FDA Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting: Introductory Remarks

NDA 210166, prucalopride: for the treatment of chronic idiopathic constipation (CIC) in adults

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Product Overview

- Drug: prucalopride
- Class: selective serotonin (5-HT_4) receptor agonist
- Mode of administration: oral tablet
- Proposed indication: treatment of chronic idiopathic constipation (CIC) in adults

Disease Overview

- Chronic idiopathic constipation (CIC), also known as functional constipation, characterized by the Rome criteria
  - Straining during defecation, hard stools, sensation of incomplete evacuation, fewer than three spontaneous bowel movements per week, loose stools rarely present without the use of laxatives
- Prevalence in North America is approximately 15%, increases with age
- CIC can have a profound impact on patient quality of life
- Additional treatment options are needed

FDA-Approved Treatments for CIC

FDA Approved Treatments	Year of CIC Approval	Class	Contraindications and Common Adverse Events
lubiprostone (Amitiza®)	2006	Apical chloride channel activator	Contraindication: known or suspected mechanical GI obstruction Common AEs: nausea, diarrhea, headache, abdominal pain, abdominal distension, flatulence
linaclotide (Linzess®)	2012	Guanylate cyclase-C agonist	Contraindication: known or suspected mechanical GI obstruction, patients <6 years old due to risk of serious dehydration Common AEs: diarrhea, abdominal pain, flatulence, abdominal distension, viral gastroenteritis, headache
plecanatide (Trulance®)	2017	Guanylate cyclase-C agonist	Contraindication: known or suspected mechanical GI obstruction, patients <6 years old due to risk of serious dehydration Common AEs: diarrhea

Prucalopride Regulatory History

- 2009: EMA approved prucalopride for CIC in women for whom laxatives were ineffective; indication expanded to males in 2014
- 1998: IND submitted to FDA
- 2004: IND inactivated
- 2012: IND reactivated by Shire
  - Phase 3 trials completed in the United States (1999); other trials ongoing/completed outside of the United States
  - Concern that the extent of prucalopride exposure and design of the clinical trials conducted may not be adequate to evaluate the potential cardiovascular (CV) safety signal associated with the 5-HT_4 receptor agonist class of drugs

Regulatory History (continued)

- DGIEP agreed that safety data appeared sufficient to support NDA submission
- DGIEP noted that lack of controlled trials of 12 months in duration was an important review issue
- DGIEP suggested that a possible path forward would be to include data from completed and ongoing trials, as well as available post-market data from Europe and countries in which prucalopride is approved
- Safety database adequacy would be discussed at an AC meeting

Regulatory History (continued)

- Primary efficacy endpoint in completed CIC trials:
  - Percentage of patients with a mean of ≥3 spontaneous complete bowel movements (SCBM) per week
- FDA's currently recommended endpoint for CIC trials:
  - Overall 12-week SCBM responder, defined as a patient who is a SCBM weekly responder ≥9 out of 12 weeks of the treatment period
    - SCBM weekly responder is a patient who has a SCBM weekly frequency rate of ≥3 and increased by ≥1 from baseline
    - Patients must have at least 4 days of evaluable response data to be considered a weekly responder

Contents of NDA Submission: Clinical Trial Efficacy Data

- Two 12-week,randomized (R), double-blind (DB), placebo-controlled (PC), phase 3 trials (Studies 3001 and 302)
  - Primary basis to demonstrate efficacy in support of FDA approval
  - Completed in 2011 and 2013, and enrolled primarily non-U.S. patient populations
- Three 12-week, R, DB, PC phase 3 legacy trials (Studies INT-6, USA-11 and -13)
  - Completed in 1999 and enrolled U.S. patient populations (USA-11,-13)
  - Trial results from the U.S. trials mirror results of the non-U.S. trials
- One 24-week phase 4 trial, conducted in Europe (Study 401)
  - Completed in 2012

Contents of NDA Submission: Safety Data

- Safety data from completed double-blind and open-label, phase 2 through 4 trials in CIC patients
- A non-interventional epidemiologic study (Study 802) conducted to estimate the standardized incidence rate ratio and 95% CI for major adverse cardiovascular events (MACE) in prucalopride compared to polyethylene glycol (PEG)
- Nonclinical toxicology data
- Clinical pharmacology data
- Platelet aggregation study
- Thorough QT study

Questions to Committee (1)

Question #1 (Voting):

Do the clinical trial data provide substantial evidence of effectiveness of prucalopride for the treatment of adults with chronic idiopathic constipation (CIC)? Discuss your answer.

Questions to Committee (2)

Question #2 (Voting):

Has the potential risk of cardiovascular adverse events with the use of prucalopride in adults with CIC been adequately addressed by the Applicant? Discuss your answer.

Questions to Committee (2a)

Question #2a (Discussion):

If you answered NO to Question #2, what additional safety data do you recommend? Discuss your answer.

Questions to Committee (3)

Question #3 (Voting):

Does the risk-benefit profile of prucalopride support the approval of this application?


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Nonclinical Safety Findings of Prucalopride

Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting
October 18, 2018

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Pharmacology

Receptor Binding Profile at Therapeutic Concentrations

Drug	5-HT_4	5-HT_3	5-HT_2	5-HT_1	hERG
Prucalopride	+				
Cisapride	+	+	+		+
Tegaserod	+	+	+	+	

+ indicates affinity for the receptor subtype that is clinically relevant at concentrations necessary for therapeutic action

Source: Tack J et al. Aliment Pharmacol Ther. 2012 Apr; 35(7):745-767

Cardiovascular Safety Studies: In Vitro

- Prucalopride had no effect on hERG potassium current (I_{kr}) in HEK293 cells at concentrations up to 1µM (50X therapeutic C_{max} of 7.5 ng/mL or 20nM); the IC_{50} for inhibition of hERG potassium current was 22µM (1100X therapeutic C_{max})
- Prucalopride had little or no effect on:
  - outward or inward potassium current
  - slow inward potassium current
  - fast sodium current
  - L-type calcium current in isolated guinea pig ventricular myocytes
- Prucalopride at concentrations ≥3µM prolonged AP duration by:
  - 14 to 20% in isolated guinea pig papillary muscles
  - 14 to 20% in canine and rabbit Purkinje fibers
  - 14 to 20% in rabbit hearts

Cardiovascular Safety Studies: In Vitro (Cont.)

- In isolated human atrial muscle strips, prucalopride caused a minor increase in contractile force (20% of 5-HT induced contractions) at concentrations ≥100nM
- Prucalopride (1nM to 10µM) had no contractile activity on porcine, canine, and human isolated coronary arteries
- Prucalopride at 200nM had no significant effect on human platelet aggregation in vitro

Cardiovascular Safety Studies: In Vivo

- Prucalopride at single IV doses of ≥1.25 mg/kg (44x human C_{max}), prolonged the duration of the QTc interval (by 11%) in anesthetized guinea pigs.
- In conscious dogs, IV or oral doses of ≥2.5 mg/kg (89x human C_{max}), caused a slight and transient increase in BP and HR, but no effect on ECG.
- In anesthetized dogs, IV prucalopride up to 1.25 mg/kg (137x human C_{max}), had no adverse effects on BP or ECG parameters.
- Oral prucalopride at 30 mg/kg for 12 months, had no apparent effect on ECG characteristics in dogs (872 X human C_{max}).

Cardiovascular Safety Studies: In Vivo (Cont.)

- In juvenile pigs, IV prucalopride, at 1.25 mg/kg (101 x human C_{max}), had **no effect** on CV parameters or QT and QTc intervals
- In anesthetized pro-arrhythmogenic rabbits, IV prucalopride, at up to 18.6 mg/kg (600X human C_{max}), **did not cause** tachycardia, torsades de pointes, or cardiac arrhythmias

Genetic Toxicity Study

- Prucalopride was positive in the Ames test in Salmonella TA100 at concentrations ≥500 µg/plate, with or without metabolic activation.
- However, prucalopride was negative in the following:
  - in vitro human lymphocyte chromosome aberration assay
  - in vitro unscheduled DNA synthesis assay in primary rat hepatocytes
  - in vivo mouse lymphoma assay
  - mouse micronucleus test
  - Big Blue transgenic rat gene mutation study

Carcinogenicity Studies

- In the 2-year carcinogenicity study in mice, the incidences of mammary gland adenocarcinoma in females were significantly higher than controls at the high dose (80 mg/kg; 194x the clinical exposure)
- In the 2-year carcinogenicity study in rats, the incidences of pituitary, thyroid, pancreatic, mammary gland, pheochromocytoma (adrenal), and hepatic tumors were significantly higher at 229x and 196x the clinical exposure
- Mechanistic studies suggest that the tumors observed in rodents are likely through epigenetic mechanisms

Summary

- Nonclinical safety of prucalopride has been assessed in an extensive battery of studies
- Nonclinical studies do not suggest a significant cardiovascular safety concern for prucalopride at the proposed clinical dose
- Positive carcinogenicity findings were observed with doses at very high multiples of human exposure


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Clinical Pharmacology Findings of Prucalopride for the Treatment of Chronic Idiopathic Constipation

Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting
October 18, 2018

Shen (Steven) Li, PhD
Division of Clinical Pharmacology III
Office of Clinical Pharmacology, Office of Translational Sciences
Center for Drug Evaluation and Research

Outline

- Pharmacokinetics (PK) of prucalopride
  - Absorption, distribution, metabolism, and excretion
- Intrinsic and extrinsic factors
  - Organ impairment
  - Drug-drug interaction
- Dose selection rationale
- Effects on QT prolongation
- Effects on platelet aggregation

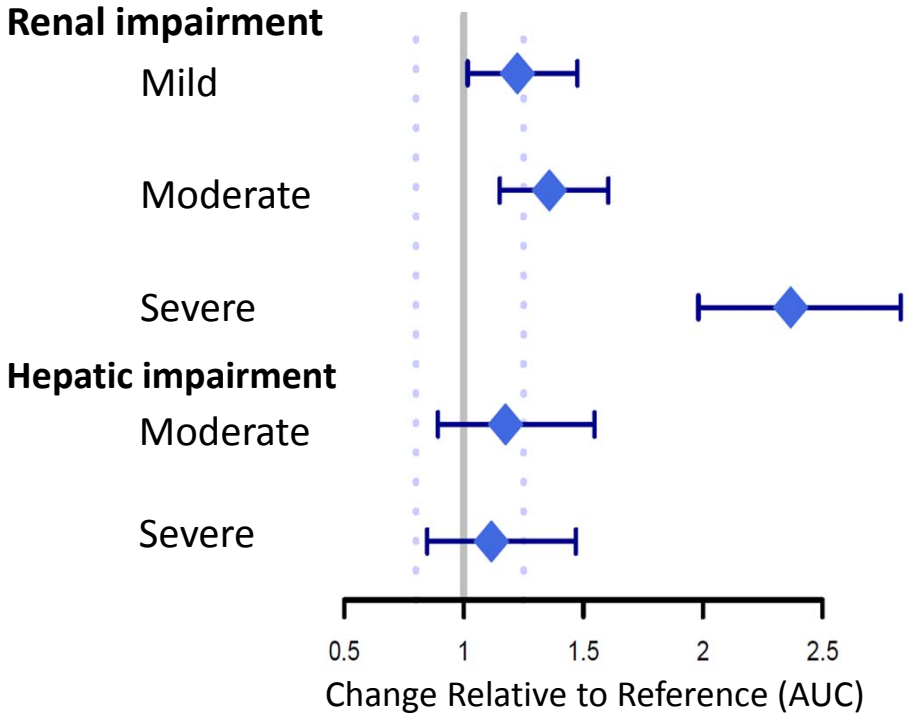
Pharmacokinetics of Prucalopride

Prucalopride PK in patients with chronic idiopathic constipation and healthy subjects are similar

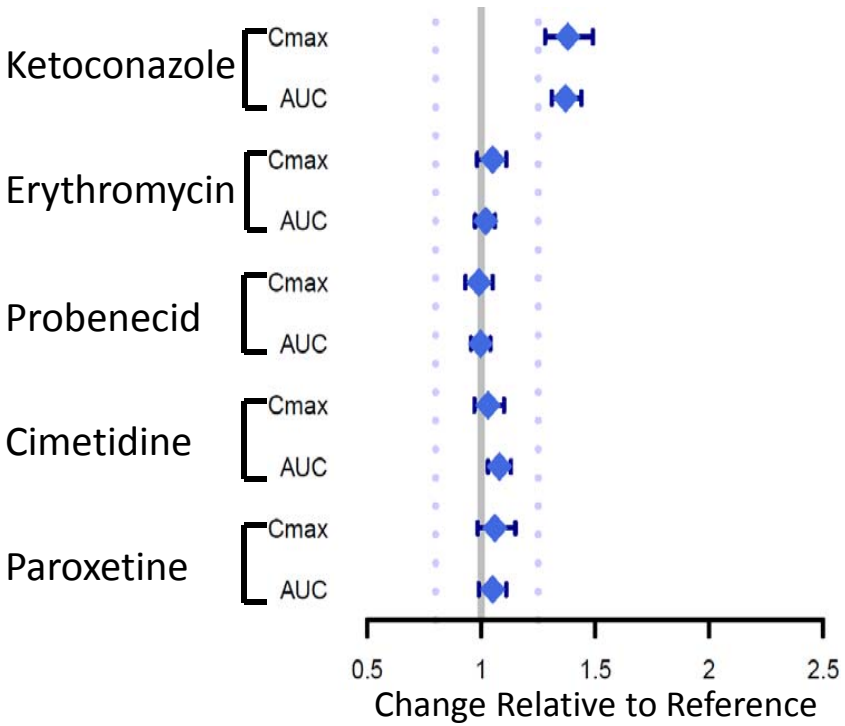
Absorption	• T_{max} 2 to 3 hours • Dose proportionality: 1 mg – 20 mg • Steady state: achieved within 3 to 4 days with QD dosing • No food effect on C_{max} and AUC
Distribution	• Protein binding ~28.9%.
Metabolism	• In plasma, prucalopride accounted for 92% to 94% of the total radioactivity • Substrate of CYP3A • No major metabolite
Excretion	• Urinary excretion: major elimination pathway. 84% of the dose excreted in urine, including 64% of the dose as unchanged prucalopride • t1/2 ~ 24 hours

Effects of Intrinsic and Extrinsic Factors on Prucalopride PK

Organ Impairment



Effects of other drugs on prucalopride



Source: Reviewer's analysis

Dose Selection Rationale for 2-mg QD

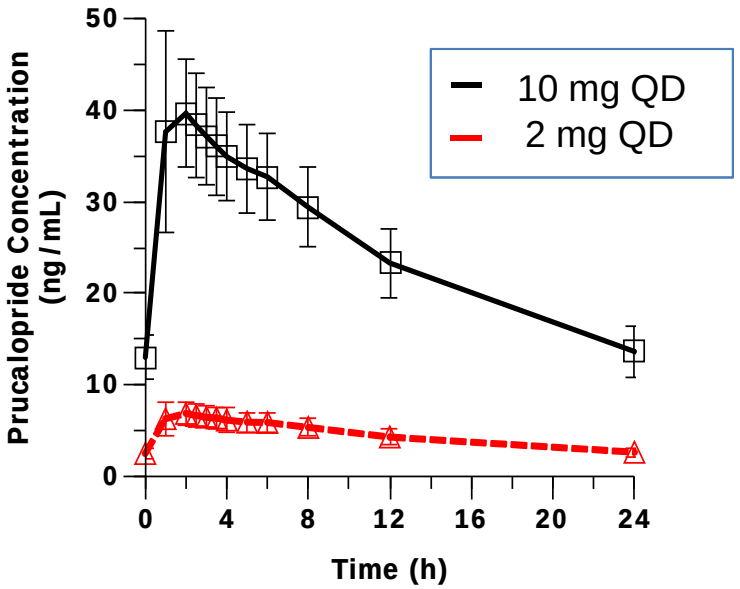
Proportion of Patients with an Average of ≥3 SCBMs/Week Over 12 Weeks

Study	Placebo, n/N (%)	2 mg QD, n/N (%)	4 mg QD, n/N (%)
PRU-INT-6	23/240 (9.6)	46/236 (19.5)	56/237 (23.6)
PRU-USA-11	25/193 (13.0)	55/190 (28.9)	54/187 (28.9)
PRU-USA-13	25/207 (12.1)	50/209 (23.9)	48/204 (23.5)

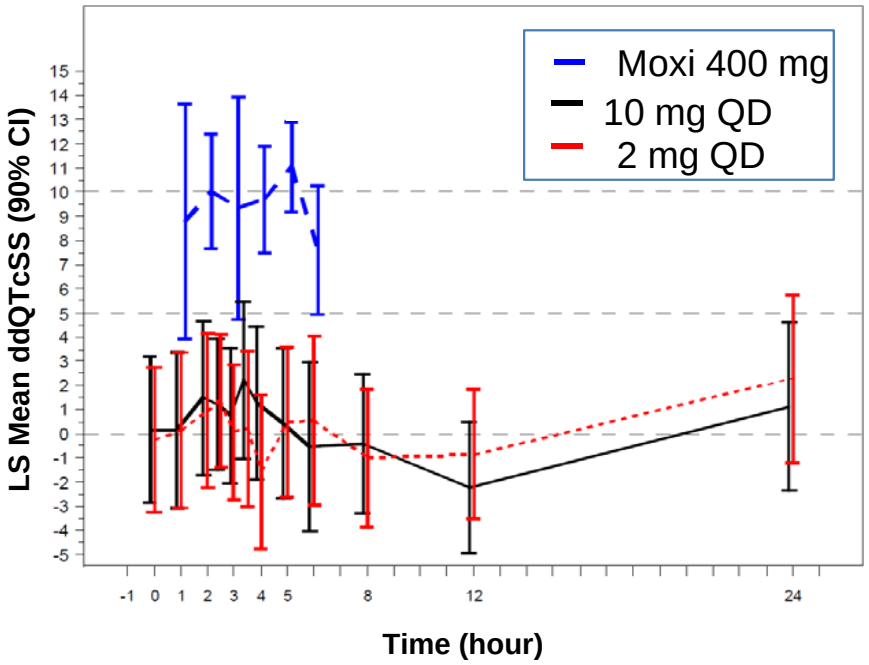
SCBM: spontaneous complete bowel movement
Source: Clinical study reports for Studies PRU-INT-6, PRU-USA-11, and PRU-USA-13

No Clinically Relevant Effects on QT Prolongation in Thorough QT Study

Concentration-time profile



ddQTcSS-time profile

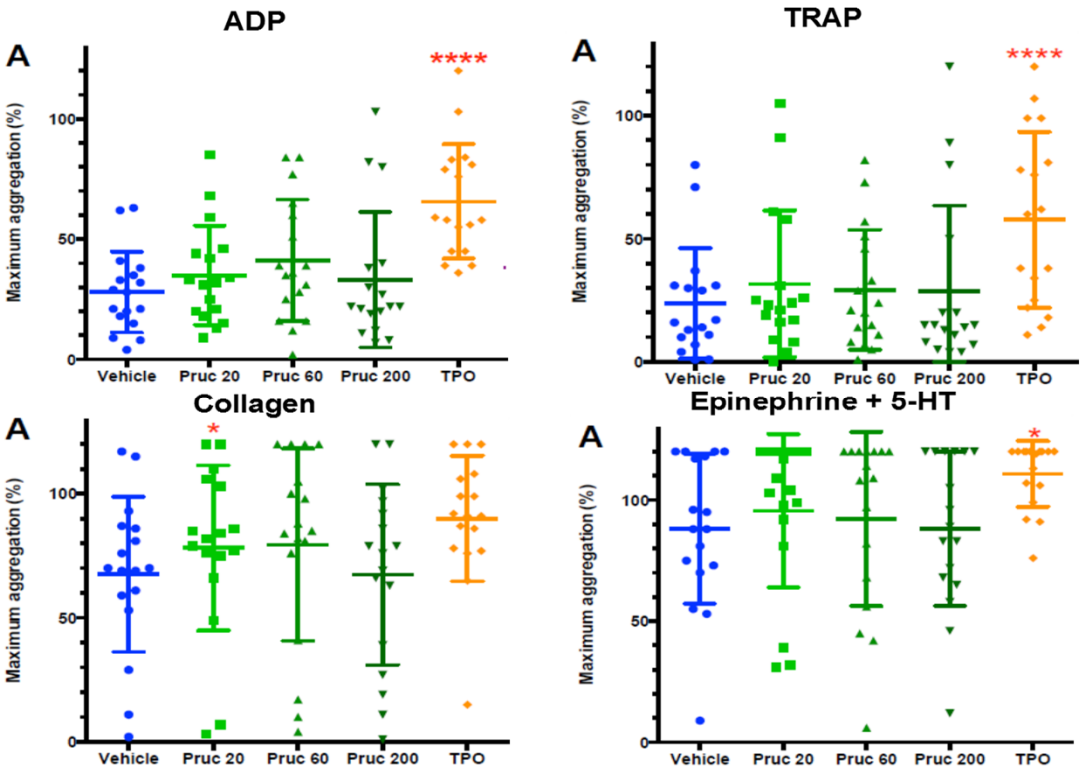


Source: Reviewer's plot using data provided for Study M0001-C102

ddQTcSS: placebo-, baseline-corrected QTc based on a study-specific QT correction

Source: FDA QT-IRT review

No Significant Effects on Platelet Aggregation



In vitro platelet aggregation:

- Blood from healthy subjects (N=20)
- Agonists: ADP, TRAP, collagen, epinephrine and 5-HT
- Prucalopride 20, 60, and 200 nM (i.e., 1x, 3x, 10x C_{max})
- Thrombopoietin (TPO): positive control

* p <0.05. ADP=adenosine diphosphate; TRAP=thrombin receptor activating peptide

Source: Applicant's report V6002M-SPD555, Figures 1 through 4.

Summary

- Severe renal impairment: dose reduction to 1 mg QD is recommended
- No clinically relevant effects on the QT interval were observed at the proposed dose of 2 mg QD and 10 mg QD (5 times the proposed dosage) in healthy subjects
- In vitro prucalopride did not significantly potentiate the platelet aggregation induced by platelet agonists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Analysis of Prucalopride Efficacy Data for the CIC Program

Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting

October 18, 2018

Ling Lan, PhD

OTS/OB/DBIII, Statistician

Outline

- Overview of efficacy trials
- Baseline demographics and characteristics
- Efficacy endpoints and results
- Summary of efficacy

Overview: Clinical Development Program

Study ID	Design	Inclusion Criteria	Dosage* and Sample Size	Year
3001	Phase 3: 12-wk MC, R, DB, PC R by various stratification factors	≤2 SBMs/wk	PRU 2 mg: placebo=249:252	2011
302		≤2 SCBMs/wk and other similar criteria	PRU 1 mg: 1-2 mg: 2 mg: placebo=14:65:98:181	2013
INT-6			PRU 2 mg: 4 mg: placebo =236:238:240	1999
USA-11			PRU 2 mg: 4 mg: placebo =190:204:193	1999
USA-13			PRU 2 mg: 4 mg: placebo =214:214:212	1999
401	Phase 4: 24-wk MC R DB PC		PRU 1 mg: 1-2 mg: 2 mg: placebo=7:23:141:169	2012

* This application focused on dosage of PRU ≤ 2 mg. Source: Reviewer's analyses

Abbreviations: SBM=spontaneous bowel movement (a BM is not followed by previous intake of laxative with 24 hours), SCBM=a completed SBM, DB=double-blind, MC=multi-center, PC=placebo-controlled, PG=parallel group, PRU=prucalopride, R=randomized, wk=week

Overall Demographics and Baseline Characteristics

Characteristic	Study ID					
	3001	302	INT-6	USA-11	USA-13	401
Sex	Female	Male	Female (primarily)			
Race	Asian	Caucasian				
Region	Asia	EU		US		EU
Age ≥65 years	0	42%	11% - 18%			
Years of Constipation (median)	5-15			20		15
Previous use bulk-forming laxatives	≈27%		≥57%			NA
≤1 SBMs/week for 6 months	≈50%		≈75%			NA

Source: Reviewer's analyses
NA: not available

Primary Efficacy Endpoint

- **Primary endpoint**: percentage of responders, defined as patients with a mean of ≥3 spontaneous complete bowel movements (SCBMs) per week over the 12-week treatment period

- **Calculation of weekly SCBM** during an interval (week, month, or 12 weeks): (# of SCBM in interval)*7 / (# of evaluable days in interval)
  - For a week with ≤3 days of data, SCBM/week = 'missing'
  - For a 12-wk period with ≤13 days of data, SCBM/week = 'missing'

Statistical Analysis Method

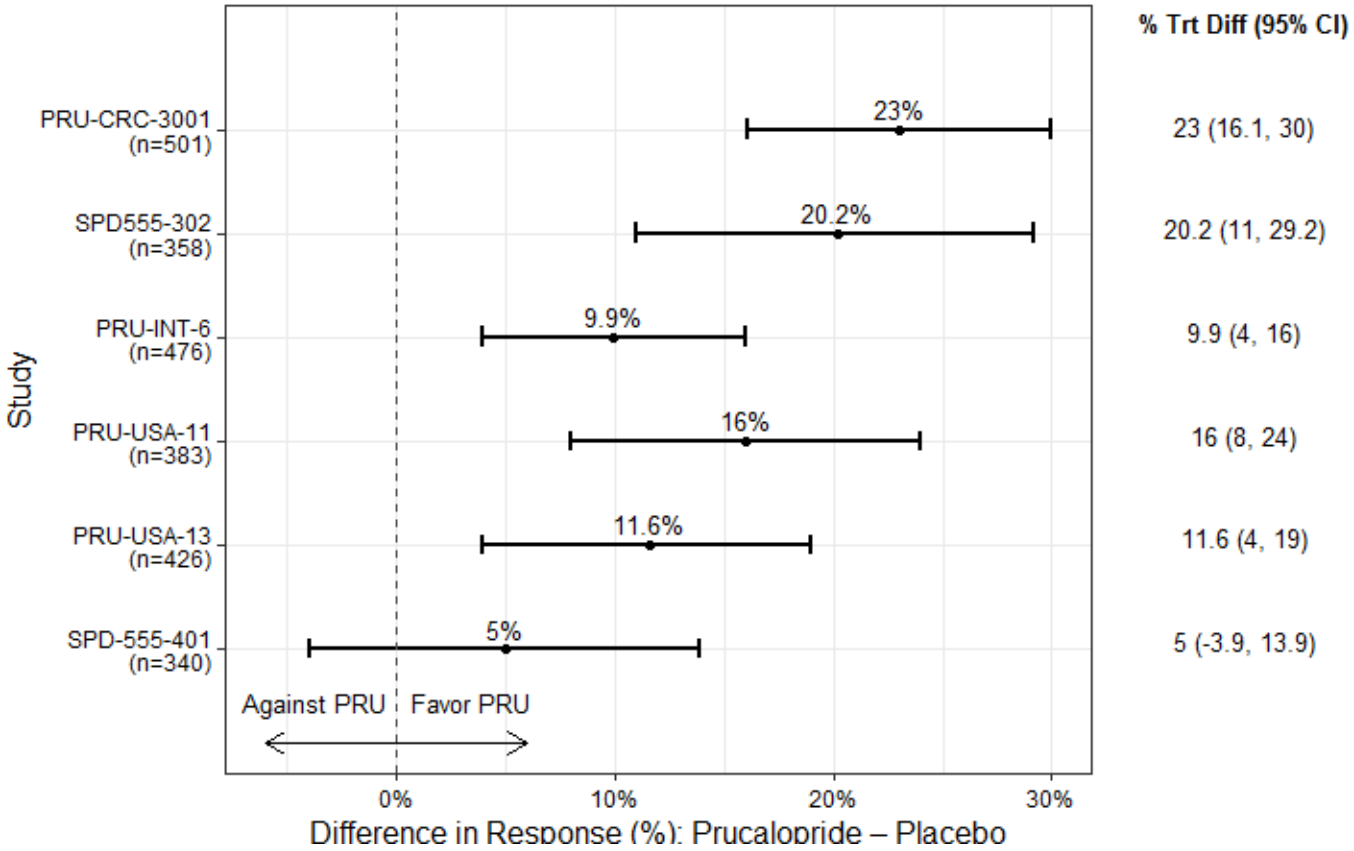
Primary analysis: Cochran-Mantel-Haenszel (CMH) test controlling for randomization stratification factors used in each study

Primary population: Randomized subjects received at least one dose of treatment, while Study 302 excluded one study site

Data used:

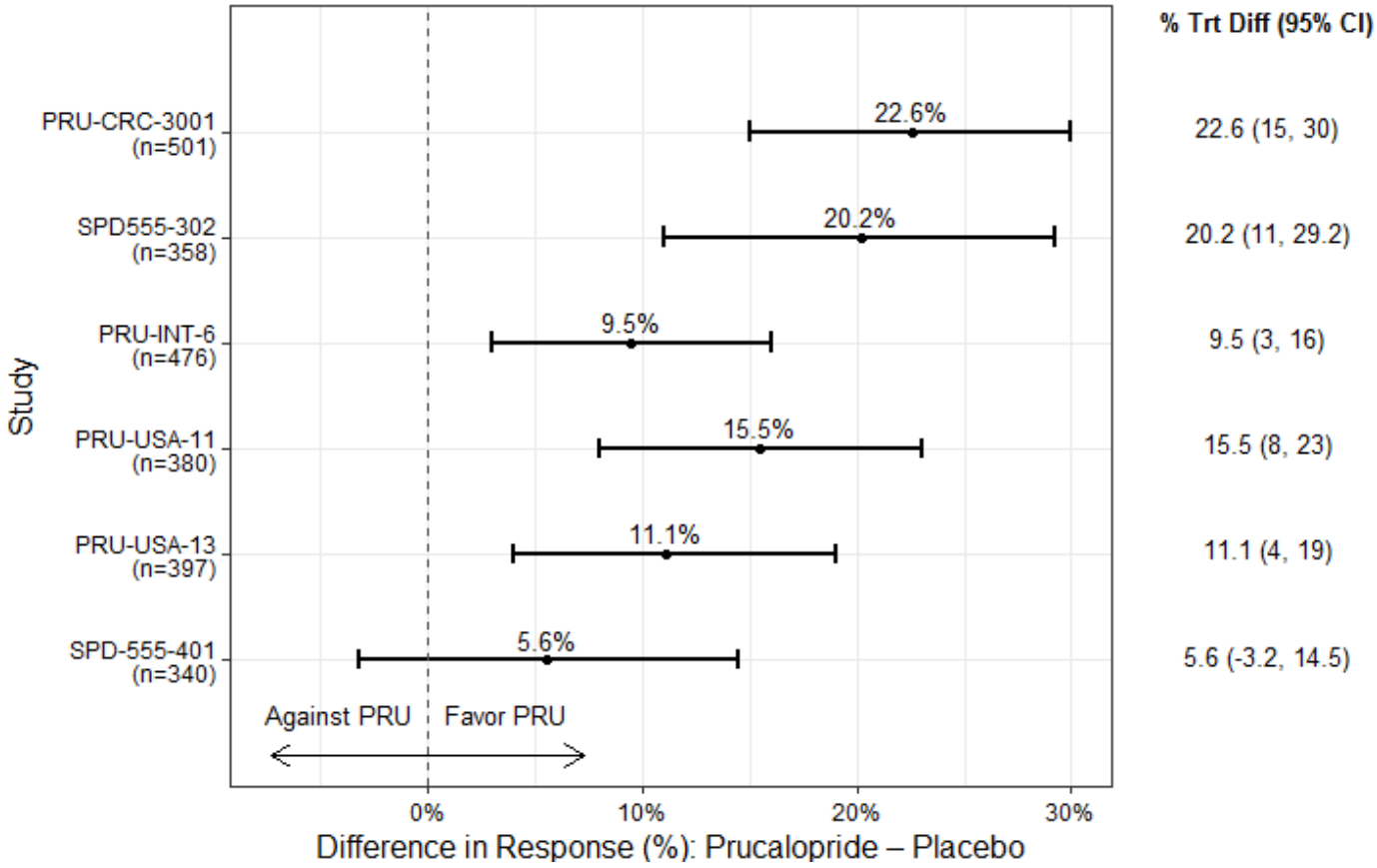
- Given 9% to 17% missing weekly diary data, the Agency's primary analyses used observed case data (defined as observed case data for subjects with ≥37 days of data and non-responder imputation for <37 days of data)
- Applicant's primary analysis: Last observation carried forward (LOCF) by SAP
- Various sensitivity analyses for missing data

Applicant's Primary Efficacy Results



Source: Applicant's IR response on March 30, 2018, verified by the Reviewer using LOCF data

Agency's Primary Efficacy Results

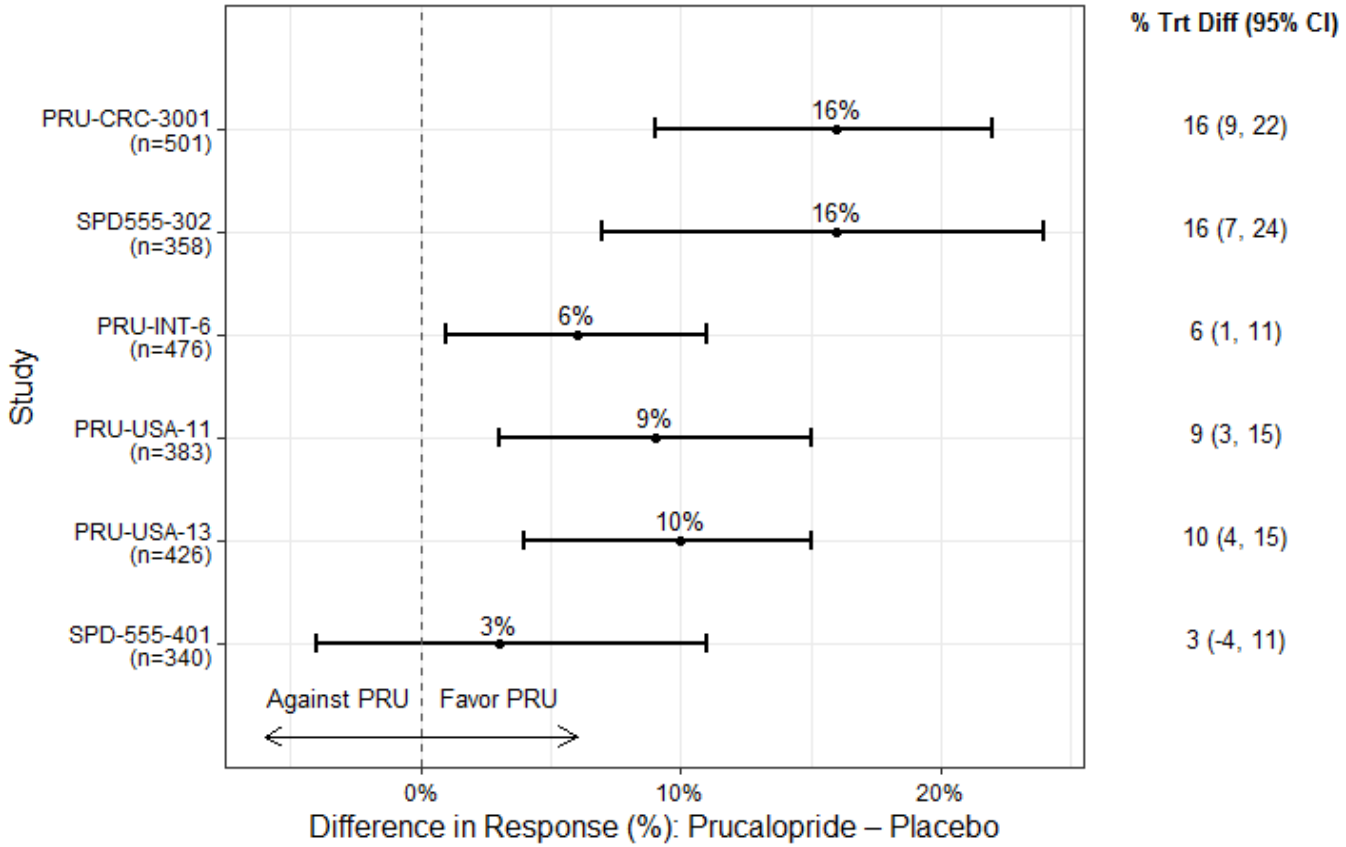


Source: Reviewer's analyses using observed case data and non-responder imputation.

Alternative Endpoint A

- **Definition:** An overall 12-week SCBM responder is a patient who is a SCBM weekly responder for ≥9 out of 12 treatment weeks
  - SCBM weekly responder: ≥3 SCBM/wk and ≥1 SCBM/wk increase from baseline
  - With ≥4 evaluable days/wk to be considered a weekly responder
- FDA recommendation at a meeting on July 15, 2014
- CMH test stratified by pooled country, sex, and number of CBMs/week at baseline (0 or >0), based on observed case data (i.e., no imputation, based on ISE SAP)

Alternative Endpoint A Results

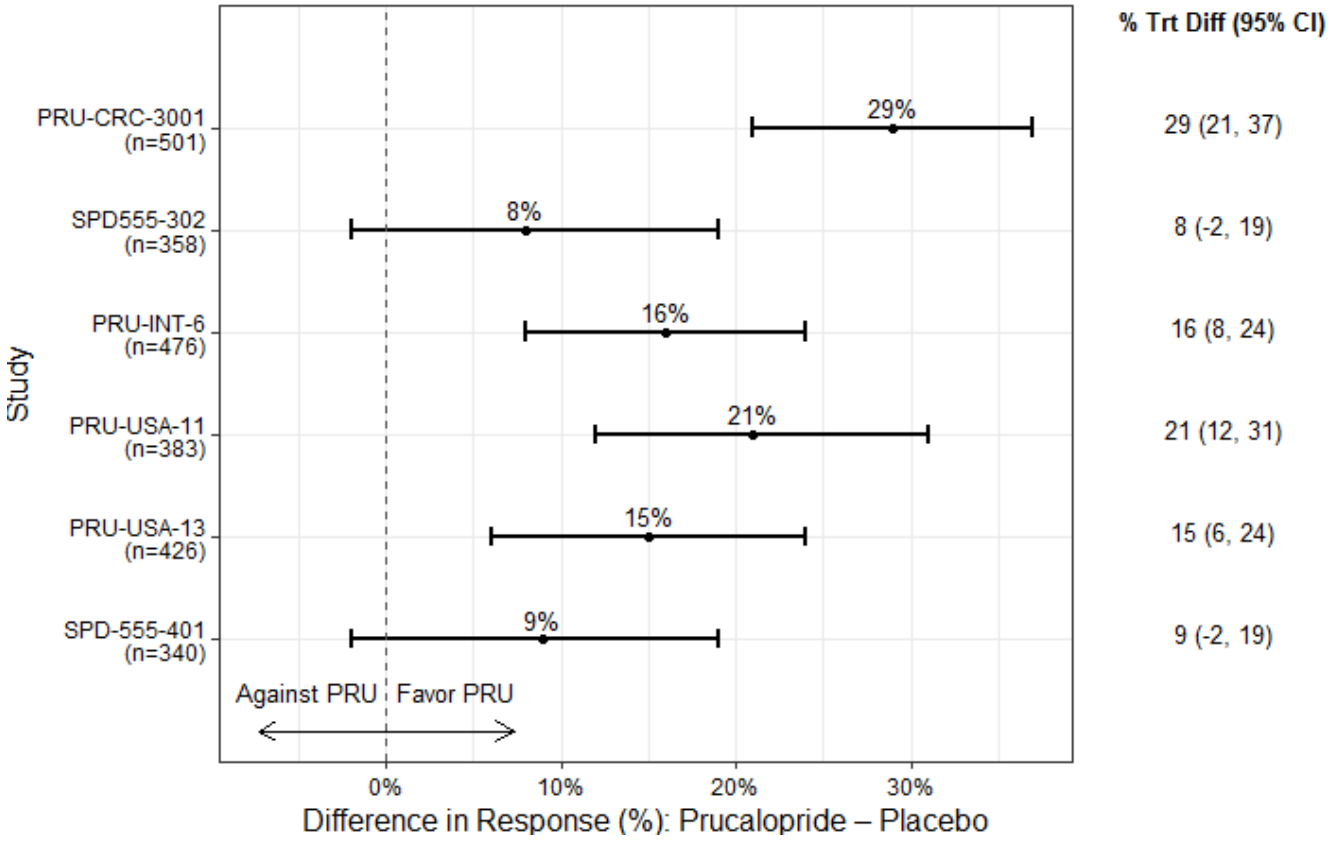


Source: Applicant's Table 2 of the IR response dated 6/8/2018, verified by the Reviewer

Major Secondary Endpoint

- The Applicant also focused on one of the secondary endpoints: proportion of subjects with an average increase of ≥1 SCBM/week from baseline over a 12-week treatment period
- This endpoint was listed as the key secondary endpoint in Studies INT-6, USA-11, and USA-13, and one of the secondary endpoints in the other efficacy trials

Secondary Endpoint Results



Source: Table 7 of the Applicant's IR response dated 6/26/2018, verified by the Reviewer

Efficacy Summary

- All trials, except for Study 401, demonstrated statistically significant treatment effects for prucalopride compared with placebo as measured by the primary endpoint and Alternative Endpoint A
- Robust results for the primary endpoint
  - Sensitivity analyses for missing data were consistent with the primary efficacy findings
  - Subgroup analyses by age, sex, and race were consistent across all studies with reasonable subgroup sizes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Safety Evaluation of the Clinical Trial Data for the CIC Program

Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting
October 18, 2018

Charles Line, MD
Medical Officer
Division of Gastroenterology and Inborn Errors Products
Center for Drug Evaluation and Research

Presentation Overview

- Clinical Trial Safety Database
- Exposure
- Deaths
- Serious Treatment-Emergent Adverse Events (TEAEs)
- Common Adverse Events
- Discontinuations
- Adverse Events of Special Interest
  - Major Adverse Cardiovascular Events (MACE)
  - Other Cardiac Events of Interest
  - Psychiatric Events of Interest
- Summary
- Benefit-Risk

Clinical Trial Safety Database

- The phase 2 through 4, double-blind, placebo controlled, trials in chronic idiopathic constipation (CIC) patients included 16 of the 20 completed trials of at least 4 weeks duration conducted in adult patients (Pool D)
  - 4 trials were excluded based on their design
  - There were no controlled trials of 12 months duration
- The phase 2 and 3 open-label trials in CIC patients were also considered for purposes of evaluating deaths, attempted and completed suicide, and MACE (Pool E)
  - Included 7 of the 9 completed open-label trials
  - 2 expanded access trials were excluded

Exposure by Treatment Group

Phase 2 through 4 Double-Blind Trials in Adults with CIC*

	Placebo 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	Total N=5278
n	1973	110	328	1512	1345	3295	5268
Duration of Exposure (weeks)							
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)	9.6 (5.23)
Median	11.9	4.0	4.0	12.0	8.1	11.7	11.9
Min, Max	0, 28	0, 6	0, 24	0, 26	0, 16	0, 26	0, 28

Source: Reviewer's table adapted from Applicant submission, Integrated Summary of Safety, Table 7, page 98/504
PRU=prucalopride, SD=standard deviation, Min=minimum, Max=maximum
*Pool D Trials
#n=Number of subjects who took at least one dose of prucalopride

Exposure: Open-Label Trials*

- 2,759 subjects received prucalopride
- Majority received at least 180 days of prucalopride regardless of dose (62.0%)
  - 38.1% : 365 days or more
  - 21.1% : 545 days or more
  - 3.5% : 730 days or more

* Pool E Trials

Deaths: Double-Blind and Open-Label CIC Trials

Treatment Group	Age/Sex (M/F)	Cause of Death	Treatment Duration (Days)
Phase 2-4 Double-Blind Trials			
1 mg dose	83 M	Lobar pneumonia	11 days
2 mg dose	86 F	Respiratory failure/ *S. aureus b*ronchitis	31 days
Placebo	89 M	Myocardial infarction/arrhythmia	7 days
Phase 2-3 Open-Label Trials			
2 mg dose	81 M	Myocardial infarction*	272 days (death 67 days after last dose)
2 mg dose	89 F	Pneumonia	226 days (death 4 days after last dose)
4 mg dose	56 M	Myocardial infarction*	48 days (OL; 75 days total, including prior DB trial)
1 mg twice a day	70 M	Completed suicide via gunshot wound	101 days (death 29 days after last dose)
1 mg four times a day	40 F	Completed suicide via hanging	242 days (death 52 days after last dose)

* Subject was adjudicated as cardiovascular death, standard MACE
Source: Reviewer's analysis

Select Serious Treatment-Emergent Adverse Events

Events Occurring in the prucalopride 2mg group and greater than placebo* (Total N=5278)

Primary System Organ Class	Dictionary Derived Term	Placebo (N=1973)	PRU 2mg (N=1516)
Cardiac Disorders	Mitral Valve Prolapse	0 (0.0%)	1 (0.1%)
	Supraventricular Tachycardia	0 (0.0%)	1 (0.1%)
Gastrointestinal Disorders	Abdominal Distention	0 (0.0%)	1 (0.1%)
	Constipation	0 (0.0%)	1 (0.1%)
	Obstruction Gastric	0 (0.0%)	1 (0.1%)
Investigations	Blood Pressure Decreased	0 (0.0%)	1 (0.1%)
	ECG Signs of Myocardial Ischemia	0 (0.0%)	1 (0.1%)
	Electrocardiogram QT Prolonged	0 (0.0%)	1 (0.1%)
Metabolism and Nutritional Disorders	Hypokalemia	0 (0.0%)	1 (0.1%)
Nervous System Disorders	Cerebrovascular Accident	0 (0.0%)	1 (0.1%)
Psychiatric Disorders	Abnormal Behavior	0 (0.0%)	1 (0.1%)
	Anxiety	0 (0.0%)	1 (0.1%)
Respiratory, Thoracic and Mediastinal Disorders	Asthma	0 (0.0%)	1 (0.1%)
	Respiratory Failure	0 (0.0%)	1 (0.1%)

*Pool D Trials: Double-Blind Placebo Controlled Trials

Source: Reviewer's analysis

Common Adverse Events

Events in the prucalopride 2mg group and greater than placebo*

Dictionary Derived Term	Placebo (N=1973)	PRU 2mg (N=1516)
Headache	186 (9.4%)	265 (17.5%)
Nausea	126 (6.4%)	206 (13.6%)
Diarrhea	72 (3.6%)	179 (11.8%)
Abdominal Pain	153 (7.8%)	151 (10.0%)

* Pool D Trials: Double-Blind Placebo Controlled Trials
Source: Reviewer's analysis

Discontinuations Due to Adverse Events in the Double-Blind Placebo Controlled Trials

- Patients completing trials
  - 86.1% total prucalopride group versus 87.1% placebo group
- Discontinuations due to AEs
  - 6.7% total prucalopride group
    - 5.5% prucalopride 2 mg group
  - 2.8% placebo group
- Other reasons for discontinuation fairly well balanced between prucalopride (all dose groups) and placebo

MACE Analysis: Adjudication

- 19 double-blind placebo controlled and 9 open-label trials were analyzed (N=4476) for:
  - Standard MACE – cardiovascular mortality (including sudden cardiac death, death due to acute myocardial infarction, heart failure, stroke, and other cardiovascular causes), nonfatal myocardial infarction (MI), nonfatal stroke
  - Extended MACE – standard MACE + unstable angina requiring hospitalization
- A Cardiovascular Endpoint Committee (CEC) was established
  - 2 Cardiologists and 1 Neurologist specializing in strokes
- A pre-specified process was used to identify cases for blinded adjudication
  - All deaths, serious TEAEs, and non-serious cardiovascular TEAEs underwent blinded adjudication
- The chair reviewed 1,916 events (703 patients) across all trials that included 881 events (532 patients) in trials that enrolled patients with CIC
  - 218 potential MACE cases (173 patients) were selected for adjudication

MACE Analysis: Selected Baseline CV Risk Characteristics

	DB Placebo N=2019	DB PRU			All PRU[c] (DB and OL) N=4476
		DB PRU All Doses[b] N=3366	DB PRU 2mg N=1545	DB PRU 4 mg N=1369	
At least 1 risk factor[a]	753 (37.3)	1361 (40.4)	613 (39.7)	540 (39.4)	1697 (39.2)
Group 1: Ischemic heart disease	117 (5.8)	214 (6.4)	101 (6.5)	71 (5.2)	258 (5.8)
Group 2: Ischemic heart disease and/or >1 CV risk factor	376 (18.6)	739 (22.0)	327 (21.2)	261 (19.1)	888 (19.8)
Group 3: Age >65 Years	296 (14.7)	637 (18.9)	280 (18.1)	201 (14.7)	753 (16.8)
Group 4: Ischemic heart disease and/or ECC <60 ml/min and/or PVD	263 (13.0)	571 (17.0)	235 (15.2)	201 (14.7)	675 (15.1)
High-risk groups 1 to 4 combined	481 (23.8)	928 (27.6)	410 (26.5)	336 (24.5)	1127 (25.2)

Source: Reviewer's table, adapted from Applicant submission, MACE report, Table 4, page 15
PRU=prucalopride, DB=double-blind, OL=open-label. Patients rolling over from DB to OL/crossover trials are counted only once.
[a] Risk factors=ischemic cardiac disease, elevated blood pressure, elevated cholesterol, type 2 diabetes, peripheral vascular disease (including aortic and femoral artery disease), cerebrovascular accident or carotid disease, age >65, BMI >30Kg/m^2, and estimated creatinine clearance (Cockcroft-Gault) <60mL/min
[b] Includes the 0.5, 1, 2, and 4 mg prucalopride groups
[c] All PRU group includes all subjects who have taken at least 1 dose of prucalopride in DB or OL trials included in the MACE analysis dataset

Summary of Adjudication Information

Double-Blind and Open-Label Trials in CIC patients

	DB PLA N=2019		DB PRU						All PRU[b] (DB and OL) N=4476	
			DB PRU All Doses[a] N=3366		DB PRU 2 mg N=1545		DB PRU 4 mg N=1369			
	n (%)	*m*	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*	**9 (0.2)**	*9*
Extended MACE[c]	**2 (0.1)**	*2*	**4 (0.1)**	*4*	**1 (0.1)**	*1*	**3 (0.2)**	*3*	**15 (0.3)**	*16*
MACE (Separate Categories)										
CV death	1 (0.0)	*1*	0	*0*	0	*0*	0	*0*	2 (0.0)	*2*
Nonfatal myocardial infarction	0	*0*	1 (0.0)	*1*	0	*0*	1 (0.1)	*1*	2 (0.0)	*2*
Nonfatal stroke	1 (0.0)	*1*	1 (0.0)	*1*	1 (0.1)	*1*	0	*0*	5 (0.1)	*5*
Unstable angina requiring hosp.	0	*0*	2 (0.1)	*2*	0	*0*	2 (0.1)	*2*	6 (0.1)	*7*
Non-MACE Event										
Non-ischemic arrhythmia	1 (0.0)	*1*	12 (0.4)	*14*	6 (0.4)	*6*	3 (0.2)	*4*	24 (0.5)	*27*
Arterial thromboemboli	1 (0.0)	*1*	2 (0.1)	*2*	1 (0.1)	*1*	0	*0*	6 (0.1)	*6*
Hospitalized CHF	0	*0*	1 (0.0)	*1*	0	*0*	1 (0.1)	*1*	3 (0.1)	*3*
TIA	0	*0*	1 (0.0)	*1*	1 (0.1)	*1*	0	*0*	2 (0.0)	*2*
Vascular revascularization	0	*0*	1 (0.0)	*1*	1 (0.1)	*1*	0	*0*	7 (0.2)	*8*
Other CV event[d]	6 (0.3)	*6*	5 (0.1)	*5*	0	*0*	4 (0.3)	*4*	28 (0.6)	*31*
Non-CV event or death	8 (0.4)	*8*	9 (0.3)	*10*	5 (0.3)	*5*	3 (0.2)	*4*	36 (0.8)	*42*
Insufficient Information to Adjudicate	2 (0.1)	*4*	3 (0.1)	*3*	2 (0.1)	*2*	1 (0.1)	*1*	12 (0.3)	*13*
Subjects NOT adjudicated	2002 (99.2)	*NA*	3332 (99.0)	*NA*	1529 (99.0)	*NA*	1357 (99.1)	*NA*	4365 (97.5)	*NA*

CHF=congestive heart failure; CV=cardiovascular; DB=double-blind; hosp.=hospitalization; MACE=major adverse cardiovascular event; N=total number of MACE in each treatment group; m=number of events; n=number of subjects with an event; NA=not applicable; OL=open-label; PLA=placebo; PRU=prucalopride; TIA=transient ischemic attack

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

[b] The ALL PRU group includes all subjects who have taken at least 1 dose of prucalopride in DB or OL studies included in the MACE analysis. Subjects rolling over from DB to OL/crossover studies are counted only once.

[c] Extended MACE includes all standard MACE events plus unstable angina requiring hospitalization.

[d] Other CV event includes syncope, angina (excluding unstable angina requiring hospitalization), and chest pain.

Source: Applicant's submission, MACE report, Table 6, page 20

Summary of Non-Ischemic Events, Other CV Events, and Cases With Insufficient Information to Adjudicate

Adjudication Class Preferred Term	DB PLA (N = 2019)		DB PRU (N = 3366)		DB PRU 2mg (N = 1545)		DB PRU 4mg (N = 1369)		ALL PRU (N = 4476)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Non-ischemic arrhythmia	**1 (0.0)**	**1**	**12 (0.4)**	**14**	**6 (0.4)**	**6**	**3 (0.2)**	**4**	**24 (0.4)**	**27**
Atrial fibrillation	1 (0.0)	1	4 (0.1)	4	3 (0.2)	3	1 (0.1)	1	10 (0.2)	11
Atrial flutter	0	0	2 (0.1)	2	0	0	1 (0.1)	1	3 (0.0)	3
Supraventricular tachycardia	0	0	1 (0.0)	2	0	0	1 (0.1)	2	3 (0.0)	4
Ventricular tachycardia	0	0	2 (0.1)	2	0	0	0	0	2 (0.0)	2
Arrhythmia supraventricular	0	0	1 (0.0)	1	1 (0.1)	1	0	0	1 (0.0)	1
Atrial tachycardia	0	0	0	0	0	0	0	0	1 (0.0)	1
Atrioventricular block second degree	0	0	1 (0.0)	1	0	0	0	0	1 (0.0)	1
Nodal arrhythmia	0	0	0	0	0	0	0	0	1 (0.0)	1
Palpitations	0	0	1 (0.0)	1	1 (0.1)	1	0	0	1 (0.0)	1
Syncope	0	0	1 (0.0)	1	1 (0.1)	1	0	0	1 (0.0)	1
Tachycardia	0	0	0	0	0	0	0	0	1 (0.0)	1
Other CV event	**6 (0.3)**	**6**	**5 (0.1)**	**5**	**0**	**0**	**4 (0.3)**	**4**	**28 (0.4)**	**31**
Syncope	5 (0.2)	5	5 (0.1)	5	0	0	4 (0.3)	4	23 (0.4)	24
Angina pectoris	0	0	0	0	0	0	0	0	4 (0.1)	4
Atrial fibrillation	0	0	0	0	0	0	0	0	1 (0.0)	1
Cardiac pacemaker insertion	1 (0.0)	1	0	0	0	0	0	0	0	0
Loss of consciousness	0	0	0	0	0	0	0	0	1 (0.0)	2
Insufficient info to adjudicate	**2 (0.1)**	**4**	**3 (0.1)**	**3**	**2 (0.1)**	**2**	**1 (0.1)**	**1**	**12 (0.2)**	**13**
Thrombosis	0	0	0	0	0	0	0	0	2 (0.0)	3
Transient ischaemic attack	0	0	0	0	0	0	0	0	2 (0.0)	2
Angina pectoris	0	0	0	0	0	0	0	0	1 (0.0)	1
Blindness transient	0	0	1 (0.0)	1	0	0	1 (0.1)	1	1 (0.0)	1
Blood creatine phosphokinase increased	1 (0.0)	1	0	0	0	0	0	0	0	0
Cerebrovascular insufficiency	0	0	0	0	0	0	0	0	1 (0.0)	1
Chest pain	1 (0.0)	1	0	0	0	0	0	0	0	0

Source: Applicant's submission, response to FDA information request, received 05/14/2018

Subjects Exposed to Prucalopride Who Were Adjudicated as Standard MACE

Event	Age/Sex (M/F)	On Treatment at the Time of the Event	Dose/Trial Type at the Time of the Event	Treatment Duration
Nonfatal MI	71 F	No	4mg/ Open-Label	DB (placebo) and OL (112 days)
Nonfatal MI	70 F	Yes	4mg/ Double-Blind	DB (12 weeks)
Nonfatal Stroke	77 M	Yes	2mg/ Double-Blind	DB (22 days)
Nonfatal Stroke	70 F	Yes	4mg/ Open-Label	DB (12 weeks) and OL (190 days)
Nonfatal Stroke	64 M	Yes	2mg/ Open-Label	DB (4 weeks) and OL (860 days)
Nonfatal Stroke	78 F	Yes	3mg/ Open-Label	DB (12 weeks) and OL (21 days)
Nonfatal Stroke	61 M	Yes	3mg/ Open-Label	DB (placebo) and OL (76 days)
Cardiovascular Death	56 M	Yes	4mg / Open-Label	DB (4 weeks) and OL (48 days), 75 days total
Cardiovascular Death	81 M	No	2mg/ Open-Label	DB (4 weeks) and OL (244 days), 272 days total (died 67 days after discontinuing)

Source: Reviewer's Table

Other Cardiac Events of Interest in the Double-Blind Placebo-Controlled Trials

Palpitations

- Total prucalopride group 1.3% versus placebo group 0.7%

QT prolongation, related ventricular arrhythmias, syncope

- In the total prucalopride group, QT prolongation, related ventricular arrhythmias, and syncope/pre-syncope events occurred in <0.3% of subjects
- Percentages of these events in the total prucalopride group were comparable to placebo

ECG abnormalities including atrial fibrillation

- Various ECG abnormalities occurred in ≤1% of subjects in the total prucalopride group
- Percentages of these events in the total prucalopride group were comparable to placebo

Psychiatric Events of Interest

Completed and Attempted Suicides Double-Blind and Open-Label Trials (N=4476)

Description of Event	Treatment Duration	Other Relevant Historical
Completed suicide - 70-year-old male, via self-inflicted gunshot wound	101 days (death 29 days after the last dose)	History of depression and insomnia. Started on antidepressants 1 month prior to the event
Completed suicide - 40-year-old female, via hanging (asphyxia)	242 days (death 52 days after the last dose)	History of depression and drug abuse
Attempted suicide - 29-year-old female, by ingesting cocaine and rivotril (clonazepam)	42 days	History of depression. This event occurred 7 days after the end of prucalopride treatment
Attempted suicide - 38-year-old female, due to "personal problems"	Approximately 269 days (OL) (28 days in prior DB trial)	No documented past medical history. The subject was still hospitalized with repeated suicide attempts at follow-up
Attempted suicide - 37-year-old female	142 days (OL) (placebo in prior DB trial)	History of anxiety and multiple pain diagnoses. On multiple psychiatric medications
Attempted suicide - 24-year-old male, hospitalized for psychosis and a suicide attempt	452 days (OL) (84 days in prior DB trial)	Other reported adverse events included homicidal thoughts, insomnia, hallucination, and depression

Source: Reviewer's Table

Summary of Safety Analysis from Clinical Trials

- The majority of the double-blind trials were of 12 weeks in duration. 38.1% were exposed for more than a year in the open-label trials. None of these trials prospectively evaluated MACE
- There were 7 deaths in patients with CIC treated with prucalopride; and none were attributed to the study drug
- The differences between the placebo and prucalopride 2 mg groups were small for serious treatment emergent adverse events
- The most common adverse events occurring in subjects receiving the prucalopride 2 mg dose were headache, nausea, abdominal pain, and diarrhea. The percentages of these events were higher in the prucalopride 2 mg group compared to placebo
- There was a dose associated increase in diarrhea
  - There was no clear association between diarrhea and dehydration or hemodynamic instability
  - There was no clear indication that any of the reported adverse cardiac events resulted from diarrhea, dehydration, or electrolyte imbalances
- In general, the percentages of Standard and Extended MACE cases were low for the double-blind and open-label label trials
  - This is in alignment with the Applicant's analysis
- The Adjudication Process classified several events as "insufficient information to adjudicate" including myocardial infarction, myocardial ischemia, angina pectoris, hemiparesis, etc.
  - The rationale for not adjudicating these events as MACE was reviewed and appears reasonable
  - Insufficient information or insufficient evidence to confirm the respective reported diagnosis in these cases
  - The numbers of cases that had "insufficient information to adjudicate" were low and comparable between the prucalopride and placebo groups
- The numbers of other cardiovascular events of interest were low and comparable between the prucalopride and placebo groups
- The numbers of subjects with either attempted or completed suicide were low and most of them had underlying risk factors

Benefit and Risk Assessment: Clinical Trials

Benefit:

- 5 out of 6 double-blind placebo controlled trials have shown the prucalopride 2 mg group to have a statistically significant higher percentage of responders compared to placebo in adults with CIC

Risk Analysis:

- Numbers of MACE events, completed/attempted suicides, and other cardiovascular events of interest in the overall safety database (including double-blind placebo-controlled and open-label trials) were low and comparable between the prucalopride and placebo groups


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An Assessment of Study 802, A Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort

Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting
October 18, 2018

Joel Weissfeld, MD, MPH
Medical Officer
Division of Epidemiology I, Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology, CDER FDA

Data Sources

	Data Source				
Data source feature	**SNR**	**ISD**	**CPRD**	**THIN**	**GePaRD**
Study period	2012-2015	2010-2016	2010-2016	2010-2016	2010-2014
Region	Sweden	Scotland	U.K. except Scotland	U.K. except Scotland	Germany
Data type	Claims	Claims	GP EHR	GP EHR	Claims
Exposure	Prescriptions dispensed	Prescriptions dispensed	Prescriptions written	Prescriptions written	Prescriptions dispensed
MACE adjudication procedure	Not applicable	Medical chart review	Profile with questionnaire	Profile with EHR free text	Not applicable

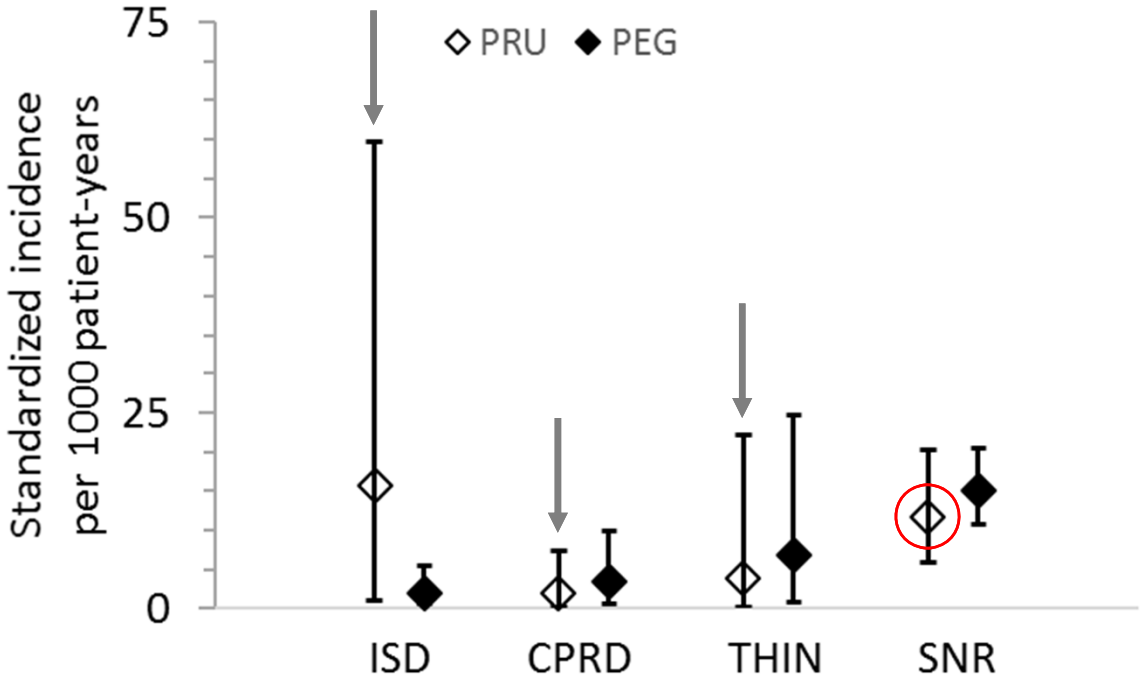
Source: Reviewer's table

Number of Study Patients

Data Source	Before trimming	
	PRU	PEG
GePaRD	5,636	28,017
SNR	3,656	18,280
ISD	1,249	6,245
CPRD	952	4,758
THIN	537	2,685

Source: Reviewer's table

MACE Incidence (Per 1000 Patient-Years)



Source: Reviewer's figure prepared from data in Supplemental Full Results File, Table 10a

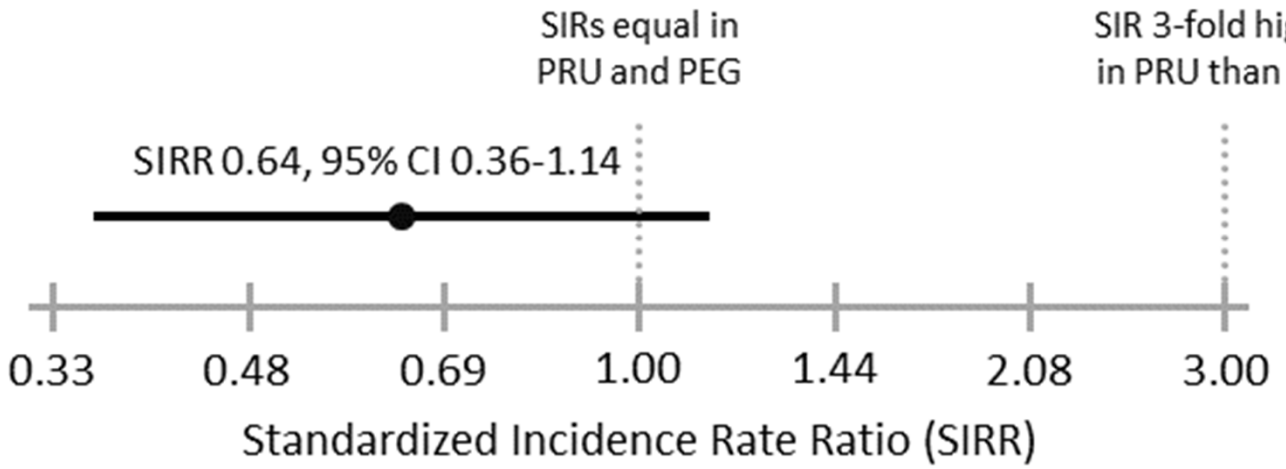
Number of Study Patients

Data Source	After trimming	
	PRU	PEG
~~GePaRD~~	~~5,326~~	~~25,388~~
SNR	3,194	16,769
ISD	1,154	5,806
CPRD	866	4,254
THIN	501	2,543

N=5,715 patients in SNR, ISD, CPRD, or THIN with mean 5.7-month exposure to prucalopride

Source: Reviewer's table

Result from Primary Analysis for MACE



Applicant's conclusion: No evidence of increased risk of MACE in patients using prucalopride as compared with PEG.

Source: Reviewer's figure

FDA's Assessment of Study 802

- A useful source of reassuring evidence about the cardiovascular safety of prucalopride
- Satisfies a pre-NDA expectation for an observational study that reasonably excludes 3-fold MACE risk from prucalopride

Important Problems in Study 802

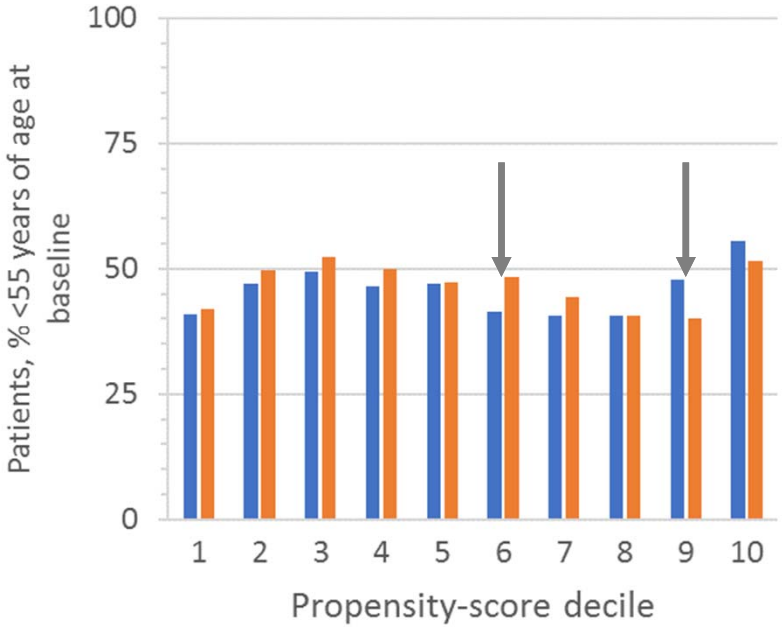
Especially susceptible to confounding,

- PEG as a comparator for prucalopride
- Observation time (i.e., patient-years) in prucalopride and PEG cohorts distributed differently on age and other baseline factors

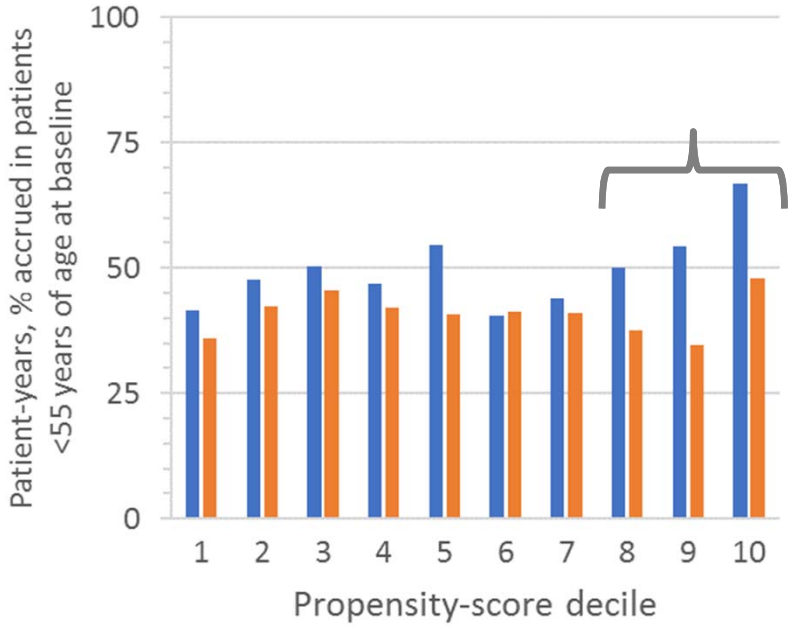
Swedish National Registers

Patient-Years in SNR Distributed Differently on Age

Patients, % <55 years, PRU *vs.* PEG, 45.7% *vs.* 46.8%



Patient-years, % <55 years, PRU *vs.* PEG, 49.9% *vs.* 40.4%



PRU PEG

Source: Reviewer's figure prepared from data in Supplemental Full Results File, Table 13

Conclusion

- Important problems making Study 802 especially susceptible to confounding
- FDA accepted Study 802 as a useful source of evidence that reasonably excludes greater than three-fold MACE risk from prucalopride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FDA Backup Slides Shown

Results Integrating Four Data Sources

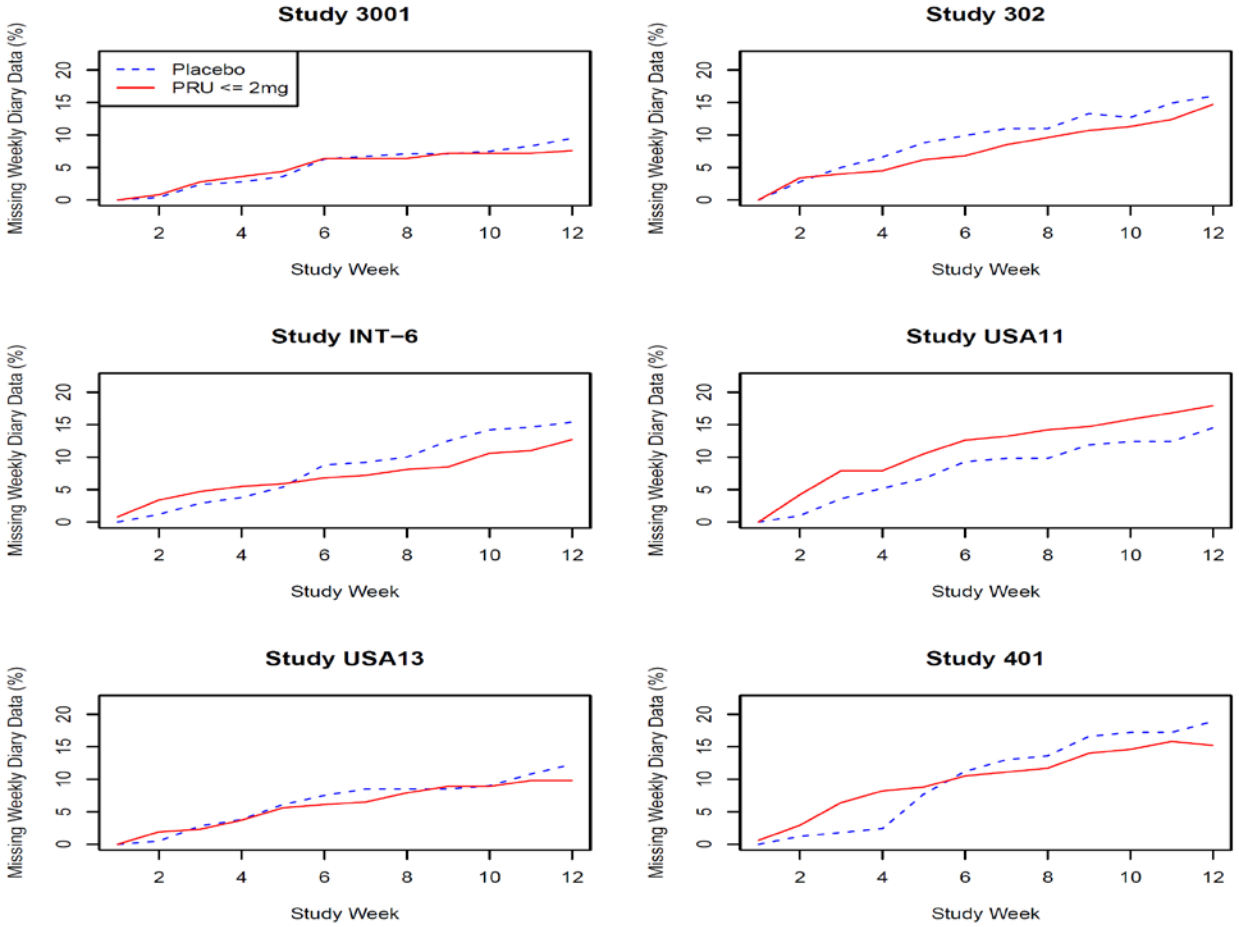
Result	Events, N PRU	Events, N PEG	SIRR	95% CI
MACE				
U.K. and SNR (Primary)	18	73	0.64	0.36-1.14
United Kingdom (U.K.[1)]	4	9	0.68	0.19-2.38
Sweden (SNR)	14	64	0.63	0.33-1.20
Secondary Analyses				
nonfatal AMI	7	21	0.95	0.38-2.39
nonfatal stroke	8	35	0.54	0.23-1.29
in-hospital CV death	3	19	0.47	0.13-1.67
Subgroup Analyses (MACE)				
18-54 year-old women	1	8	0.22	0.03-1.90
≥55 year-old women	13	53	0.71	0.37-1.37
18-54 year-old men	0	1		
≥55 year-old men	4	11	2.57	0.71-9.26

Source: Table assembled from Tables 15a and 15b in Supplemental Full Results File

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event as a composite of nonfatal AMI, non-fatal stroke, or in-hospital CV death; PRU, prucalopride; PEG, polyethylene glycol 3350; SIRR, standardized incidence rate ratio; CI, confidence interval; SNR, Swedish National Registers

[1] Combining Information Services Division (ISD) of Scotland, Clinical Practice Research Datalink (CPRD), and The Health Improvement Network (THIN)

Percentage of Subjects without Diary Records per Week during Weeks 1-12 in Efficacy Studies



Source: Reviewer's analyses results