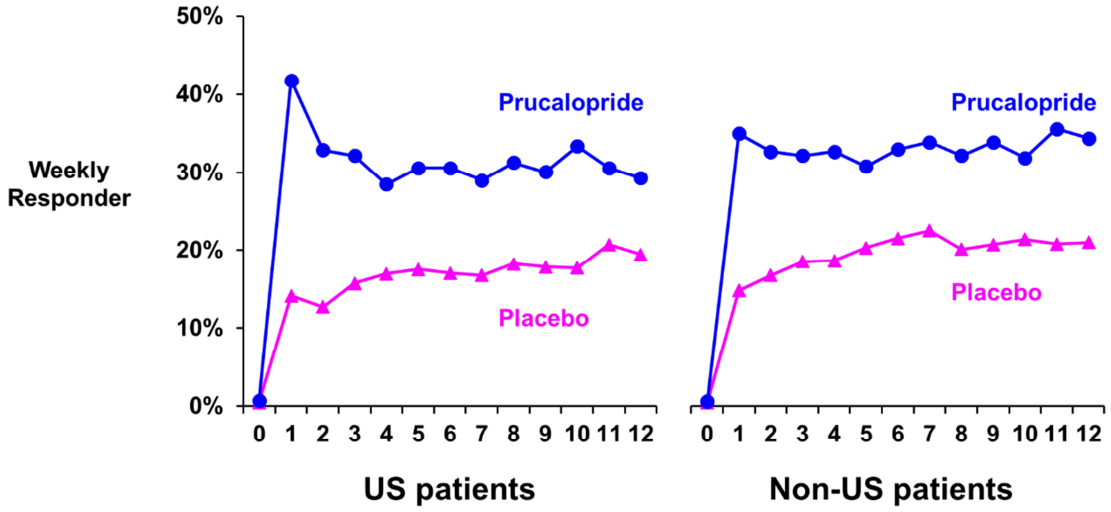
Furthermore, the response rates in each of the individual 12 weeks were comparable between patients in the US and non-US population; the response rates were consistently higher in the prucalopride group than in the placebo group in both groups.

Table 37: Primary Endpoint: Percentage of Patients with ≥3 CSBMs/Week in Week 1-12 in Studies Conducted in the United States versus Outside the United States

	US Patients		Non-US Patients		Difference in Proportion p-value [a]	
	PLA N=405	PRU 2 mg* N=404	PLA N=842	PRU 2 mg* N=831	US Patients	Non-US Patients
	% of patients				95% CI	
Proportion of Patients with ≥ 3 CSBMs	12.4	26.0	13.8	28.8	13.6 (8.3; 19.0)	15.0 (11.1, 18,8)

CI=confidence interval; CSBM=complete spontaneous bowel movement; US=United States; PLA=placebo; PRU=prucalopride
*Includes all patients titrated from prucalopride 1 mg to 2 mg
Source: Shire Pre-NDA briefing book SN 208/54, (question 3)

Figure 26: Proportion of Patients with a Mean Frequency of ≥3 CSBMs/Week (Response Rate) Over the 12-Week Treatment Period in Studies Conducted in the United States Versus Outside the United States



CSBM=complete spontaneous bowel movement; US=United States

6.7 Efficacy Conclusions

In 5 of 6 studies (3001, 302, 6, USA-11, and USA-13), the primary efficacy endpoint, the proportion of patients with ≥ 3 CSBMs/week after 12 weeks of treatment, was met, showing a statistically significant improvement with prucalopride 2 mg* vs placebo (Figure 27). In Study 401, the primary efficacy results were not statistically significant at 24-weeks or 12-weeks.

The primary efficacy endpoint was also analyzed using the alternative response definitions that the FDA currently recommends for studies in CIC: the proportion of patients with ≥3 CSBMs/week and an increase of ≥ 1 CSBM/week for ≥9 out of the 12 weeks (or 18 out of the 24 weeks for Study 401) including 3 of the last 4 weeks. Five of 6 studies were statistically significant for Alternative Endpoint A (3001, 302, 6, USA-11, and USA-13); this endpoint was not met in Study 401.

In addition, prucalopride showed numerically and/or statistically significantly better results compared with placebo on a variety of secondary efficacy endpoints across Studies 3001, 302, 6, USA-11, and USA-13, including the proportion of patients with an average increase of ≥1 CSBM, the increase in average number of CSBMs, and improvement in PAC-SYM and PAC-QOL scores. Prucalopride decreased the time to first CSBM in all 6 studies.

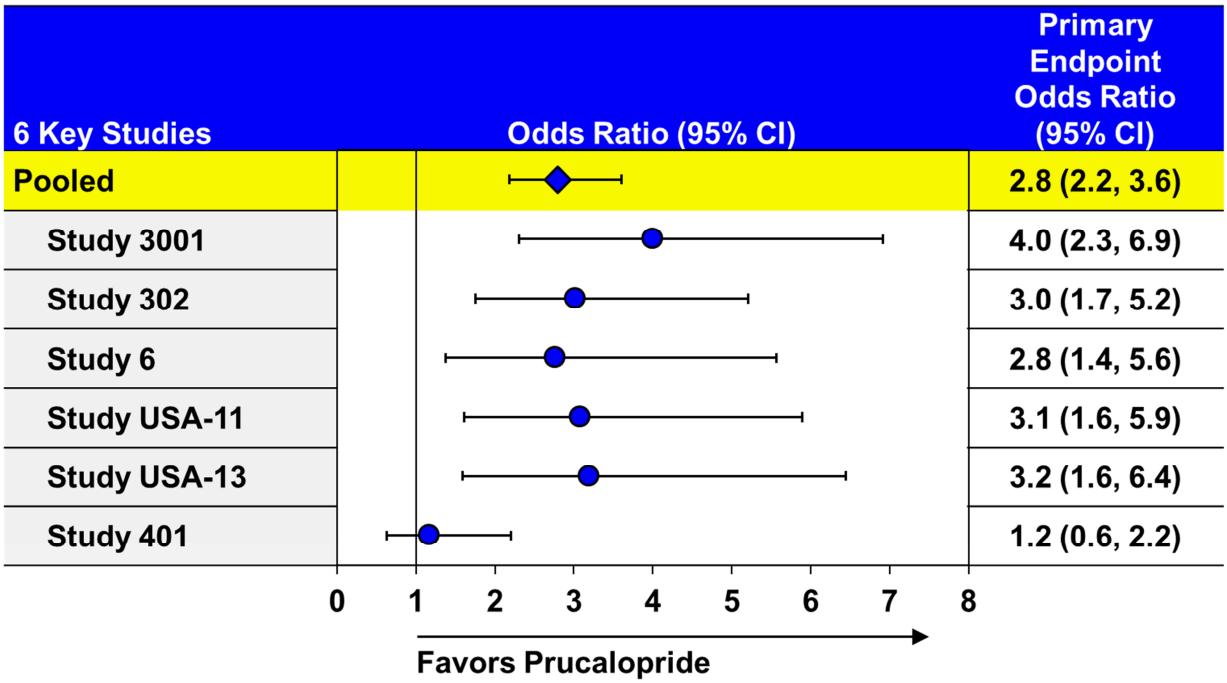
The therapeutic gain of prucalopride over placebo (as odds ratios) from the 6 individual studies are presented in a Forest plot, as published by Camilleri et al., (2016) (Figure 27). The overall odds ratio was 2.68 (95 % CI 2.16-3.33). The authors evaluated heterogeneity between studies using the I^2 statistic and the Breslow-Day test (Higgins and Thompson, 2002), resulting in a p-value of 0.0406 and an I^2 statistic of 56%, indicating moderate heterogeneity. This heterogeneity was due to the results of Study 401. When this study was excluded, still involving

86% of patients, results were highly homogeneous (I^2=6.8%), demonstrated homogeneity across studies conducted in Asian, American, and European populations.

The efficacy of prucalopride was similar in both US and non-US patients. Current findings support the generalizability of the findings observed in a population of patients with CIC treated with prucalopride outside the US to patients in the US.

In conclusion, results from the clinical program indicate that prucalopride is an effective treatment for patients with CIC.

Figure 27: Forest Plot of Primary Efficacy Endpoint Results in Randomized Double-blind Placebo-controlled Studies ≥12 Weeks



CI=confidence interval; OR=odds ratio
Source: Camilleri et al., 2016

7. CLINICAL SAFETY

Summary

- In Phase 2-4 Pooled Randomized DBPC studies 4 weeks duration in patients with CIC, a total of 3,295 patients were exposed to prucalopride (doses of 0.5-4 mg QD or BID) for a mean of 64.2 days.
- In addition to the Pooled Randomized DBPC studies ≥4 weeks, 939 patients were exposed to prucalopride in Phase 1 studies, 2,595 in open-label studies, and 5,715 in pharmacoepidemiology study, Study 802.
- Overall in the Pooled Randomized DBPC studies ≥4 weeks, 946 patients (62%) in the prucalopride 2 mg* group and 1,058 patients (54%) in the placebo group experienced ≥1 AE. The most common AEs in the prucalopride 2 mg* group were headache (17%), nausea (14%), diarrhea (12%), and abdominal pain (10%).
- Few AEs were reported as severe in ≥2% of patients in the prucalopride 2 mg* group: headache (3%), nausea (2%), diarrhea (2%), and abdominal pain (2%).
- Adverse events were generally transient and lasted <5 days; few patients reported headache, nausea, diarrhea, or abdominal pain lasting >5 days in the prucalopride 2 mg* group (6%, 6%, 3%, and 4%, respectively).
- The rate of SAEs was low and similar between prucalopride and placebo groups. Most SAEs occurred in ≤2 patients. The most frequently reported SAEs in ≥3 patients in the prucalopride group were abdominal pain, vaginal hemorrhage, and hysterectomy, which were all reported in <1% of prucalopride 2 mg* patients.
- There were 3 AEs leading to discontinuation reported in ≥1% of patients taking 2 mg* prucalopride: headache, diarrhea, and nausea.
- There were 8 events with fatal outcome reported in the Pooled Randomized DBPC studies ≥4 weeks and their open-label extensions: 3 occurred during the randomized studies (2 prucalopride, 1 placebo), and 5 occurred during open-label extensions on prucalopride. All events with fatal outcome were considered by the investigator as not related to prucalopride treatment.
- Systematic and comprehensive investigations from studies with intense cardiac monitoring including a TQT study, clinical studies, and more than 8 years of post-marketing experience did not demonstrate an increase in cardiovascular risk.
- A rigorous epidemiological observational study (Study 802) did not show an increased cardiovascular risk with prucalopride compared with PEG (IRR=0.64 [95% CI, 0.36-1.13]).
- From first launch in 2009 through October 2017, there are >280,000 patient years of experience with prucalopride, with no new identified safety risks.

7.1 Treatment Exposure

A total of 5,268 patients were included in the Phase 2-4 Pooled Randomized DBPC studies ≥4 weeks duration in adult patients with CIC. Of these patients, 3,295 were treated with prucalopride (at doses of 0.5-4 mg QD; BID in PRU-INT-2) and 1,973 were treated with placebo.

The mean (SD) exposure was 64.2 (36.46) days in the total prucalopride group and 72.1 (36.32) days in the placebo group. In the total prucalopride group, 3,295 patients (99.7%) were exposed for at least 1 day, 3,166 patients (95.8%) were exposed for at least 7 days, and 2,786 patients (84.3%) were exposed for at least 28 days. In the placebo group, 1,973 patients (100%) patients were exposed for at least 1 day, 1,962 patients (99.4%) were exposed for at least 7 days, and 1,816 patients (92.0%) were exposed for at least 28 days.

As shown in Table 38, 4 doses were included in the clinical safety studies; however, the safety presentation focuses on the 1 mg and 2 mg doses. As previously discussed, the 4 mg dose did not provide significant benefit over the 2 mg dose, and only the 2 mg dose (and 1 mg in patients with severe renal insufficiency) is included in the proposed indication.

Table 39 shows prucalopride exposure in open-label extension studies. Overall, 2,595 patients were exposed to prucalopride for at least 1 day in open-label extension studies, with 1,052 patients exposed to prucalopride for at least 1 year.

Table 38: Exposure by Treatment Group in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)

	PLA N=1973	PRU 0.5 mg N=110	PRU 1 mg N=330	PRU 2 mg* N=1516	PRU 4 mg N=1349	Total PRU N=3305
Duration of exposure (days)						
n	1973	110	328	1512	1345	3295
Mean (SD)	72.1 (36.32)	27.0 (6.12)	40.4 (29.06)	79.1 (38.00)	56.3 (29.37)	64.2 (36.46)
Median	83.0	28.0	28.0	84.0	57.0	82.0
Min, Max	1, 193	1, 42	1, 170	1, 182	1, 113	1, 182
Duration of exposure (weeks)						
n	1973	110	328	1512	1345	3295
Mean (SD)	10.3 (5.19)	3.9 (0.87)	5.8 (4.15)	11.3 (5.43)	8.0 (4.20)	9.2 (5.21)
Median	11.9	4.0	4.0	12.0	8.1	11.7
Min, Max	0, 28	0, 6	0, 24	0, 26	0, 16	0, 26
Duration of exposure category (days), n (%)						
At least 1	1973 (100)	110 (100)	328 (99.4)	1512 (99.7)	1345 (99.7)	3295 (99.7)
At least 7	1962 (99.4)	108 (98.2)	316 (95.8)	1474 (97.2)	1268 (94.0)	3166 (95.8)
At least 28	1816 (92.0)	79 (71.8)	252 (76.4)	1363 (89.9)	1092 (80.9)	2786 (84.3)
At least 90	292 (14.8)	0	17 (5.2)	250 (16.5)	96 (7.1)	363 (11.0)
At least 180	1 (< 1)	0	0	4 (< 1)	0	4 (< 1)

Max=maximum; Min=minimum; PLA=placebo; PRU=prucalopride; SD=standard deviation

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Note: Exposure was calculated as the date of the last dose of study medication - the date of the first dose of study medication + 1 within each treatment period.

Note: Where a patient participated in multiple treatment periods, the exposure was calculated as the sum of exposures across treatment periods.

Source: Module 5.3.5.3, Table SAF D.07

Table 39: Exposure in Open-label Extension Studies

	Open-label N=2759
Duration of exposure category (days)	
At least 1	2595 (94.1)
At least 7	2561 (92.8)
At least 28	2455 (89.0)
At least 90	2151 (78.0)
At least 180	1710 (62.0)
At least 365	1052 (38.1)
At least 545	583 (21.1)
At least 730	96 (3.5)
At least 910	16 (<1)

Source: Module 5.3.5.3, Table SAF. E.07

7.2 Safety Pooling Strategy

The safety presentation includes an integrated analysis of Phase 2-4 Pooled Randomized DBPC studies of ≥4 weeks duration in patients with CIC, which includes the 6 studies supporting efficacy (Studies 3001, 302, 6, USA-11, USA-13, and 401), Phase 2 studies (PRU-INT-1, PRU-INT-2, PRU-USA-3, PRU-BEL-6, PRU-GBR-4, PRU-USA-26, and PRU-FRA-1), and Phase 3 studies (PRU-USA-25, PRU-USA-28, and PRU-INT-12).

7.3 Overview of Adverse Events in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks

Table 40 shows an overview of AEs in the Pooled Randomized DBPC studies. Overall, 64.9% of patients in the total prucalopride group, and 53.6% of patients in the placebo group reported ≥ 1 AE. Adverse events leading to discontinuation of study medication occurred in 6.7% of patients in the total prucalopride group and 2.9% of patients in the placebo group. Serious AEs occurred in 2.0% of patients in the total prucalopride group and 1.9% of patients in the placebo group. Two events with fatal outcome (<1%) occurred in the total prucalopride group, and 1 event with a fatal outcome (<1%) occurred in the placebo group.

The "total prucalopride" AE rates represent a conservative safety profile since the rates of AEs, severe AEs, AEs leading to dose adjustment, and AEs leading to discontinuation are increased by the inclusion of data from the 4 mg arms from Studies 6, USA-11, USA-13 and 401. The most relevant representation of prucalopride safety profile is shown by the pooled 2 mg data.

In the total prucalopride 2 mg* group, 62.4% reported ≥ 1 AE, 5.3% experienced an AE leading to permanent discontinuation of study medication, and 1.8% reported an SAE. Additionally, the 1 mg dose was given exclusively to elderly patients (≥65 years old) and does not show an increased rate of AEs.

Table 40: Overall Treatment-emergent Adverse Events by Treatment Group in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)

	PLA N=1973	PRU 0.5 mg N=110	PRU 1 mg N=330	PRU 2 mg* N=1516	PRU 4 mg N=1349	Total PRU N=3305
			n (%)			
≥ 1 AE	1058 (53.6)	60 (54.5)	184 (55.8)	946 (62.4)	956 (70.9)	2146 (64.9)
≥ 1 mild AE	693 (35.1)	40 (36.4)	108 (32.7)	665 (43.9)	630 (46.7)	1443 (43.7)
≥ 1 moderate AE	571 (28.9)	32 (29.1)	114 (34.5)	498 (32.8)	594 (44.0)	1238 (37.5)
≥ 1 severe AE[a]	208 (10.5)	18 (16.4)	48 (14.5)	193 (12.7)	267 (19.8)	526 (15.9)
≥ 1AE leading to dose adjustment	7 (< 1)	0	2 (< 1)	3 (< 1)	18 (1.3)	23 (< 1)
≥ 1 AE leading to temporary discontinuation of study medication	35 (1.8)	3 (2.7)	4 (1.2)	52 (3.4)	75 (5.6)	134 (4.1)
≥ 1 AE leading to permanent discontinuation of study medication	58 (2.9)	6 (5.5)	17 (5.2)	81 (5.3)	116 (8.6)	220 (6.7)
≥ 1 SAE	38 (1.9)	2 (1.8)	9 (2.7)	27 (1.8)	28 (2.1)	66 (2.0)
≥ 1 event with fatal outcome	1 (< 1)	0	1 (< 1)	1 (< 1)	0	2 (< 1)

PLA=placebo; PRU=prucalopride; AE=adverse event

[a] If the severity of the AE was missing, it was imputed as "severe".

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Note 1: Percentages were based on all patients in the safety set for Phase 2-4 double-blind, placebo-controlled studies of ≥ 4 weeks duration

Note 2: Patients were counted by the treatment most recently taken when the event occurred. Patients were counted once per category per treatment.

Source: Module 5.3.5.3, Table SAF D.08

7.3.1 Common Adverse Events (≥2%)

A summary of the most common AEs (i.e., occurring in ≥2% of patients in all prucalopride groups) in the Pooled Randomized DBPC studies is provided in Table 41. The most common AEs in the total prucalopride group were GI disorders (diarrhea, nausea, and abdominal pain) and nervous system disorders (headache). These 4 preferred terms were the only AEs reported in more than 5% of patients treated with the 2 mg* dose.

- Headache occurred in 19.4% of patients in the total prucalopride group and 9.4% of patients in the placebo group. A dose-dependent increase in AE incidence was observed for headache: 10.9% in the prucalopride 0.5 mg group, 13.3% in the prucalopride 1 mg group, 17.5% in the prucalopride 2 mg* group, and 23.8% in the prucalopride 4 mg group.
- Nausea occurred in 15.4% of patients in the total prucalopride group and 6.4% of patients in the placebo group. A dose-dependent increase in AE incidence was observed: 6.4% in

the prucalopride 0.5 mg group, 9.7% in the prucalopride 1 mg group, 13.6% in the prucalopride 2 mg* group, and 19.6% in the prucalopride 4 mg group.

- Diarrhea occurred in 12.0% of patients in the total prucalopride group and 3.6% of patients in the placebo group. A dose-dependent increase in AE incidence was observed: 4.5% in the prucalopride 0.5 mg group, 8.2% in the prucalopride 1 mg group, 11.8% in the prucalopride 2 mg* group, and 13.7% in the prucalopride 4 mg group.
- Abdominal pain occurred in 9.7% of patients in the total prucalopride group and 7.8% of patients in the placebo group and did not appear to be dose-dependent.

The majority of headache, nausea, abdominal pain, and diarrhea AEs was mild to moderate in severity. The incidence of severe AEs of headache, nausea, diarrhea, or abdominal pain was low, with only 2-3% of patients reporting severe events in any treatment group.

Table 41: Adverse Events Occurring in ≥2% of Patients in the Total Prucalopride Treatment Group by System Organ Class, Preferred Term, and Treatment Group in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)

	PLA N=1973	PRU 0.5 mg N=110	PRU 1 mg N=330	PRU 2 mg* N=1516	PRU 4 mg N=1349	Total PRU N=3305
	n (%)					
≥ 1 AE	1058 (53.6)	60 (54.5)	184 (55.8)	946 (62.4)	956 (70.9)	2146 (64.9)
Gastrointestinal disorders	519 (26.3)	32 (29.1)	94 (28.5)	561 (37.0)	607 (45.0)	1294 (39.2)
Nausea	126 (6.4)	7 (6.4)	32 (9.7)	206 (13.6)	264 (19.6)	509 (15.4)
Diarrhoea	72 (3.6)	5 (4.5)	27 (8.2)	179 (11.8)	185 (13.7)	396 (12.0)
Abdominal pain	153 (7.8)	7 (6.4)	22 (6.7)	151 (10.0)	141 (10.5)	321 (9.7)
Abdominal pain upper	49 (2.5)	4 (3.6)	13 (3.9)	52 (3.4)	72 (5.3)	141 (4.3)
Vomiting	42 (2.1)	5 (4.5)	7 (2.1)	51 (3.4)	70 (5.2)	133 (4.0)
Abdominal distention	78 (4.0)	0	5 (1.5)	63 (4.2)	58 (4.3)	126 (3.8)
Flatulence	55 (2.8)	3 (2.7)	11 (3.3)	47 (3.1)	66 (4.9)	127 (3.8)
Dyspepsia	34 (1.7)	2 (1.8)	4 (1.2)	28 (1.8)	42 (3.1)	76 (2.3)
Nervous system disorders	254 (12.9)	16 (14.5)	56 (17.0)	342 (22.6)	388 (28.8)	802 (24.3)
Headache	186 (9.4)	12 (10.9)	44 (13.3)	265 (17.5)	321 (23.8)	642 (19.4)
Dizziness	36 (1.8)	2 (1.8)	9 (2.7)	52 (3.4)	56 (4.2)	119 (3.6)
Infections and infestations	318 (16.1)	18 (16.4)	33 (10.0)	247 (16.3)	256 (19.0)	554 (16.8)
Nasopharyngitis	64 (3.2)	1 (< 1)	3 (< 1)	44 (2.9)	39 (2.9)	87 (2.6)
Influenza	47 (2.4)	1 (< 1)	5 (1.5)	36 (2.4)	34 (2.5)	76 (2.3)
Sinusitis	42 (2.1)	3 (2.7)	4 (1.2)	27 (1.8)	42 (3.1)	76 (2.3)
General disorders and administration site conditions	114 (5.8)	7 (6.4)	25 (7.6)	114 (7.5)	152 (11.3)	298 (9.0)
Fatigue	25 (1.3)	1 (< 1)	8 (2.4)	30 (2.0)	42 (3.1)	81 (2.5)
Musculoskeletal and connective tissue disorders	142 (7.2)	6 (5.5)	20 (6.1)	124 (8.2)	109 (8.1)	259 (7.8)
Back pain	48 (2.4)	1 (< 1)	11 (3.3)	37 (2.4)	31 (2.3)	80 (2.4)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PLA=placebo; PRU=prucalopride; PT=preferredterm; SOC=system organ class

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Note 1: Percentages were based on all patients in the safety set for Phase 2-4 double-blind, placebo-controlled studies of≥ 4 weeks duration

Note 2: Patients were counted by the treatment most recently taken when the event occurred. Patients were counted once perSOC and once per PT, per treatment group

Note 3: AEs were classified into SOC and PT using Version 16.0 of MedDRA.

Note 4: AEs were ordered by decreasing frequency in the total PRU group.

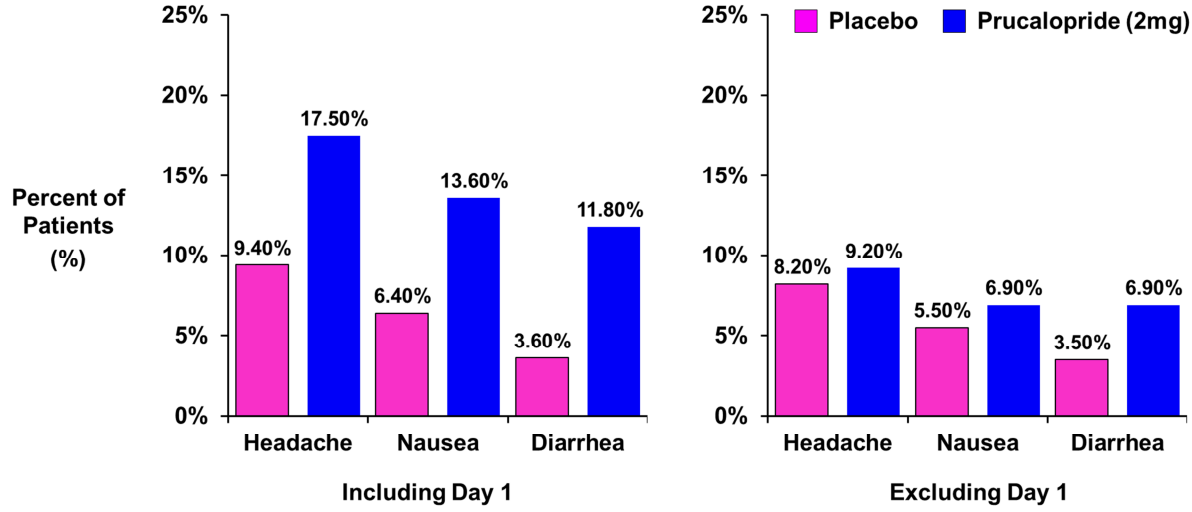
Source: Module 5.3.5.3, Table SAF D.09

7.3.2 Onset and Duration of Adverse Events

A large proportion of the events began on the first day of treatment and were transient in nature (lasting <5 days; Table 42). When excluding events that began with first dose (Figure 28), headache occurred in 9.2% of patients in the prucalopride 2 mg* group and 8.2% of patients in the placebo group; nausea occurred in 6.9% and 5.5% of patients, respectively; diarrhea occurred

in 6.9% and 3.5% of patients, respectively. These data suggest that the likelihood of an AE is markedly decreased after Day 1 of prucalopride treatment.

Figure 28: Incidence of Headache, Nausea, and Diarrhea Including Day 1 (Left Panel) and Excluding Day 1 (Right Panel) in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)



Source: Module 5.3.5.3, Table SAF D.09 and Table SAF D.15

Table 42: Incidence of Headache, Nausea, and Diarrhea Lasting >5 days

	PLA N=1973	PRU 0.5 mg N=110	PRU 1 mg N=330	PRU 2 mg* N=1516	PRU 4 mg N=1349	Total PRU N=3305
	n (%)					
Headache	88 (4.5)		12 (3.6)	93 (6.1)	91 (6.7)	197 (6.0)
Nausea	50 (2.5)		11 (3.3)	95 (6.3)	85 (6.3)	192 (5.8)
Abdominal pain	58 (2.9)		6 (1.8)	64 (4.2)	53 (3.9)	128 (3.9)
Diarrhea	10 (<1)		5 (1.5)	42 (2.8)	38 (2.8)	89 (3.7)

Note 1: Percentages were based on all subjects in the safety set for Phase 2-4 double-blind, placebo-controlled studies of ≥ 4 weeks duration

Note 2: Subjects were counted by the treatment most recently taken when the event occurred. Subjects were counted once per SOC and once per PT, per treatment group.

Source: Module 5.3.5.3, Table SAF D.16

7.4 Serious Adverse Events in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks

Overall, the incidence of SAEs in the Pooled Randomized DBPC studies was low and was not dose-dependent; 2.0% of patients in the total prucalopride group, 1.8% in the prucalopride 2 mg* group, and 1.9% in the placebo group reported ≥1 SAE.

An overview of the most common (i.e., ≥2 patients in the total prucalopride group) SAEs occurring in studies included in the Pooled Randomized DBPC studies ≥4 weeks is provided in Table 43.

In the prucalopride 2 mg* arm, no SAEs were reported more than once with the exception of abdominal pain, which occurred in 3 patients, and vaginal hemorrhage, which occurred in 2 patients.

Table 43: Serious Adverse Events Occurring in ≥2 Patients in the Total Prucalopride Treatment Group in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)

	PLA N=1973	PRU 0.5 mg N=110	PRU 1 mg N=330	PRU 2 mg* N=1516	PRU 4 mg N=1349	Total PRU N=3305
	n (%)					
≥ 1 SAE	38 (1.9)	2 (1.8)	9 (2.7)	27 (1.8)	28 (2.1)	66 (2.0)
Gastrointestinal disorders	7 (< 1)	1 (< 1)	1 (< 1)	5 (< 1)	4 (< 1)	11 (< 1)
Abdominal pain	3 (< 1)	0	0	3 (< 1)	1 (< 1)	4 (< 1)
Constipation	0	0	0	1 (< 1)	1 (< 1)	2 (< 1)
Infections and infestations	3 (< 1)	1 (< 1)	2 (< 1)	3 (< 1)	5 (< 1)	11 (< 1)
Bronchitis	0	0	0	2 (< 1)	0	2 (< 1)
Pneumonia	0	0	1 (< 1)	0	1 (< 1)	2 (< 1)
Surgical and medical procedures	7 (< 1)	0	1 (< 1)	2 (< 1)	8 (< 1)	11 (< 1)
Abdominoplasty	0	0	0	0	2 (< 1)	2 (< 1)
Hysterectomy	3 (< 1)	0	1 (< 1)	0	1 (< 1)	2 (< 1)
Umbilical hernia repair	0	0	0	0	2 (< 1)	2 (< 1)
Nervous system disorders	7 (< 1)	0	3 (< 1)	1 (< 1)	2 (< 1)	6 (< 1)
Headache	0	0	1 (< 1)	0	1 (< 1)	2 (< 1)
Reproductive system and breast disorders	3 (< 1)	0	0	4 (< 1)	1 (< 1)	5 (< 1)
Vaginal haemorrhage	1 (< 1)	0	0	2 (< 1)	1 (< 1)	3 (< 1)
Cardiac disorders	4 (< 1)	0	0	2 (< 1)	3 (< 1)	5 (< 1)
Atrial fibrillation	1 (< 1)	0	0	1 (< 1)	1 (< 1)	2 (< 1)
Supraventricular tachycardia	0	0	0	1 (< 1)	1 (< 1)	2 (< 1)
General disorders and administration site conditions	4 (< 1)	0	0	1 (< 1)	3 (< 1)	4 (< 1)
Chest pain	2 (< 1)	0	0	1 (< 1)	1 (< 1)	2 (< 1)
Psychiatric disorders	0	0	1 (< 1)	2 (< 1)	1 (< 1)	4 (< 1)
Anxiety	0	0	0	1 (< 1)	1 (< 1)	2 (< 1)

Table 43: Serious Adverse Events Occurring in ≥2 Patients in the Total Prucalopride Treatment Group in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)

	PLA N=1973	PRU 0.5 mg N=110	PRU 1 mg N=330	PRU 2 mg* N=1516	PRU 4 mg N=1349	Total PRU N=3305
	n (%)					

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PLA=placebo; PRU=prucalopride; PT=preferred term; SOC=system organ class

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Note 1: Percentages were based on all patients in the safety set for Phase 2-4 double-blind, placebo-controlled studies of ≥ 4 weeks duration

Note 2: Patients were counted by the treatment most recently taken when the event occurred. Patients were counted once per SOC and once per PT, per treatment group

Note 3: AEs were classified into SOC and PT using Version 16.0 of MedDRA.

Note 4: AEs were ordered by decreasing frequency in the total PRU group.

Source: Module 5.3.5.3, Table SAF D.10

7.5 Adverse Events Leading to Discontinuation in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks

Overall, 6.7% of patients in the total prucalopride group, 5.3% in the prucalopride 2 mg* group, and 2.9% in the placebo group reported ≥1 AE leading to discontinuation of study medication.

An overview of the most common AEs leading to discontinuation of study medication (i.e., occurring in ≥5 patients in the total prucalopride group) is provided in Table 44.

The most common AEs leading to discontinuation were GI disorders (diarrhea, nausea, and abdominal pain) and nervous system disorders (headache). All other individual AEs that led to the permanent discontinuation of study medication occurred in < 1% of patients in the total prucalopride group.

The incidence of events leading to discontinuation showed a dose-response, with incidences increasing with increasing doses of prucalopride. In the prucalopride 2 mg* dose group, diarrhea leading to discontinuation occurred in 1.5% of patients, nausea leading to discontinuation occurred in 1.3%, and headache leading to discontinuation occurred in 1.5%; all other events leading to discontinuation occurred in <1% of patients.

Table 44: Adverse Events Leading to Permanent Discontinuation of Study Medication Occurring in ≥5 Patients in the Total Prucalopride Treatment Group in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)

	PLA N=1973	PRU 0.5 mg N=110	PRU 1 mg N=330	PRU 2 mg* N=1516	PRU 4 mg N=1349	Total PRU N=3305
	n (%)					
≥ 1 AE leading to permanent discontinuation of study medication	58 (2.9)	6 (5.5)	17 (5.2)	81 (5.3)	116 (8.6)	220 (6.7)
Gastrointestinal disorders	29 (1.5)	3 (2.7)	9 (2.7)	53 (3.5)	87 (6.4)	152 (4.6)
Diarrhoea	2 (< 1)	1 (< 1)	5 (1.5)	22 (1.5)	43 (3.2)	71 (2.1)
Nausea	9 (< 1)	1 (< 1)	4 (1.2)	20 (1.3)	37 (2.7)	62 (1.9)
Abdominal pain	8 (< 1)	1 (< 1)	3 (< 1)	15 (< 1)	23 (1.7)	42 (1.3)
Vomiting	2 (< 1)	1 (< 1)	2 (< 1)	5 (< 1)	15 (1.1)	23 (< 1)
Abdominal pain upper	3 (< 1)	0	0	5 (< 1)	13 (< 1)	18 (< 1)
Abdominal discomfort	0	0	0	1 (< 1)	6 (< 1)	7 (< 1)
Nervous system disorders	16 (< 1)	2 (1.8)	6 (1.8)	27 (1.8)	56 (4.2)	91 (2.8)
Headache	9 (< 1)	2 (1.8)	5 (1.5)	22 (1.5)	41 (3.0)	70 (2.1)
Dizziness	2 (< 1)	0	1 (< 1)	5 (< 1)	13 (< 1)	19 (< 1)
Migraine	2 (< 1)	0	0	0	5 (< 1)	5 (< 1)
General disorders and administration site conditions	6 (< 1)	0	4 (1.2)	9 (< 1)	19 (1.4)	32 (< 1)
Fatigue	2 (< 1)	0	1 (< 1)	3 (< 1)	5 (< 1)	9 (< 1)
Asthenia	1 (< 1)	0	0	2 (< 1)	5 (< 1)	7 (< 1)
Musculoskeletal and connective tissue disorders	6 (< 1)	0	1 (< 1)	8 (< 1)	9 (< 1)	18 (< 1)
Muscle spasms	2 (< 1)	0	0	3 (< 1)	5 (< 1)	8 (< 1)
Cardiac disorders	3 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)	7 (< 1)	11 (< 1)
Palpitations	2 (< 1)	0	0	1 (< 1)	5 (< 1)	6 (< 1)
Metabolism and nutrition disorders	0	0	2 (< 1)	3 (< 1)	2 (< 1)	7 (< 1)
Decreased appetite	0	0	2 (< 1)	2 (< 1)	2 (< 1)	6 (< 1)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with AE; PLA=placebo; PRU=prucalopride; PT=preferred term; SOC=system organ class

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Note 1: Percentages were based on all patients in the safety set for Phase 2-4 double-blind, placebo-controlled studies of ≥ 4 weeks duration

Note 2: Patients were counted by the treatment most recently taken when the event occurred. Patients were counted once per SOC and once per PT, per treatment group.

Note 3: AEs were classified into SOC and PT using Version 16.0 of MedDRA.

Note 4: AEs were ordered by decreasing frequency in the total PRU group.

Source: Module 5.3.5.3, Table SAF D.13

7.6 Fatal Events

Overall, there were 8 events with fatal outcome across all Phase 2, 3, and 4 prucalopride studies, including the 16 Pooled Randomized DBPC studies in CIC (N=5,268) as well as open-label extensions of those studies (N=2,759). Of these 8 events with fatal outcome, 6 occurred in patients ≥70 years of age.

There were 3 events with fatal outcome during the Pooled Randomized DBPC studies (Table 45). Two of these events occurred in patients receiving prucalopride and 1 receiving placebo, all were elderly patients, and review of the cases did not indicate any relationship to treatment. The patient in the placebo group died from myocardial infarction and arrhythmia that were not considered related to the study medication by the investigator. The patients on prucalopride died from complications of lobar pneumonia and respiratory failure (prucalopride 1 mg group) and an AE of bronchitis (prucalopride 2 mg group). Both AEs were considered not related to study medication by the investigator. Full narratives for these events are found in Appendix 11.1.

Five events with fatal outcome occurred during the open-label extensions of the randomized studies, in which all patients were receiving prucalopride. Three events occurred after patients had discontinued prucalopride for 29, 52 and 67 days, respectively. All 5 events during the open-label extension studies were considered not related to study medication by the investigator.

Table 45: Summary of Events with Fatal Outcome in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks and Open-label Extensions

Age/Sex	Cause of Death	Dose	Studies	Duration of Treatment	Related
83 / M	Lobar pneumonia	1 mg	Randomized DBPC	11 days	Not related
86 / F	Bronchitis	2 mg	Randomized DBPC	31 days	Not related
89 / M	MI	Placebo	Randomized DBPC	7 days	Not related
81 / M	MI	2 mg	Open-label	67 days after discontinuation	Not related
89 / F	Pneumonia	2 mg	Open-label	218 days	Not related
56 / M	MI	2 mg	Open-label	48 days	Not related
70 / M	Suicide	2 mg	Open-label	29 days after discontinuation	Not related
40 / F	Suicide	4 mg	Open-label	52 days after discontinuation	Not related

F= female; M=male; MI=myocardial infarction

7.7 Cardiovascular Safety Evaluations

Cardiovascular safety investigations were conducted from 6 different sources:

- Substantive non-clinical testing at supra-therapeutic doses
- Thorough QT study and Phase 1 monitoring showing no clinically relevant cardiac repolarization effect
- Comprehensive review of the Phase 2-4 Pooled Randomized DBPC studies ≥ 4 weeks examining all reported preferred terms for cardiovascular AEs
- Independent, blinded expert adjudication of MACE in the Phase 2-4 Pooled Randomized DBPC studies ≥ 4 weeks
- A retrospective observational study (Study 802; Section 7.7.5) comparing prucalopride to matched controls treated with PEG
- Pharmacovigilance monitoring from 8 years post-marketing experience

Each data source supports the cardiovascular safety of prucalopride, and the totality of the data could not establish an increase in cardiovascular risk in patients with CIC treated with prucalopride. Additionally, negative findings from nonclinical studies on the effects of prucalopride on coronary artery contractility and platelet aggregation further support the cardiovascular safety.

7.7.1 In Vitro and In Vivo Nonclinical Testing

As part of safety pharmacology and toxicology programs, a comprehensive set of non-clinical studies with prucalopride at concentrations covering and exceeding the therapeutic dose was conducted in a variety of in vitro and in vivo models.

These investigations included studies to exclude all potential non-5-HT_4 receptor-mediated cardiovascular interactions that have been observed with cisapride and tegaserod.

The in vitro and in vivo non-clinical studies included:

- In vitro hERG channel studies (human)
- In vitro ion channel studies (guinea pig)
- In vitro electrophysiological studies (guinea pig, rabbit, and dog)
- In vitro platelet aggregation studies (human)
- In vitro coronary artery contractility studies (dog, pig, and human)
- In vitro chronotropic and inotropic effects studies (piglet and human)
- In vivo cardiovascular assessment studies (guinea pig, dog, and juvenile pig)
- In vivo proarrhythmia studies (rabbit)
- In vivo chronic toxicity studies (rat and dog)

The nonclinical safety pharmacology and toxicology evidence from these studies supports a wide cardiovascular safety margin. No relevant effects were seen on cardiovascular or cardiac electrophysiological parameters at concentrations of at least 50 times the therapeutic plasma concentrations in humans. In an in vitro study of human platelet aggregation, prucalopride (up to 200 nM; 10 times the therapeutic plasma concentrations) did not cause a statistically significant increase in platelet aggregation responses to a range of physiologically relevant platelet activators. In addition, at concentrations up to 10 μM (500 times the therapeutic plasma concentrations), there were no effects on contraction in porcine, canine, or human isolated left anterior descending coronary arteries, further demonstrating that prucalopride has no significant affinity or selectivity for 5-HT_{2A} and 5-HT_{1B} receptors. Importantly, there was no effect on the hERG channel at prucalopride concentrations up to 50 times the recommended clinical dose. There were no effects of prucalopride on other ion channels or proarrhythmia tendencies at concentrations up to 500 times the therapeutic dose.

These results support the conclusion that there is no apparent mechanism for an excess in cardiovascular risk with prucalopride – as supported by the high selectivity for the 5-HT_4 receptor.

7.7.2 Thorough QT and Phase 1 and 2 Studies with Enhanced ECG Monitoring

7.7.2.1 ECG and QT Clinical Investigations

Five studies were conducted to assess ECG and QT in subjects and patients treated with prucalopride at doses up to 20 mg QD. These studies demonstrated no relevant changes in blood pressure (systolic and diastolic) or QT in subjects and patients treated with supratherapeutic doses. However, a small, transient increase in HR (mean increase=3-8 bpm) was observed and returned to baseline before the next dose in most subjects (healthy volunteers). Based on systematic and comprehensive clinical cardiovascular review, these changes appear to have no effect on cardiovascular safety.

Thorough QT Study C102

The TQT Study C102 was a double-blind, randomized, placebo- and positive comparator-controlled, parallel study (with a 2-sequence crossover nested in the placebo arm) evaluating the effect of therapeutic and supratherapeutic multiple (2-10 mg dose escalation) doses of prucalopride on cardiac repolarization in 120 healthy subjects (males and females).

Subjects were administered a single dose of 2 mg prucalopride on each of Days 1 to 5, with dosing escalated by 2 mg/day to a maximum dose level of 10 mg on Days 6 to 9, and continued QD dosing with 10 mg prucalopride from Days 10 to 13. For prucalopride (2 mg and 10 mg), a small increase in HR relative to placebo was observed, but the increase did not exceed 6 bpm at any time point. This small increase in HR associated with exposure to prucalopride is a known effect and was not considered to be clinically relevant. The results from Study C102 confirm the absence of any clinically significant effect of prucalopride on cardiac repolarization: for both the therapeutic prucalopride dose of 2 mg and for the supratherapeutic dose of 10 mg, the mean differences in time-matched QTcSS change from baseline between prucalopride and placebo were all <5 msec and the upper limits of the corresponding 90% CIs were all <10 msec. A negative 'thorough QT/QTc study' is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 msec. This definition is chosen to provide reasonable assurance that the mean effect of the study drug on the QT/QTc interval is not greater than around 5 msec [ICH E14].

Furthermore, no subject had a QTcSS increase of > 60 msec that resulted in QTcSS >500 msec following either prucalopride 2 mg or prucalopride 10 mg. No significant correlation was demonstrated between plasma concentration and change in QTcSS interval. Based on the regression model, no QT interval increase is expected with increasing prucalopride plasma concentrations, at least up to 5 times the therapeutic dose.

No significant differences were seen between prucalopride and placebo in ECG morphologic changes or arrhythmias, and observed abnormalities were not considered to be of clinical relevance.

In conclusion, administration of prucalopride was safe and well tolerated in up-titrating doses up to supratherapeutic doses of 10 mg QD.

Study 26

Study 26 was a randomized, double-blind, dose-escalation safety study with extensive ECG assessments including Holter monitoring in 89 high-risk elderly patients with constipation who were living in a nursing facility. The mean age of the patients was 83 years, and 87.6% of these patients had a history of cardiovascular disease. Patients were treated with 0.5 mg, 1 mg, or 2 mg prucalopride QD or placebo for 4 weeks.

A resting 12-lead ECG was recorded immediately before and 3 hours after the first intake of study medication on Day 1, and again just prior to and 3 hours after study medication administration on Day 4, Day 7, Day 14, and Day 28 or at discontinuation.

Cardiologists performing the central reading of the ECGs evaluated abnormalities in the following areas: rhythm, arrhythmia, conduction, morphology, myocardial infarction, ST segment, T-waves and U-waves. All ECG measurements and interpretations were validated by a cardiologist experienced in ECG reading.

No relevant changes over time or differences between treatments were observed in supine pulse rate and systolic and diastolic blood pressure.

There was no relevant difference in HR between active and placebo treatment. No consistent or clinically relevant treatment-related differences were noted for PR, QT, QTcB, QTcF, linear corrected QT or QT dispersion. With regard to QRS, statistically significant differences were obtained for the prucalopride 0.5 mg vs. placebo comparison. A decrease in median QRS values was observed in the prucalopride 0.5 mg treatment group (range -8.00 to -3.00 msec) that was not seen in the placebo group (range -1.00 to +3.00 msec) or in the other prucalopride groups (range -1.00 to +5.00 msec and -1.00 to +1.00 msec for prucalopride 1 mg and 2 mg, respectively).

During Holter monitoring, no clinically significant differences in the incidence of possible proarrhythmic or supraventricular effects were observed, with the exception of a higher occurrence of non-sustained ventricular tachycardia in the placebo group vs. the prucalopride 2 mg group on Day 7. There were no events of sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes.

In conclusion, administration of prucalopride up to 2 mg QD for 4 weeks was well tolerated in this patient population.

Study 9

Study 9 was a double-blind, placebo-controlled, 2-period crossover study documenting the cardiovascular safety (measured by ECG and Holter monitoring) of prucalopride at doses up to 10 mg in 33 healthy subjects. Subjects' mean age was 26.2 years. Each treatment period consisted of a run-in day for baseline assessments, 8 treatment days, and 5 additional days for assessments. Subjects were randomized to start with either prucalopride or placebo treatment. During the prucalopride treatment period, the dose was consecutively escalated by 2 mg per day, starting from 2 mg up to 10 mg QD (supra-therapeutic dose=5 times the therapeutic dose) or until severe drug-related AEs occurred.

An increase in mean HR compared to baseline was observed during exposure to both prucalopride and placebo. The mean increase was higher when exposed to prucalopride compared to placebo, particularly at the 3-hour post-dose time-points (C_{max}), when the within-subject difference ranged from + 4.0 bpm (Day 7) to + 6.8 bpm (Day 2). The mean increase at 3 hours post-dose on Days 1 to 8 ranged from + 7.1 bpm (Day 2) to + 10.5 bpm (Day 7) with placebo and from + 12.8 bpm (Day 4) to + 17.0 bpm (Day 8) when exposed to prucalopride. Despite the daily increase in dose for prucalopride up to 10 mg, the difference in HR between treatment periods decreased. At steady-state (Day 8), the difference in HR between the study arms at 3 hours post-dose was + 6.1 bpm.

There was no effect of prucalopride on blood pressure, and there were no findings that were indicative of orthostatic hypotension. The ECG findings confirmed the effect on HR. Consistent with the increases in HR, decreases in QT values were observed. The QT shortening observed was appropriate and similar during both the prucalopride and placebo treatment periods, indicating a physiological reduction in QT upon increased HR. When correcting QT for HR using Fridericia's formula, only decreases from baseline were observed, during both the placebo and prucalopride treatment periods. No correlation was found between shifts in ECG parameters (HR, QT, QTc) and the corresponding prucalopride plasma concentrations.

All Holter monitoring results were normal.

This study demonstrates that prucalopride at doses up to 5 times the proposed therapeutic dose does not prolong QT. Overall, administration of prucalopride was safe and well tolerated in up-titrating doses up to supratherapeutic doses of 10 mg QD.

Study 10

Study 10 was a double-blind, placebo-controlled, 2-period crossover study documenting the cardiovascular safety (measured by ECG and Holter monitoring) of prucalopride at doses up to 20 mg in 32 healthy subjects. Subjects' mean age was 26.2 years. Each treatment period consisted of a run-in day for baseline assessments, 13 treatment days, and 5 additional days for assessments. Subjects were randomized to start with either prucalopride or placebo. During the prucalopride treatment period, the dose was consecutively escalated by 2 mg step per day, starting from 2 mg up to 20 mg QD (supra-therapeutic dose=10 times the expected recommended therapeutic dose) or until severe drug-related AEs occurred. There was a wash-out period of 14 to 21 days between the 2 treatment periods.

Heart rate increased 3 hours post-dose both during the placebo and prucalopride treatment periods. The mean increase was slightly higher during the prucalopride treatment period and more pronounced on Day 1. At 3 hours post dose (C_{max}), the increase in HR ranged from 4.1 bpm (Day 11 for the 20 mg prucalopride group) to 8.1 bpm (Day 1 for the 2 mg prucalopride group). These increases in HR returned toward baseline before the next dose, with pre-dose differences in HR ranging from 0.5 bpm (Day 13 for the 20 mg prucalopride group) to 4.8 bpm (Day 2 for the 2 mg prucalopride group). Despite a daily increase in prucalopride dose up to 20 mg, the difference in pulse rate between the treatments became less pronounced, and the effect was no longer present when treatment discontinued. There was no effect on blood pressure, and there were no findings that were indicative of orthostatic hypotension. The ECG findings confirm the effect on HR. Consistent with the increases in HR, decreases in QT values were observed. The QT shortening observed was appropriate and similar during both the prucalopride and placebo treatment periods, indicating a physiological reduction in QT upon increased HR. When correcting QT for HR using Fridericia's formula, only decreases from baseline were observed, during both the placebo and prucalopride treatment periods. No correlation was found between shifts in ECG parameters (HR, QT, QTc) and the corresponding prucalopride plasma concentrations.

This study demonstrates that prucalopride at doses up to 10 times the proposed therapeutic dose does not prolong QT, and there is a transient increase in HR. Overall, administration of prucalopride was safe and well tolerated in up-titrating doses up to supratherapeutic doses of 20 mg QD.

Study 15

Study 15 was a double blind, randomized, placebo-controlled, 2-period crossover study in 32 healthy subjects. The objectives of the study were to evaluate safety, with special regard to blood pressure and HR, after single and repeated doses of 2 mg and 4 mg prucalopride compared with placebo.

Each period started with a run-in day (Day 0). A single dose of prucalopride or placebo was taken on Day 1, followed by a 7-day once-daily regimen from Day 5 until Day 11. There was a washout period of at least 14 days between periods.

This study showed that the increases in HR seen at C_{max} were no longer present at the 8-hour timepoint.

The results of Study 15 demonstrated a small increase in HR, which was usually maximally observed within 1-3 hours after the first dose of prucalopride and lasted for 5-8 hours. The small increase in HR was observed again on Day 5 after a wash-out period of 4 days. The short-term increase did not disappear with repeated dosing (Day 11), although the effect at steady state tended to be somewhat less. Increases in HR were not considered to be clinically relevant and were not associated with any specific complaint. Additionally, a dose-relationship was not apparent.

In studies of longer duration longer, such as the Pooled randomized DBPC studies, vital signs were taken at monthly visits. In many of these studies, the timing of the measurement was not specified in relationship to the timing of the dose, so the vital signs and ECG were likely after dosing, at any point in the day. Table 46 shows the mean HR at baseline and week 12. The mean HR shows a 1 bpm increase over baseline at week 12 in the all PRU group compared to a 1.3 bpm increase in placebo patients.

Table 46: Mean Heart Rate (ECG) in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)

	PLA (N=1973)	PRU 2 mg* (N=1516)	PRU 4 mg (N=1349)	Total PRU (N=3305)
Baseline, Mean (SD)	66.8 (10.5)	67.5 (10.7)	67.2 (10.5)	67.6 (10.7)
Week 12, Mean (SD)	68.1 (11.0)	68.7 (10.3)	68.7 (10.6)	68.6 (10.4)

PLA=placebo, PRU=prucalopride

*Includes all patients titrated from prucalopride 1 mg to 2 mg

7.7.3 Cardiovascular Adverse Events in Clinical Studies

The database was searched for events related to cardiovascular and cerebrovascular ischemic-events, which included a search for the following adverse event terms:

> *ACUTE MYOCARDIAL INFARCTION, ANGINA PECTORIS, ANGINA UNSTABLE, CORONARY ARTERY DISEASE, CORONARY ARTERY OCCLUSION, CORONARY ARTERY STENOSIS, MYOCARDIAL INFARCTION, MYOCARDIAL ISCHAEMIA, TRANSIENT ISCHAEMIC ATTACK, ECG SIGNS OF MYOCARDIAL ISCHAEMIA, CEREBROVASCULAR ACCIDENT, ISCHAEMIC STROKE, ELECTROCARDIOGRAM ST SEGMENT DEPRESSION, CORONARY BYPASS THROMBOSIS, CORONARY ANGIOPLASTY, CORONARY ARTERY BYPASS, PARAPARESIS, PARESIS, HEMIPARESIS*

In the Pooled Randomized DBPC studies ≥ 4 weeks, the number of cardiovascular and cerebrovascular ischemic-related events was low, and incidences were comparable between the total prucalopride group (9 patients [0.3%]) and the placebo group (5 patients [0.3%]). The incidence of cardiovascular AEs in the prucalopride 2 mg* group was 0.4% (Table 47).

Two cases in the placebo group and no cases in the prucalopride group were considered severe. Two cases (0.1%) in the placebo group and 1 case in the prucalopride 2 mg* group (0.1%) led to permanent discontinuation of the study medication.

There were 6 serious cardiovascular AEs (3 each in the placebo and the prucalopride treatment group); narratives for the prucalopride events are provided in Appendix 11.5.

No events with fatal outcome associated with ischemic events were observed in the prucalopride group, 1 event with fatal outcome was reported in the placebo group (myocardial infarction in an 89-year-old patient with a history of atrial fibrillation on placebo).

All but 1 patient with an AE related to cardiovascular or cerebrovascular ischemic events had a past medical history that included cardiovascular risk factors. The patient (prucalopride 2 mg group) without a clear history showed ECG signs of myocardial ischemia that were later judged by a cardiologist to be insignificant. A narrative for this patient is found in Appendix 11.5.

Table 48 provides a breakdown of cardiovascular and cerebrovascular ischemic events by SOC and PT in the Pooled Randomized DBPC studies ≥4 weeks.

Table 47: Adverse Events Related to Cardiovascular and Cerebrovascular Ischemic Events (Unadjudicated Data) in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)

	PLA N=1973	PRU 0.5 mg N=110	PRU 1 mg N=330	PRU 2 mg* N=1516	PRU 4 mg N=1349	Total PRU N=3305
	n (%)					
≥ 1 AE	5 (0.3)	0	0	6 (0.4)	3 (0.2)	9 (0.3)
≥ 1 severe AE [a]	2 (0.1)	0	0	0	0	0
≥ 1 SAE	3 (0.2)	0	0	2 (0.1)	1 (0.1)	3 (0.1)
≥ 1 event with fatal outcome	1 (0.1)	0	0	0	0	0
≥ 1AE leading to dose adjustment	0	0	0	0	0	0
≥ 1 AE leading to temporary discontinuation of study medication	0	0	0	0	1 (0.1)	1 (0.03)
≥ 1 AE leading to permanent discontinuation of study medication	2 (0.1)	0	0	1 (0.1)	0	1 (0.03)

AE= adverse event; PLA=placebo; PRU=prucalopride; SAE=serious adverse event

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

If the severity of the AE was missing, it was imputed as "severe".

Note 1: Percentages were based on all patients in the safety set for Phase 2-4 double-blind, placebo-controlled studies of ≥ 4 weeks duration

Note 2: Patients were counted by the treatment most recently taken when the event occurred. Patients were counted once per category per treatment.

Source: Module 5.3.5.3, Table SAF.DX04.0

Table 48: Cardiovascular and Cerebrovascular Ischemic Events by System Organ Class and Preferred Term (Unadjudicated Data) in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)

	PLA N=1973	PRU 0.5 mg N=110	PRU 1 mg N=330	PRU 2 mg* N=1516	PRU 4 mg N=1349	Total PRU N=3305
	n (%)					
≥ 1 AE	5 (0.3)	0	0	6 (0.4)	3 (0.2)	9 (0.3)
Cardiac disorders	4 (0.2)	0	0	3 (0.2)	3 (0.2)	6 (0.2)
Coronary artery occlusion	0	0	0	2 (0.1)	0	2 (0.1)
Angina pectoris	1 (0.1)	0	0	0	1 (0.1)	1 (0.0)
Angina unstable	0	0	0	0	1 (0.1)	1 (0.0)
Coronary artery disease	1 (0.1)	0	0	0	1 (0.1)	1 (0.0)
Myocardial infarction	1 (0.1)	0	0	0	1 (0.1)	1 (0.0)
Myocardial ischaemia	1 (0.1)	0	0	1 (0.1)	0	1 (0.0)
Investigations	0	0	0	1 (0.1)	0	1 (0.0)
ECG signs of myocardial ischaemia	0	0	0	1 (0.1)	0	1 (0.0)
Nervous system disorders	1 (0.1)	0	0	2 (0.1)	0	2 (0.1)
Cerebrovascular accident	0	0	0	1 (0.1)	0	1 (0.0)
Transient ischemic attack	0	0	0	1 (0.1)	0	1 (0.0)
Ischaemic stroke	1 (0.1)	0	0	0	0	0

AE=adverse event; PLA=placebo; PRU=prucalopride; PT=preferred term; SOC=system organ class;

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Note 1: Percentages were based on all patients in the safety set for Phase 2-4 DBPC studies of ≥ 4 weeks duration

Note 2: Patients were counted by the treatment most recently taken when the event occurred. Patients were counted once per SOC and once per PT.

Note 3: AEs were classified into SOC and PT using Version 19.1 of MedDRA.

Source: Module 5.3.5.3, Table SAF.DX.04

7.7.4 Independent Adjudication for MACE in Clinical Program

Shire commissioned an independent adjudication committee to evaluate all potential MACE from the Pooled Randomized DBPC studies ≥ 4 weeks duration in patients with CIC as part of the extensive evaluation of the cardiovascular safety of prucalopride. The independent panel of experts established prespecified selection criteria used to screen the entire dataset for possible MACE. This panel reviewed and adjudicated all identified cases of possible MACE, as well as unstable angina requiring hospitalization (extended MACE), and either confirmed or refuted the events using strict, prespecified criteria.

Overall, the incidence of MACE during the CIC clinical studies was low and demonstrated no difference in ischemic cardiovascular events between placebo and prucalopride. A total of 218 cases in 173 patients were selected for MACE adjudication. From these cases selected for MACE adjudication, 170 cases (in 128 patients) were cases in patients with CIC.

In the randomized DBPC CIC studies, there were only 2 patients with standard MACE and 2 additional patients with extended MACE in the prucalopride group, as well as 2 patients with standard MACE in the placebo group (Table 49). These numbers translate to an incidence rate of 3.5 patients and 5.2 patients per 1,000 patient-years in the prucalopride and placebo group, respectively, for standard MACE and 7.1 and 5.2 per 1,000 patient years, respectively, for extended MACE (Table 50).

Independent adjudication of the open-label extension studies aligns with and supports the conclusions from the randomized, placebo-controlled portion of studies.

Table 49: Summary of Adjudication Information in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)

	PLA N=2019		PRU					
			PRU All Doses [a] N=3366		PRU 2 mg* N=1545		PRU 4 mg N=1369	
	n (%)	***m***	**n (%)**	***m***	**n (%)**	***m***	**n (%)**	***m***
Standard MACE	**2 (0.1)**	***2***	**2 (0.1)**	***2***	**1 (0.1)**	***1***	**1 (0.1)**	***1***
Extended MACE	**2 (0.1)**	***2***	**4 (0.1)**	***4***	**1 (0.1)**	***1***	**3 (0.2)**	***3***
MACE (Separate Categories)								
Cardiovascular event with fatal outcome	1 (0.0)	*1*	0	*0*	0	*0*	0	*0*
Nonfatal MI	0	*0*	1 (0.0)	*1*	0	*0*	1 (0.1)	*1*
Nonfatal stroke	1 (0.0)	*1*	1 (0.0)	*1*	1 (0.1)	*1*	0	*0*
Unstable angina requiring hospitalization	0	*0*	2 (0.1)	*2*	0	*0*	2 (0.1)	*2*

CV=cardiovascular; MACE=major adverse cardiac event; MI=myocardial infarction; m=number of events; n=number of patients with an event; NA=not applicable; PLA=placebo; PRU=prucalopride

a Includes the prucalopride 0.5-1, 2, and 4 mg treatment groups

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Source: Module 5.3.5.3, MACE Report, Section 3.1.4.1, Table 6

Table 50: Incidence of Standard and Extended MACE (Safety Population)

	PLA N=2019		PRU						All PRU [b] (DB and OL) N=4476	
			PRU All Doses [a] N=3366		PRU 2 mg* N=1545		PRU 4 mg N=1369			
	Patient-years Exposure	*Incidence (Rate/1000 PYE)*	Patient-years Exposure	*Incidence (Rate/1000 PYE)*	Patient-years Exposure	*Incidence (Rate/1000 PYE)*	Patient-years Exposure	*Incidence (Rate/1000 PYE)*	Patient-years Exposure	*Incidence (Rate/1000 PYE)*
Standard MACE	384.0	5.2	565.2	3.5	319.3	3.1	202.5	4.9	2768.9	3.3
Extended MACE	384.0	5.2	565.2	7.1	319.3	3.1	202.5	14.8	2768.9	5.4

DB=double-blind; MACE=major adverse cardiac event; OL=open-label; PLA=placebo; PRU=prucalopride; PYE=patient-years exposure

*Includes all patients titrated from prucalopride 1 mg to 2 mg.

Source: Module 5.3.5.3, MACE Report, Section 3.1.4.2, Table 9

Additional analyses of MACE by sex and age in the double-blind studies showed no evidence of an excess in cardiovascular risk in any demographic (Table 51).

Table 51: Incidence of Standard and Extended MACE by Sex and Age (Safety Population)

	Standard MACE							
	PLA		PRU 2 mg*		PRU 4 mg		PRU Total	
	N	MACE	N	MACE	N	MACE	N	MACE
Standard MACE								
Male	410	2	339	1	177	0	583	1
Female	1609	0	1206	0	1192	1	2783	1
≤ 65 years	1723	0	1265	0	1168	0	2729	0
> 65 years	296	2	280	1	201	1	637	2
Extended MACE								
Male	410	2	339	1	177	1	583	2
Female	1609	0	1206	0	1192	2	2783	2
≤ 65 years	1723	0	1265	0	1168	1	2729	1
> 65 years	269	2	280	1	201	2	637	3

MACE=major adverse cardiac event; PLA=placebo; PRU=prucalopride;
*Includes all patients titrated from prucalopride 1 mg to 2 mg.
Source:
Module 5.3.5.3, MACE Report, Section 3.1.4.2, Table 10

7.7.5 Pharmacoepidemiology Study 802: Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort

7.7.5.1 Study Design

Study 802 was an observational (noninterventional) population-based cohort study of patients initiating prucalopride or PEG from UK, Sweden, and Germany.

This study was implemented in 5 administrative health care data sources in 3 countries: in the UK, 2 data sources derived from electronic medical records from general practices – the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN) – and the Information Services Division (ISD) of Scotland, an administrative health care data source; in Sweden, the Swedish National Registers (SNR) including health data from the National Patient Register, the Prescribed Drug Register, the National Cancer Register, the Cause-of-Death Register, and information from the Total Population Register; and in Germany, the German Pharmacoepidemiological Research Database (GePaRD), constructed from claims of statutory health insurance agencies. Patients and practices that could potentially be included in multiple UK data sources were retained in only 1 data source.

The incidence rate of MACE for prucalopride and PEG users and the adjusted IRRs and incidence rate differences (IRDs) of MACE comparing prucalopride to PEG use were calculated individually for each data source and after pooling the aggregated results from UK and Sweden. Data from Germany was excluded from the pooled analyses, as the patient population was markedly different compared to the other countries in terms of comorbidities because of differences in prescribing and reimbursement practices between prucalopride and PEG.

Subjects and Study Size

The prucalopride cohort consisted of adult patients who had a dispensing (for claims data sources) or prescription (as recorded in electronic medical record data sources) for prucalopride within the study period with at least 12 months of data coverage in the data source before this first dispensing or prescription, no evidence in the data source of prior use of prucalopride, and no evidence of short use of PEG (i.e., < 5 days) within 12 months before this first prucalopride prescription/dispensing.

The PEG cohort consisted of patients who had a dispensing or prescription for PEG of at least 5 days within the study period, at least 12 months of data coverage in the data source before this first dispensing or prescription, and no evidence of prior use of PEG for chronic constipation in the data source. The first prescription for PEG was the index prescription, prescribed or dispensed on the index date. Up to 5 PEG initiators were selected for each prucalopride initiator, matched by age, sex, and calendar year of first prescription of prucalopride or PEG. (The SNR also matched patients by recent hospitalization and specialty of the prescribing physician to increase comparability between PEG and prucalopride users). At the time of study initiation, PEG was the most commonly prescribed reimbursable medication for chronic constipation in Europe.

The study size was driven by the number of prucalopride initiators and associated duration of exposure that was available in the selected data sources during the study period. Per study protocol, it was estimated that 10,950 prucalopride new users would be sufficient to reach, with 80% probability, an upper bound of the two-sided 95% CI of the IRR of less than 3 if the true IRR is 1.0 and the baseline rate of MACE is 2 per 1,000, with assumed average prucalopride treatment duration of 130 days.

Variables and Data Sources

Prucalopride or PEG exposure was ascertained from general practitioner prescriptions in the CPRD and THIN data and by outpatient dispensing in the ISD, GePaRD, and SNR data. Cardiovascular risk factors and other covariates were identified from the available health care utilization codes before the index date.

The primary endpoint, MACE, comprised the first occurrence of any of its individual components during follow-up. The cardiovascular endpoints of interest were identified by applying modified versions of existing algorithms of diagnosis codes from published pharmacoepidemiologic studies to data from hospital admissions and discharge diagnoses. In the CPRD and THIN, validation of outcomes was conducted by obtaining, as available, linkage to Hospital Episode Statistics discharge diagnoses and to Office for National Statistics death records (CPRD only), general practitioner questionnaires (CPRD only), and review of free-text comments (THIN only). In the ISD of Scotland, validation of outcomes was conducted through medical chart abstraction. For cases in the UK data sources, an adjudication committee of 3 clinical experts determined final status. Cases included in Sweden were identified using modifications of electronic algorithms previously validated in the Swedish registers.

Analyses

For each cohort, the prevalence of known risk factors for MACE at baseline was described. Crude and standardized incidence rates of each outcome of interest were calculated for the prucalopride and PEG cohorts by categories of each covariate of interest, and corresponding crude and standardized IRRs and IRDs were estimated.

Within each data source, propensity scores were developed using logistic regression with prucalopride versus PEG as the outcome and included variables shown to be potential confounders, including cardiovascular risk factors. To optimize comparability of cohorts, the propensity score distributions of prucalopride and PEG cohorts were evaluated, and individuals below percentile 1 of the prucalopride distribution and above percentile 99 of the PEG distribution were trimmed from the cohorts, which eliminated all patients with nonoverlapping propensity score. Incidence rates, IRRs, and IRDs were standardized against person-years in the prucalopride cohort and stratified by data source and propensity score decile. For the main analysis, incidence was calculated as number of events/time of treatment plus 7 days, assuming any treatment-related cardiovascular risk would not carry over after treatment discontinuation. Sensitivity analyses included extended time (30 days and all follow-up time (after discontinuation).

For the UK data sources, where validation was conducted, a sensitivity analysis of the primary analysis was performed in which cases classified as "probable" were additionally included as events following review by the adjudication committee. An additional sensitivity analysis was conducted for all data sources to assess the impact of including out-of-hospital cardiovascular events with fatal outcome in the MACE composite endpoint. A bias analysis was conducted to determine the potential impact of unmeasured confounding assuming different scenarios of prevalence of the confounders and their association with the outcome.

Post hoc subgroup analyses by sex, age, sex by age, and history of cardiovascular disease were conducted for the primary pooled analysis per FDA request after the planned analyses had been initiated.

Results

The pooled analyses of aggregate data included 35,087 patients with chronic constipation treated with prucalopride (n=5,715) or PEG (n=29,372), including 5,120 matched patients from the CPRD, 3,044 from THIN, 6,960 from the ISD, and 19,963 from the SNR. The average duration of cumulative prucalopride and PEG use after the index date was approximately 175 days and 82 days, respectively. For details of patient attrition, see Table 61 in Appendix 11.6.

In all data sources, the vast majority of patients were women (i.e., 95% in the CPRD and THIN, 96% in ISD of Scotland, and 91% in Sweden), and the proportion of patients aged 55 years and older was roughly similar in the UK data sources (34% in the CPRD, 31% in THIN, and 21% in ISD) and higher in Sweden (53%). In general, patients on prucalopride had more baseline GI comorbidities, whereas PEG patients tended to have more baseline cardiovascular diseases in

CPRD, THIN, and SNR and more baseline history of cancer in all data sources (see Table 62 in Appendix 11.6).

Crude and standardized incidence rates, incidence rate ratios and incidence rate differences overall and by country are presented in Table 52. The higher incidence rates in Sweden may reflect the older age distribution and the fact that case ascertainment was based only on electronic records using previously validated algorithms without further case adjudication.

The pooled standardized incidence rates (95% CI) of MACE among patients initiating prucalopride per 1,000 person-years was 6.57 (3.90-10.39) and 10.30 (7.03-14.19) for PEG. The overall pooled adjusted IRR for MACE (i.e., combining the 3 UK data sources and the SNR) was 0.64 (95% CI, 0.36-1.13). The pooled adjusted IRD for MACE combining the 3 UK data sources and the SNR was –3.73 per 1,000 person-years (95% CI, –8.34 to 0.89). The pooled adjusted IRRs for individual components of MACE were 1.06 (95% CI, 0.44-2.57) for hospitalization for nonfatal acute myocardial infarction, 0.58 (95% CI, 0.25 1.31) for hospitalization for nonfatal stroke, and 0.47 (95% CI, 0.13-1.67) for in hospital cardiovascular events with fatal outcome.

Table 52: Incidence Rates, Incidence Rate Ratios, and Incidence Rate Differences of Major Adverse Cardiovascular Events, Acute Myocardial Infarction, Stroke, and Cardiovascular Events with Fatal Outcome in the Prucalopride and PEG Cohorts

	Prucalopride				PEG					
Outcome	N	No. Events	Person Years	Standardized Incidence Rate per 1,000 person years (95% CI)[a]	N	No. Events	Person Years	Standardized Incidence Rate per 1,000 Person Years (95% CI)[a]	Standardized Incidence Rate Ratio (95% CI)[a]	Standardized Incidence Rate Difference per 1,000 Person Years (95% CI)[a]
MACE[b]	5,715	18	2,738	6.57 (3.90, 10.39)	29,372	74	6,564	10.30 (7.03, 14.19)	0.64 (0.36, 1.13)	-3.73 (-8.34, 0.89)
Hospitalization for non-fatal acute MI	5,715	8	2,741	2.92 (1.26, 5.75)	29,372	22	6,586	2.74 (1.41, 4.58)	1.06 (0.44, 2.57)	0.18 (-2.34, 2.69)
Hospitalization for non-fatal stroke	5,715	9	2,741	3.28 (1.50, 6.23)	29,372	39	6,573	5.70 (3.10, 9.01)	0.58 (0.25, 1.31)	-2.42 (-5.97, 1.13)
In-hospital cardiovascular events with fatal outcome	5,715	3	2,744	1.09 (0.23, 3.20)	29,372	19	6,595	2.35 (1.11, 4.10)	0.47 (0.13, 1.67)	-1.26 (-3.13, 0.62)

CI=confidence interval; MACE=major adverse cardiovascular events; MI=myocardial infarction; PEG=polyethylene glycol.

[a] Incidence rates, incidence rate ratio, and incidence risk difference are standardized against the person-years in the prucalopride cohort, stratified according to study source and propensity score decile.

[b] MACE includes the following components: hospitalization for non-fatal acute MI, hospitalization for non-fatal stroke, and in-hospital cardiovascular death.

The IRR and IRD results were robust to the alternative definitions of the MACE endpoints that added out-of-hospital cardiovascular events with fatal outcome (IRR: 0.43 (95% CI, 0.25 to 0.73)) in all data sources and probable cases to the definition of MACE (and possible in-hospital cardiovascular events with fatal outcome) in the UK and probable cases to the definition of MACE (and possible in-hospital cardiovascular events with fatal outcome), as well as to bias analyses that considered the hypothetical impact of unmeasured confounding in different scenarios of confounder prevalence and association with the outcomes. The results were also consistent across all subgroups favoring prucalopride over PEG with the exception of men older than 55 years where an IRR of 2.57 (95% CI, 0.71-9.27) was observed based on 4 events in the prucalopride cohort (n=247) and 11 events in the PEG cohort (n=1176).

Although Germany was not included in the main analyses, results are included for transparency. In Germany, after trimming, 30,714 matched patients from GePaRD (88% female and 66% aged 55 years and older) were identified. In general, fewer patients on prucalopride had history of comorbid conditions at baseline compared to PEG patients. The standardized incidence rate of MACE per 1,000 person-years was 11.05 (95% CI, 8.03-14.69) for prucalopride and 21.53 (95% CI, 18.52-24.78) for PEG. The adjusted IRR for MACE was 0.51 (95% CI, 0.37-0.71), and the adjusted IRD for MACE was –10.48 (95% CI, –14.99 to –5.98

Discussion

The primary objective of this study was to estimate, in real-world settings, the IRR and 95% CI for MACE in initiators of prucalopride compared with initiators of PEG, adjusting for potential confounders. More specifically, the study aimed to investigate whether the upper bound of the two-sided 95% CI for the adjusted IRR was less than 3.00. The pooled point estimate of the IRR was 0.64 (95% CI, 0.36-1.13), with a 95% CI that included the null value and an upper limit below 3.00. Thus, the results do not show evidence of an increased risk of MACE overall among patients with chronic constipation using prucalopride. Differences in baseline comorbidities between the prucalopride and PEG cohorts were minimized after standardization by propensity score decile and data source included in the final pooled analyses.

In the sensitivity analyses using alternative definitions of the MACE study endpoint, the results were consistent with those from the main, pooled analysis. The main results were also robust to potential unmeasured confounders.

7.8 Laboratory Findings

A summary of biochemistry and hematology parameters at Baseline and Week 12 is provided in Table 63 in Appendix 11.7. Laboratory parameters were reviewed to detect changes over time. Overall, there were no consistent or clinically relevant treatment-related trends. Mean changes were generally small, and comparable between prucalopride and placebo treatment groups. No clinically relevant dose-effect was observed.

7.9 Potential for Withdrawal and Rebound

The potential withdrawal and rebound effects of prucalopride were investigated in Studies PRU-USA-3 and PRU-USA-28 and showed no evidence that prucalopride induced withdrawal or rebound effects and most subjects' bowel status returned to pre-treatment levels.

Examination of the safety parameters (AE profile and abnormalities for clinical laboratory, vital signs and ECG) during washout periods and during follow-up periods after last intake of study medication showed that the overall safety/tolerability profile of prucalopride was not impacted by interruption or discontinuation of treatment. These findings suggest that interruption or discontinuation of prucalopride is unlikely to result in worsening of constipation.

7.10 Safety Conclusions

In Pooled Randomized DBPC studies ≥4 weeks, a total of 3,295 patients with CIC were exposed to prucalopride for a mean of 64.2 days. In addition, in the long-term open-label studies, 2,595 patients were exposed to prucalopride.

In the Pooled Randomized DBPC studies ≥4 weeks, 62% of patients in the prucalopride 2 mg* group reported ≥1 AE compared to 54% in the placebo group. Only headache, nausea, diarrhea, and abdominal pain were reported with an incidence of greater than 5%. These events occurred at a higher rate with prucalopride compared to placebo and were consistently reported in the 16 randomized controlled studies.

The majority of events were mild to moderate in intensity, and the incidence of severe AEs was low (13% prucalopride 2 mg* and 11% placebo). Most events were transient and lasted <5 days.

The rate of SAEs was similar between prucalopride 2 mg* and placebo (2% for both). Abdominal pain, vaginal hemorrhage, and hysterectomy were the only SAEs reported in ≥3 patients. Compared to placebo, slightly more patients receiving prucalopride experienced AEs leading to discontinuation (5% prucalopride and 3% placebo). The most common AEs leading to discontinuation were headache, nausea, and diarrhea.

There was a total of 8 events with fatal outcome across all Phase 2-4 studies including Pooled Randomized DBPC studies ≥4 weeks and their open-label extension studies. Three events with fatal outcome occurred during the randomized studies: 2 with prucalopride (1 with 1 mg and 1 with 2 mg) and 1 with placebo. All 3 of these events were evaluated by the investigator as not related to treatment. An additional 5 events with fatal outcome occurred during open-label extension studies when all patients received prucalopride, all of which were evaluated by the investigator as not related to treatment.

An in-depth safety assessment demonstrated that prucalopride does not increase the risk for cardiovascular events. A comprehensive review of the pooled randomized studies showed a low cardiovascular risk with prucalopride, similar to that with placebo. Independent expert adjudication of all potential MACE and extended MACE cases confirmed very low rates of events and similarity between the prucalopride and placebo groups. The independent adjudication committee concluded that there are no signs suggestive of increased cardiovascular

risk with prucalopride. Prucalopride is not associated with QT prolongation or attendant sequelae. In healthy subjects, a transient increase in heart at C_{max} (3 hours) resolved before the next dose and was not observed in random measurements of HR in studies with patients.

Shire also sponsored a pharmacoepidemiology study (Study 802) comparing MACE among patients treated with prucalopride and patients treated with PEG. The study found no signal of increased cardiovascular risk with prucalopride.

The clinical safety profile of prucalopride is also supported by over 282,000 years of patient exposure since its initial approval in the EU in 2009. Across 8 years of real-world experience, the majority of reported post-marketing AEs have been non-serious, and no cardiovascular signal has been detected.

Overall, prucalopride consistently demonstrated a well-tolerated safety profile.

8. NON-US POST-MARKETING PRUCALOPRIDE EXPERIENCE

Safety concerns are monitored with routine pharmacovigilance activities including the use of targeted questionnaires to follow-up on cases of palpitations, cardiovascular and cerebrovascular ischemic events, QT prolongation, torsades de pointes and syncope, and safety in patients with severe and unstable cardiovascular disease.

The benefit-risk profile of prucalopride is thoroughly reviewed on an ongoing basis, via regular (and ad hoc) cross-functional review of clinical, post-marketing, nonclinical, literature, and other data. Shire's Global Drug Safety performs continuous signal detection, safety monitoring, and evaluations for prucalopride, as governed by Shire's standard operating procedures. Safety data from all sources including literature are monitored, reviewed, and evaluated to identify potential safety signals. Results of signal detection are presented to and assessed by a multi-disciplinary panel of subject matter experts at Safety Review Team meetings, which take place routinely (biannually), as well as on an ad hoc basis as necessary. Postmarketing data also include safety reported from investigator-sponsored studies.

Periodic safety update reports (PSURs) are produced for prucalopride annually, providing a review of worldwide safety data from both Shire territories (i.e., the US, EU, Switzerland, Lichtenstein, Iceland, and Norway) and Janssen territories (i.e., the rest of the world). Shire maintains a robust Safety Exchange agreement with Janssen, detailing all aspects relating to the exchange of safety information between the 2 marketing authorization holders.

As of 14 Oct 2017 (the data-lock point for the last PSUR), 6 biannual and 4 annual PSURs were produced for prucalopride. To supplement the NDA submission to the FDA, Shire is providing an overview of safety data since the international birthdate of prucalopride (15 Oct 2009), which includes a summary of the identified/potential risks, patient exposure data, changes to product labeling, and a review of the ADR reporting pattern observed in the postmarketing environment. This information provides supportive evidence of the stable safety profile and favorable benefit-risk profile of prucalopride, and Shire's commitment to thorough monitoring of safety data.

In addition to routine pharmacovigilance, special questionnaires are sent out to request follow-up for the following cases:

- Palpitations
- Cardiovascular and cerebrovascular ischemic events
- QT prolongation, torsade de pointes and syncope
- Safety in patients with severe and unstable cardiovascular disease
- Safety in pregnant women

Routine risk minimization measures by means of the Summary of Product Characteristics and package leaflet are deemed sufficient to ensure appropriate use and manage the risks of prucalopride. No additional risk minimization activities are mandated or requested by health authorities.

Based on the marketing data, the estimate of cumulative patient exposure to prucalopride is 58,940 person years of treatment in the current interval and 282,535 person-years of treatment through October 2017 since launch. As of 30 Apr 2017, a total of 5072 postmarketing ADRs were reported in patients receiving prucalopride. The majority of postmarketing ADRs are non-serious, spontaneously reported, and most are listed in accordance with the company core data sheet.

No postmarketing ADRs were added to the product labeling based on the safety evaluations since launch.

Overall, information received from postmarketing sources does not support an increased risk for cardiovascular or ischemic events with the use of prucalopride. Furthermore, in real-world epidemiological Study 802 (Section 7.7.5) the overall preplanned pooled analyses did not reveal an increased risk of MACE in patients using prucalopride compared with PEG.

No changes to reference safety information by any non-US health authority were recommended based on any of the postmarketing safety evaluations.

9. BENEFIT RISK ANALYSIS

Prucalopride is the first highly selective and high-affinity 5-HT_4 receptor agonist that has shown prokinetic effects in both dogs and humans. The product's mechanism of action is different than that of other available treatments for CIC. Treatment with prucalopride leads to improvements in frequency of BMs, bowel symptoms, and health-related quality of life. The potential risks to the patient consist predominantly of GI symptoms, such as nausea, diarrhea, and headache. These symptoms are mostly mild to moderate in intensity and unlikely to lead to discontinuation. Prucalopride has a favorable PK profile, with no significant drug-drug interactions.

In all 6 studies included in the efficacy evaluation, the primary efficacy endpoint was the proportion of patients with ≥3 CSBMs/week over 12 weeks (or 24 weeks in Study 401) of treatment. The primary endpoint was met in 5 of these studies. In Study 401, the primary efficacy results were not statistically significant, though the results from this study were inconsistent with what has been previously demonstrated in the other studies. In all 6 studies, alternatives for the primary endpoint using different responder definitions were consistent with what was observed in the prespecified analyses.

Furthermore, prucalopride demonstrated numerically and/or statistically significantly different results compared with placebo on a variety of secondary efficacy endpoints across studies. Secondary endpoints included the proportion of patients with an average increase of ≥ 1 CSBM, the increase in average number of CSBMs, the time to first CSBM, and improvement in PAC-SYM and PAC-QOL scores.

Prucalopride established a consistent treatment effect across studies on the primary, alternative, and secondary endpoints. Overall, these results provide conclusive evidence of the efficacy of prucalopride in a population of patients with CIC.

In Pooled Randomized DBPC studies ≥4 weeks, a total of 3,295 patients were exposed to prucalopride (doses of 0.5-4 mg QD or BID) for a mean of 64.2 days.

The most common AEs were GI disorders (diarrhea, nausea, and abdominal pain) and nervous system disorders (headache).

The cardiovascular safety, and more particularly, the risk of ischemic (MACE) events was further investigated through the adjudication of all potential MACE from completed Phase 2-4 clinical studies and open-label extensions with prucalopride by an independent adjudication committee. Following detailed adjudication, there were 2 patients with standard MACE (cardiovascular event with fatal outcome, nonfatal myocardial infarction, and nonfatal stroke) and 2 additional patients with extended MACE (standard MACE plus unstable angina requiring hospitalization) in the prucalopride group and 2 patients with standard MACE in the placebo group.

The risk of ischemic MACE assessed in a pharmacoepidemiology study (Study 802) evaluating the relative incidence of MACE in patients using prucalopride versus that in a matched comparator cohort showed no evidence of an overall increased risk of MACE in patients using prucalopride compared with patients using PEG for chronic constipation.

Taken together, results from the evaluation of cardiovascular and cerebral ischemic events in the clinical database, the separate independent adjudication of MACE, and the epidemiology study evaluating the incidence of MACE do not indicate that prucalopride use is associated with an increased incidence of ischemic cardiovascular events. Furthermore, prucalopride is not associated with QT prolongation or arrhythmia.

The generalizability of the data to a population of patients from the US was assessed by comparing the rate of responders on the primary efficacy endpoint and the incidence of AEs in patients from within and outside of the US. An analysis comparing North America vs Western Europe, Eastern Europe, and Asia-Australia showed that the proportion of patients with ≥ 3 CSBMs per week over the 12-week treatment period was statistically significantly higher in the prucalopride 2 mg* treatment group compared with placebo in patients across all 4 regions. Additionally, the most frequent reported AEs were similar in patients from within and outside of the US, i.e., headache, nausea, diarrhea, abdominal pain, and abdominal distension. However, these AEs were observed more frequently in the US population, both in the prucalopride and placebo groups. When correcting for placebo, the incidence of the reported AEs was very similar in patients from the US and those from outside of the US.

In addition, based on postmarketing data in the EU, the estimated patient exposure to prucalopride through January 2018 is more than 280,000 person-years cumulatively since launch. The safety data collected to date from worldwide sources are consistent with that seen in the clinical studies.

Furthermore, the conclusion from the review of the available worldwide safety data for prucalopride from clinical studies, post-marketing, and literature sources, suggest that the cardiovascular risks associated with other non-selective drugs from the same 5-HT_4 agonist class are highly unlikely with the highly-selective prucalopride.

Overall, prucalopride continues to maintain a favorable benefit-risk profile.

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11. APPENDICES

11.1 Narratives of Events with Fatal Outcome

Study PRU-INT-12 placebo group: An 89-year-old male patient died due to the severe TEAEs of myocardial infarction and arrhythmia. These AEs occurred on Day 7 and were not considered related to the study medication.

Study 26 prucalopride 1 mg group: An 83-year-old White male resident of a nursing home with a medical history of congestive heart failure, hypertension, premature ventricular contractions, and circulatory disease was started on prucalopride 1 mg for constipation. On Day 1, he had a severely deteriorated cardiac status (AE of cardiac failure, considered to be doubtfully related to the study medication). Blood pressure, pulse and ECG remained unchanged until Day 8. On Day 3 the patient started cisapride and metoclopramide for gastritis and esophagitis. On Day 8, the patient developed a severe tachycardia that was considered not to be related to the study medication. On Day 11, the patient had hyperkinesia (restless lower extremities), jaundice, pneumonia lobar, pulmonary edema, and somnolence (all SAEs) and lapsed into a coma. All SAEs were severe in intensity and were considered not related or doubtfully related to the study medication. Treatment with prucalopride was discontinued. The patient died on Day 13. The cause of death (lobar pneumonia) was not considered related to the study medication.

Study 26 prucalopride 2 mg group: A 86-year-old White female resident of a nursing home had a medical history of left lower lobe pneumonia, chronic atrial fibrillation, congestive heart failure, hypertension, peripheral vascular disease, circulatory disorder, depression and dementia. Her concomitant medication included acetylsalicylic acid (for circulatory disorder), citalopram hydrobromide (for depression), digoxin and nifedipine (for atrial fibrillation), enalapril maleate (for hypertension), nabumetone (for arthritis), nizatidine (for peptic ulcer disease), *plantago ovata* (psyllium for constipation), risperidone (for dementia with psychosis), treatment of wounds and ulcers (for stage 2 decubitus ulcers) and multivitamins. She was started on prucalopride 2 mg for constipation. On Day 28 (also last day of study), she developed an acute bronchitis secondary to *Staphylococcus aureus* that resulted in hospitalization. These events were all considered to not be related to prucalopride. On Day 31, the patient died due to severe respiratory failure secondary to bronchitis with *S. aureus.* This SAE was considered to be not related to the study medication.

Study PRU-INT-10 prucalopride 2 mg group: An 81-year-old male with a history of ischemic heart disease and transient ischemic attack died of a MI 67 day after his last dose of prucalopride 2 mg. He was on prucalopride from July 17, 1999 to April 14, 2000 (244 days) during open label phase and including a 29 days of short treatment interruptions. Prior to the open-label study the subject was participating in a double-blind trial where he received 4mg prucalopride for 4 weeks for 28 days) with prucalopride 4 mg in a prior. Concomitant medications during the studies included; acetylsalicylic acid, and dipyridamole used as prophylaxis, oxazepam for insomnia, Bisacodyl for constipation lansoprazole, and omeprazole for reflux disease. Sixty-seven days after the last intake of prucalopride, he died of myocardial infarction. The event was considered not related to the study medication by the investigator.

Study PRU-INT-10 prucalopride 2 mg group: An 89-year-old woman with a history of coronary heart disease, organic psychosis, and mild anemia died of pneumonia 4 days after discontinuing

prucalopride 2 mg (previously treated with 1 mg in the 4-week double-blind trial for 30 days). She developed bronchitis on day 218 of treatment with prucalopride and subsequently, was diagnosed with of severe pneumonia 8 days later considered a serious AE. She was treated for the pneumonia and not hospitalized. Treatment with Augmentin, metamizole, and cefotiam hydrochloride was initiated for bronchitis and pneumonia. Concomitant medications during the studies included; furosemide for Parkinson's symptom, Madopar, Olanzapine and sertraline for organic psychosis, Treatment with prucalopride was discontinued on day 226 and she died 4 days later. This event was not considered related to be related to the study medication by the investigator.

Study PRU-USA-22 prucalopride 2 mg group: A 56-year-old man with a history of cardiomyopathy, atrial fibrillation, hypertension, hypercholesterolemia, non-insulin dependent diabetes mellites (NIDDM) and cerebrovascular accident died from an MI on day 49 of an open label study. He was on prucalopride 2 mg. His total exposure to prucalopride was 75days; administered prucalopride at doses of 2, 3 and 4mg for 49 days during open-label study and 4mg for 27 days during the 4-week double-blind trial (27 days)). Concomitant medications during the studies included; atorvastatin for hypercholesterolemia, bumetadine as a diuretic, digoxin for cardiac maintenance, fosinopril for hypertension, glipizide and metformin for NIDDM, isosorbide mononitrate for cardiac prophylaxis, metipranolol for cardiac arrhythmia, warfarin sodium as anticoagulant and tocopherol for health maintenance. The investigator deemed this event not be related to the study drug.

Study PRU-USA-22 prucalopride 2 mg group: A 69-year-old man with a long history of abdominal pain associated with chronic idiopathic constipation (CIC) .and depression committed suicide via a self-inflicted gunshot wound (GSW) to the chest and abdomen. Prucalopride was discontinued approximately 29 days prior to this event (total prucalopride exposure of 101 days; including previously exposure to prucalopride: 2mg for 46 days during open-label study (30Oct99-13Dec99) and 4 mg for 55 days during preceding DB study (2 treatment periods of 4 weeks with interruption of 17 days), resulting in a total exposure of 101 days to prucalopride (no interruption between DB and open-label). He was started on antidepressants 1 month prior to the event. Other medical history includes abdominal pain and chronic idiopathic constipation with previous hospitalizations for abdominal pain, dehydration, depression, insomnia, anorexia, nausea, vomiting, and diarrhea. Concomitant medications during the studies included; furosemide for leg edema, dexamethasone for confusion, diclofenac for bowel pain, levomepromazine for nausea, valproate sodium for fitting, medazepam for agitation, haloperidol for confusion, dorbanex for constipation and lansoprazole for stomach protection.

Study PRU-USA-22 prucalopride 4 mg group: A 40-year-old woman with a history of depression, drug dependency and drug abuse committed suicide by hanging resulting in asphyxiation and death 52 days post-exposure to prucalopride. Used 4 mg of prucalopride for approximately 7 months (160 days) during open-label study and 4 mg for 82 days during preceding DB study, resulting in a total exposure to prucalopride of 242 days. Concomitant medications during the studies included; famotidine for heartburn, amoxicillin and clarithromycin for strep throat, Tylenol sinus medication for a sinus infection, paracetamol and acetylsalicylic acid for headache, sinutab for allergic rhinitis and Alka-Seltzer plus for flu symptoms. The investigator considered this event to not be related to the study medication.

11.2 Efficacy Tables for Prucalopride up to 4 mg

Table 53: Patient Demographics in Studies 6, USA-11, USA-13 (ITT Population) Including 4 mg Dose

	Study 6			Study USA-11			Study USA-13		
	PLA N=240	PRU 2 mg N=238	PRU 4 mg N=238	PLA N=209	PRU 2 mg N=207	PRU 4 mg N=204	PLA N=212	PRU 2 mg N=214	PRU 4 mg N=215
Age, years									
Mean (SE)	43.7 (0.99)	42.7 (0.98)	45.4 (0.97)	48.9 (0.9)	48.2 (0.98)	47.8 (0.96)	46.2 (0.89)	48.6 (0.97)	49.1 (0.93)
Median (min, max)	43 (18, 80)	40 (17, 83)	45 (18, 89)	48 (18, 81)	48 (20, 83)	47 (18, 85)	45 (18, 82)	46.5 (20, 95)	47 (21, 86)
Age category, n (%)									
<18	0	1 (0.4)	0	0	0	0	0	0	0
[18,40]	107 (44.6)	122 (51.3)	94 (39.5)	60 (28.7)	62 (30.0)	65 (31.9)	70 (33.0)	56 (26.2)	60 (27.9)
[41,64]	109 (45.4)	88 (37.0)	117 (49.2)	118 (56.5)	118 (57.0)	110 (53.9)	119 (56.1)	124 (57.9)	121 (56.3)
≥65	24 (10.0)	27 (11.3)	27 (11.3)	31 (14.8)	27 (13.0)	29 (14.2)	23 (10.8)	34 (15.9)	34 (15.8)
Sex, n (%)									
Female	222 (92.5)	213 (89.5)	215 (90.3)	183 (87.6)	188 (90.8)	174 (85.3)	189 (89.2)	181 (84.6)	185 (86.0)
Male	18 (7.5)	25 (10.5)	23 (9.7)	26 (12.4)	19 (9.2)	30 (14.7)	23 (10.8)	33 (15.4)	30 (14.0)
Weight, kg									
Mean (SE)	66.7 (0.84)	68.8 (0.93)	68.0 (0.88)	68.4 (1.02)	69.3 (0.96)	68.6 (1.04)	70.7 (0.99)	71.1 (1.04)	69.6 (1.03)
Height, cm									
Mean (SE)	165.1 (0.45)	165.8 (0.5)	165.7 (0.52)	164.7 (0.63)	164.7 (0.63)	165.0 (0.63)	165.3 (0.58)	165.2 (0.6)	165.7 (0.62)
Race, n (%)									
White	226 (94.2)	223 (93.7)	220 (92.4)	182 (87.1)	188 (90.8)	186 (91.2)	197 (92.9)	183 (85.5)	184 (85.6)
Black	2 (0.8)	3 (1.3)	4 (1.7)	18 (8.6)	13 (6.3)	9 (4.4)	9 (4.2)	24 (11.2)	21 (9.8)
Hispanic	2 (0.8)	0	2 (0.8)	4 (1.9)	5 (2.4)	8 (3.9)	5 (2.4)	3 (1.4)	7 (3.3)
Asian	2 (0.8)	5 (2.1)	1 (0.4)	2 (1.0)	1 (0.5)	1 (0.5)	0	3 (1.4)	0
Other	8 (3.3)	7 (2.9)	11 (4.6)	3 (1.4)	0	0	1 (0.5)	1 (0.5)	3 (1.4)

max=maximum; min=minimum; N=number of patients in treatment group; n=number of patients with characteristic; PLA=placebo; PRU=prucalopride; SE=standard error

Source: Module 5.3.5.1, PRU-INT-6, Section 14, Display SUB.7; PRU-USA-11, Section 14, Display SUB.7; PRU-USA-13, Section 14, Display SUB.7

Table 54: Baseline Disease Characteristics in Studies 6, USA-11, and USA-13 (ITT Population) Including 4 mg Dose

	Study 6			Study USA-11			Study USA-13		
	PLA N=240	PRU 2 mg N=238	PRU 4 mg N=238	PLA N=209	PRU 2 mg N=207	PRU 4 mg N=204	PLA N=212	PRU 2 mg N=214	PRU 4 mg N=215
History of constipation, years									
Mean (SD)	18.5 (0.9)	15.9 (0.97)	18.3 (0.99)	21.6 (1.19)	21.1 (1.10)	20.5 (1.14)	21.4 (1.06)	22.7 (1.08)	22 (1.17)
Median (Min; Max)	18 (1; 68)	10 (1; 70)	15 (1; 79)	20 (1; 77)	20 (1; 78)	20 (1; 79)	20 (1; 71)	20 (1; 63)	20 (0; 82)
<1	8 (3.3)	9 (3.8)	3 (1.3)	5 (2.4)	4 (1.9)	8 (3.9)	3 (1.4)	2 (0.9)	3 (1.4)
1-<10	66 (27.5)	83 (34.9)	73 (30.7)	59 (28.2)	51 (24.6)	61 (29.9)	54 (25.5)	52 (24.3)	64 (29.8)
10-<20	51 (21.3)	69 (29.0)	61 (25.6)	37 (17.7)	47 (22.7)	31 (15.2)	42 (19.8)	41 (19.2)	36 (16.7)
20-<30	63 (26.3)	36 (15.1)	45 (18.9)	40 (19.1)	40 (19.3)	38 (18.6)	46 (21.7)	40 (18.7)	37 (17.2)
30-<40	25 (10.4)	18 (7.6)	28 (11.8)	30 (14.4)	32 (15.5)	34 (16.7)	33 (15.6)	38 (17.8)	33 (15.3)
40-<50	17 (7.1)	12 (5.0)	16 (6.7)	21 (10.0)	18 (8.7)	20 (9.8)	22 (10.4)	24 (11.2)	23 (10.7)
≥50	10 (4.2)	11 (4.6)	12 (5.0)	17 (8.1)	15 (7.2)	12 (5.9)	12 (5.7)	17 (7.9)	19 (8.8)
Main complaint, n (%)									
Infrequent defecation	59 (24.6)	57 (23.9)	58 (24.4)	71 (34.0)	86 (41.5)	69 (33.8)	61 (28.8)	66 (30.8)	60 (27.9)
Abdominal bloating	64 (26.7)	73 (30.7)	57 (23.9)	45 (21.5)	30 (14.5)	55 (27.0)	58 (27.4)	53 (24.8)	56 (26.0)
Abdominal pain	61 (25.4)	58 (24.4)	54 (22.7)	19 (9.1)	18 (8.7)	13 (6.4)	19 (9.0)	27 (12.6)	20 (9.3)
Feeling not completely empty	29 (12.1)	26 (10.9)	26 (10.9)	38 (18.2)	30 (14.5)	28 (13.7)	30 (14.2)	29 (13.6)	44 (20.5)
Straining	17 (7.1)	18 (7.6)	29 (12.2)	24 (11.5)	28 (13.5)	26 (12.7)	30 (14.2)	22 (10.3)	26 (12.1)
Hard stools	10 (4.2)	6 (2.5)	14 (5.9)	12 (5.7)	15 (7.2)	13 (6.4)	14 (6.6)	17 (7.9)	9 (4.2)
Previous use of diet adjustments as constipation treatment, n (%)									
Yes	140 (58.3)	154 (64.7)	148 (62.2)	137 (65.6)	150 (72.5)	141 (69.1)	144 (67.9)	139 (65.0)	141 (65.6)
No	100 (41.7)	84 (35.3)	90 (37.8)	72 (34.4)	57 (27.5)	63 (30.9)	68 (32.1)	75 (35.0)	74 (34.4)
Previous use of laxatives, n (%)									
Yes	198 (82.5)	191 (80.3)	183 (76.9)	183 (87.6)	185 (89.4)	180 (88.2)	189 (89.2)	189 (88.3)	192 (89.3)
No	42 (17.5)	47 (19.7)	55 (23.1)	26 (12.4)	22 (10.6)	24 (11.8)	23 (10.8)	25 (11.7)	23 (10.7)
Previous use of bulk-forming laxatives, n (%)									
Yes	141 (58.8)	143 (60.1)	121 (50.8)	138 (66.0)	136 (65.7)	138 (67.6)	122 (57.5)	123 (57.5)	119 (55.3)
No	99 (41.3)	95 (39.9)	117 (49.2)	71 (34.0)	71 (34.3)	66 (32.4)	90 (42.5)	91 (42.5)	96 (44.7)
Number of SBMs during the last 6 months, n (%)									
0	99 (41.3)	86 (36.1)	91 (38.2)	79 (37.8)	77 (37.2)	76 (37.3)	85 (40.1)	96 (44.9)	101 (47.0)
>0 - ≤1	84 (35.0)	78 (32.8)	69 (29.0)	78 (37.3)	79 (38.2)	77 (37.7)	65 (30.7)	73 (34.1)	66 (30.7)
>1 - ≤3	51 (21.3)	65 (27.3)	70 (29.4)	49 (23.4)	50 (24.2)	46 (22.5)	60 (28.3)	43 (20.1)	43 (20.0)
>3	6 (2.5)	9 (3.8)	8 (3.4)	3 (1.4)	1 (0.5)	5 (2.5)	2 (0.9)	2 (0.9)	5 (2.3)

Table 54: Baseline Disease Characteristics in Studies 6, USA-11, and USA-13 (ITT Population) Including 4 mg Dose

BM=bowel movement; max=maximum; min=minimum; N= number of patients in treatment group; n=number of patients with characteristic; PLA=placebo; PRU=prucalopride; ; SBM=spontaneous bowel movement SD=standard deviation

[a] Not applicable for 39 patients in Study 6, 18 patients in USA-11, and 11 patients in USA-13 as they did not use previous therapy

Source: Module 5.3.5.1, PRU-INT-6, Section 14, Display SUB.9; PRU-USA-11, Section 14, Display SUB.9; PRU-USA-13, Section 14, Display SUB.9

Table 55: Patient Disposition in Studies 6, USA-11, and USA-13 (ITT Population) Including 4 mg Dose

	Study 6			Study USA-11			Study USA-13		
	PLA N=240	PRU 2 mg N=238	PRU 4 mg N=238	PLA N=209	PRU 2 mg N=207	PRU 4 mg N=204	PLA N=212	PRU 2 mg N=214	PRU 4 mg N=215
	n (%)								
Completed	207 (86.3)	207 (87.0)	183 (76.9)	182 (87.1)	172 (83.1)	173 (84.8)	188 (88.7)	194 (90.7)	185 (86.0)
Withdrawn	33 (13.8)	31 (13.0)	55 (23.1)	27 (12.9)	35 (16.9)	31 (15.2)	24 (11.3)	20 (9.3)	30 (14.0)
Withdrawal of consent	5 (2.1)	5 (2.1)	8 (3.4)	7 (3.3)	3 (1.4)	5 (2.5)	5 (2.4)	4 (1.9)	7 (3.3)
AE	16 (6.7)	15 (6.3)	35 (14.7) [a]	4 (1.9)	18 (8.7)	16 (7.8)	5 (2.4)	8 (3.7)	13 (6.0)
Noncompliance	1 (0.4)	0	2 (0.8)	4 (1.9)	4 (1.9)	4 (2.0)	1 (0.5)	4 (1.9)	3 (1.4)
Lost to follow-up	1 (0.4)	3 (1.3)	2 (0.8)	3 (1.4)	3 (1.4)	2 (1.0)	2 (0.9)	3 (1.4)	2 (0.9)
Lack of efficacy [b]	7 (2.9)	3 (1.3)	5 (2.1)	5 (2.4)	2 (1.0)	1 (0.5)	3 (1.4)	1 (0.5)	0
Other	2 (0.8)	4 (1.7)	2 (0.8)	4 (1.9)	2 (1.0)	3 (1.5)	5 (2.4)	0	5 (2.3)
Ineligible to continue	1 (0.4)	1 (0.4)	1 (0.4)	0	3 (1.4)	0	3 (1.4)	0	0

AE=adverse event; N=number of patients in treatment group; n=number of patients who completed/withdrew; PLA=placebo; PRU=prucalopride

[a] Thirty-six patients stopped treatment for AEs; in 1 patient, the study termination reason given was 'withdrew consent', while on the AE Form, 'permanently stopped' was recorded.

[b] Labeled insufficient response in these studies.

Source: Module 5.3.5.1, PRU-INT-6, Section 14, Display SUB.4; PRU-USA-11, Section 14, Display SUB.4; PRU-USA-13, Section 14, Display SUB.4

Table 56: Proportion of Patients with an Average of ≥3 CSBMs/week in Studies 6, USA-11, USA-13 (ITT Population) Including 4 mg Dose

	Study 6			Study USA-11			Study USA-13		
	PLA N=240	**PRU 2 mg N=236**	**PRU 4 mg N=237**	**PLA N=193**	**PRU 2 mg N=190**	**PRU 4 mg N=187**	**PLA N=212**	**PRU 2 mg N=214**	**PRU 4 mg N=215**
Week 1-12, n (%)	23 (9.6)	46 (19.5)	56 (23.6)	25 (13.0)	55 (28.9)	54 (28.9)	25 (12.1)	50 (23.9)	48 (23.5)
p-value		0.002 [a]	≤0.001		< 0.001 [a]	≤0.001		0.002 [a]	≤0.01

CBM=complete bowel movement; CMH=Cochrane-Mantel-Haenszel; ITT=intent-to-treat; PLA=placebo; PRU=prucalopride; CSBM=complete spontaneous bowel movement

[a] p-value based on a CMH test controlling for country/investigator

[b] p-value based on a CMH test controlling for country, sex, and the average number of CBMs during the run-in period

Table 57: Proportion of Patients with an Average of ≥3 CSBMs/week and an Increase of ≥ 1 CSBM/week for ≥ 9 out of the 12 Weeks (18 out of 24 weeks for Study 401) Including 3 of the Last 4 Weeks in Studies 6, USA-11, USA-13 (ITT Population) Including 4 mg Dose

	Study 6			Study USA-11			Study USA-13		
	PLA N=240	**PRU 2 mg N=236**	**PRU 4 mg N=237**	**PLA N=193**	**PRU 2 mg N=190**	**PRU 4 mg N=187**	**PLA N=212**	**PRU 2 mg N=214**	**PRU 4 mg N=215**
n (%)	13 (5.4)	30 (12.7)	34 (14.3)	15 (7.8)	37 (19.5)	36 (19.3)	11 (5.2)	34 (15.9)	33 (15.3)
Weeks 1-12									
Diff. in proportion		0.073	0.089		0.117	0.115		0.107	0.102
95% CI		0.022, 0.124	0.036, 0.142		0.049, 0.185	0.047, 0.183		0.050, 0.164	0.045, 0.158
p-value [a]		0.0050	0.0027		0.0005	0.0014		0.0002	0.0013

CBM=complete bowel movement; CI=confidence interval; CMH=Cochrane Mantel Haenszel; Diff.=difference; ITT=intent-to-treat; PLA=placebo; PRU=prucalopride; CSBM=complete spontaneous bowel movement

[a] p-value based on a CMH test for general association controlling for (pooled) country (Studies 6 and 401)/center (Studies USA-11 and USA-13), sex (Study 401), and number of CBMs/week at baseline (Study 401)

Table 58: Proportion of Patients with an Average Increase of ≥1 CSBMs/week in Studies 6, USA-11, USA-13 (ITT Population) Including 4 mg Dose

	Study 6			Study USA-11			Study USA-13		
	PLA N=240	**PRU 2 mg N=236**	**PRU 4 mg N=237**	**PLA N=193**	**PRU 2 mg N=190**	**PRU 4 mg N=187**	**PLA N=212**	**PRU 2 mg N=214**	**PRU 4 mg N=215**
Week 1-12, n (%)	49 (20.9)	86 (38.1)	94 (44.1)	49 (25.9)	89 (50.3)	90 (51.1)	57 (27.5)	89 (42.6)	95 (46.6)
p-value		≤ 0.001[a]	≤ 0.001		≤ 0.001[a]	≤ 0.001[a]		≤ 0.001[a]	≤ 0.001[a]

CBM=complete bowel movement; CMH=Cochrane-Mantel-Haenszel; ITT=intent-to-treat; PLA=placebo; PRU=prucalopride; CSBM=complete spontaneous bowel movement

[a] p-value based on a CMH test controlling for country/investigator

[b] p-value based on a CMH test controlling for country, sex, and the average number of CBMs during the run-in period

Table 59: Time to First Bowel Movement in in Studies 6, USA-11, USA-13 (ITT Population) Including 4 mg Dose

	Study 6			Study USA-11			Study USA-13		
	PLA N=240	**PRU 2 mg N=169**	**PRU 4 mg N=237**	**PRU 2 mg* N=171**	**PRU 2 mg N=190**	**PRU 4 mg N=187**	**PLA N=212**	**PRU 2 mg N=214**	**PRU 4 mg N=215**
	Median (95% CI)								
Time to first CSBM (hours)									
Since Day 1	493 (362, 646)	113 (57.75, 174)	49.45 (3, 815)	297 (220, 484)	32.50 (13.83; 53)	25.1 (2, 336)	311 (214; 425)	54.83 (29.35; 97.08)	46.25 (3, 395)
p-value [a]		≤ 0.001	≤ 0.001		≤ 0.001	≤ 0.001		≤ 0.001	≤ 0.001
Time to first SBM (hours)									
Since Day 1	26.53 (24.25, 32.25)	2.25 (1.92, 3.08)	1.92 (1, 12)	27.50 (25.25, 36)	2.00 (1.50, 2.50)	1.58 (1, 5)	24.92 (14.83; 28.50)	3.00 (2.33; 4.25)	2.00 (1, 7)
p-value [a]		≤ 0.001	≤ 0.001		≤ 0.001	≤ 0.001		≤ 0.001	≤ 0.001

CI=confidence interval; ITT=intent-to-treat; PLA=placebo; PRU=prucalopride; CSBM=complete spontaneous bowel movement

[a] p-value based on a log-rank test

[b] p-value based on a stratified log-rank test containing country and the average number of CBMs/week during the run-in period as stratification factors

Table 60: Average Number of Bowel Movements in in Studies 6, USA-11, USA-13 (ITT Population) Including 4 mg Dose

	Study 6			Study USA-11			Study USA-13		
	PLA N=240	PRU 2 mg N=236	PRU 4 mg N=237	PLA N=193	PRU 2 mg N=190	PRU 4 mg N=187	PLA N=212	PRU 2 mg N=214	PRU 4 mg N=215
	Mean Actual Value (Mean Change)								
Average number of CSBMs per week									
RI	0.4	0.4	0.5	0.4	0.5	0.5	0.4	0.4	0.5
Week 1-12	1.0 (0.5)	1.6 (1.2)	1.9 (1.4)	1.3 (0.8)	2.3 (1.9)	2.4 (1.9)	1.2 (0.8)	1.9 (1.5)	2.0 (1.5)
p-value[a]		≤ 0.001	≤ 0.001		≤ 0.001	≤ 0.001		≤ 0.001	≤ 0.001
Average number of SBMs per week									
RI	3.6	4.0	3.6	3.0	3.5	3.8	3.3	3.7	3.2
Week 1-12	4.4 (0.7)	6.2 (2.4)	6.1 (2.5)	4.0 (1.0)	6.6 (3.2)	6.9 (3.2)	4.2 (0.9)	6.0 (2.3)	6.1 (3.1)
p-value[a]		≤ 0.001	≤ 0.001		≤ 0.001	≤ 0.001		≤ 0.001	≤ 0.001
Average number of BMs per week									
RI	5.6	5.4	5.2	5.2	5.7	5.7	5.1	5.6	5.2
Week 1-12	6.1 (0.4)	7.1 (1.8)	7.1 (1.9)	6.0 (0.8)	7.7 (2.0)	8.1 (2.5)	5.8 (0.7)	7.4 (1.8)	7.4 (2.3)
p-value[a]		≤ 0.001	≤ 0.001		≤ 0.001	≤ 0.001		≤ 0.001	≤ 0.001

ANCOVA=analysis of covariance; BM=bowel movement; CBM=complete bowel movement; ITT=intent-to-treat; PLA=placebo; PRU=prucalopride; RI=run-in; SBM=spontaneous bowel movement; CSBM=complete spontaneous bowel movement

[a] p-value based on an ANCOVA model with factors treatment, baseline value, and country/region for Studies 6, USA-11, and USA-13 and average number of CBMs during the run-in period, country, and sex for Study 401

Note: Numbers were rounded.

11.3 Inclusion and Exclusion Criteria

11.3.1 Study 3001 Inclusion and Exclusion Criteria

Inclusion Criteria for Screening

- Men or women aged 18 to 65 years, inclusive.
  History of chronic constipation: the patient reported, on average, 2 or fewer SBMs per week and 1 or more of the following for at least a quarter of the time for the preceding 3 months, while symptom onset was more than 6 months before the screening visit:
  - very hard (little balls) and/or hard stools in more than 25% of BMs
  - sensation of incomplete evacuation in more than 25% of BMs
  - straining at defecation in more than 25% of BMs
  - sensation of ano-rectal obstruction or blockade in more than 25% of BMs
  - a need for digital manipulation to facilitate evacuation in more than 25% of BMs

  The above criteria were only applicable for SBMs, i.e., not preceded within a period of 24 hours by the intake of a laxative agent or by the use of an enema.
- Patients who never had SBMs were considered to be constipated and were eligible for the study.
- The patient's constipation was functional (see the first 2 exclusion criteria). Patients must have been investigated by barium enema within the past 1 year and/or colonoscopic examination within the past 3 years, as described in the second exclusion criteria.
- Patients with the diagnosis of irritable bowel syndrome with constipation and with no other organic diseases could potentially be included depending on the decision of the investigator.
- Before entry, women must have been:
  - postmenopausal (for at least1 year),
  - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy),
  - practicing a highly effective method of birth control, if sexually active, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g., condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for patients participating in clinical studies, for the duration of their participation in the study, or
  - not heterosexually active

Note: patients who were not heterosexually active at screening must have agreed to utilize a highly effective method of birth control if they became heterosexually active during their participation in the study.

Women must have agreed to continue using these methods of contraception throughout the study. Prucalopride may cause severe transient diarrhea, hence women of childbearing potential

who use oral contraceptives should use additional effective contraceptive methods throughout the study.

- Women of childbearing potential must have had a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening.
- Men must have agreed to use a double barrier method of birth control and to not donate sperm during the study and for 1 month after receiving the last dose of study drug.
- Willing/able to adhere to the prohibitions and restrictions specified in this protocol.
- Willing/able to fill out his/her own diary and questionnaires.
- Must have been available for follow-up during the study period as determined in the protocol.
- Patients must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and were willing to participate in the study. Written informed consent must have been signed by the patient and by the Investigator.

Exclusion Criteria

Potential patients who met any of the following criteria were excluded from participating in the study:

- Patients in whom constipation was thought to be drug-induced.
- Patients suffering from secondary causes of chronic constipation; for example:
  - Endocrine disorders: insulin-dependent diabetes mellitus, hypopituitarism, hypothyroidism, hypercalcemia, pseudo-hypoparathyroidism, pheochromocytoma, glucagon-producing tumors. Endocrine disorders that were controlled by appropriate medical therapy were not excluded except insulin-dependent diabetes mellitus.
  - Metabolic disorders: porphyria, uremia, hypokalemia, amyloid neuropathy. Metabolic disorders that were controlled by appropriate medical therapy were not excluded.
  - Neurologic disorders: Parkinson's disease, cerebral tumors, cerebrovascular accidents, multiple sclerosis, meningocele, aganglionosis, hypoganglionosis, hyperganglionosis, autonomic neuropathy, spinal cord injury, Chagas disease, major depression.
  - Patients with a megacolon/megarectum or a diagnosis of pseudo-obstruction.
  - Constipation as a result of surgery.
  - Known or suspected organic disorders of the large bowel, i.e., obstruction, carcinoma, or inflammatory bowel disease. Results of a barium enema or of a colonoscopic examination performed within the past 1 year were required to rule out organic disorders. A colonoscopic examination performed within the last 3 years was acceptable if the examination was performed for evaluation of constipation and there was no history or evidence of weight loss, anemia, or rectal

bleeding. Patients who had polyps discovered on the colonoscopy that were untreated (i.e., by polypectomy) were excluded from the study.

- Use of or intent to use disallowed medications that influence the bowel habits during the study (i.e., anticholinergics [not including antihistamines], opioids, spasmolytics, prokinetics, and tricyclic antidepressants).
- Patients with severe and clinically uncontrolled cardiovascular, liver, or lung disease, neurologic or psychiatric disorders (including active alcohol or drug abuse), cancer or AIDS, or other GI or endocrine disorders.
- Patients with impaired renal function, i.e., serum creatinine > 2 mg/dL (> 180 µmol/L).
- Patients with clinically significant abnormalities of hematology, urinalysis, or blood chemistry.
- Known allergies, hypersensitivity, or intolerance to prucalopride or its excipients.
- Women who were pregnant or breast-feeding.
- Had received an investigational drug or used an investigational medical device in the 30 days preceding the screening visit.
- Any condition that, in the opinion of the Investigator, would compromise the well-being of the patient or the study or prevent the patient from meeting or performing study requirements.
- Employees of the Investigator or study center, with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, as well as family members of the employees or the Investigator.

11.3.2 Study 302 Inclusion and Exclusion Criteria

Inclusion Criteria

A patient was eligible for the study if all of the following applied at the Screening Visit (Visit 1):

1. The patient was a male outpatient ≥18 years of age (no upper age limit).
2. The patient had a history of constipation. The patient reported an average of ≤2 SBMs/week that resulted in a feeling of complete evacuation (CSBM) and 1 or more of the following for at least 6 months before the selection visit:
   - Very hard (little balls) and/or hard stools for at least a quarter of the stools
   - Sensation of incomplete evacuation following for at least a quarter of the stools
   - Straining at defecation for at least a quarter of the time.

   This included patients who never had SBMs. The above criteria were only applicable for SBMs, i.e., BMs not preceded by the intake of a laxative agent or by the use of an enema within a period of 24 hours.
3. The patient agreed to stop his current laxative treatment and was willing to use rescue medication according to the rescue rule (bisacodyl/enemas).
4. The patient's constipation was chronic (see also exclusion criteria).
5. The patient was able and willing to complete the questionnaires (if a validated version in the language of the patient was available) and the e-diary.
6. The patient voluntarily signed the written informed consent form in accordance with the regional laws/regulations, prior to the first study-related activity.
7. The patient was willing to adhere to all study requirements (amongst others colonoscopy/sigmoidoscopy, if required).

Exclusion Criteria

A patient meeting any of the following criteria at the Screening Visit (Visit 1) was excluded from the study:

1. Patients in whom constipation was thought to be drug-induced.
2. Patients using any disallowed medication.
3. Patients suffering from secondary causes of chronic constipation, such as:
   - Endocrine disorders (e.g., hypopituitarism, hypothyroidism, hypercalcemia, pseudohypoparathyroidism, pheochromocytoma, or glucagon-producing tumors; unless these conditions were controlled by appropriate medical therapy) Patients with insulin-dependent diabetes mellitus always had to be excluded, also if the patients were under appropriate medical therapy.
   - Metabolic disorders (e.g., porphyria, uremia, hypokalemia, or amyloid neuropathy; unless these conditions were controlled by appropriate medical therapy)
   - Neurological disorders (e.g., Parkinson's disease, cerebral tumors, cerebrovascular accidents, multiple sclerosis, meningocele, aganglionosis, hypoganglionosis, hyperganglionosis, autonomic neuropathy or neuropathy due to chemotherapy, spinal cord injury, Chagas disease, or major depression)

- Surgery.

Note: if a patient was experiencing chronic constipation prior to the onset of a condition listed above and the constipation had not been worsened by this condition, the patient was eligible for screening. However, if the constipation had started after the onset of 1 of the above conditions and the relation between both could not be excluded (i.e., it was not certain whether it was secondary to it or not), or when the constipation had worsened after the onset of 1 of the above conditions, the patient was not allowed to be screened for this study. Patients with insulin-dependent diabetes mellitus always had to be excluded, irrespective of whether the constipation started prior to or after the onset of diabetes.

4. Patients with a significant history of cancer (i.e., <5-year disease-free survival).
5. Patients with intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract, such as Crohn's disease, and ulcerative colitis and toxic megacolon/megarectum.

Results of an endoscopy or radiologic bowel evaluation were required to rule out polyps, cancer, stricture, or other structural or organic disease:

- For patients ≤50 years: a flexible sigmoidoscopy or colonoscopy after the onset of constipation symptoms and within the previous 5 years
- For patients > 50 years: a flexible sigmoidoscopy/double contrast barium enema or colonoscopy after the onset of constipation symptoms and within the previous 5 years
- For patients, regardless of age, even if results of this test were available within the previous 5 years but if the patient had alarm symptoms such as anemia, weight loss, heme positive stool, or rectal bleeding: a flexible sigmoidoscopy and double contrast barium enema or colonoscopy was needed after the onset of symptoms
- If abnormalities were detected during the sigmoidoscopy or colonoscopy, e.g., because of polyps, the patient could be included in the study if the polyps were removed. If clinically indicated, a repeat colonoscopy/sigmoidoscopy needed to be performed at latest within 1 week after the Screening Visit (Visit 1).

If no barium enema with flexible sigmoidoscopy or a colonoscopy had been performed within the period as described above, the assessment was to be scheduled on the Screening Visit (Visit 1) or within the following week. When it was clinically indicated that a repeat colonoscopy/sigmoidoscopy was needed to confirm results of a colonoscopy/sigmoidoscopy performed after the Screening Visit (Visit 1), the patient was considered a screen failure.

6. Patients with known serious illness: clinically significant cardiac, vascular, liver, pulmonary, or psychiatric disorders (as evaluated by the investigator).
7. Patients with any condition that in the opinion of the investigator would complicate or compromise the study or the wellbeing of the patient or evidence of clinically relevant pathology that could interfere with the study results or put the patient's safety at risk.
8. Patients known to have human immunodeficiency virus infection or acquired immunodeficiency syndrome, hepatitis B, or hepatitis C.
9. Patients with impaired renal function, i.e., serum creatinine concentration > 180µmol/L or calculated Cl_{CR} ≤30mL/min, including patients requiring dialysis.

10. Patients with clinically significant abnormalities of hematology, urinalysis, or blood chemistry as determined by the investigator.

If the results of the hematology, biochemistry, or urinalysis tests were not within the laboratory's reference ranges, the patient could be included only on the condition that the investigator judged that the deviations were not clinically significant. This had to be clearly recorded in the eCRF.

11. Patients with a known history of alcohol or drug abuse in the previous 6 months.
12. Patients with lactose intolerance for whom it was expected that low doses of lactose could lead to diarrhea or a known allergy to ingredients or excipients of the investigational product.
13. Patients who received an investigational drug in the 30 days preceding the Run-in Period of the study.
14. Patients who previously used prucalopride.

11.3.3 Study 6 Inclusion and Exclusion Criteria

Inclusion Criteria

Patients meeting all of the following requirements were allowed to enter the study:

1. Male and non-pregnant, non-breast-feeding female outpatients at least 18 years of age (no upper age limit).
2. History of constipation; the patient reported having, on average, 2 or fewer spontaneous bowel movements per week that resulted in a feeling of complete evacuation as well as the occurrence of 1 or more of the following for at least 6 months before the selection visit:

   - very hard (little balls) and/or hard stools at least a quarter of the stools;

   - sensation of incomplete evacuation following at least a quarter of the stools;

   - straining at defecation at least a quarter of the time.

   The above criteria were only applicable for spontaneous bowel movements, i.e. not preceded within a period of 24 hours by the intake of a laxative agent or by the use of an enema.
   Patients who never had spontaneous bowel movements were considered to be constipated and were eligible for the study.

3. Constipation that was not induced by secondary causes of constipation (see exclusion criteria 1 through 5).
4. Willingness and ability to fill out his/her own diary and questionnaires without help.
5. Written informed consent, signed by the patient and by the investigator.
6. Availability for follow-up during the study period as determined in the protocol.

Exclusion Criteria

Patients were to be excluded if any of the following applied:

1. Patients in whom constipation was thought to be drug-induced, or who were using any disallowed medication.
2. Patients suffering from secondary causes of chronic constipation; for example:
   Endocrine disorders: insulin-dependent diabetes mellitus, hypo-pituitarism, hypothyroidism, hypercalcaemia, pseudohypopara-thyroidism, pheochromocytoma, or glucagon-producing tumours. Endocrine disorders controlled by appropriate medical therapy were not excluded with the exception of insulin-dependent diabetes mellitus.

   Metabolic disorders: porphyria, uraemia, hypokalaemia, or amyloid neuropathy. Metabolic disorders controlled by appropriate medical therapy were not excluded.

   Neurologic disorders: Parkinson's disease, cerebral tumours, cerebrovascular accidents, multiple sclerosis, meningocele, aganglionosis, hypoganglionosis, hyper-ganglionosis, autonomic neuropathy, spinal cord injury, Chagas disease, or major depression.
3. Presence of a megacolon/megarectum or a diagnosis of pseudo-obstruction.
4. Constipation as a result of surgery.
5. Known or suspected organic disorders of the large bowel (i.e. obstruction, carcinoma, or inflammatory bowel disease). Results of a barium enema or of a colonoscopic examination performed within the last 12 months were needed to rule out organic disorders. A colonoscopic examination performed within the last 3 years was acceptable if the examination was performed for an evaluation of constipation, and there was no history or evidence of weight loss, anaemia, or rectal bleeding. Patients with polyps discovered by colonoscopy that were untreated (i.e. by polypectomy) were to be excluded.
6. Presence of severe and clinically uncontrolled cardiovascular, liver, or lung disease, neurologic or psychiatric disorders (including active alcohol or drug abuse), cancer or AIDS, and other gastro-intestinal or endocrine disorders.
7. Impaired renal function, i.e. serum creatinine concentration > 2 mg/dL (> 180 µmol/L).
8. Clinically significant abnormalities of haematology, urinalysis, or blood chemistry.
9. Females of child-bearing potential without adequate contraceptive protection during the study. Oral contraceptives, Depo Provera®, Norplant®, intrauterine device (IUD), sterilization, or a double barrier method were acceptable methods of birth control.
10. Treatment with an investigational drug in the 30 days preceding the run-in phase

of the study.

11. Previous treatment with either prucalopride formulation.

11.3.4 Study USA-11 Inclusion and Exclusion Criteria

Inclusion Criteria

Patients meeting all of the following requirements were allowed to enter the study:

1. Male and non-pregnant, non-breast-feeding female outpatients at least 18 years of age (no upper age limit).
2. History of constipation; the patient reported having, on average, 2 or fewer spontaneous bowel movements per week that resulted in a feeling of complete evacuation as well as the occurrence of 1 or more of the following for at least 6 months before the selection visit:

   - very hard (little balls) and/or hard stools at least a quarter of the stools;

   - sensation of incomplete evacuation following at least a quarter of the stools;

   - straining at defecation at least a quarter of the time.

   The above criteria were only applicable for spontaneous bowel movements, i.e. not preceded within a period of 24 hours by the intake of a laxative agent or by the use of an enema.
   Patients who never had spontaneous bowel movements were considered to be constipated and were eligible for the study.
3. Constipation that was not induced by secondary causes of constipation (see exclusion criteria 1 through 5).
4. Willingness and ability to fill out his/her own diary and questionnaires without help.
5. Written informed consent, signed by the patient and by the investigator.
6. Availability for follow-up during the study period as determined in the protocol.

Exclusion Criteria

Patients were to be excluded if any of the following applied:

1. Patients in whom constipation was thought to be drug-induced, or who were using any disallowed medication.
2. Patients suffering from secondary causes of chronic constipation; for example:
   Endocrine disorders: insulin-dependent diabetes mellitus, hypo-pituitarism, hypothyroidism, hypercalcaemia, pseudohypopara-thyroidism, pheochromocytoma, or glucagon-producing tumours. Endocrine disorders controlled by appropriate medical therapy were not excluded with the exception of insulin-dependent diabetes mellitus.

   Metabolic disorders: porphyria, uraemia, hypokalaemia, or amyloid neuropathy. Metabolic disorders controlled by appropriate medical therapy were not excluded.

Neurologic disorders: Parkinson's disease, cerebral tumours, cerebrovascular accidents, multiple sclerosis, meningocele, aganglionosis, hypoganglionosis, hyper-ganglionosis, autonomic neuropathy, spinal cord injury, Chagas disease, or major depression.

3. Presence of a megacolon/megarectum or a diagnosis of pseudo-obstruction.
4. Constipation as a result of surgery.
5. Known or suspected organic disorders of the large bowel (i.e. obstruction, carcinoma, or inflammatory bowel disease). Results of a barium enema with flexible sigmoidoscopy or of a colonoscopic examination performed within the last 12 months were needed to rule out organic disorders. A colonoscopic examination or barium enema with flexible sigmoidoscopy performed within the last 3 years was acceptable if the examination was performed for an evaluation of constipation, and there was no history or evidence of weight loss, anaemia, or rectal bleeding, and the patient had at least 3 consecutively negative stool occult blood tests at screening. Patients with polyps discovered by colonoscopy that were untreated (i.e. by polypectomy) were to be excluded.
6. Presence of severe and clinically uncontrolled cardiovascular, liver, or lung disease, neurologic or psychiatric disorders (including active alcohol or drug abuse), cancer or AIDS, and other gastro-intestinal or endocrine disorders.
7. Impaired renal function, i.e. serum creatinine concentration > 2 mg/dL (> 180 µmol/L), or $Cl_{CR} \leq 50$ mL/min.
8. Clinically significant abnormalities of haematology, urinalysis, or blood chemistry.
9. Females of child-bearing potential without adequate contraceptive protection during the study. Oral contraceptives, Depo Provera®, Norplant® (used for at least 3 months prior to randomization), intrauterine device (IUD), sterilization, or a double barrier method were acceptable methods of birth control.
10. Treatment with an investigational drug in the 30 days preceding the run-in phase of the study.
11. Previous treatment with either prucalopride formulation.

11.3.5 Study USA-13 Inclusion and Exclusion Criteria

Inclusion Criteria

Patients meeting all of the following requirements were allowed to enter the study:

1. Male and non-pregnant, non-breast-feeding female outpatients at least 18 years of age (no upper age limit).
2. History of constipation; the patient reported having, on average, 2 or fewer spontaneous bowel movements per week that resulted in a feeling of complete evacuation as well as the occurrence of 1 or more of the following for at least 6 months before the selection visit:

   - very hard (little balls) and/or hard stools at least a quarter of the stools;

   - sensation of incomplete evacuation following at least a quarter of the stools;

   - straining at defecation at least a quarter of the time.

The above criteria were only applicable for spontaneous bowel movements, i.e. not preceded within a period of 24 hours by the intake of a laxative agent or by the use of an enema.

Patients who never had spontaneous bowel movements were considered to be constipated and were eligible for the study.

3. Constipation that was not induced by secondary causes of constipation (see exclusion criteria 1 through 5).
4. Willingness and ability to fill out his/her own diary and questionnaires without help.
5. Written informed consent, signed by the patient and by the investigator.
6. Availability for follow-up during the study period as determined in the protocol.

Exclusion Criteria

Patients were to be excluded if any of the following applied:

1. Patients in whom constipation was thought to be drug-induced, or who were using any disallowed medication.
2. Patients suffering from secondary causes of chronic constipation; for example:
   Endocrine disorders: insulin-dependent diabetes mellitus, hypo-pituitarism, hypothyroidism, hypercalcaemia, pseudohypopara-thyroidism, pheochromocytoma, or glucagon-producing tumours. Endocrine disorders controlled by appropriate medical therapy were not excluded with the exception of insulin-dependent diabetes mellitus.

   Metabolic disorders: porphyria, uraemia, hypokalaemia, or amyloid neuropathy. Metabolic disorders controlled by appropriate medical therapy were not excluded.

Neurologic disorders: Parkinson's disease, cerebral tumours, cerebrovascular accidents, multiple sclerosis, meningocele, aganglionosis, hypoganglionosis, hyper-ganglionosis, autonomic neuropathy, spinal cord injury, Chagas disease, or major depression.

3. Presence of a megacolon/megarectum or a diagnosis of pseudo-obstruction.
4. Constipation as a result of surgery.
5. Known or suspected organic disorders of the large bowel (i.e. obstruction, carcinoma, or inflammatory bowel disease). Results of a barium enema or of a colonoscopic examination performed within the last 12 months were needed to rule out organic disorders. A colonoscopic examination performed within the last 3 years was acceptable if the examination was performed for an evaluation of constipation, and there was no history or evidence of weight loss, anaemia, or rectal bleeding, and the patient had at least 3 consecutively negative stool occult blood tests at screening. Patients with polyps discovered by colonoscopy that were untreated (i.e. by polypectomy) were to be excluded.
6. Presence of severe and clinically uncontrolled cardiovascular, liver, or lung disease, neurologic or psychiatric disorders (including active alcohol or drug abuse), cancer or AIDS, and other gastro-intestinal or endocrine disorders.
7. Impaired renal function, i.e. serum creatinine concentration > 2 mg/dL (> 180 μmol/L) or $Cl_{CR} \leq 50$ mL/min.
8. Clinically significant abnormalities of haematology, urinalysis, or blood chemistry.
9. Females of child-bearing potential without adequate contraceptive protection during the study. Oral contraceptives, Depo Provera®, Norplant® (used for at least 3 months prior to randomization), intrauterine device (IUD), sterilization, or a double barrier method were acceptable methods of birth control.
10. Treatment with an investigational drug in the 30 days preceding the run-in phase of the study.
11. Previous treatment with either prucalopride formulation.

11.3.6 Study 401 Inclusion and Exclusion Criteria

Inclusion Criteria

A patient was eligible for the study if all of the following applied:

1. Patient was a male or non-pregnant, non-breastfeeding female outpatient ≥18 years of age (no upper age limit).
2. Patient had a history of constipation. The patient reported an average of ≤2 CSBMs per week and 1 or more of the following for at least 6 months before the selection visit:
   - Very hard (little balls) and/or hard stools at least a quarter of the stools.
   - Sensation of incomplete evacuation following at least a quarter of the stools.
   - Straining at defecation at least a quarter of the time.

   The above criteria were only applicable for SBMs (i.e., BMs not preceded within a period of 24 hours by the intake of a laxative agent or by the use of an enema). Patients who never had SBMs were considered to be constipated and were eligible for the study.
3. Patient agreed to stop his/her current laxative treatment and was willing to use rescue medication according to the rescue rule (bisacodyl/enemas).
4. Patient's constipation was chronic.
5. Patient was able and willing to complete the questionnaires (if a validated version in the language of the patient was available) and the e-diary.
6. Women of childbearing potential had a negative serum pregnancy test at Visit 1 (the Screening Visit) and used an efficient method of birth control for the entire duration of the study and until the first menses after a 30-day period after the last dose of investigational product. They must have been on a stable regimen for at least 1 month of oral contraceptives, contraceptive implant or depot injection, contraceptive patch, intrauterine device, condom and spermicidal agent, or diaphragm and spermicidal agent, or agreed upon continuous abstinence from heterosexual sexual contact and have been willing to continue this contraception.
7. Patient voluntarily signed the written ICF in accordance with the regional laws/regulations, prior to the first study-related activity.
8. Patient was willing to adhere to all study requirements.

Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

1. Patients in whom constipation was thought to be drug-induced.
2. Patients who used any disallowed medication.
3. Patients who previously used prucalopride.

4. Patients who suffered from secondary causes of chronic constipation, such as:

   - Endocrine disorders, eg, hypopituitarism, hypothyroidism, hypercalcemia, pseudo-hypoparathyroidism, pheochromocytoma, or glucagon-producing tumors, unless these were controlled by appropriate medical therapy. Patients with insulin-dependent diabetes mellitus were excluded, also if the patients were under appropriate medical therapy.
   - Metabolic disorders, eg, porphyria, uremia, hypokalemia, or amyloid neuropathy, unless these were controlled by appropriate medical therapy.
   - Neurological disorders, eg, Parkinson's disease, cerebral tumors, cerebrovascular accidents, multiple sclerosis, meningocele, aganglionosis, hypoganglionosis, hyperganglionosis, autonomic neuropathy or neuropathy due to chemotherapy, spinal cord injury, Chagas disease, major depression.
   - Surgery.

   Note: If a patient had chronic constipation prior to the onset of a condition listed above and the constipation had not worsened by this condition, the patient was eligible for screening. However, if the constipation had started after the onset of 1 of the above conditions and the relation between both could not be excluded (ie, it was not certain whether it was secondary to it or not), or when the constipation worsened after the onset of 1 of the above conditions, the patient was not allowed to be screened for this study. Patients with insulin-dependent diabetes mellitus were excluded, irrespective of whether the constipation started prior to or after the onset of diabetes.

5. Patients with a significant history of cancer (ie, less than a 5-year disease-free survival).
6. Patients with intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract, such as Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum.
   Results of an endoscopy or radiologic bowel evaluation was required to rule out polyps, cancer, stricture, or other structural or organic disease:

   - For patients ≤50 years: a flexible sigmoidoscopy or colonoscopy after the onset of constipation symptoms and within the previous 5 years.
   - For patients > 50 years: a flexible sigmoidoscopy/double-contrast barium enema or colonoscopy after the onset of constipation symptoms and within the previous 5 years.
   - For patients, regardless of age, even if results of this test were available within the previous 5 years but if the patient had alarm symptoms such as anemia, weight loss, heme positive stool, or rectal bleeding: a flexible sigmoidoscopy and double-contrast barium enema or colonoscopy was needed after the onset of symptoms.
   - If abnormalities had been detected during the sigmoidoscopy or colonoscopy (eg, because of polyps), the patient could have been included in the study if the polyps

were removed. If clinically indicated, a repeat colonoscopy/sigmoidoscopy needed to be performed at the latest within 1 week after the Screening Visit (Visit 1).

If no barium enema with flexible sigmoidoscopy or a colonoscopic examination had been performed within the period as previously described, the assessment was to be scheduled on the Screening Visit or within the week following the Screening Visit (Visit 1). When it was clinically indicated that a repeat colonoscopy/sigmoidoscopy was needed to confirm results of a colonoscopy/sigmoidoscopy performed after the Screening Visit (Visit 1), the patient should have been a screen failure.

7. Patients with clinically significant cardiac, vascular, liver, pulmonary, endocrine, neurological, or psychiatric disorders (as evaluated by the investigator), or metabolic disturbances.
8. Patients with any condition that, in the opinion of the investigator, would have complicated or compromised the study or the well-being of the patient or evidence of clinically relevant pathology that could have interfered with the study results or put the patient's safety at risk.
9. Patients known to have a human immunodeficiency virus infection, acquired immunodeficiency syndrome, hepatitis B, or hepatitis C.
10. Patients with impaired renal function (serum creatinine concentration > 180µmol/L or calculated Cl_{CR} ≤30mL/min), including patients requiring dialysis.
11. Patients with clinically significant abnormalities of hematology, urinalysis, or blood chemistry as determined by the investigator.
    If the results of the hematology, biochemistry, or urinalysis tests were not within the laboratory's reference ranges, the patient could have been included only on the condition that the investigator judged that the deviations were not clinically significant. This should have been clearly recorded in the e-CRF.
12. Patients with a history of alcohol or drug abuse in the previous 6 months.
13. Patients with lactose intolerance for whom it was expected that low doses of lactose could have led to diarrhea, or a known allergy to ingredients or excipients of the investigational product.
14. Patients who received an investigational drug in the 30 days preceding the Run-in Phase of the study.

11.4 PAC-SYM and PAC-QOL Instruments

PAC-SYM PATIENT ASSESSMENT OF CONSTIPATION

This questionnaire asks you about your constipation symptoms in the **past 2 weeks**. Answer each question according to your symptoms, as accurately as possible. There are no right or wrong answers.

For each symptom below, please indicate **how severe** your symptoms have been during the **past 2 weeks**. If you have not had the symptom during the past 2 weeks, tick 0. If the symptom seemed mild, tick 1. If the symptom seemed moderate, tick 2. If the symptom seemed severe, tick 3. If the symptom seemed very severe, tick 4. Please be sure to answer every question.

How severe have each of these symptoms been in the past 2 weeks?	**Absent 0**	**Mild 1**	**Moderate 2**	**Severe 3**	**Very severe 4**
1. discomfort in your stomach	☐	☐	☐	☐	☐
2. pain in your stomach	☐	☐	☐	☐	☐
3. bloating in your stomach	☐	☐	☐	☐	☐
4. stomach cramps	☐	☐	☐	☐	☐
5. painful bowel movements	☐	☐	☐	☐	☐
6. rectal burning during or after a bowel movement	☐	☐	☐	☐	☐
7. rectal bleeding or tearing during or after a bowel movement	☐	☐	☐	☐	☐
8. incomplete bowel movement, as though you didn't "finish"	☐	☐	☐	☐	☐
9. stools that were too hard	☐	☐	☐	☐	☐
10. stools that were too small	☐	☐	☐	☐	☐
11. straining or squeezing to try to pass stools	☐	☐	☐	☐	☐
12. feeling like you had to pass a stool but couldn't (false alarm)	☐	☐	☐	☐	☐

PAC-QOL PATIENT ASSESSMENT OF CONSTIPATION

The following questions are designed to measure the impact constipation has had on your daily life **during the past 2 weeks**. For each question, please tick one box.

The following questions ask you about the intensity of your symptoms. To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
1. have you felt bloated to the point of bursting?	☐	☐	☐	☐	☐
2. have you felt heavy because of your constipation?	☐	☐	☐	☐	☐

The next few questions ask you about the effects of constipation on your daily life. How much of the time, during the past 2 weeks...	**None of the time 0**	**A little of the time 1**	**Some of the time 2**	**Most of the time 3**	**All of the time 4**
3. have you felt any physical discomfort?	☐	☐	☐	☐	☐
4. have you felt the need to open your bowel but not been able to?	☐	☐	☐	☐	☐
5. have you been embarrassed to be with other people?	☐	☐	☐	☐	☐
6. have you been eating less and less because of not being able to have bowel movements?	☐	☐	☐	☐	☐

The next few questions ask you about the effects of constipation on your daily life. To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
7. have you had to be careful about what you eat?	☐	☐	☐	☐	☐
8. have you had a decreased appetite?	☐	☐	☐	☐	☐
9. have you been worried about not being able to choose what you eat (for example, at friend's)?	☐	☐	☐	☐	☐
10. have you been embarrassed about staying in the toilet for so long when you were away from home?	☐	☐	☐	☐	☐
11. have you been embarrassed about having to go to the toilet so often when you were away from home?	☐	☐	☐	☐	☐
12. have you been worried about having to change your daily routine (for example, travelling, being away from home)?	☐	☐	☐	☐	☐

The next few questions ask you about your feelings. How much of the time, during the past 2 weeks...	None of the time 0	A little of the time 1	Some of the time 2	Most of the time 3	All of the time 4
13. have you felt irritable because of your condition?	☐	☐	☐	☐	☐
14. have you been upset by your condition?	☐	☐	☐	☐	☐
15. have you felt obsessed by your condition?	☐	☐	☐	☐	☐
16. have you felt stressed by your condition?	☐	☐	☐	☐	☐
17. have you been less self-confident because of your condition?	☐	☐	☐	☐	☐
18. have you felt in control of your situation?	☐	☐	☐	☐	☐

The next questions ask you about your feelings. To what extent, during the past 2 weeks...	Not at all 0	A little bit 1	Moderately 2	Quite a bit 3	Extremely 4
19. have you been worried about not knowing when you are going to be able to open your bowels?	☐	☐	☐	☐	☐
20. have you been worried about not being able to open your bowels when you needed to?	☐	☐	☐	☐	☐
21. have you been more and more bothered by not being able to open your bowels?	☐	☐	☐	☐	☐

The next questions ask about your life with constipation. How much of the time, during the past 2 weeks...	**None of the time 0**	**A little of the time 1**	**Some of the time 2**	**Most of the time 3**	**All of the time 4**
22. have you been afraid that your condition will get worse?	☐	☐	☐	☐	☐
23. have you felt that your body was not working properly?	☐	☐	☐	☐	☐
24. have you had fewer bowel movements than you would like?	☐	☐	☐	☐	☐

The next questions ask you about how satisfied you are. To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
25. have you been satisfied with how often you open your bowels?	☐	☐	☐	☐	☐
26. have you been satisfied with the regularity with which you open your bowels?	☐	☐	☐	☐	☐
27. have you been satisfied with your bowel function?	☐	☐	☐	☐	☐
28. have you been satisfied with your treatment?	☐	☐	☐	☐	☐

11.5 Cardiovascular Adverse Event Narratives

Study 3001 prucalopride 2 mg treatment group: A 63-year-old Asian male had a protocol-specified ECG (27 days after the first intake of the study medication) which showed an abnormal T-wave, possible inferior ischemia, or possible anterolateral ischemia. He was diagnosed with heart ischemia on ECG with no symptoms. The patient had no history of cardiovascular disease, and the ECG at baseline did not show evidence of myocardial ischemia. The event led to the discontinuation of study medication. The patient was seen by a cardiologist on Day 42 (14 days after the last intake of study medication), who indicated that the ECG change was abnormal but not significant and did not require treatment. The SAE was reported as resolved. The investigator assessed this event as mild in intensity and possibly related to study medication.

Study USA-13 prucalopride 4 mg treatment group: A 60-year-old female patient with a history of angina pectoris, myocardial infarction, coronary artery disease and Grave's disease who was treated with medications to treat ischemic heart disease was hospitalized due to an increase in the severity of her pre-existing angina, which was reported as of moderate intensity. The investigator assessed this event as not related to the study medication. The study medication was temporarily interrupted due to the event. The next day, a cardiac catheterization was performed (results unspecified). Her condition improved, and she was discharged from the hospital. Thereafter the patient was re-started with prucalopride and the event did not reoccur.

Study 401 prucalopride 2 mg treatment group: A 77-year-old male with a history of hypertension who was diagnosed with a SAE of cerebrovascular accident and was admitted to the hospital. No action was taken with the study medication. Cerebrovascular accident was reported to be moderate in severity and was assessed as unlikely related to the study medication by the investigator. The patient's condition improved (no paresis, speech or swallowing difficulties, or urinary or fecal incontinence) and he was discharged from the hospital after 4 days. The event was reported as resolved with sequelae on discharge; the patient had not regained full functionality of his left arm but was able to walk without aids. The patient withdrew consent and was discontinued from the study.

11.6 Additional Tables from Study 802

Table 61: Cohort Selection for Prucalopride and PEG Groups in Study 802

	Prucalopride No. patients (% remaining)	PEG No. patients (% remaining)
Total (prior to exclusions, matching, and trimming)	8,782 (100%)	2,168,213 (100%)
Eligible patients after exclusions[a]	6,394 (72.81%)	1,063,841 (49.07%)
Eligible patients after matching	6,394 (100%)	31,968 (3.00%)
Patients in the trimmed population	5,715 (89.38%)	29,372 (91.88%)

No.=number; PEG=polyethylene glycol.

[a] Patients were excluded due to the following reasons: registration in Scottish practices [applies to the Clinical Practice Research Datalink (CPRD) and The Health Information Network (THIN) only], registration in duplicate practices (applies to CPRD and THIN only), <12 months of data prior to index date, age <18 years, short index episode (<12 days, PEG only), prior use of the study drug (prucalopride or PEG), short episode (<12 days) of PEG within 12 months of index date, new users of PEG and prucalopride on the same date, or all follow-up time occurred during overlapping exposure in both study cohorts.

Table 62: Demographics and Cardiovascular and Gastrointestinal Risk Factors in the Prucalopride and PEG Study Cohorts

	Prucalopride No. patients (% total) N=5715	PEG No. patients (% total) N=29,372
Sex		
Female	5,296 (92.67%)	27,363 (93.16%)
Male	419 (7.33%)	2,009 (6.84%)
Age		
18-54	3,263 (57.10%)	17,031 (57.98%)
≥ 55	2,452 (42.90%)	12,341 (42.02%)
Sex and Age		
18-54 year-old women	3,091 (54.09%)	16,198 (55.15%)
≥ 55 year-old women	2,205 (38.58%)	11,165 (38.01%)
18-54 year-old men	172 (3.01%)	833 (2.84%)
≥ 55 year-old men	247 (4.32%)	1,176 (4.00%)
History of hospitalization for cardiovascular disease		
Yes	345 (6.04%)	1,610 (5.48%)
No	5,370 (93.96%)	27,762 (94.52%)
Any revascularization procedures		
Yes	139 (2.43%)	723 (2.46%)
No	5,576 (97.57%)	28,649 (97.54%)
Aspirin and other antiplatelets		
Yes	1,001 (17.52%)	4,826 (16.43%)
No	4,714 (82.48%)	24,546 (83.57%)
Statins		
Yes	1,200 (21.00%)	5,780 (19.68%)
No	4,515 (79.00%)	23,592 (80.32%)
Antihypertensives		
Yes	2,646 (46.30%)	12,336 (42.00%)
No	3,069 (53.70%)	17,036 (58.00%)
Antidiabetics		
Yes	482 (8.43%)	2,393 (8.15%)
No	5,233 (91.57%)	26,979 (91.85%)
Anticoagulants		
Yes	606 (10.60%)	2,958 (10.07%)
No	5,109 (89.40%)	26,414 (89.93%)
Hyperlipidemia diagnosis		
Yes	449 (7.86%)	2,116 (7.20%)
No	5,266 (92.14%)	27,256 (92.80%)
Hypertension diagnosis		
Yes	1,018 (17.81%)	5,374 (18.30%)
No	4,697 (82.19%)	23,998 (81.70%)
Obesity, BMI > 30 kg/m^2 (CPRD/THIN/SNR only)[a]		
Yes	262 (5.74%)	1,534 (6.51%)
No	4,299 (94.26%)	22,032 (93.49%)
Obesity treatments		
Surgical or pharmaceutical intervention		
Yes	203 (3.55%)	913 (3.11%)
No	5,512 (96.45%)	28,459 (96.89%)

Table 62: Demographics and Cardiovascular and Gastrointestinal Risk Factors in the Prucalopride and PEG Study Cohorts

	Prucalopride No. patients (% total) N=5715	PEG No. patients (% total) N=29,372
Diabetes diagnosis		
Yes	430 (7.52%)	2,136 (7.27%)
No	5,285 (92.48%)	27,236 (92.73%)
Chronic renal disease diagnosis		
Yes	124 (2.17%)	636 (2.17%)
No	5,591 (97.83%)	28,736 (97.83%)
Cancer		
Yes	439 (7.68%)	2,590 (8.82%)
No	5,276 (92.32%)	26,782 (91.18%)
Smoking (CPRD/THIN only)[b]		
Never smoker	671 (49.09%)	3,278 (48.23%)
Former smoker	424 (31.02%)	2,007 (29.53%)
Current smoker	262 (19.17%)	1,438 (21.16%)
Unknown	10 (0.73%)	74 (1.09%)
COPD diagnosis		
Yes	209 (3.66%)	1,133 (3.86%)
No	5,506 (96.34%)	28,239 (96.14%)
Asthma without COPD diagnosis		
Yes	710 (12.42%)	2,806 (9.55%)
No	5,005 (87.58%)	26,566 (90.45%)
Number of outpatient medical visits with constipation diagnoses (CPRD/THIN/SNR only)[c]		
0	2,423 (53.12%)	19,578 (83.08%)
≥ 1	1,623 (35.58%)	2,907 (12.34%)
Number of medical visits with IBS diagnoses (CPRD/THIN/SNR only)[c]		
0	3,712 (81.39%)	21,975 (93.25%)
≥ 1	609 (13.35%)	1,301 (5.52%)
Number of unique other GI related outpatient diagnoses (CPRD/THIN/SNR only)[d]		
0	2,457 (53.87%)	15,987 (67.84%)
1-12	1,209 (26.51%)	3,800 (16.12%)
Prescription or dispensing for opioid medications[e]		
Yes	1,730 (30.27%)	9,810 (33.40%)
No	3,985 (69.73%)	19,562 (66.60%)
Chronic opioid use[f]		
Yes	1,551 (27.14%)	7,708 (26.24%)
No	4,164 (72.86%)	21,664 (73.76%)
Recent hospitalization[g]		
Yes	248 (4.34%)	1,366 (4.65%)
No	5,467 (95.66%)	28,006 (95.35%)
Economic deprivation category (CPRD/THIN/ISD only)		
Q1 (least deprived)	556 (22.05%)	2,432 (19.30%)
Q2	480 (19.04%)	2,322 (18.42%)
Q3	506 (20.07%)	2,586 (20.52%)

Table 62: Demographics and Cardiovascular and Gastrointestinal Risk Factors in the Prucalopride and PEG Study Cohorts

	Prucalopride No. patients (% total) N=5715	PEG No. patients (% total) N=29,372
Q4	478 (18.96%)	2,639 (20.94%)
Q5 (most deprived)	474 (18.80%)	2,480 (19.68%)
Unknown	27 (1.07%)	144 (1.14%)
Economic deprivation category (SNR only)		
Q1 (least deprived)	795 (24.89%)	3,648 (21.75%)
Q2	784 (24.55%)	4,149 (24.74%)
Q3	808 (25.30%)	4,104 (24.47%)
Q4 (most deprived)	807 (25.27%)	4,868 (29.03%)
At least 1 cardiovascular risk factor[h]		
Yes	3,297 (57.69%)	16,136 (54.94%)
No	2,418 (42.31%)	13,236 (45.06%)
Constipation inpatient diagnosis (CPRD/ISD/SNR only)		
Yes	1,014 (19.45%)	869 (3.24%)
No	4,200 (80.55%)	25,960 (96.76%)
IBS inpatient diagnosis (CPRD/ISD/SNR only)		
Yes	168 (3.22%)	236 (0.88%)
No	5,046 (96.78%)	26,593 (99.12%)
Other GI related inpatient diagnosis (CPRD/ISD/SNR only)		
Yes	1,564 (30.00%)	4,499 (16.77%)
No	3,650 (70.00%)	22,330 (83.23%)

BMI=body mass index; COPD=chronic obstructive pulmonary disease; CPRD=Clinical Practice Research Datalink; CV=cardiovascular; GI=gastrointestinal; IBS=irritable bowel syndrome; ISD=Informational Service Division; MI=myocardial infarction; NA=variable not available in the database; No.=Number; PEG=polyethylene glycol; SNR=Swedish National Registers; THIN=The Health Information Network.

[a] Identified using the information reported closest in time to the cohort entry date within the prior 3 years.

[b] Identified using the information reported closest in time to the cohort entry date within the prior 10 years.

[c] Diagnoses occurring any time before taking the index study medication.

[d] Total number of unique other GI diagnoses occurring any time before the index study medication. Other GI diagnoses considered were esophageal conditions, gastroduodenal conditions, appendicitis, hernias, intestinal conditions, peritonitis, liver conditions, biliary conditions, pancreatic conditions, GI hemorrhage, malabsorption, and inflammatory bowel disease.

[e] Occurring in the 6 months before cohort entry.

[f] Chronic opioid use was defined as more than 1 unique prescription or dispensing (i.e., occurring on separate days) for an opioid during the 12 months before the index date.

[g] Any hospitalization, regardless of diagnosis, in the 14 days immediately preceding cohort entry.

[h] History of cardiovascular disease (including all MACE component endpoints), hypertension, smoking, hyperlipidemia, diabetes, aged more than 55 years, or BMI greater than 30 kg/m^2.

11.7 Laboratory Parameters

Table 63: Biochemistry Parameters over Time in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)

	PLA N=1973				PRU 1 mg N=330				PRU 2 mg* N=1516			
	Baseline		Week 12		Baseline		Week 12		Baseline		Week 12	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Calcium (mmol/L)	1733	2.3 (0.16)	1047	2.3 (0.15)	328	2.4 (0.12)	68	2.3 (0.11)	1507	2.3 (0.13)	990	2.3 (0.15)
Chloride (mmol/L)	1727	103.3 (3.05)	1046	103.2 (2.85)	328	103.5 (3.48)	68	104.3 (2.91)	1508	103.2 (3.25)	988	103.3 (2.79)
Magnesium (mmol/L)	1673	0.9 (0.10)	1031	0.9 (0.10)	273	0.8 (0.09)	51	0.8 (0.08)	1491	0.9 (0.10)	973	0.9 (0.10)
Phosphate (mmol/L)	1689	1.2 (0.28)	1040	1.2 (0.21)	289	1.2 (0.24)	65	1.2 (0.18)	1504	1.2 (0.28)	983	1.2 (0.20)
Potassium (mmol/L)	1726	4.3 (0.5)	1039	4.3 (0.46)	328	4.4 (0.53)	68	4.2 (0.45)	1500	4.3 (0.54)	981	4.2 (0.45)
Sodium (mmol/L)	1732	140.2 (2.91)	1047	140.0 (2.83)	328	139.4 (2.87)	68	140.0 (3.07)	1508	140.3 (2.86)	988	140.0 (2.64)
Protein (g/L)	1693	71.6 (4.92)	1046	71.5 (4.75)	289	72.2 (5.24)	68	71.6 (4.06)	1508	71.8 (4.94)	990	71.7 (4.59)
Albumin (g/L)	1679	43.1 (3.76)	1046	42.6 (3.71)	279	41.8 (4.21)	68	43.3 (3.31)	1496	43.2 (3.98)	988	42.9 (3.69)
BUN (mmol/L)	878	4.3 (1.49)	629	4.5 (1.35)	72	5.3 (2.73)	0	NA	744	4.5 (1.69)	589	4.5 (1.4)
Urea (mmol/L)	854	4.9 (1.91)	418	4.8 (1.90)	256	5.0 (1.88)	68	4.7 (1.54)	765	4.8 (1.90)	401	4.7 (1.86)
Urate (µmol/L)	1731	271.8 (79.49)	1047	268.0 (77.12)	328	266.3 (83.95)	68	248.5 (71.03)	1509	271.0 (77.58)	989	265.1 (76.62)
Creatinine (µmol/L)	1734	74.2 (18.48)	1047	73.1 (18.06)	328	84.4 (18.91)	68	79.3 (15.10)	1509	74.5 (18.50)	990	72.7 (17.40)
Glucose (mmol/L)	1686	5.1 (1.29)	1036	5.1 (1.16)	286	5.4 (2.01)	68	4.8 (0.64)	1498	5.1 (1.27)	985	5.0 (1.17)
Cholesterol (mmol/L)	1694	5.2 (1.06)	1046	5.1 (1.03)	289	5.6 (1.17)	68	5.6 (1.08)	1508	5.2 (1.04)	989	5.1 (0.98)
Triglycerides (mmol/L)	1506	1.5 (1.05)	989	1.4 (1.02)	122	1.7 (0.89)	10	1.5 (0.78)	1347	1.4 (0.93)	938	1.4 (0.88)
Direct bilirubin (µmol/L)	1341	2.6 (1.33)	836	2.7 (1.44)	225	2.2 (1.53)	68	3.1 (1.93)	1207	2.6 (1.34)	761	2.7 (1.5)
Bilirubin (µmol/L)	1727	9.6 (4.82)	1042	9.4 (4.55)	326	9.7 (4.56)	68	9.3 (4.37)	1500	9.6 (4.83)	984	9.4 (4.77)
ALP (U/L)	1732	67.6 (28.28)	1045	64.8 (22.94)	328	73.9 (34.70)	68	60.0 (22.46)	1505	67.8 (26.5)	984	66.6 (25.17)
GGT (U/L)	1480	22.4 (22.06)	819	23.7 (22.36)	328	24.3 (31.35)	68	29.0 (32.56)	1259	21.8 (19.37)	760	22.5 (19.11)
LDH (U/L)	1586	171.2 (58.99)	983	166.6 (56.16)	209	193.3 (90.27)	10	190.6 (16.65)	1393	169.3 (56.28)	931	169.7 (58.64)
AST (U/L)	1731	20.7 (8.71)	1046	20.6 (7.24)	328	19.4 (7.32)	68	22.4 (7.89)	1509	20.6 (7.27)	989	20.8 (7.75)
ALT (U/L)	1730	19.3 (12.82)	1046	20.2 (13.52)	327	18.7 (10.60)	68	24.4 (10.53)	1509	19.0 (10.73)	989	19.7 (11.53)
Creatine kinase	761	110.2 (87.77)	555	108.7 (89.08)	37	84.1 (81.34)	10	176.5 (130.77)	615	110.3 (111.23)	503	108.7 (75.67)

Table 63: Biochemistry Parameters over Time in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks (Safety Set)

	PLA N=1973				PRU 1 mg N=330				PRU 2 mg* N=1516			
	Baseline		Week 12		Baseline		Week 12		Baseline		Week 12	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
(U/L)												
Prolactin (ng/mL)	378	9.2 (8.57)	174	9.2 (6.36)	22	8.9 [a] (3.30)	10	17.3[a] (22.75)	355	10.0 (12.78)	163	9.7 (5.98)
Bicarbonate (mmol/L)	1480	26.0 (2.96)	989	26.4 (3.48)	99	25.9 (3.23)	10	26.3 (2.68)	1316	25.9 (3.05)	931	26.3 (3.27)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BL=baseline; BUN=blood urea nitrogen; GGT=gamma glutamyltransferase; LDH=lactate dehydrogenase; W=week

[a] The high mean level at Week 12 is caused by outlier values. The median values at Baseline (8.75 ng/mL) and Week 12 (9.95 ng/mL) were similar and showed less variation over time.

[b] The high mean level at Baseline is caused by outlier values. The median values at Baseline (5.80 ng/mL) and Week 12 (5.00 ng/mL) were similar and showed less variation over time.

* Includes all patients titrated from 1 mg to 2 mg.

Source: Module 5.3.5.3, Table SAF D.17