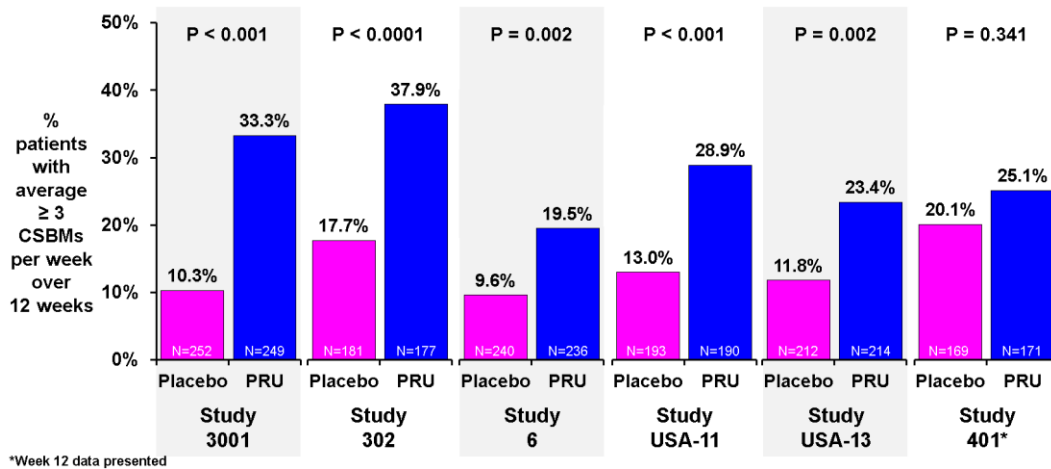


Errata to Shire's FDA Briefing Document issued for the Advisory Committee meeting October 18, 2018. The erroneous text is identified by a strikethrough, with correction following in bold, unless otherwise specified.

1. Page 26 and Page 80

Figure 4 and Figure 19; response rate percentage for Placebo and PRU for study USA13 was corrected. Footnote correction to Figure 19

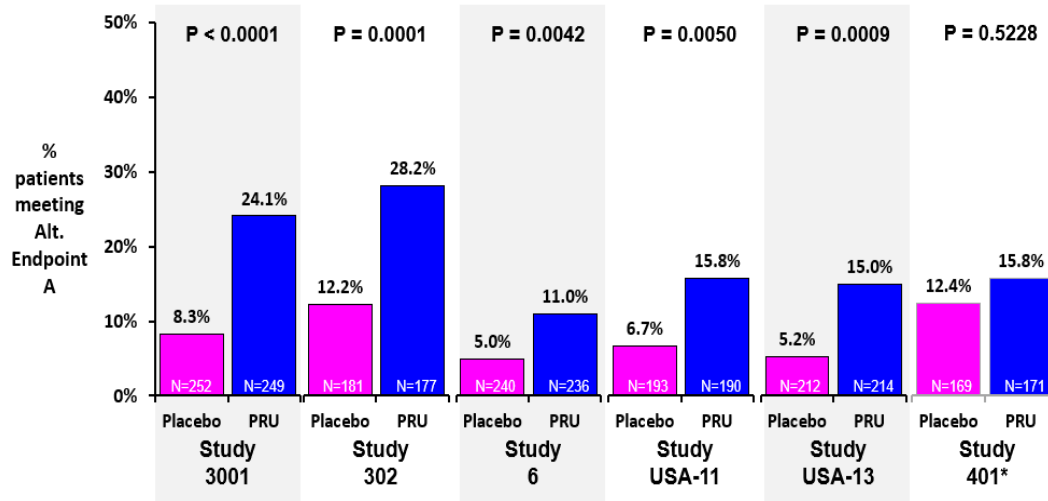


PRU=prucalopride; CSBM=complete spontaneous bowel movement

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~~ (updated IR 3/30/2018), and Study SPD555-401, Section 9.2.1, Table 8

2. Page 28 and page 83

Figure 6 and Figure 20; response rates and p-values were corrected with non-imputed data and using a Cochran-Mantel-Haenszel test (~~controlling for country, sex) and number of CSBMs/week at baseline (0 or >0) controlling for pooled country/center, sex and number of CBMs/week at baseline (0 or >0). Missing number N=181 in the bar for Placebo, Study 302 added to Figure 6 and 20.~~



3. Page 82

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 **0.5228** and p=0.3735 **0.1944** respectively)

4. Page 62

Table 19 Study 302, column 3 ~~370~~ **358**

5. Page 78

Table 22, Study 302 PLA N=~~252~~ **187**, PRU N=~~249~~ **187**

6. Page 84

Table 24 corrected using results based on **non-imputed data** for all studies and using a Cochran-Mantel-Haenszel test controlling for **pooled country/center**, sex and number of **CSBMs/week** at baseline (0 or >0).

**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 - Imputation: None)**

	Study 3001		Study 302 <sup>1)</sup>		Study INT-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 (%)	21 (8.3)	60 (24.1)	22 (12.2)	50 (28.2)	12 (5.0)	26 (11.0)	13 (6.7)	30 (15.8)	11 (5.2)	32(15.0)	21 (12.4)	27 (15.8)
<b>Weeks 1-12</b>												
Diff. in proportion		0.158		0.161		0.060		0.091		0.098		0.034
95% CI		0.094, 0.221		0.079, 0.243		0.012, 0.109		0.028, 0.153		0.041, 0.154		-0.040, 0.108
p-value <sup>a</sup>		< 0.0001		0.0001		0.0042		0.0050		0.0009		0.5228
<b>Weeks 1-24</b>												
Diff. in proportion												0.051
95% CI												-0.020, 0.123
p-value <sup>a</sup>												0.1944

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

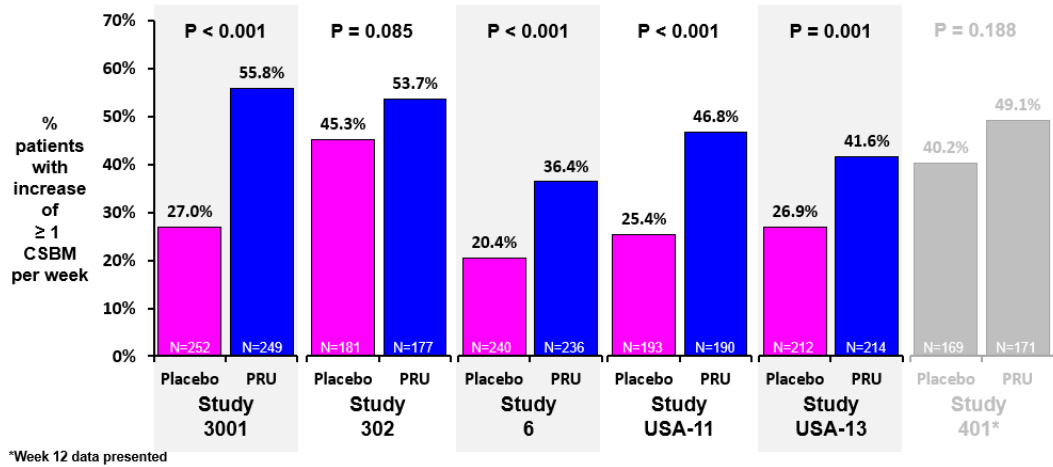
**The analysis was performed on the intent-to-treat (ITT) population for study 3001, study INT-6, study USA-11, study USA-13 and study 401, and modified-intent-to-treat (mITT) population for study 302.**

<sup>a</sup> p-value based on a CMH test for general association controlling for ~~age category (< 65 versus ≥ 65), (pooled)~~ pooled country (Study 6, Study 401, Study 302, Study 3001)/center (Study USA-11, Study USA-13), ~~race~~, sex and number of CSBMs/week at baseline (0 or >0).

\*Includes also patients titrated from prucalopride 1 mg to 2 mg.

7. Page 29

Figure 7, revised to include the results of study 401, and revised **response rates** and **p-values**



8. Page 22

Table 1: Add Footnote; Population numbers consistent with study reports: all treated patients (USA-11, USA-13 and INT-6), safety population (401), modified intent-to-treat population (mITT, 302) and intent-to-treat population (ITT, 3001).

9. Page 70

Section 6.1.1 line 2, ...occurrence of  $\leq 2$  SBM/Week and at least ~~2~~ **1** of the following...

10. Page 44

Table 11 Column 3, row 4, 56/M, MI, ~~2~~ mg **4** mg

11. Page 48

Table 13 percentage ~~0.07%~~ **0.06%**

12. Page 15

..and demonstrated ~~none of the~~ **that** off-target interactions **only occurred at concentrations greatly exceeding those** of previously approved nonselective 5-HT4 agonists.

13. Page 60

..it demonstrates ~~none of the~~ **that** off-target mediated cardiovascular interactions **occur at concentrations that greatly exceed those of previously approved nonselective 5-HT4 agonist.** ~~that have been observed with cisapride and tegaserod~~

14. Page 37

... Study 802 (~~5,717~~ **5,715** patients exposed to prucalopride).

15. Page 49

Section 1.5.2.5 ....; ~~10.30 (7.03-14.19)~~ **10.24 (6.97-14.13)** for PEG (Table 15). The pooled adjusted IRR for MACE was 0.64 (95% CI, 0.36, ~~1.13~~ **1.14**).

16. Page 50

**Table 15**

	<b>Prucalopride (N=<del>5717</del> 5715)</b>	<b>PEG (N=<del>2938</del> 29,372)</b>
MACE rate/1000 PYE (95% CI)	6.57 (3.90, 10.39)	<del>10.30 (7.03, 14.19)</del> <b>10.24 (6.97-14.13)</b>
Adjusted IRR (95% CI)	0.64 (0.36, <del>1.13</del> , <b>1.14</b> )	

17. Page 116,

Section 7, 10<sup>th</sup> bullet ..... (IRR=0.64 [95% CI,0.36-~~1.13~~, **1.14**]).

18. Page 130

Table 45: Column 3 row 7, 56/M, MI, ~~2~~ mg **4** mg; Column 5, row 6, ~~218~~ **226**

19. Page 145

Second Paragraph, starting with second line ... ~~10.30 (7.03-14.19)~~**10.24 (6.97-14.13)** 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~~ **1.14**). The pooled adjusted IRD for MACE combining the 3 UK data sources and the SNR was ~~-3.73~~ **-3.66** per 1,000 person-years (95% CI, ~~-8.34 to 0.89~~ **-8.27 to 0.95**). The pooled adjusted IRRs for individual components of MACE were ~~1.06 (95% CI, 0.44-2.57)~~ **0.95 (95% CI, 0.38-2.39)** for hospitalization for nonfatal acute myocardial infarction, ~~0.58 (95% CI, 0.25-1.31)~~ **0.54 (95% CI, 0.23, 1.29)**....

20. Page 146

Table 52

Outcome	No. Events	Standardized Incidence Rate per 1,000 person years (95% CI) <sup>a</sup>	No. Events	Standardized Incidence Rate per 1,000 Person Years (95% CI) <sup>a</sup>	Standardized Incidence Rate Ratio (95% CI) <sup>a</sup>	Standardized Incidence Rate Difference per 1,000 Person Years (95% CI) <sup>a</sup>
MACE <sup>b</sup>	18	6.57 (3.90, 10.39)	<del>74</del> 73	<del>10.30 (7.03, 14.19)</del> 10.24 (6.97- 14.13)	0.64 (0.36, <del>1.13</del> , 1.14)	<del>-3.73 (-8.34, 0.89)</del> -3.66 (-8.27, 0.95)
Hospitalization for non-fatal acute MI	<del>8</del> -7	<del>2.92 (1.26, 5.75)</del> 2.55 (1.03, 5.26)	<del>22</del> 21	<del>2.74 (1.41, 4.58)</del> 2.70 (1.37, 4.54)	<del>1.06 (0.44, 2.57)</del> 0.95 (95% CI, 0.38-2.39)	<del>0.18 (-2.34, 2.69)</del> -0.14 (-2.55, 2.27)
Hospitalization for non-fatal stroke	<del>9</del> -8	<del>3.28 (1.50, 6.23)</del> 2.92 (1.26, 5.75)	<del>39</del> 35	<del>5.70 (3.10, 9.01)</del> 5.39 (2.82, 8.71)	<del>0.58 (0.25, 1.31)</del> 0.54 (95% CI, 0.23, 1.29)	<del>-2.42 (-5.97, 1.13)</del> -2.47 (-5.93, 0.99)

21. Page 147

First paragraph, line 9. .... IRR of 2.57 (95% CI, 0.71-~~9.27~~ **9.26**)

22. Page 147

Third paragraph, line 5 .....was 0.64 (95% CI,0.36-~~1.13~~, **1.14**).

23. Page 144

Second Paragraph, last sentence....Sensitivity analyses included extended time (~~30 days and i.e.~~ all follow-up time (after discontinuation).

24. Page 158

Line 10 and 13, ~~2 mg~~ **4 mg**

25. Page 191

**Table 62**

	<b>Prucalopride No. patients (% total) N=5715</b>	<b>PEG No. patients (% total) N=29,372</b>
<b>Number of outpatient medical visits with constipation diagnoses (CPRD/THIN/SNR only)<sup>c</sup></b>		
0	2,423 (53.12%)	19,578 (83.08%)
≥ 1	<del>1,623 (35.58%)</del> <b>2,138 (46.88)</b>	<del>2,907 (12.34%)</del> <b>3,988 (16.92)</b>
<b>Number of medical visits with IBS diagnoses (CPRD/THIN/SNR only)<sup>c</sup></b>		
0	3,712 (81.39%)	21,975 (93.25%)
≥ 1	<del>609 (13.35%)</del> <b>849 (18.61)</b>	<del>1,301 (5.52%)</del> <b>1,591 (6.75)</b>
<b>Number of unique other GI related outpatient diagnoses (CPRD/THIN/SNR only)<sup>d</sup></b>		
0	2,457 (53.87%)	15,987 (67.84%)
1-12	<del>1,209 (26.51%)</del> <b>2,104 (46.13)</b>	<del>3,800 (16.12%)</del> <b>7,579 (32.16)</b>