FDA Briefing Document
Gastrointestinal Drug Advisory Committee Meeting

October 18, 2018

The committee will discuss new drug application (NDA) 210166, for prucalopride tablets for oral administration, submitted by Shire Development, LLC, proposed for the treatment of chronic idiopathic constipation (CIC) in adults.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the application for prucalopride (Motegrity) proposed for the treatment of chronic idiopathic constipation (CIC) in adults to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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1. EXECUTIVE SUMMARY

This Advisory Committee (AC) meeting was requested by the Division of Gastroenterology and Inborn Errors Products for the purposes of discussing the benefit/risk assessment of prucalopride (Motegrity) as proposed by the Applicant (Shire Development, LLC) for the treatment of chronic idiopathic constipation (CIC) in adults. The currently available treatment options do not completely meet the needs of patients with CIC; the available approved products have a modest treatment benefit over placebo and over-the-counter and nondrug therapies are not specifically approved for CIC. If approved, prucalopride, a selective 5-hydroxytryptamine (serotonin) type 4 receptor (5-HT_4) agonist, would offer a different class of drugs for the treatment of CIC compared to the currently available therapies in the United States (U.S.) for CIC. Not all available treatments are effective in all patients and some may have limited tolerability.

The European Medicines Agency (EMA) approved prucalopride (under the name Resolor) in 2009 for chronic constipation in women in whom laxatives have been ineffective, and the indication was later expanded in 2014 to include males. Prucalopride is approved in 82 countries. Due to the concern for cardiovascular risks potentially associated with the 5-HT_4 agonist class of drugs, these risks have been monitored since the initial product approval in 2009 by the EMA. In 2010, Shire acquired the product and continued marketing prucalopride in Europe. In 2012, Shire obtained the right to develop prucalopride in the U.S.

This New Drug Application (NDA) includes data from two 12-week phase 3 trials (PRU-CRC-3001 [Study 3001] and SPD555-302 [Study 302]) that were completed in 2011 and 2013, respectively, as the primary basis to demonstrate efficacy in support of FDA approval and labeling. Both trials were conducted in non-U.S. populations. The NDA also contains data from three other 12-week phase 3 legacy trials, completed in 1999, to support the generalizability of efficacy results to the U.S. patient population. In addition, data were submitted from a sixth trial, a 24-week phase 4 trial conducted in Europe (SPD555-401 [Study 401]).

All of the trials achieved statistical significance for the primary efficacy endpoint except for Study 401, which did not achieve statistical significance at week 12 or 24. The treatment effect, which was similar at week 12 and 24, was lower in this trial as compared to the others. The reasons for the smaller treatment effect in this study remain unclear. The treatment benefit of prucalopride compared to placebo for the five successful trials ranged from 10 to 23 percent of patients meeting the responder definition for the primary endpoint (defined by a mean of ≥3 spontaneous complete bowel movements [SCBMs] per week over the 12-week treatment period). The prucalopride treatment group had a numerically higher response rate at week 12 compared to the placebo group (25% versus 20%) in Study 401. The efficacy analyses conducted using the FDA's currently recommended efficacy endpoint for trials evaluating treatment of CIC (i.e., "Alternative Endpoint A") demonstrated a treatment benefit of prucalopride over placebo with a range of 6 to 16 percent of patients meeting the responder definition. Alternative Endpoint A defines an overall 12-week SCBM responder as a patient who is a SCBM weekly responder for ≥9 out of 12-weeks of the treatment period. A SCBM weekly responder is a patient who has a SCBM weekly frequency rate of ≥3 and increased by ≥1 from baseline. This treatment difference is generally consistent with what has been demonstrated for other approved products

using similar efficacy endpoints (approximate range 8 to 17% treatment difference from placebo).

Additional sensitivity analyses on the primary endpoint (different imputation approaches, per-protocol and completer analyses) confirmed the efficacy of prucalopride as compared to the placebo arm. Subgroup analyses (presented in the Appendix) demonstrated consistent efficacy trends by age, sex, and race across all studies with reasonable subgroup sizes.

There are no long-term (at least 12 months duration) controlled trials to inform the safety of this product, which is intended to treat a chronic disease. Because prucalopride had been approved in Europe since 2009, DGIEP agreed that the Applicant could submit results of a non-interventional pharmacoepidemiology study that used national claims data from four European countries (five data sources) in lieu of obtaining controlled clinical data on patients treated for up to one-year pre-marketing (refer to Regulatory History Section below). However, the Applicant was advised the adequacy of this information for purposes of long term safety, would need to be discussed at an Advisory Committee Meeting. Therefore, the safety database includes data from a non-interventional epidemiologic study (SPD555-802) conducted to estimate the adjusted incidence ratio and 95% CI for major adverse cardiac events (MACE) in prucalopride compared to polyethylene glycol (PEG). The findings from this study reasonably exclude a greater than three-fold MACE risk from prucalopride use. Because of the serious potential for bias due to confounding, the study does not reliably bound MACE risk at levels lower than three-fold.

In short-term clinical trials, the most commonly identified treatment-emergent adverse events (TEAEs) among prucalopride treated patients included diarrhea, headache, abdominal pain, and nausea. The serious TEAEs and discontinuations due to adverse events occurred in small numbers based on analyses of the safety database that includes completed phase 2 through 4 double-blind trials of at least 4 weeks duration in adults with CIC. These findings are generally aligned with the findings from the safety analyses of the trials submitted in the NDA 210166 application to provide evidence of efficacy to support product approval and labeling (Studies 302, 3001, INT-6, USA-11, USA-13, and 401).

There were a small number of deaths in patients treated with prucalopride at multiple doses (0.5 mg, 1 mg, 2 mg, and 4 mg). There were seven deaths out of 6064 patients treated with prucalopride in all phase 2 through 4 trials combined verses one death out of 1973 placebo treated patients: two deaths in the prucalopride group and one death in the placebo group among double-blind trials; five deaths in prucalopride open-label trials. The patients who died in the open-label trials had a longer duration of prucalopride exposure since they continued treatment in the open-label trials after completing double-blind trials.

There were small numbers of cases of standard MACE: two (0.1%) for the placebo group (N=2019) and two (0.1%) for the double-blind all doses of prucalopride group (N=3366). Furthermore, there were low percentages of patients with Standard and Extended MACE in the overall safety database, and the majority of these patients had baseline cardiovascular risk factors, thereby possibly confounding the causality determination.

The limitations of the safety database included the absence of controlled trial data beyond 12-weeks (except for one 24-week trial). DGIEP has been recommending applicants submitting NDAs for 5-HT4 agonists to treat gastrointestinal disorders provide controlled data for at least 12 months duration due to potential cardiovascular (CV) safety concerns in this class of drugs. In addition, the clinical trials safety database appeared to include patients that may have a lower risk for cardiovascular disease, given the available data on baseline risk factors and low rates of events in the placebo group. To address this issue, Study SPD555-802, a retrospective observational study evaluating MACE, defined as the composite of hospitalization for acute myocardial infarction (AMI), hospitalization for stroke, and in-hospital cardiovascular death, was submitted in lieu of a premarket safety study. In general, the safety data submitted for patients treated with prucalopride at multiple doses (0.5 mg, 1 mg, 2 mg, and 4 mg) from clinical trials in CIC patients resulted in small numbers of patients with cardiovascular adverse events.

The additional information relevant to the evaluation of CV safety in this review include non-clinical data, a thorough QT study, platelet aggregation studies, additional data from completed comparative studies, and an analysis of post-market observational data. The non-clinical data did not identify clinically meaningful findings at therapeutic doses of prucalopride and no significant QTc prolongation effect of prucalopride (2 mg and 10 mg) was detected in a thorough QT (TQT) study. In one platelet aggregation study, prucalopride did not significantly potentiate platelet aggregation inducted by a range of physiologically relevant platelet activators. Taking these findings and the safety findings from the broad safety database (completed phase 2 through 4 double-blind trials of at least 4 weeks duration in adults with CIC (Pool D), supplemented with the results of the analysis of study SPD555-802, the observational pharmacoepidemiology study, the Division is requesting advice from the Committee to determine whether the safety data adequately characterize the potential CV safety risk, and if this information taken together with the efficacy results provide an acceptable benefit/risk balance for treatment with prucalopride in patients with CIC.

Finally, a review of the safety database revealed a small number of events related to completed suicide and suicidal ideation which are also reviewed as a potential class issue. In general, the safety data submitted for patients treated with prucalopride at multiple doses (0.5 mg, 1 mg, 2 mg, and 4 mg) resulted in small numbers of patients with psychiatric adverse events.

2. DRAFT POINTS TO CONSIDER

The Division requests that you consider the following points when reviewing the briefing documents for this AC meeting:

1. The strengths and limitations of the safety and efficacy data submitted in support of:
    - The proposed dosing regimen for treatment of adult patients with chronic idiopathic constipation (CIC)
    - Dose adjustment (1 mg) in patients with severe renal impairment

2. The adequacy of the safety database, including the data obtained from the pharmacoepidemiology study (SPD555-802), given that there exists a potential CV safety concern with this class of drugs, and there are no controlled trials of 12 months duration.

3. INTRODUCTION

The Applicant submitted New Drug Application (NDA) 210166 for prucalopride tablets on December 21, 2017 to the Division of Gastroenterology and Inborn Errors Products (DGIEP). The proposed indication is treatment of chronic idiopathic constipation (CIC) in adults. The product is administered as an oral tablet.

Prucalopride, a selective serotonin type 4 (5-HT_4) receptor agonist, is a gastrointestinal prokinetic agent that stimulates colonic peristalsis by increasing bowel motility. There are safety concerns regarding the potential for cardiovascular and psychiatric risk with this class of 5-HT_4 agonists being developed to treat gastrointestinal motility disorders.

The Applicant's proposed labeling for prucalopride treatment for adults with CIC includes the following dosage and administration recommending:

- Adults: 2 mg once daily
- Geriatric patients (65 years and older): 1 mg once daily. Based on clinical response, increase to 2 mg once daily.
- Patients with severe renal impairment (glomerular filtration rate less than 30 ml/min/1.73 m^3): 1 mg once daily.

This AC meeting was requested by the Division of Gastroenterology and Inborn Errors Products for the purposes of discussing the benefit/risk assessment of prucalopride as proposed by the Applicant (Shire) for the treatment of adults with CIC. If approved, prucalopride, a selective 5-HT_4 agonist, would offer a therapy for CIC in a different class of drugs from the currently available therapies in the U.S. for CIC (lubiprostone [Amitiza], linaclotide [Linzess], plecanatide [Trulance]). The currently available treatment options do not completely meet the needs of patients with CIC. The available approved products have a modest treatment benefit over placebo, and over-the-counter and nondrug therapies are not specifically approved for CIC. Therefore, additional treatment options are needed.

4. BACKGROUND

4.1. Condition of Interest

Chronic idiopathic constipation (CIC), also known as functional constipation, is characterized according to the Rome diagnostic criteria, based upon the presence of the following symptoms for at least three months with symptom onset at least six months prior to diagnosis (Longstreth et al. 2006; Mearin et al. 2016):

(1) Must include two or more of the following:

- Straining during more than 25% of defecations
- Lumpy or hard stools (Bristol Stool Scale Form 1-2) in more than 25% of defecations
- Sensation of incomplete evacuation for more than 25% of defecations
- Sensation of anorectal obstruction/blockage for more than 25% of defecations
- Manual maneuvers to facilitate more than 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
- Fewer than three spontaneous bowel movements per week

(2) Loose stools are rarely present without the use of laxatives.

(3) Insufficient criteria for irritable bowel syndrome (IBS).

The prevalence of chronic constipation in North America is estimated to vary between 2 to 27 percent (average of approximately 15 percent) depending on how the disease is defined (Higgins and Johanson 2004; Suares and Ford 2011). A systematic review, published in 2004, estimated that 63 million people in North America fulfilled the Rome II criteria for constipation (Higgins and Johanson 2004). Surveys of physician visits for constipation have found more visits by women, nonwhite patients, patients with lower incomes, and those with less than 12 years of education (Sonnenberg and Koch 1989). The prevalence of chronic constipation rises with age, most notably in patients 65 years of age or older (Sonnenberg and Koch 1989; Talley et al. 1996; Higgins and Johanson 2004). In this older age group, approximately 26 percent of men and 34 percent of women report constipation (Talley et al. 1992; Talley et al. 1996). Ultimately, chronic idiopathic constipation remains a considerable health issue and can have a profound impact on patient quality of life. Additional treatment options are needed for patients with CIC.

4.2. Relevant Prucalopride Regulatory History

The EMA approved prucalopride (under the name Resolor) in 2009 for chronic constipation in women in whom laxatives have been ineffective, and the indication was later expanded in 2014 to include males. Prucalopride is approved in 82 countries. The regulatory history below describes the relevant history of the development program in the U.S. for CIC indication. Recommendations and discussions that are relevant to the adequacy of the efficacy and safety analyses are summarized below.

- 1998: The initial IND 055078 was submitted to the FDA by Johnson and Johnson.

- 2000-2004: The IND was placed on a partial hold due to genotoxicity and carcinogenicity concerns and was inactivated on July 30, 2004.

- October 15, 2009: EMA approval of prucalopride (Resolor).

- October 2010: Shire (the current Applicant) acquired the prucalopride development program and continued the marketing of prucalopride in Europe.

- July 25, 2012: A Type C meeting was held to discuss the partial hold issues as well as additional questions about the clinical development program.

    - FDA communicated 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.

    - FDA informed the Applicant that on November 17, 2011, the Gastrointestinal Drugs Advisory Committee (GIDAC) met to provide recommendations on the design and size of premarketing CV development programs necessary to support the approval of the 5-HT_4 receptor agonists for the proposed indications of CIC, IBS-C, gastroparesis, and gastroesophageal reflux disease that does not respond to a proton pump inhibitor. Given the history of this class of drugs and the discussion at the 2011 AC meeting, FDA has requested that the safety development program for 5-HT_4 agonists include initiation of a premarketing trial with adequate CV safety evaluation as its primary objective. FDA communicated that this trial would not need to be completed prior to an NDA submission; however, it would be likely that a GIDAC would meet to determine whether the level of evidence submitted for CV safety is sufficient to allow approval before completing a CV safety trial or whether additional enrollment in such a trial may or may not be necessary. FDA noted that the overall targeted sample size for the CV safety objective be large enough to collect sufficient CV events to rule out an upper bound of a hazard ratio of major adverse cardiovascular events (MACE) of 2.0 to provide general assurance of CV safety.

    - FDA acknowledged that the Applicant had already completed phase 3 trials and communicated that it was not clear at that time if sufficient data had been collected to provide an equivalent level of assurance to meet the requirements for a CV safety database; however, the Division suggested that a possible path forward would be to include data from completed and ongoing trials, as well as available post-market data.

    - FDA communicated concerns that the primary efficacy endpoint used in the completed trials differed from the recommended endpoint for trials for CIC. The primary efficacy endpoint in the completed trials was percentage of subjects with a mean of ≥3 SCBMs per week; however, FDA's recommended primary efficacy endpoint for CIC is defined by the following (referred to as Alternative Endpoint A in this document):

      Alternative Endpoint A: Overall 12-week SCBM responder, defined as a patient who is a SCBM weekly responder for ≥9 out of 12-weeks of the treatment period. A SCBM weekly responder is a patient who has a SCBM weekly frequency rate of ≥3 and increased by ≥1 from baseline. Patients must also have at least 4 days of evaluable response data to be considered a weekly responder.

- August 2012: Shire submitted a compete response to the partial hold (due to genotoxicity and carcinogenicity concerns); the hold was lifted, and the IND was reactivated in September 2012.

- January 22, 2013: A Type C meeting focused on the need for further evaluation for MACE, potential need for an AC, and concerns with the post-approval pharmacoepidemiology study design. FDA communicated that the preliminary review of the Applicant's analysis of MACE events in previously conducted trials may not provide a sufficient level of assurance regarding prucalopride's CV safety. Specifically, the two adjudicated MACE events in the double-blind trials were well below the requisite number needed to rule out even a large hazard ratio. Therefore, the analysis presented a challenge for inferring safety given that the controlled studies were not prospectively designed to assess MACE and were of short duration (12-weeks). The Applicant proposed extending the UK THIN pharmacoepidemiology study pre-approval to other countries to provide safety data to support an NDA. The FDA agreed to discuss this further with the Applicant.

- July 15, 2014: During a Type C meeting, the FDA made the following recommendations for the NDA submission:

    - Persuasive justification for generalizability to the U.S. population for the two proposed "pivotal" randomized controlled trials (SPD555-302 [Study 302]), PRU-CRC-3001 [Study 301]) should be provided, given that one trial was conducted in males in Europe and one trial enrolled primarily an Asian population.
    - Alternative Endpoint A would be considered the key supportive post hoc endpoint analysis as this endpoint aligns with FDA's current endpoint recommendations for CIC trials.

- March 29, 2017: A Type C meeting, written response, included discussion of inspection site selection, and further clarification on data submission/ verification.

- August 8, 2017: A Type B pre-NDA meeting was conducted. FDA communicated the following recommendations for the planned NDA submission included:

    - Reiteration of the previous recommendations that the NDA should include persuasive justification for relying on trials conducted outside of the U.S. patient population, and that Alternative Endpoint A will be considered the key supportive analysis endpoint since this endpoint aligns with current recommendations.
    - Study SPD555-802 (post-marketing pharmacoepidemiology safety study), designed to rule out an incidence rate ratio (IRR) of 3, appeared reasonable. Depending on the results of SPD555-802, a post-marketing observational study to rule out an IRR of 2 may be required.

      FDA agreed with the proposed strategy to analyze results of study SPD555-802 as individual country data and pooled data with the exclusion of the German data, due to the age skewness of the German data.
    - FDA agreed that the safety data appeared sufficient to support NDA submission, and noted that a significant review issue would be the lack of controlled trials of 12 months duration, as the Division had moved towards requiring controlled trials of 12

months duration in a drug class for which there have been cardiovascular safety concerns.

- September 26, 2017: The FDA notified Shire of agreement on the iPSP.

- December 21, 2017: Shire submitted NDA 210166.

4.3. Currently Approved Therapies for Chronic Idiopathic Constipation

The general goal of CIC treatment is to increase the frequency of bowel movements, improve stool consistency, and reduce straining associated with bowel movements. The currently approved therapies for CIC are summarized in the table below. In addition to these therapies, probiotics, osmotic and stimulant laxatives, stool softeners, fiber, diet and lifestyle modification, are often used for treatment but none are approved for chronic constipation.

Table 1. Currently Approved Treatments for CIC

Drug	Indications	Dosing/Administration	Mechanism of Action	Contraindications and Common AEs	Year Approved
lubiprostone (Amitiza)	CIC (adults) OIC (adults) IBS with constipation in women ≥18 years of age	CIC: 24 mcg oral twice daily OIC: 24 mcg oral twice daily IBS-C: 8 mcg oral twice daily	Apical chloride-2 channel activator	Contraindicated in known or suspected mechanical GI obstruction. Common AEs: nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence	CIC: 2006 IBS-C: 2008 OIC: 2013
linaclotide (Linzess)	CIC (adults) IBS-C (adults)	CIC: 145 mcg oral once daily, 72 mcg once daily may be used based on individual presentation or tolerability. IBS-C: 290 mcg oral once daily	Guanylate cyclase-C agonist	Contraindicated in known or suspected mechanical GI obstruction, patients less than 6 y/o due to the risk of serious dehydration Common AEs: diarrhea, abdominal pain, flatulence, abdominal distension, viral gastroenteritis, and headache	2012
plecanatide (Trulance)	CIC (adults) IBS-C (adults)	CIC: 3 mg oral once daily IBS-C: 3 mg oral once daily	Guanylate cyclase-C agonist	Contraindicated in known or suspected mechanical GI obstruction, patients less than 6 years of age due to the risk of serious dehydration. Most Common AE: Diarrhea	CIC: 2017 IBS-C: 2018

Source: Reviewer's Table
Abbreviations: AE, adverse event; CIC, chronic idiopathic constipation; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome – constipation; OIC, opioid-induced constipation; y/o, year-old

5. EFFICACY

5.1. Overview

In this NDA submission, the Applicant submitted data from five phase 3 trials and one phase 4 trial to support product approval and labeling for prucalopride 2 mg (Table 1). The two trials considered to be the primary basis for demonstration of efficacy (Studies PRU-CRC-3001 [Study 3001] and SPD555-302 [Study 302]) were conducted outside of the U.S. and primarily enrolled female Asian or male Caucasian subjects and were completed in 2011 and 2013, respectively. The submission contains data from three phase 3 trials to support the generalizability of results from non-U.S. pivotal studies to the U.S. patient population (PRU-INT-6 [Study INT-6], PRU-USA-11 [Study USA-11] and PRU-USA-13 [Study USA-13]). The NDA also contains a sixth trial, a phase 4, 24-week trial (SPD555-401 [Study 401]). Except for the duration of Study 401 (24 weeks), the study design was generally similar for all efficacy studies: 12-week, randomized; double-blind; placebo-controlled design evaluating safety; efficacy; and quality of life.

Studies 3001, INT-6, USA-11 and USA-13 evaluated prucalopride 2 mg versus placebo. Studies 302 and 401 evaluated prucalopride 2 mg in patients <65 years of age; and patients ≥65 years of age were initiated on 1 mg with the option to dose-escalate to 2 mg if insufficient response to therapy occurred; insufficient response was defined as an average of <3 SCBM/week during the preceding 2 weeks of treatment (i.e., since the previous visit) at the week 2 or week 4 Visit.

A bowel movement was considered to be “spontaneous” (i.e., SBM) if the bowel movement was not preceded by the intake of a laxative agent or enema within a period of 24 hours. A SBM was considered complete (SCBM) if the subject responded “yes” to the e-diary question about completely emptying his/her bowels.

Table 2. Study design for Phase 3/4 efficacy studies

Trial ID	Design/ Randomization factors	Dose**/ Sample size	Population	Region	Year Completed
PRU-CRC-3001 (Study 3001)	12-wk MC R DB PC Phase 3 trial By Country and baseline spontaneous bowel movement (SBM) (<1 or ≥1 and ≤2 SBM/week)	PRU 2 mg: placebo =249:252	90% females and 92% Asian	Asia/ Australia	2011
SPD555-302 (Study 302)	12-wk MC R DB PC Phase 3 trial by country and the average number of complete bowel movements (CBMs) at 2-wk baseline period (0 or >0 CBM/week)	PRU 1 mg: PRU 1 mg to 2 mg: PRU 2 mg: placebo = 14:65:98:181	100% male with 97% white	Europe (Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, The Netherlands, Poland, Romania, UK)	2013
PRU-INT-6 (Study INT-6)	12-wk MC R DB PC Phase 3 study By country	PRU 2 mg: PRU 4 mg: placebo =236:238:240	91% female and 93% white	Australia, Belgium, Canada, Great Britain, The Netherlands, Norway, South Africa, Sweden	1999
PRU-USA-11 (Study USA-11)	12-wk MC R DB PC Phase 3 study By investigator	PRU 2 mg: PRU 4 mg: placebo =190:204:193	88% female and 90% white	All USA	1999
PRU-USA-13 (Study USA-13)	12-wk MC R DB PC Phase 3 study By investigator	PRU 2 mg: PRU 4 mg: placebo =214:214:212	87% female and 88% white	All USA	1999
SPD555-401 (Study 401)	24-wk MC DB PC Phase 4 study By country, sex and the baseline CBM (0 or >0 CBM/wk)	PRU <2 mg: PRU 2 mg: placebo =30:141:169	85% female and 93% white	Europe (Romania, Poland, Slovakia, Italy, Belgium, Spain, Sweden, Czech Republic)	2012

Source: Reviewer's analyses
Abbreviations: CBM, complete bowel movement; DB, double-blind; MC, multi-center; PC, placebo-controlled; PG, parallel group; PRU, prucalopride; R, randomized; SBM, spontaneous bowel movement; wk, week
** This application focused on dosage of PRU 1 mg, 1 mg to 2 mg and 2 mg.

5.2. Enrollment Criteria

The enrollment criteria for the submitted trials were generally similar with slight differences that are unlikely to influence the interpretability or outcome of the trials. For example, the enrollment criteria for Study 3001 relied on a history of spontaneous bowel movements (SBMs), whereas Study 302 relied on a history of spontaneous complete bowel movements (SCBMs). In both trials, a bowel movement was considered to be spontaneous if not preceded by the use of a laxative or enema within 24 hours. The similarities and differences in the enrollment criteria are summarized below.

In Study 3001, CIC was defined as ≤2 SBMs/week and patients were required to meet ≥1 of the following criteria for at least a quarter of the time for the preceding 3 months with symptom onset >6 months prior to screening:

- very hard (little balls) and/or hard stools in >25% of bowel movements (BMs)
- sensation of incomplete evacuation following in >25% of BMs
- straining at defecation in >25% of BMs
- sensation of anorectal obstruction or blockade in >25% of BMs
- a need for digital manipulation to facilitate evacuation in >25% of BMs

At randomization, the following criteria needed to be met:

- An average of ≤2 SBMs/week during the 2-week run-in period
- Presence of one or more of the criteria listed above

In Study 302, CIC was defined as ≤2 SCBMs/week and patients were required to meet ≥1 of the following criteria for ≥6 months before the screening visit:

- very hard (little balls) and/or hard stools for at least a quarter of the stools
- sensation of incomplete evacuation following in at least a quarter of the stools
- straining at defecation for at least a quarter of the time

At randomization, the following criteria needed to be met:

- An average of ≤2 SCBMs/week during the 2- week run-in period.
- Discontinuation of laxative treatment and no rescue medication use on more than 75% of the days during the run-in period
- No use of prohibited medication during the run-in period

For both trials, patients who never had a SBM were considered eligible. All other enrollment criteria were generally similar between the 2 trials.

The definition of CIC used in Studies INT-6, USA-11, USA-13, and 401 was the same as the definition used in Study 302. The other enrollment criteria were generally similar.

5.3. Demographic and Baseline Disease Characteristics

In general, the patients' demographics and baseline characteristics were comparable between the prucalopride arms and the placebo arm within each study. For details refer to the summary tables in the Appendix.

The six phase 3/4 trials were completed between 1999 and 2013 and enrolled CIC patients with various demographic and baseline characteristics as summarized by study below (Table 3):

- Sex: Five of the six efficacy studies included primarily female CIC patients. The percentage of females ranged from 86% to 91%, except for Study 302 which was conducted in a male population.
- Race: The majority of subjects in Study CRC-3001 were of Asian origin (92%, 463 of 501 patients). The other five studies enrolled mainly Caucasian patients (88% to 97%).

- Region: The six trials included one trial conducted primarily in Asia, two trials conducted in the U.S., and three international trials (mainly from EU).
- Age: Study 302 included the highest proportion of patients ≥65 years of age (42%). Study 3001 did not recruit patients ≥65 year of age by design. Studies INT-6, USA-11, and 401 included 11% to 18% patients ≥65 years of age.
- History of constipation: The patients enrolled in the two U.S. trials reported a longer disease duration (mean/median is approximately 20 years) than those in other efficacy trials (mean/median is between 5 to 15 years).
- Previous use of bulk forming laxatives: A larger percentage of patients enrolled in the two U.S. trials reported use of bulk forming laxatives previously (67% and 57%) as compared to those in the two pivotal trials (26% and 27%).
- SBMs in last 6 months: A larger proportion of patients enrolled in the two U.S. trials reported 0 or 0 to ≤1 SBMs/week in last 6 months (about 75%), as opposed to 39% and 50% in the two phase 3 pivotal trials.

Table 3. Summary of Demographic and Baseline Characteristics for Phase 3/4 Trials

	PRU-CRC-3001 N=501	SPD555-302 N=358	PRU-INT-6 N=476	PRU-USA-11 N=383	PRU-USA-13 N=426	SPD555-401 N=340
Sex						
Male	51 (10.2)	358 (100)	43 (9)	40 (10.4)	56 (13.1)	49 (14.4)
Female	450 (89.8)	0	433 (91)	343 (89.6)	370 (86.9)	291 (85.6)
Race						
White	31 (6.2)	346 (96.6)	447 (93.9)	337 (88.0)	380 (89.2)	316 (92.9)
Asian	463 (92.4)	1	7	3	3	1
Age groups						
≥65 years	2 (0.4)	150 (41.9)	51 (10.7)	53 (13.8)	57 (13.4)	61 (17.9)
<65 years	499 (99.6)	208 (58.1)	425 (89.3)	330 (86.2)	369 (86.6)	279 (82.1)
Age in years						
Median (range)	43 (18, 65)	62 (18, 91)	43 (17, 89)	48 (18, 85)	46 (18, 95)	48 (18, 93)
Baseline weekly average on SBM and SCBM						
≤2 SBM/week	483 (96.4)	177 (49.4)	192 (40.3)	175 (45.7)	194 (45.5)	170 (50)
≤2 SCBM/week	499 (99.6)	341 (95.3)	461 (96.8)	374 (97.7)	418 (98.1)	328 (96.5)
>6 SBM/week	0	47 (13.1)	98 (20.6)	58 (9.9)	83 (19.5)	27 (7.9)
History of Constipation (years)						
Median (range)	10 (0.5, 60)	5 (0.5, 65)	15 (1, 79)	20 (1, 79)	20 (0, 82)	15 (NA)
Previous use bulk-forming laxatives* (%)	26	27	57	67	57	NA
Number of SBMs/week during the last 6 months (%)						
0	23	10	39	37	44	NA
>0 & ≤1	27	29	32	38	32	NA

Source: Reviewer's analyses, primary analysis population
Abbreviations: SBM, spontaneous bowel movement; SCBM, spontaneous complete bowel movement

5.4. Collective Evidence of Efficacy

5.4.1. Efficacy Results for the Primary Endpoint

The primary endpoint for all six phase 3/4 trials was the percentage of responders, defined as patients with a mean of ≥3 spontaneous complete bowel movements (SCBMs) per week over the 12-week treatment period.

The efficacy analysis population was the intent-to-treat (ITT) population for five of the six studies, and modified ITT (mITT) population for Study 302 excluding subjects enrolled at site 350012 due to a serious good clinical practice breach. The ITT population included randomized subjects who had at least one administration of the investigational product.

The primary analysis was to compare the difference in responder rates between prucalopride ≤2 mg (1 mg and 2 mg) and the placebo using a Cochran-Mantel-Haenszel (CMH) test, controlling for the randomization stratification factors used in each study. Details of the missing data imputation and calculation of weekly SBM and SCBM frequencies in the presence of missing daily e-diary data are discussed in the Appendix.

The primary efficacy analysis results are presented in Table 4. In the two pivotal trials, Study 3001 and Study 302, prucalopride demonstrated statistically significant treatment effects compared to placebo with increased percentages of responders (23% and 20.2%, respectively) and with both p-values of <0.001. Three out of the four supportive efficacy studies, Studies INT-6, USA-11, and USA-13, also demonstrated statistically significant treatment effects with treatment differences of 9.9%, 16%, and 11.6%, respectively, and p-values of <0.01; and Study 401 reported a numerically higher response rate at week 12 in the prucalopride arm (25.1%) as compared to the placebo arm (20.1%) with a response difference of 5% and a p-value of 0.34. Of note, Study 401 was a phase 4 trial conducted in Europe to evaluate prucalopride for 24 weeks. The primary efficacy endpoint failed to achieve statistical significance at both week 12 and 24; however, statistical significance was achieved in the other five trials submitted to support product approval.

Table 4. Primary Efficacy Analysis Results for Phase 3/4 Studies (ITT/mITT Population)

	PLA		PRU ≤2 mg		Percent Difference PRU–PLA	
Study	**N**	**n (%)**	**N**	**n (%)**	**(95% CI)**	**P-value[1]**
PRU-CRC-3001	252	26 (10.3)	249	83 (33.3)	23 (16.1, 30)	<0.0001
SPD555-302	181	32 (17.7)	177	67 (37.9)	20.2 (11, 29.2)	<0.0001
PRU-INT-6	240	23 (9.6)	236	46 (19.5)	9.9 (4, 16)	0.002
PRU-USA-11	193	25 (13.0)	190	55 (28.9)	16 (8, 24)	<0.001
PRU-USA-13	212	25 (11.8)	214	50 (23.4)	11.6 (4, 19)	0.0015
SPD-555-401	169	34 (20.1)	171	43 (25.1)	5 (-3.9, 13.9)	0.341

Source: Table 2 on Page 13 of the draft-labeling-text.pdf and Applicant's IR response on March 30, 2018, verified by the reviewer.
Abbreviations: CI, confidence interval; PLA, placebo; PRU, prucalopride
[1] P-value based on primary analyses method for each study. Note that the proportions of subjects on PRU <2 mg were 46% (79 of 177) for Study 302 and 15% (30 of 171) for Study 401.

Results of sensitivity analyses for missing data and additional supportive analyses (per-protocol and completer analyses) were consistent with the primary efficacy findings on the comparison between the prucalopride and the placebo arm. Subgroup analyses (presented in the Appendix) demonstrated consistent efficacy trend by age, sex and race across all studies with reasonable subgroup sizes.

5.4.2. Efficacy Results of the Alternative Endpoint A

As noted previously in the Regulatory History, the pre-specified primary endpoint in the six phase 3/4 trials differed from the FDA's currently recommended primary efficacy endpoint for the CIC indication. Therefore, at a meeting on July 15, 2014, FDA requested an additional post hoc efficacy analysis using the recommended overall responder endpoint (referred to as Alternative Endpoint A).

- Alternative Endpoint A: An overall 12-week SCBM responder is a patient who is a SCBM weekly responder for ≥9 out of 12-weeks of the treatment period. A SCBM weekly responder is a patient who has a SCBM weekly frequency rate of ≥3 and increased by ≥1 from baseline. Patients must also have at least 4 days of evaluable response data to be considered a weekly responder.

The analysis of the Alternative Endpoint A is considered the key supportive analysis. There was no multiplicity control pre-specified for the Alternative Endpoint A.

This alternative endpoint was analyzed by CMH tests adjusted by pooled country, sex and number of CBMs/week at baseline (0 or >0). The nominal p-values for treatment differences in five of the phase 3/4 studies were less than 0.001; and the p-value equals 0.52 for Study 401 (Table 5).

Table 5. Alternative Endpoint A Analyses Results for Phase 3/4 studies (ITT/mITT Population)

	PLA		PRU ≤2 mg		Percent Difference PRU–PLA	
Study	N	n (%)	N	n (%)	95% CI (%)	P-value[1]
PRU-CRC-3001	252	21 (8)	249	60 (24)	16 (9, 22)	<0.0001
SPD555-302	181	22 (12)	177	49 (28)	16 (7, 24)	0.0002
PRU-INT-6	240	12 (5)	236	26 (11)	6 (1, 11)	0.0042
PRU-USA-11	193	13 (7)	190	30 (16)	9 (3, 15)	0.0050
PRU-USA-13	212	11 (5)	214	32 (15)	10 (4, 15)	0.0009
SPD-555-401	169	21 (12)	171	27 (16)	3 (-4, 11)	0.5228

Source: Applicant's Table 2 of the IR response dated June 8, 2018, verified by the reviewer
Abbreviations: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intent-to-treat; mITT, modified intent-to-treat; PLA, placebo; PRU, prucalopride
[1] P-value based on CMH test adjusted by pooled country, sex and number of CBMs/week at baseline (0 or >0) using non-imputed data (based on Section 12.1 of the ISE SAP)

5.4.3. Secondary Endpoints

Each efficacy study protocol listed multiple exploratory secondary endpoints. There was no multiplicity control pre-specified for the secondary endpoints. Overall, the secondary endpoint results were consistent with the primary endpoint in favor of prucalopride over placebo.

The Applicant proposed to label one of the secondary endpoints: proportion of subjects with an average increase of ≥1 SCBM/week from baseline over a 12-week treatment period.

Table 6 presents efficacy analyses results on this secondary endpoint. Four of the phase 3/4 trials demonstrated treatment effect of prucalopride as compared to placebo in terms of this endpoint with a nominal level <0.001, except for Studies SPD555-302 and SPD555-401.

This endpoint was listed as the key secondary endpoints in Studies INT-6, USA-11, and USA-13 and one of the secondary endpoints in the other phase 3/4 trials.

Table 6. Secondary Analyses Result on Proportion of Subjects with an Average Increase of ≥1 SCBM/Week from Baseline over a 12-Week Treatment Period for Phase 3/4 Studies in the ITT/mITT Population

	PLA		PRU ≤2 mg		Percent Difference PRU–PLA (95% CI)	
Study	N	n (%)	N	n (%)		P-value[1]
PRU-CRC-3001	252	68 (27)	249	139 (56)	29 (21, 37)	<0.001
SPD555-302	181	82 (45)	177	95 (54)	8 (-2, 19)	0.085
PRU-INT-6	240	49 (20)	236	86 (36)	16 (8, 24)	<0.001
PRU-USA-11	193	49 (25)	190	89 (47)	21 (12, 31)	<0.001
PRU-USA-13	212	57 (27)	214	89 (42)	15 (6, 24)	0.001
SPD-555-401	169	68 (40)	171	84 (49)	9 (-2, 19)	0.188

Source: Table 7 on Page 9 of the Applicant's IR response dated June 26, 2018, verified by the reviewer
Abbreviations: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intent-to-treat; mITT, modified intent-to-treat; PLA, placebo; PRU, prucalopride; SCBM, spontaneous complete bowel movement
[1] P-value is based on the pre-specified CMH test for the primary analysis for each study using non-responder imputation

5.4.4. Efficacy Summary

Overall, all trials demonstrated a statistically significant treatment effect for prucalopride compared with placebo, except for Study SPD-555-401, which did not achieve statistical significance at week 12 or 24. The treatment effect, at week 12 and 24, was lower in this trial as compared to the others. The exact reasons for failure of this study remain unclear; however, efficacy of prucalopride compared with placebo was demonstrated in five other trials submitted to support product approval.

The statistical reviewer conducted sensitivity analyses for missing data using different imputation approaches, per-protocol, and completer analyses. The findings were consistent with the primary efficacy results and demonstrated efficacy in prucalopride arm relative to the placebo arm in five phase 3 studies (except Study 401), thereby, further supporting demonstration of efficacy.

Data Quality and Integrity

The efficacy studies were completed in 1999 or between 2010 and 2013. Most of the supportive studies, Studies INT-6, USA-11 and USA-13, completed in 1999, had more than 68% data with no source documentation from the study sites (Table 7).

Table 7. Summary of Missing Source Data for Phase 3/4 Studies in the ITT/mITT Population

Study	Sites/Total number of Sites (%)	Subjects/study size n/N (%)
PRU-CRC-3001	6/28 (21.4)	35/501 (7.0)
SPD555-302	7/65 (10.8)	51/358 (14.2)
PRU-INT-6	44/66 (66.7)	324/476 (68.1)
PRU-USA-11	25/36 (69.4)	261/383 (68.1)
PRU-USA-13	31/40 (77.5)	299/426 (70.2)
SPD-555-401	10/51 (19.6)	76/340 (22.4)

Source: Reviewer's analyses
Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat

The data from Studies 302 and 3001 are considered reliable based on inspectional findings. The reliability of the data from Studies USA-11 and USA-13 could not be determined by inspection alone because most of the original study records were not available for inspection due to age of the studies. For Studies 3001 and 302, the statistical review team conducted analyses to further evaluate the data in light of the missing source documentation at certain study sites. Based on the statistical reviewer's exploratory analysis, the statistical significance of the primary endpoint in Studies 3001 and 302 was not affected when the data with no source documentation were excluded from the primary analysis. For Studies USA-11, USA-13 and INT-6, a similar analysis was not feasible because of the amount of missing source documentation (see table above). Generally, there were no major numerical inconsistencies between the efficacy data from study sites without source documentation and the rest of the efficacy data.

Inspections for this NDA consisted of inspections of five clinical investigator sites and the Applicant. No significant regulatory findings or data integrity issues were noted during the clinical site and Application inspections.

Two of the clinical trials submitted in support of the application, Studies USA-11 and USA-13, were conducted from 1998 to 1999 by Janssen Research Foundation. The data from these trials was submitted to the EMA, and the product was approved for marketing in the EMA in 2009. These data were purchased by the current Applicant. During pre-NDA discussions with FDA, the Applicant notified FDA that a limited amount of source data (see table above) for Studies USA-11 and USA-13 would be available for inspection and data verification due to the long period of time since the studies had been conducted. More importantly, source data from only one site in each of the top ten enrolling sites would be available for review. There was a lack of source data at most clinical sites from Studies USA-11 and USA-13. However, the results of the inspections at the sites where source data were available, the results of the Applicant inspection including review of monitoring reports, and the history of the monitoring from Janssen Research Foundation indicate that these studies were adequately conducted at the sites inspected and can be used in support of the application.

5.4.5. Efficacy Conclusion

Based on the data submitted by the Applicant, prucalopride demonstrated efficacy as compared to placebo as measured by the percentage of responders meeting the primary endpoint, the Alternative Endpoint A, and secondary endpoints. For the primary endpoint, in five of the six

efficacy trials, the prucalopride arm had a statistically significantly higher percent of responders than that in the placebo arm; one study, Study 401, did not have statistically significant findings.

6. SAFETY OVERVIEW

6.1. Summary of Safety Analyses

The most common identified treatment-emergent adverse events (TEAEs) in patients treated with prucalopride included diarrhea, headache, abdominal pain, and nausea. The short-term treatment (≤12 weeks) with prucalopride at multiple doses (0.5 mg, 1 mg, 2 mg, and 4 mg) resulted in low numbers of deaths, serious TEAEs, and discontinuations due to adverse events in the overall safety database. Note that the 2 mg dose is proposed for the indication (1 mg in patients with severe renal impairment). These findings were also seen in the trials to support product approval and labeling (Studies 302, 3001, INT-6, USA-11, USA-13, and 401).

The limitation of the clinical trials safety database is that there are no controlled trials of 12 months duration given that this product is intended to treat a chronic disease. To address this issue, Study SPD555-802, a retrospective observational study evaluating major adverse cardiac events (MACE), defined as the composite of hospitalization for AMI, hospitalization for stroke, and in-hospital cardiovascular death, was submitted in lieu of a randomized clinical trial of longer duration. This study is discussed in the Division of Epidemiology Review of Observational Study Section below. Additional analyses were also performed to determine CV safety in the studies noted above as well as the double-blind placebo-controlled and open label studies in the Applicant's overall safety database. The results of the CV safety analysis are discussed in detail in the Adverse Events of Special Interest Section. Given the concerns for cardiac and psychiatric adverse events with the drug class, a focused evaluation of cardiac and psychiatric events was conducted and is discussed in detail in the Adverse Events of Special Interest Section.

In general, the safety data submitted for patients treated with prucalopride at multiple doses (0.5 mg, 1 mg, 2 mg, and 4 mg) resulted in small numbers of patients who experienced cardiovascular and psychiatric adverse events. Furthermore, there were low percentages of patients with Standard (and Extended) MACE in the overall safety database. Given the findings from the clinical trial database and the results of the analysis of the observational study SPD555-802, the Division is requesting advice from the Committee regarding whether the safety data adequately characterize the potential CV safety risk when considering the totality of the data.

6.2. Safety Analyses Methodology

In this document, the safety review for prucalopride was performed using the Applicant's safety database that includes 16 of the 20 completed double-blind, placebo-controlled, phase 2 through 4 trials of at least 4 weeks duration conducted in adult patients with CIC (Pool D). Four trials were excluded based on the design; two trials had a cross-over design with small sample sizes (28 and 8 patients), one enrolled a pediatric population, and one was 7 days duration (40 patients). The following safety review will summarize deaths, serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), and discontinuations due to adverse events (AEs).

In general, TEAEs include all AEs which start on or after the first dose and those that occur up to 5 days after the date of the last dose; however, slightly different rules were used across the trials for the cut-off date after the last dose. For the integrated safety analyses, the Applicant defined a TEAE based on the rules applied for each trial and included SAEs or deaths for at least 30 days post-study.

The safety review also includes focused safety analyses of adverse events of special interest, including cardiovascular and psychiatric events, given the potential safety concerns with the 5-HT_4 receptor agonist drug class. The trials included in the broad safety database (Pool D) evaluated a range of doses (0.5 mg, 1 mg, 2 mg, and 4 mg); the 2 mg dose is being proposed for approval and labeling with 1 mg proposed for patients with severe renal impairment. The safety results for all the evaluated doses are shown in this document; however, FDA focused on the 2 mg dose since it is the primary dose being considered for approval and labeling.

The five phase 3 trials (Studies 302, 3001, INT-6, USA-11, USA-13) and one phase 4 trial (study 401) that were submitted as the primary basis for efficacy and safety in the NDA are included in the broader safety database (Pool D). The safety data from these six trials (5 phase 3 trials and 1 phase 4 trial) were reviewed individually and the overall type and frequency of adverse events were generally aligned with the safety findings from the broader safety database (Pool D). Additionally, the six trials submitted to demonstrate efficacy to support product approval contributed the largest number of patients to the broader safety database (Pool D) (noted in boxes Table 8). As there were no meaningful differences and to obtain a larger sample of patients to help characterize the safety of prucalopride, the broader safety analyses (Pool D) are presented in this document.

Table 8. Patients by Treatment Group: Pool D (phase 2 through 4 double-blind, controlled trials of at least 4 weeks duration in adults with CIC)

	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	Total N = 5278
				n (%)			
All studies	1973	110	330	1516	1349	3305	5278
PRU-INT-6	240 (12.2)	0	0	238 (15.7)	238 (17.6)	476 (14.4)	716 (13.6)
PRU-USA-13	212 (10.7)	0	0	214 (14.1)	215 (15.9)	429 (13.0)	641 (12.1)
PRU-USA-11	209 (10.6)	0	0	207 (13.7)	204 (15.1)	411 (12.4)	620 (11.7)
PRU-USA-28	257 (13.0)	0	0	0	253 (18.8)	253 (7.7)	510 (9.7)
PRU-CRC-3001	252 (12.8)	0	0	249 (16.4)	0	249 (7.5)	501 (9.5)
PRU-INT-12	72 (3.6)	0	76 (23.0)	75 (4.9)	80 (5.9)	231 (7.0)	303 (5.7)
PRU-USA-25	117 (5.9)	0	0	0	225 (16.7)	225 (6.8)	342 (6.5)
PRU-INT-2	63 (3.2)	0	67 (20.3)	62 (4.1)	61 (4.5)	190 (5.7)	253 (4.8)
PRU-USA-3	46 (2.3)	43 (39.1)	48 (14.5)	48 (3.2)	46 (3.4)	185 (5.6)	231 (4.4)
SPD555-302	186 (9.4)	0	15 (4.5)	169 (11.1)	0	184 (5.6)	370 (7.0)
SPD555-401	180 (9.1)	0	7 (2.1)	174 (11.5)	0	181 (5.5)	361 (6.8)
PRU-INT-1	45 (2.3)	46 (41.8)	43 (13.0)	40 (2.6)	0	129 (3.9)	174 (3.3)
PRU-USA-26	18 (<1)	21 (19.1)	24 (7.3)	26 (1.7)	0	71 (2.1)	89 (1.7)
PRU-GBR-4	38 (1.9)	0	39 (11.8)	0	0	39 (1.2)	77 (1.5)
PRU-BEL-6	26 (1.3)	0	0	0	27 (2.0)	27 (<1)	53 (1.0)
PRU-FRA-1	12 (<1)	0	11 (3.3)	14 (<1)	0	25 (<1)	37 (<1)

PLA = placebo; PRU = prucalopride
Note: Percentages were based on all subjects in the safety set for Phase 2-4 double-blind, placebo-controlled studies of ≥ 4 weeks duration
Source: Applicant table, Integrated Summary of Safety, Table 12, page 106/504
Abbreviation: CIC, chronic idiopathic constipation

Of note, Study PRU-USA-21 was a double-blind, placebo-controlled trial in 40 patients, which was excluded from Pool D by the Applicant because the duration was limited to 7 days. This trial was reviewed by FDA as part of the safety analysis for cardiovascular events of interest (excluding Standard and Extended MACE), and psychiatric adverse events, discussed later in this document.

The phase 2 and 3 open-label trials (Pool E) were also considered for purposes of evaluating deaths and MACE to obtain a more complete evaluation of these events. However, causality is difficult to determine in the absence of a comparator arm. For a listing of the trials included in Pool E, refer to the Appendix (Table 30).

Additional analyses of adverse events of special interest (cardiovascular and psychiatric) were performed. Cardiovascular adverse events reviewed included MACE (standard and extended), palpitations, QT prolongation, ventricular arrhythmias, syncope, cardiovascular and cerebrovascular ischemic events, and electrocardiogram abnormalities. The review of psychiatric adverse events emphasized attempted and completed suicide. An additional evaluation of other reported common psychiatric events (anxiety, depression, insomnia, etc.) was conducted.

As previously noted, there are no controlled trial data of 12 months duration. Given that prucalopride has been approved in Europe since 2009, the safety analysis also includes results from study SPD555-802, a post-marketing retrospective cohort (observational) study to measure the incidence of MACE in European patients with exposure to prucalopride (PRU) or polyethylene glycol 3350 (PEG). The study was designed to exclude a three-fold risk from prucalopride; a primary analysis pooled results from studies separately conducted in four European data sources. This study is reviewed below in section 7.4, Division of Epidemiology Review of Observational Study SPD555-802.

6.3. Exposure

Overall, there appears to be adequate exposure to prucalopride in the clinical trials of the CIC population for the evaluation of common AEs and events associated with use ≤12 weeks. However, the evaluation of rare or infrequent AEs of special interest and/or those that may occur after a longer duration of use may not be adequately characterized in this clinical trial database. For this reason, additional post-marketing CV safety data were reviewed to address long-term exposure as noted above.

For Pool D (phase 2 through 4 double-blind, placebo-controlled trials), Table 9 shows that 3295 patients were exposed to prucalopride (doses 0.5 mg, 1 mg, 2 mg, or 4 mg); of these patients, 1512 patients were exposed to the 2 mg dose. The majority of the patients who received the 2 mg dose had at least 28 days of exposure (1363 [89.9%]). While there were subjects with longer durations of exposure to the 2 mg dose (250 patients [16.5%] for at least 90 days and 4 patients [<1%] for at least 180 days), there were no patients with at least 12 months duration of use in the controlled trials. The exposure to prucalopride in the double-blind, placebo-controlled trials in adults with CIC (Pool D) is summarized in the table below.

Table 9. Exposure Duration (Weeks) by Treatment Group—Phase 2 through 4 Double-Blind Studies in Adults with CIC (Pool D)

Duration	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
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
Abbreviations: CIC, chronic idiopathic constipation; PRU, prucalopride; SD, standard deviation; Min, minimum; Max, maximum

In Pool E (open label trials), a total of 2759 subjects were exposed to the study drug. The majority of the subjects received the study drug for at least 180 days (1710 [62.0%]). In addition, 1052 (38.1%) subjects had at least 365 days of exposure, 583 (21.1%) had at least 545 days of exposure, and 96 (3.5%) had at least 730 days of exposure.

6.4. Deaths

There were 8 total deaths among patients in Pool D and Pool E; 7 deaths occurred in patients receiving prucalopride. In Pool D, there were 2 deaths in the prucalopride group, and 1 in placebo, and in Pool E, there were 5 deaths (in open-label trials). The causes of death included lobar pneumonia, respiratory failure, bronchitis, myocardial infarction (MI), and suicide. No deaths occurred in the six phase 3/4 efficacy trials that were submitted to support product approval and labeling (Studies 3001, 302, INT- 6, USA-11, USA-13, and 401).

The following describes the 2 deaths which occurred in Pool D. Both patients were enrolled in Study USA-26, which was a 4-week CV safety trial in frail, geriatric patients living in a nursing facility):

- An 83-year-old male with a history of congestive heart failure, hypertension, and circulatory disease died of lobar pneumonia on day 13. He was treated with prucalopride 1 mg. He developed deteriorated cardiac status (cardiac failure) on day 1 of drug administration, followed by severe tachycardia (day 8), hyperkinesia (restless lower extremities), jaundice, pneumonia lobar, pulmonary edema and somnolence. Ultimately, he lapsed into a coma (day 11). The investigator deemed these events as not or doubtfully related to the study drug.

- An 86-year-old female with a history of hypertension, circulatory disorder, peripheral vascular disease, left lower pneumonia, congestive heart failure, and atrial fibrillation developed *Staphylococcus aureus* bronchitis and died from respiratory failure on day 31 of being treated with prucalopride 2 mg. None of these events were considered to be related to the study drug by the investigator.

The following describes five deaths which occurred in Pool E (open-label trials). These patients were enrolled from 4-week double-blind trials into longer-term (at least 12 months duration) phase 3, open-label trials. [1]

- An 81-year-old male with a history of ischemic heart disease and transient ischemic attack died of a MI 67 days after discontinuing prucalopride 2 mg. He was treated with prucalopride from (b) (6) to (b) (6), including 29 days of treatment interruption and 4 weeks of prucalopride 4 mg in a prior double-blind trial. The event was considered not related to the study medication by the investigator.

- An 89-year-old female with a history of coronary heart disease died of pneumonia 4 days after discontinuing treatment with prucalopride 2 mg administration (previously treated with 1 mg in the 4-week double-blind trial). She developed bronchitis on day 218 of prucalopride and subsequently, was diagnosed with a serious AE of severe pneumonia 8 days later. She was not hospitalized and was treated for pneumonia. The prucalopride treatment was discontinued, and she died 4 days later. This event was not considered related to the study medication by the investigator.

- A 56-year-old male with a history of cardiomyopathy, atrial fibrillation, hypertension, hypercholesterolemia, non-insulin dependent diabetes, and cardiovascular accident died of an MI on day 48 of the open-label study while on prucalopride 2 mg (total prucalopride exposure 75 days; previously treated with prucalopride 2, 3, and 4 mg in the open-label trial, and 4 mg in a 4-week double-blind trial). The investigator deemed this event to be not related to the study drug.

- A 70-year-old male with a history of depression completed a suicide via a self-inflicted gunshot wound (GSW) to the chest and abdomen. Prucalopride was discontinued approximately 30 days prior to this event (total prucalopride exposure of 101 days; previously treated with prucalopride 2 mg for 46 days in an open-label trial, and 4 mg for 55 days in a 4-week plus 4-week retreatment double-blind trial with interruption of 17 days). 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.

- A 40-year-old female with a history of depression, drug-dependency, and drug abuse died by completed suicide by hanging 52 days post-treatment with prucalopride 4 mg group (total prucalopride exposure 242 days; previously treated with prucalopride for approximately 160 days in an open-label trial, and 4 mg for 82 days in a double-blind trial). The investigator deemed this serious TEAE to be not related to the study drug.

None of these cases were attributed to the study drug by the investigators.

[1] The deaths occurred in 2 phase 3, open-label trials, PRU-INT-10 and PRU-USA-22.

6.5. Serious Treatment-Emergent Adverse Events

In Pool D (double-bind, placebo-controlled trials of ≥4 weeks in adults with CIC), 66 of 3305 patients (2.0%) in the total prucalopride group (0.5 mg, 1 mg, 2 mg, 4 mg), 27 of 1516 patients (1.8%) in the prucalopride 2 mg group, and 38 of 1973 patients (1.9%) in the placebo group experienced at least one serious TEAE. The overall number of events was small and gastrointestinal disorders were the most commonly reported serious event. The serious treatment-emergent events that occurred in Pool D are summarized in Table 10. The prucalopride 2 mg dose is noted in a box in the following table because 2 mg is the proposed dose for approval. Prucalopride 1 mg is being proposed for use in patient with severe renal impairment; the serious treatment-emergent events that occurred in the 1 mg group were generally similar and with smaller numbers of reported events as compared to the 2 mg dose. The serious treatment-emergent events occurring in either the 2 mg or 1 mg prucalopride exposed patients were similar to those occurring in placebo.

Table 10. Serious TEAEs in at Least 2 Subjects in the Phase 2 through 4 Double-blind Studies of >4 weeks Duration in Adults with CIC (Pool D, 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
≥ 1 serious TEAE	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)

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

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

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

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

Source: Applicant's submission, Integrated Summary of Safety, Table 38, pages 158-159
For Psychiatric disorders, the 2 events that were not represented in the table were drug abuse in the 1 mg group and abnormal behavior in the 2 mg group.

6.6. Treatment- Emergent Adverse Events

In Pool D, 2146 of 3305 patients (64.9%) in the total prucalopride group (0.5 mg, 1 mg, 2 mg, 4 mg), 946 of 1516 patients (62.4%), and 1058 of 1973 patients (53.6%) in the placebo group experienced ≥1 TEAE. The most common TEAEs in the prucalopride 2 mg group (proposed

dose for approval) were gastrointestinal disorders (nausea, diarrhea, abdominal pain) and nervous system disorders (headache). Headache occurred in 265 of 1516 patients (17.5%) in the prucalopride 2 mg group, and in 186 of 1973 patients (9.4%) in the placebo group. Nausea occurred in 206 of 1516 patients (13.6%) in the prucalopride 2 mg group, and 126 of 1973 patients (6.4%) in the placebo group. A dose-dependent increase in the number of patients reporting one or more events of diarrhea across prucalopride groups was seen; 5 of 110 patients (4.5%), 27 of 330 patients (8.2%), 179 of 1516 patients (11.8%), 185 of 1349 patients (13.7%) in the 0.5 mg, 1 mg, 2 mg, and 4 mg prucalopride groups, respectively. Diarrhea events were reported in 72 of 1973 patients (3.6%) in the placebo group. Finally, the majority of headache, nausea, abdominal pain, and diarrhea TEAEs were transient in nature (lasting <5 days). All other TEAEs occurred in <10% of subjects in the total prucalopride group.

The TEAEs that occurred in Pool D were generally similar in type and frequency to the TEAEs that occurred in the phase 3 trials submitted to support approval.

6.7. Discontinuations due to Adverse Events

The majority of patients (2847 (86.1%) in the total prucalopride group (0.5 mg, 1 mg, 2 mg, 4 mg) and 1719 (87.1%) in the placebo group) completed the phase 2 through 4 double-blind, placebo-controlled trials (Pool D).

The main reason for discontinuation was the occurrence of AEs: 222 of 3305 patients (6.7%) exposed to any dose of prucalopride compared to 55 of 1973 patients (2.8%) in the placebo group. In the prucalopride 2 mg group, 83 of 1516 (5.5%) discontinued due to AEs compared to 55 of 1973 patients (2.8%) in the placebo group.

In general, the other reasons for discontinuation were fairly balanced between the placebo and total and 2 mg prucalopride groups.

7. CARDIOVASCULAR SAFETY

7.1. Non-clinical

Prucalopride is a selective 5-hydroxytryptamine type 4 (5-HT_4) receptor agonist being developed for the treatment of CIC in adults. It has motility stimulating properties in the gastrointestinal tract with pronounced effects in the large intestine, where it stimulates peristalsis and accelerates colonic transit.

Prucalopride has shown high affinity and selectivity for the human 5-HT_4 receptors expressed in human embryonic kidney 293 cells (HEK-293) with an inhibition constant [K_i] of 2.5 to 8nM. The affinity of prucalopride for other receptors, channels or transporters was very low and only detected at concentrations exceeding the affinity for the 5-HT_4 receptor by 150 to 10,000 fold. Other 5-HT_4 receptor agonists in the same class, such as tegaserod and cisapride, have affinities for other receptors/channels such as the 5-HT_{1-2} (tegaserod) and the 5-HT_2 (cisapride) in a similar concentration range as their affinity for the 5-HT_4 receptor. The half maximal effective concentrations for the in vitro pharmacological effects were low in all the animal species tested,

including human gastric and colon tissues, ranging from 16 to 32nM, and these effects were blocked by a selective 5-HT_4 receptor antagonist. In rats and dogs, prucalopride was shown to stimulate gastrointestinal motility and induce contractions of the colon at oral doses ≥0.04 mg/kg. The binding affinities of prucalopride for different serotonin receptor subtypes as compared to cisapride and tegaserod are shown in the Table 11 below.

Table 11. Receptor Binding Profile at Therapeutic Concentrations

Drug	5-HT_4	5-HT_3	5-HT_2	5-HT_1	D_2	hERG
Prucalopride	+					
Cisapride	+	+	+			+
Tegaserod	+	+	+	+		

Source: Tack et al. (Tack et al. 2012)
Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); hERG, potassium ion channel encoded by human ether-à-go-go-related gene; D_2, dopamine receptor
+ indicates affinity for this receptor (as either agonist or antagonist) that is likely to be clinically relevant at concentrations necessary for 5-HT_4 agonism (i.e. for therapeutic action)

In central nervous system safety pharmacology studies in rats and mice, palpebral ptosis, tremors, ataxia, clonic convulsions, hypothermia, sedation (≥160 mg/kg in mice; 390 times the clinical dose of 2 mg, based on body surface area). and salivation were noted at single oral doses of ≥320 mg/kg (780 times the clinical dose of 2 mg, based on body surface area). Ptosis was also observed in rats after repeated oral administration of ≥80 mg/kg/day (390 times the clinical dose of 2 mg, based on body surface area). In dogs, pedaling movements, sedation, ptosis, decubitus and salivation were observed following repeated dosing at ≥20 mg/kg/day (325 times the clinical dose of 2 mg, based on body surface area).

Prucalopride had no effect on the delayed rectifier current (I_{Kr}) at concentrations up to 1µM (400 ng/ml). However, at concentrations higher than 1µM, prucalopride attenuated I_{Kr} in hERG-transfected HEK-293 cells and guinea pig ventricular myocytes in a dose-dependent manner. The half maximal inhibitory concentration for I_{Kr} blockage was 22µM (8140 ng/ml), about 1100 times the human C_{max}. Prucalopride had little or no effect on other membrane ion currents at concentrations exceeding therapeutic plasma concentrations. This was true for: outward potassium current, slow inward potassium channel (I_{Ks}), inward potassium current, and fast sodium current or L-type calcium current. In tissue preparations (isolated guinea pig papillary muscles, canine and rabbit Purkinje fibers and isolated rabbit hearts), prucalopride, at concentrations ≥3µM, caused a prolongation of the action potential duration (at 90% repolarization, +14% to +22%). In isolated human atrial muscle strips, prucalopride caused a minor increase in the contractile force at concentrations ≥100nM; the mean increase was about 20% of the 5-HT induced contractions. Prucalopride had no contractile effect on porcine, canine, and human isolated coronary arteries over a concentration range of 1nM to 10µM. In an in vivo human platelet aggregation study, neither prucalopride (at up to 200nM; 10 times the human C_{max}), tegaserod (100nM) nor velusetrag (a highly selective 5-HT_4 agonist; 70nM) had consistent platelet aggregation responses.

In guinea pigs and rabbits, single intravenous (IV) doses (guinea pigs ≥1.5 mg/kg; rabbits ≥9.60 mg/kg; 44 times and 350 times, respectively, the therapeutic C_{max} in humans) of prucalopride prolonged the duration of the QTcB interval. However, in dogs (conscious and anesthetized), prucalopride had no relevant effect on ECG intervals or on the duration of the action potential of the right ventricle. In conscious dogs, following single oral dose of ≥2.5 mg/kg, a slight and

transient increase in systolic and diastolic blood pressure was observed with a small effect on heart rate, but without an effect on the ECG. There were no apparent effects of prucalopride on ECG characteristics in conscious dogs following oral dosing at 30 mg/kg/day for 12 months (872 times the human C_{max}). In anesthetized juvenile pigs, prucalopride at the highest tested single dose of 1.25 mg/kg IV, did not affect systolic and diastolic pulmonary artery pressure, cardiovascular pressure parameters, pulmonary vascular resistance, the duration of the PQ interval, the QRS complex, or the QT and QTc intervals. However, at the 0.16 mg/kg dose (9 times the human C_{max}), there was a transient increase in the heart rate (19%) which reduced gradually over 30 minutes. In anesthetized methoxamine-challenged rabbits (a drug-induced pro-arrhythmogenic animal model), IV doses of prucalopride at up to 18.6 mg/kg (plasma concentration, 4812 ng/ml or 12µM; approximately 600 times the human C_{max}) did not elicit ventricular tachycardia, torsades de pointes, or other cardiac arrhythmias.

The large exposure margins observed for CNS and CV safety studies described above, suggest limited potential for these findings at clinical exposures.

Chronic (6 months) oral administration in rats produced increased liver and heart weights, and mammary gland stimulation at ≥20 mg/kg, while higher doses (40 and 80 mg/kg) produced changes in the prostate, mammary gland, female genital tract, thyroids, heart, and thymus. The no observed adverse effect level of 5 mg/kg/day in rats provides 5 and 12 times exposures (AUC, area under the plasma concentration over time curve) for males and females, respectively, compared to the human exposure at the 2 mg/day clinical dose. In the dog, the no observed adverse effect level was 10 mg/kg/day after 12 months of dosing, which provides 244 times exposure margins for the 2 mg/day clinical dose. CNS-related adverse effects and increased liver enzymes along with histopathological changes in the liver and female genital tract were observed in dogs at exposures margins >244 times the 2 mg/day clinical dose.

In a 2-year mouse carcinogenicity study, a positive dose-related trend was observed for benign Leydig cell tumors in male mice and for endometrial sarcoma in female mice. There was also a positive trend for epithelial mammary tumors, particularly mammary adenocarcinoma. However, only the incidences of mammary gland adenocarcinoma in females at the high dose (80 mg/kg) were significantly higher than the controls. The plasma exposure ratios after 10, 20, and 80 mg/kg doses were approximately 6, 15, and 114 in the males and 3, 13, and 101 in the females, respectively, as compared to the clinical exposure at the proposed dose.

In a 2-year carcinogenicity study in rats, there were increased incidences of benign pheochromocytoma, hepatocellular tumors, pancreatic islet cell tumors, pituitary adenomas, and thyroid follicular cell tumors in the male rats. In the females, there were increased incidences of mammary gland tumors, thyroid follicular cell tumors, and hepatocellular adenomas. The incidences were only significant at the high doses, which provide 229 and 196 times exposure ratios for the clinical dose.

Thus, the significantly increased incidences of tumors in 2-year carcinogenicity studies in mice and rats were only seen at very high exposure ratios. In addition, the increased tumor incidences observed are likely through epigenetic mechanisms, and their occurrence at high exposure multiples suggests a lack of tumor risks in humans at the therapeutic dose.

7.2. Clinical Pharmacology

7.2.1. Clinical Pharmacokinetics

7.2.1.1. Absorption

Following a single oral dose of 2 mg in healthy adult subjects, peak plasma concentrations are generally observed within 2 to 3 hours after administration. The absolute bioavailability of prucalopride is 93.2% following a single oral administration of 2 mg in healthy subjects. Following once daily (QD) dosing, steady state was achieved within 3 to 4 days and the accumulation ratio ranged from 1.9 to 2.3. Following either a single dose or multiple doses given QD, approximately dose-proportional increases in the systemic exposure (C_{max} and AUC) were observed over the dose range of 1 to 20 mg in healthy subjects.

Food effect
No significant effect of food on the PK of prucalopride was observed when a single dose of 2 mg prucalopride was administered with a high fat meal. Mean C_{max} was 6% higher and mean $AUC_{0\text{-}inf}$ was 4% lower in the fed state compared to the fasted state.

7.2.1.2. Distribution

Prucalopride is 28.9% bound to human plasma proteins.

7.2.1.3. Elimination

Prucalopride is primarily eliminated via renal excretion. Following a single oral administration of 0.25 to 4 mg, mean $t_{1/2}$ of prucalopride was estimated to be 15.2 to 27.4 hours. The population PK analysis showed that creatinine clearance was a significant covariate on the apparent clearance (CL/F) of prucalopride, while sex, race, and age were not identified as significant covariates on the CL/F of prucalopride.

Metabolism
In vitro, prucalopride is a substrate of cytochrome P450 (CYP) 3A. In a mass balance study (SPD555-104) using 2 mg ^{14}C-prucalopride, unchanged prucalopride accounted for 92 to 94% of the total radioactivity in plasma. Seven metabolites were recovered in urine and feces, with the most abundant metabolite R107504 (O-desmethyl prucalopride acid) accounting for 3.2% and 3.1% of the dose in urine and feces, respectively. None of the other metabolites accounted for more than 3% of the dose. The effects of a concomitant CYP3A inhibitor, ketoconazole, are discussed below in the Drug Interaction section **Error! Reference source not found.**.

Excretion
On average, 97.5% of the dose was recovered by the end of sample collection (240 hours): 84.2% of administered radioactive dose was recovered in urine and 13.3% of the dose was recovered in feces. Mean urinary excretion of unchanged prucalopride accounted for 63.6% of the administered dose.

7.2.1.4. PK in Patients with Chronic Idiopathic Constipation:

Pharmacokinetics of prucalopride in patients with CIC were characterized using various sparse PK sampling schemes in phase 2 and phase 3 studies, while intensive PK samples at steady-state were collected in one phase 2 study (PRU-NED-13) following 4 mg QD dosing for 10 days. Overall, prucalopride PK in patients with CIC and healthy subjects were similar. Mean (±SD) trough concentrations at steady state were 1.53 (±1.09), 2.97 (±1.29), and 5.6 (±1.5) ng/mL, respectively, following 1 mg, 2 mg, and 4 mg QD dosing in patients with CIC (Studies PRU-NED-2 and PRU-NED-13) and within the ranges observed in healthy subjects (Table 12).

Table 12. Mean Prucalopride Pharmacokinetic Parameters Following Once Daily Oral Dosing in Healthy Subjects and Patients with CIC

	Healthy Subjects			Patients with CIC[1]
PK Parameter	**1 mg QD**	**2 mg QD**	**4 mg QD**	**4 mg QD (N=8)**
Range of Mean C_{max} (ng/mL)	3.19-3.63	6.32-7.76	11.6-18.0	16.0±3.1
Range of Mean C_{min} (ng/mL)	1.17-1.55	2.40-2.79	4.76-6.6	5.6±1.5
Range of Mean AUC_{tau} (ng·h/mL)	47.3-56.2	95.3-109	186-254	249±46

Source: For patients with CIC, data from Study PRU-NED-13. For healthy subjects, data from Studies PRU-NED-15, PRU-USA-2, PRU-NED-8, PRU-BEL-15, PRU-NED-5, PRU-NED-7, PRU-NED-14, PRU-NED-6, PRU-NED-12, and M0001-C102.
Abbreviations: AUC_{tau}, area under the plasma concentration over time curve during a dosing interval; CIC, chronic idiopathic constipation; C_{min}, minimum plasma concentration; PK, pharmacokinetic; QD, once daily; SD, standard deviation
Note: For healthy subjects, range of mean values from multiple studies are presented.
[1] Data presented as mean ±SD.

7.2.2. Effects on QT Prolongation

No clinically relevant effects on the QT interval were observed at the proposed dose of 2 mg QD and a supratherapeutic dose of 10 mg QD of prucalopride administered for 5 days in a thorough QT study in healthy subjects (Study M0001-C102). The largest upper bounds of the two-sided 90% confidence interval (CI) for the mean difference between prucalopride (2 mg and 10 mg) and placebo were below 10 ms (Table 13). At 10 mg QD, mean C_{max} was 5.8-fold higher than that at the proposed 2 mg QD dose.

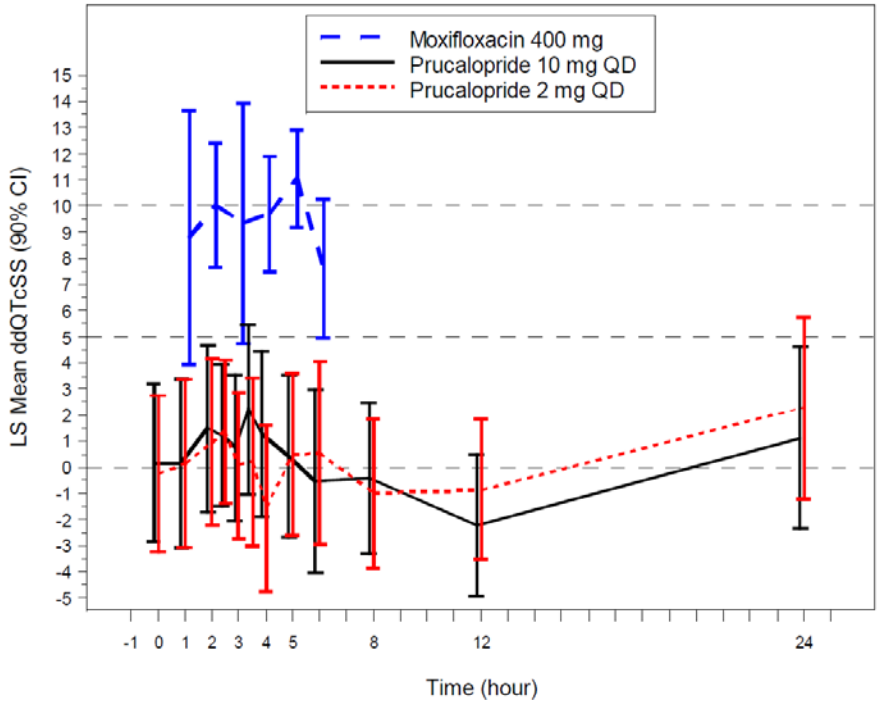
Table 13. The Point Estimates and 90% CIs Corresponding to the Largest Upper Bounds for Prucalopride (2 mg QD and 10 mg QD) and the Largest Lower Bound for Moxifloxacin

Treatment	Time (hour)	ΔΔQTcSS (ms)	90% CI (ms)
Prucalopride 2 mg	24	2.3	(-1.2, 5.7)
Prucalopride 10 mg	3.5	2.2	(-1.0, 5.4)
Moxifloxacin 400 mg[1]	5	12.9	(9.2, 16.7)

Source: FDA QT Interdisciplinary Review Team review for IND 055078, Table 1.
Abbreviations: CI; confidence interval; ΔΔQTcSS, placebo-, baseline-corrected QTc based on a study-specific QT correction; QD, once daily
[1] Multiple endpoint adjustment of three time points was applied

The time profile of ΔΔQTcSS (placebo-, baseline-corrected QTc based on a study-specific QT correction) for different treatment groups are presented in the following figure.

Figure 1. Mean and 90% CIs for ΔΔQTcSS Time Profile

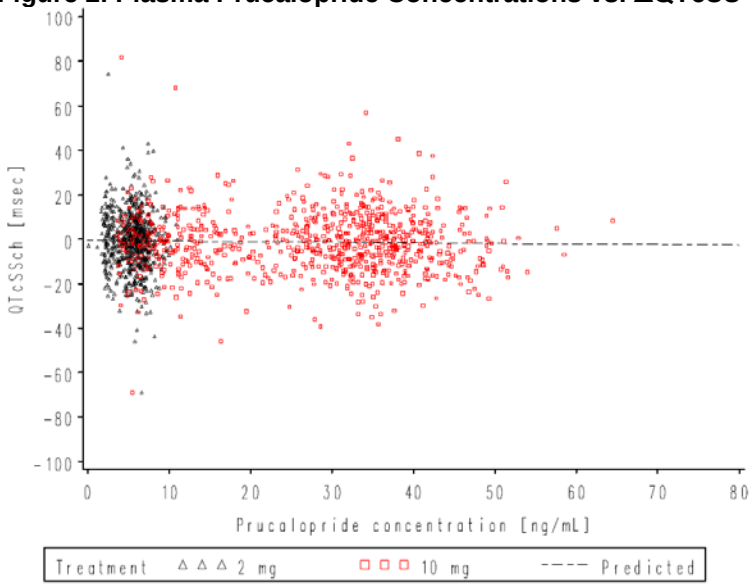


Source: FDA QT Interdisciplinary Review Team review for IND 055078, Figure 4.
Abbreviations: CI, confidence interval; ΔΔQTcSS, placebo-, baseline-corrected QTc based on a study-specific QT correction; QD, once daily

Of note, a total of 120 subjects were enrolled in this thorough QT study, with 60 subjects randomized to the prucalopride treatment (2 mg and 10 mg), 30 subjects to moxifloxacin (day 1 only) + placebo, and 30 subjects to placebo + moxifloxacin (day 15 only). As noted above, the FDA's analyses were conducted based on the mean difference between prucalopride and placebo in ΔΔQTcSS.

Additionally, there was no evident relationship between plasma prucalopride concentrations and ΔQTcSS (baseline-corrected QTc based on a study-specific QT correction) (Figure 2).

Figure 2. Plasma Prucalopride Concentrations vs. ΔQTcSS



Source: Clinical study report for Study M0001-C102, Post-Text Figure 4.2.
Abbreviation: ΔQTcSS, baseline-corrected QTc based on a study-specific QT correction

Given data for moxifloxacin were available only between 1 and 6 hours postdose, there were concerns about assay sensitivity of this thorough QT study. The time-course of the QT effects of moxifloxacin could not be adequately confirmed due to limited ECG data beyond 6 hours postdose. Therefore, to mitigate the lack of sufficient moxifloxacin data, a QT bias analysis was performed by the FDA QT Interdisciplinary Review Team. The team compared the Applicant-submitted QT measurements to the fully automatic measurements in the ECG warehouse from Study M0001-C102 for QT and QTcF, independently. The analysis results suggested an overall absence of QT bias based on the slope estimates for the difference between Applicant and ECG warehouse data versus the mean of the two measurements.

To assess the impact of this difference, the time-course and concentration-QTc relationship for the fully-automated measurements were further evaluated and no significant differences to the Applicant submitted results were observed. Therefore, the FDA QT Interdisciplinary Review Team concludes that the TQT study submitted for prucalopride is acceptable and supports excluding small mean increases (i.e., 10 ms) in the QTc interval for prucalopride.

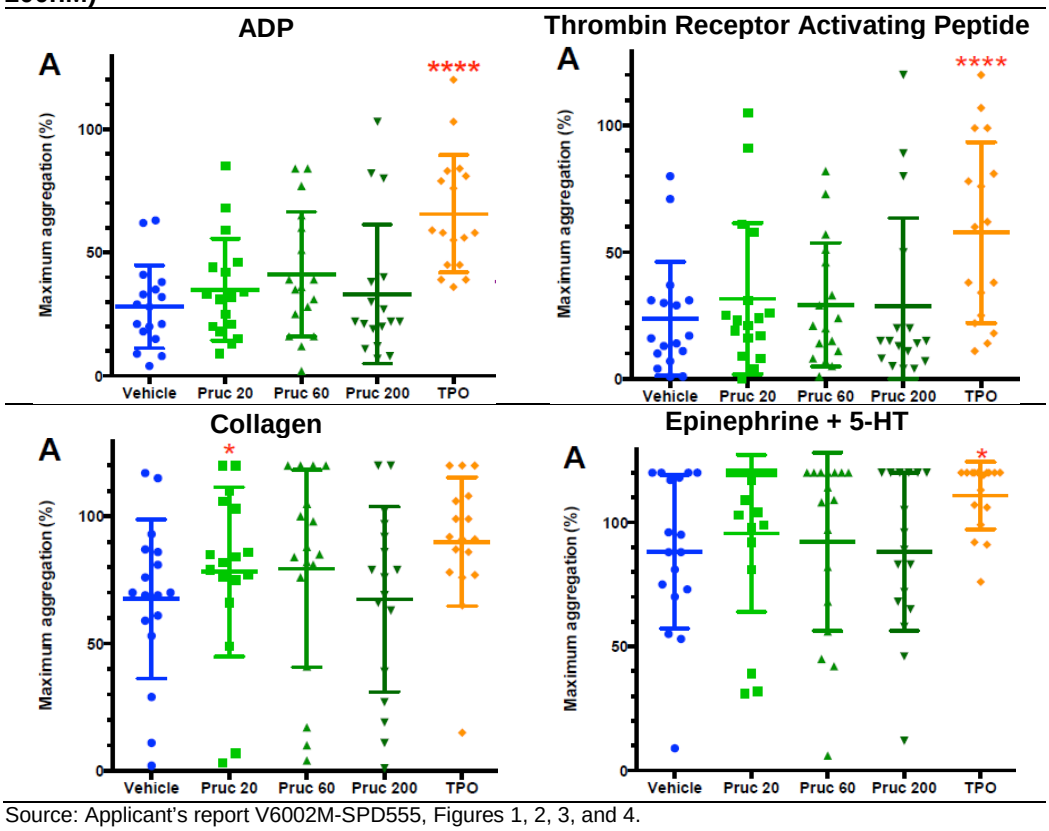
7.2.3. Effects on Human Platelet Aggregation

The potential effects of prucalopride on platelet aggregation were studied in vitro using blood samples from healthy volunteers free from drugs likely to affect platelet function (Applicant's Report V6002M-SPD555). Platelet aggregation responses were monitored using a PAP-8E aggregometer.

Study results indicated that prucalopride at concentrations of 20, 60, and 200nM (i.e., 7.4 ng/mL, 22 ng/mL, and 74 ng/mL, corresponding to up to 10-fold the mean C_{max} following 2 mg QD dosing in healthy subjects), did not significantly potentiate the platelet aggregation induced by a range of physiologically relevant platelet activators (e.g., adenosine diphosphate [ADP],

thrombin receptor activating peptide, collagen type I, and epinephrine+5-HT). It should be noted that prucalopride at 20nM did cause a statistically significant potentiation in platelet aggregation in response to collagen. However, this effect was not observed at higher prucalopride concentrations of 60 and 200nM and the clinical relevance of this finding is not yet known. Meanwhile, the positive control thrombopoietin (100 ng/mL) potentiated platelet aggregation induced by known agonists (ADP, thrombin receptor activating peptide, and epinephrine+5-HT) in this study and thus demonstrated assay sensitivity. However, thrombopoietin did not cause a statistically significant change in platelet aggregation in response to collagen, as compared with vehicle.

Figure 3. Platelet Aggregation by Agonists and by Prucalopride (Concentrations of 20, 60, and 200nM)



Source: Applicant's report V6002M-SPD555, Figures 1, 2, 3, and 4.
Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); ADP, adenosine diphosphate

7.2.4. Intrinsic and Extrinsic Factors that Affect the Systemic Exposure to Prucalopride

For patients with severe renal impairment, a reduced dosage of 1 mg QD is recommended.

7.2.4.1. Renal Impairment

The systemic exposure to prucalopride was higher in patients with renal impairment. In a dedicated renal impairment study (PRU-USA-6), the effects of renal impairment on the PK of

prucalopride were studied following a single 2 mg dose of prucalopride in subjects with renal impairment and compared with those in subjects with a normal renal function. Mean (SD) PK parameters of prucalopride from this study are presented in Table 14.

Table 14. Prucalopride Pharmacokinetic Parameters After a Single Oral Dose of 2 mg in Subjects with Renal Impairment and in Healthy Subjects

	Normal (N=9)	Mild RI (N=6)	Moderate RI (N=9)	Severe RI (N=7)	ESRD (N=3)
PK Parameter	CLcr ≥90 mL/min	CLcr 60-89 mL/min	CLcr 30-59 mL/min	CLcr 15-29 mL/min	CLcr <15 mL/min (no dialysis)
T_{max} (h)	3.3±1.2	2.9±0.7	3.2±0.9	2.4±0.7	3.8±1.3
C_{max} (ng/mL)	4.04±1.10	4.48±0.82	3.72±0.80	5.48±1.38	3.78±1.5
$AUC_{0\text{-}inf}$ (ng·h/mL)	108±16	133±21	151±45	257±48	223±104
$T_{1/2}$ (h)	29.6±6.0	32.1±2.7	39.3±9.1	46.4±7.1	50.1±10.4

Source: FDA reviewer's analysis based on the data submitted for study PRU-USA-6.
Abbreviations: CLcr, creatinine clearance; ESRD, end-stage renal disease; RI, renal impairment; PK, pharmacokinetics; SD, standard deviation
Note: Data presented as mean ±SD.

In subjects with severe renal impairment, mean C_{max} was increased by 36% compared to healthy subjects. The mean $AUC_{0\text{-}inf}$ values in patients with mild, moderate, and severe renal impairment were increased by 23%, 40%, and 138%, respectively, compared to healthy subjects. The mean $AUC_{0\text{-}inf}$ value in patients with end stage renal disease was increased by 106%, similar to that in subjects with severe renal impairment. However, this value should be interpreted with caution due to the limited sample size in this group (N=3).

Taken together, no dose adjustment is recommended for patients with mild to moderate renal impairment. For patients with severe renal impairment, dose reduction to 1 mg QD is recommended. The PK in patients with end stage renal disease have not been adequately studied due to the limited sample size.

7.2.4.2. Hepatic Impairment

In subjects with moderate to severe hepatic impairment, the PK of prucalopride were not significantly different compared to that in healthy subjects. In a dedicated hepatic impairment study (Study M0001-C103) the C_{max} and AUC in subjects with moderate (Child-Pugh B) to severe hepatic impairment (Child-Pugh C) were 10 to 20% higher than in healthy subjects after a single 2 mg dose of prucalopride. No dosage adjustment is deemed necessary for patients with mild to severe hepatic impairment.

7.2.4.3. Patients ≥65 years of age

The effect of age on the PK of prucalopride was studied in a dedicated study (PRU-NED-5). A single dose of 1 mg prucalopride was administered on day 1, followed by a 7-day treatment with 1 mg QD on days 5 to 11 in 12 healthy subjects aged 65 to 81 years and 12 healthy young

subjects (aged 20 to 32 years). Single-dose and repeated-dose PK parameters of prucalopride are presented in the table below.

Table 15. Prucalopride Pharmacokinetic Parameters after Single and Multiple Doses of 1 mg (QD) in Healthy Subjects Aged 65 Years or Older and Healthy Young Subjects

PK Parameter	Healthy Subjects Aged 65 Years or Older (N=12)	Healthy Young Subjects (N=12)
Single Dose		
T_{max} (h)	1.9±0.9	1.6±0.7
C_{max} (ng/mL)	2.17±0.67	2.24±0.79
$AUC_{0\text{-}inf}$ (ng·h/mL)	69.6±9.3	58.3±14.7
$T_{1/2}$ (h)	30.1±4.8	23.6±5.1
Steady state		
T_{max} (h)	2.3±1.1	1.8±0.7
C_{max} (ng/mL)	4.57±0.96	3.63±1.12
C_{min} (ng/mL)	2.18±0.45	1.55±0.50
AUC_{tau} (ng·h/mL)	72.2±12.5	56.2±12.5
CL_{renal} (mL/min)	156±29	190±40
CLcr (mL/min)	78.6±10.6	132±26

Source: Clinical study report for PRU-NED-5, Display 12.
Abbreviations: AUC, area under the concentration versus time curve; CLcr; creatinine clearance; PK, pharmacokinetics; SD, standard deviation; QD, once daily
Note: Data presented as mean ±SD.

Following repeated dosing at 1 mg QD, mean C_{max} and AUC_{tau} in subjects aged 65 years or older was 26% and 28% higher compared to young subjects. The mean creatinine clearance was 78.6±10.6 mL/min and 132±26.0 mL/min in healthy subjects aged 65 years or older and healthy young subjects, respectively. As such, the apparent effect of age (≥65 years old) on PK seems to be related to the decreased renal function. In subjects with mild renal impairment (creatinine clearance 60 to 89 mL/min), AUC was 23% higher than in healthy subjects in the dedicated renal impairment study (see above). Additionally, population PK analysis indicated that age was not a significant covariate on the CL/F of prucalopride, after accounting for the effect of renal function.

In two phase 3 studies SPD555-302 and SPD555-401 in which subjects aged 65 years and older initiated prucalopride therapy at a reduced dose of 1 mg QD, 81% (88 out of 109) of the subjects (ITT population) had their dose increased from 1 mg to 2 mg QD based on insufficient clinical response at week 2 or week 4. The efficacy of the 1 mg QD dose could not be established due to the limited sample size (N=21) for patients aged 65 years and older who remained on the 1 mg dose during the phase 3 trials.

Thus, the dose reduction for patients aged 65 years and older is deemed not necessary, unless they have severe renal impairment as discussed above.

7.2.4.4. Drug interactions

Effect of Other Drugs on Prucalopride
In vitro, prucalopride is a substrate of cytochrome p450 3A4 (CYP3A4), P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP).

No clinically relevant drug interactions affecting the PK of prucalopride were identified when prucalopride was co-administered with ketoconazole, erythromycin, probenecid, cimetidine, and paroxetine. In healthy subjects, co-administration of ketoconazole increased the C_{max} and AUC_{tau} of prucalopride at steady state by 38% and 37%, respectively. Of note, there was no QT prolongation at the 10 mg dose with a 5.8-fold higher C_{max} than that at the proposed 2 mg dose. Administration of erythromycin, probenecid, cimetidine, and paroxetine did not have a significant effect on the PK of prucalopride (<10% change in C_{max} and AUC).

Effect of Prucalopride on Other Drugs
Based on in vitro study results, the potential for prucalopride to inhibit major CYP enzymes (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1 and 3A4) or induce CYP enzymes (1A2, 2B6, and 3A4) is low at the anticipated clinical concentrations. Additionally, in vitro results suggest that the potential for prucalopride to inhibit transporters (P-gp, BCRP, organic anion transporter [OCT]1, OCT2, multidrug and toxin extrusion [MATE]1, and MATE2-K) is low at the anticipated clinical concentrations.

No clinically relevant effects of prucalopride on erythromycin, warfarin, digoxin, alcohol, paroxetine, and oral contraceptives (ethinyl estradiol and norethisterone) were identified when they are co-administered with prucalopride. In healthy subjects, co-administration of prucalopride increased the C_{max} and AUC_{tau} of erythromycin at steady state by 40% and 28%, respectively. No significant effect (<10% change in C_{max} and AUC) on the PK of warfarin, digoxin, alcohol, paroxetine, and oral contraceptives (ethinyl estradiol and norethisterone) was identified.

7.2.5. Rationale for Dose Selection in Phase 3 Trials

In the main phase 2 dose ranging study, PRU-USA-3, prucalopride at 0.5 mg, 1 mg, 2 mg, or 4 mg QD or placebo were administered for 4 weeks in subjects with CIC. Efficacy results from this study suggested a dose-related increase in the proportion of subjects with an average of ≥3 SCBMs/week, while the 2 mg and 4 mg dosage showed statistically significant improvements compared to placebo (Table 16).

Table 16. Proportion of Subjects with an Average of ≥3 SCBMs/Week Over 4 Weeks in Phase 2 Study PRU-USA-3

Treatment	Placebo, N=45	0.5 mg QD N=41	1 mg QD N=47	2 mg QD N=46	4 mg QD N=45
Weeks 1 to 4	13.3%	24.4%	23.4%	32.6%*	55.6%**

Source: Clinical study reports for Study PRU-USA-3, synopsis table.
Abbreviations: QD, once daily; SCBM, spontaneous complete bowel movement
** p<0.01, * p<0.05 versus placebo based on Applicant's analysis.

Therefore, prucalopride at 2 mg and 4 mg QD were studied in the initial three phase 3 studies (Studies PRU-INT-6, PRU-USA-11, and PRU-USA-13) in subjects with CIC.

Table 17. Proportion of Subjects With an Average of ≥3 SCBMs/Week Over 12-Weeks in Phase 3 Studies PRU-INT-6, PRU-USA-11, and PRU-USA-13

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)

Source: Clinical study reports for Studies PRU-INT-6, PRU-USA-11, and PRU-USA-13.
Abbreviations: ITT, intent-to-treat; QD, once daily; SCBM, spontaneous complete bowel movement
Note: Data presented are based on Applicant's ITT population.

Overall results of these three phase 3 studies suggested that the 4 mg QD provided no additional significant benefit over the 2 mg QD dose based on evaluation of the proportion of subjects with an average of ≥3 SCBMs/week over 12-week treatment period compared to placebo (Table 17). As such, the 4 mg dosage was not further evaluated by the Applicant in other phase 3 studies (SPD555-302, PRU-CRC-3001, SPD555-401).

7.3. Clinical - Cardiovascular Adverse Events of Special Interest

7.3.1. Major Adverse Cardiac Events

7.3.1.1. Methodology

The Applicant conducted a focused review of potential MACE using data from 19 double-blind (5354 patients: 3366 prucalopride and 2019 placebo) and 9 open-label (2981 patients), completed, phase 2 through 4, trials in patients with CIC. Data from other trials, including trials that evaluated other prucalopride formulations and non-CIC patient populations, were reviewed by the Applicant; the focus of this document is on patients with CIC since CIC is the proposed indication. The analysis population included all patients who had taken at least 1 dose of study medication. The data were analyzed by treatment group (prucalopride versus placebo), and the treatment periods were divided into (1) treatment during the double-blind phase to allow comparisons to placebo, and (2) overall treatment with prucalopride.

The baseline ischemic risk was determined for all patients in the MACE analysis set (completed, phase 2 through 4, double-blind, placebo-controlled, and open-label trials in patients with CIC). Ischemic risk was defined as having any of the following nine ischemic heart disease risk factors: ischemic cardiac disease, elevated blood pressure, elevated cholesterol, type 2 diabetes mellitus, peripheral vascular disease (including aortic and femoral artery disease), cerebrovascular accident or carotid disease, age >65 years, body mass index >30, and estimated creatinine clearance <60mL/min (Cockcroft-Gault). The data on baseline risk factors was limited due to the absence of smoking history and family history in the database.

A focused review of potential MACE was then conducted, using the definitions and adjudication process described below.

The Applicant separated MACE into two categories, standard and extended MACE. Standard MACE was defined by the Applicant as cardiovascular mortality (including sudden cardiac death, death due to AMI, heart failure, stroke, and other cardiovascular causes), nonfatal MI, nonfatal stroke.

Extended MACE was defined as standard MACE plus unstable angina requiring hospitalization (including cases with urgent coronary revascularization).

The Applicant established a Cardiovascular Endpoint Committee (CEC) that included 2 cardiologists and 1 stroke neurologist to perform an adjudication for each potential MACE. The CEC physicians did not participate in the trials (i.e., act as investigators or serve on data safety monitoring committees) and had no clinical relationship with any of the trial participants. Although the CEC evaluated all completed phase 2 through 4 trials, including trials conducted in non-CIC patient populations and with other formulations, the analyses that follow focus on the events identified from the completed, phase 2 through 4, double-blind, placebo-controlled and open-label trials with prucalopride in patients with CIC (the proposed indication).

A pre-specified process was utilized to identify cases for adjudication.

- Deaths. All fatal outcomes were adjudicated.
- Serious treatment-emergent adverse events (serious TEAEs).
- Non-serious cardiovascular TEAEs.

The Applicant used a pre-specified standard medical query with the Standardized Medical Dictionary for Regulatory Activities (MedDRA), version 15, to create a listing of all cardiovascular TEAEs for review by the chair of the adjudication committee. The chair reviewed 1,916 events (703 patients) across all trials that included 881 events (532 patients) in trials that enrolled patients with CIC. Treatment assignments were not provided in this database. The data included demographic information, verbatim and preferred terms, system organ class, date of onset and duration of event, outcome, and laboratory and medical history information was provided if requested. Of the 1,916 potential MACE, the chair excluded 1,698 events from adjudication, including duplicates that resulted from an overlap between the two databases. The result was 218 potential MACE (173 patients) selected for adjudication. Of these, 170 potential MACE in 128 patients with CIC underwent a detailed adjudication by the committee.

The Applicant then distributed packages of the selected possible MACE for review by each of the CEC members, including the chair, to individually review and assess whether the event represented a MACE case, defined as cardiovascular death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization. They documented their decisions by completing and signing an Individual Adjudication Form for each event. The CEC chair reviewed all Individual Adjudication Forms to determine if the committee had unanimous agreement on the classification of the event. For those events that were not agreed upon by unanimous decision or majority consensus, the committee reviewed the cases together and decided the final classification by majority vote.

7.3.1.2. Summary of Results of MACE Analysis

Nineteen double-blind (5354 patients: 3366 prucalopride and 2019 placebo) and 9 open-label (2981 patients) trials were included in the MACE analysis. The number of patients in the open-label trials includes patients who were enrolled in those trials, as well as, patients who continued

into the open-label trial from the double-blind trials. In this analysis population, the majority of patients were female (3770 of 4476 [84.2%]) comprising 1206 of 1545 patients (78.1%) in the prucalopride 2 mg group, and 1609 of 2019 patients (79.7%) in the placebo group. The median age was 46 years overall with a median age of 47 years in the prucalopride 2 mg group and 46 years in the placebo group. Overall, there were 753 of 4476 (16.8%) >65 years of age treated with prucalopride, 280 of 1545 (18.1%) in prucalopride 2 mg, and 296 of 2019 (14.7%) in the placebo group. The median body mass index was approximately 24 kg/m^2 (range: 14, 124) across all prucalopride groups and placebo. Overall, 2513 of 4476 (56.1%) patients were from North America: 595 of 1545 (38.5%) in prucalopride 2 mg, and 961 of 2019 (47.6%) in placebo.

The baseline risk factors for ischemic heart disease, based on available data, were evaluated for the patient population included in the MACE analysis. The baseline risk factors were distributed evenly across prucalopride and placebo groups, and the distribution is shown below in Table 18.

Table 18. Baseline Risk Characteristics in CIC Patients (MACE analysis)

Parameter	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	
History of Ischemic Heart Disease[c], n (%)					
No	1902 (94.2)	3152 (93.6)	1444 (93.5)	1298 (94.8)	4218 (94.2)
Yes	117 (5.8)	214 (6.4)	101 (6.5)	71 (5.2)	258 (5.8)
Number of the 9 Risk Factors for Ischemic Heart Disease[d], n (%)					
0	1266 (62.7)	2005 (59.6)	932 (60.3)	829 (60.6)	2773 (62.0)
≥1	753 (37.3)	1361 (40.4)	613 (39.7)	540 (39.4)	1697 (39.2)
1	401 (19.9)	666 (19.8)	311 (20.1)	297 (21.7)	869 (19.4)
2	207 (10.3)	393 (11.7)	167 (10.8)	157 (11.5)	489 (10.9)
3	98 (4.9)	207 (6.1)	93 (6.0)	59 (4.3)	238 (5.3)
4	35 (1.7)	70 (2.1)	30 (1.9)	20 (1.5)	81 (1.9)
5	10 (0.5)	24 (0.7)	12 (0.8)	6 (0.4)	25 (0.6)
6	2 (0.1)	1 (0.0)	0	1 (0.1)	1 (0.0)
ECC (Cockcroft-Gault), n (%)					
≥60 mL/min	1589 (78.7)	2687 (79.8)	1371 (88.7)	989 (72.2)	3673 (84.8)
<60 mL/min	191 (9.5)	446 (13.3)	167 (10.8)	156 (11.4)	526 (12.1)
Missing	239 (11.8)	233 (6.9)	7 (0.5)	224 (16.4)	131 (3.0)

BMI=body mass index; DB=double-blind; ECC=estimated creatinine clearance; Max=maximum; Min=minimum; OL=open-label; PLA=placebo; PRU=prucalopride

[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] History of Ischemic Heart Disease includes, but is not limited to, myocardial infarction, angina, coronary artery disease, coronary stent, coronary occlusion, coronary blockade, coronary atherosclerosis.

[d] Nine risk factors for ischemic heart disease include: ischemic cardiac disease, elevated blood pressure, elevated cholesterol, type 2 diabetes mellitus, peripheral vascular disease (including aortic and femoral artery disease), cerebrovascular accident or carotid disease, age >65 years, BMI >30kg/m^2, or estimated creatinine clearance (Cockcroft-Gault) <60mL/min.

Source: Applicant submission, MACE report, Table 3, page 13

As shown in the table above, the majority of patients had no history of ischemic heart disease, and approximately 60% of patients had none of the nine identified CV risk factors.

Although not all CV risk factors were available in the medical history, the available risk factors and demographics of the patient population (majority of patients <65 years of age) suggest that the patient population was generally at lower risk for MACE.

The Applicant defined patients at increased risk of ischemic heart disease by combing the risk factors into the following groups for the MACE analysis:

- Group 1: patients with a history of ischemic heart disease
- Group 2: patients with a history of ischemic heart disease or with at least 2 other cardiovascular risk factors
- Group 3: patients >65 years of age
- Group 4: patients with a history of ischemic heart disease and/or chronic renal insufficiency (estimated creatinine clearance <60 mL/min), and/ or peripheral vascular disease

Approximately 40% of patients had at least 1 risk factor and were evenly distributed across the prucalopride and placebo groups. Approximately 6% of patients had a baseline risk factor for ischemic heart disease alone. Overall, 25% of patients fell into the high-risk categories combined, further suggesting that the patient population included in the MACE analysis was generally at lower risk for ischemic heart disease.

The baseline ischemic risk according to the Applicant's risk groups is shown below in Table 19.

Table 19. Baseline Ischemic Risk – High-Risk Analysis Group Overall—Studies in CIC Patients (MACE analysis)

		DB PRU			
Baseline characteristic	**DB Placebo N=2019**	**DB PRU All Doses[b] N=3366**	**DB PRU 2 mg N=1545**	**DB PRU 4 mg N=1369**	**All PRU[c] (DB and OL) N=4476**
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
Abbreviations: BMI, body mass index; CIC, chronic idiopathic constipation; CV, cardiovascular; DB, double-blind; ECC, estimated creatinine clearance; MACE, major adverse cardiovascular event; OL, open-label; PRU, prucalopride; PVD, peripheral vascular disease
Patients rolling over from DB to OL/crossover studies 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 studies included in the MACE analysis dataset.

A small number of MACE and non-MACE events were identified by the adjudication process. This small number may be explained by the lower baseline risk characteristics of the patient population included in the MACE analysis or other limitations of the available data or the duration of the trials (≤12 weeks). This dataset included a few more studies than in the Pool D and E noted above; however, the exposure was similar to those pools.

The table below (Table 20) shows a summary of adjudication information (Standard MACE and Extended MACE). Non-MACE events are also included.

Table 20. Summary of Adjudication Information- Double-Blind and Open-Label Trials in Patients with Chronic Idiopathic Constipation (MACE analysis)

	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 submission, MACE report, Table 6, page 20

Small numbers of MACE were identified in both the prucalopride and placebo groups; however, they warrant our review in our search for a rare potential CV signal. The number of patients with Standard and Extended MACE for the combined double-blind and open-label (DB and OL) prucalopride group (standard: 9 [0.2%], extended: 15 [0.3%]) are numerically higher compared to the data obtained from the double-blind trials (double-blind placebo, standard: 2 [0.1%], extended: 2 [0.1%] versus double-blind prucalopride (all doses), standard: 2 [0.1%], extended: 4 [0.1%]). This can be noted in the description of the standard MACE cases provided in the

appendix. Still the percentage of cases is small. The most useful comparison is within the double-blind placebo grouping because of the presence of a comparator arm. However, useful information may be obtained by reviewing cases in the open-label group as well when looking at the potential CV risk across CIC patients exposed to prucalopride. See Appendix (Table 31) for individual narratives subjects treated with prucalopride with Standard MACE.

As shown in the table above, non-MACE events were also evaluated. The non-ischemic arrhythmias were numerically greater (6 [0.4%]) in the prucalopride 2 mg group (the proposed dose) compared to placebo (1 [1.0%]); however, details were not provided on the specific types of arrhythmias included in that category. FDA obtained additional information from the Applicant regarding the specific types of non-ischemic arrhythmias, other CV events, and the events with insufficient information to adjudicate to help determine whether further evaluation was warranted. The details of these categories (non-ischemic arrhythmias, other CV events, and insufficient information to adjudicate) are shown in Table 21 below.

Table 21. Summary of Non-Ischemic Events, Other CV Events, and Cases With Insufficient Information to Adjudicate

Adjudication Class	DB PLA (N = 2019)		DB PRU (N = 3366)		DB PRU 2mg (N = 1545)		DB PRU 4mg (N = 1369)		ALL PRU (N = 4476)	
Preferred Term	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
Abbreviations: CV, cardiovascular; PRU, prucalopride

In general, the numbers of events are low, and there are no clear imbalances in any event that raises concern based on the available data from the adjudication process. Atrial fibrillation in the prucalopride 2 mg group is numerically greater than placebo; however, the events and percentage of the patient population are very low given that atrial fibrillation is a fairly common finding in the general population.

Arrhythmias, syncope, cerebrovascular conditions, other clinically relevant events that are not considered MACE that are listed in this table are addressed in the subsequent sections of this

document on QT Prolongation, Related Ventricular Arrhythmias, and Syncope; Cardiovascular and Cerebrovascular Ischemic Events; and Electrocardiogram Abnormalities.

Some events that were not listed in Table 21 under "Insufficient info to adjudicate" included paralysis, myocardial ischemia, myocardial infarction, deep vein thrombosis, and hemiparesis. These events occurred in one subject each and represent the 5 events that are not reflected in total events in the All Prucalopride Group. In general, the reasons that these 13 events were not adjudicated by the committee were related to insufficient information on the event or insufficient evidence upon which to make the diagnosis.

Although the number of MACE events was small, a summary of the cardiovascular risk factors among the patients determined to have MACE are listed below. Table 22 shows the baseline risk factor groups for patients with MACE.

Table 22. Baseline Ischemic Risk: High-risk Analysis Group for Subjects With Standard MACE—Trials in Patients With CIC (MACE analysis)

		DB PRU			
	DB PLA N=2	DB PRU All Doses[a] N=2	DB PRU 2 mg N=1	DB PRU 4 mg N=1	All PRU[b] (DB and OL) N=9
Group 1: Ischemic Heart Disease	1 (50.0)	1 (50.0)	0	1 (100.0)	3 (33.3)
Group 2: Ischemic Heart Disease and/or >1 CV Risk Factor	2 (100.0)	2 (100.0)	1 (100.0)	1 (100.0)	6 (66.7)
Group 3: Age >65 Years	2 (100.0)	2 (100.0)	1 (100.0)	1 (100.0)	6 (66.7)
Group 4: Ischemic Heart Disease and/or ECC <60mL/min and/or PVD	2 (100.0)	1 (50.0)	0	1 (100.0)	3 (33.3)
High-risk Groups 1 to 4 Combined	2 (100.0)	2 (100.0)	1 (100.0)	1 (100.0)	8 (88.9)

CV=cardiovascular; DB=double-blind; ECC=estimated creatinine clearance; OL=open-label; PLA=placebo; PRU=prucalopride; PVD=peripheral vascular disease

Source: Applicant submission, MACE report, Table 7, page 21

In the prucalopride 2 mg dose group, the patient with MACE had a history of ischemic heart disease and was >65 years of age. The available data on baseline risk factors suggests that all of the patients from the double-blind trials who had MACE also had baseline risk factors for ischemic heart disease. Of the nine patients with standard MACE that received prucalopride in the combined double-blind and open-labels trials, eight (88.9%) were in one or more of the high-risk groups. As previously noted, interpretation of open-label data is difficult in the absence of a comparator arm. These results suggest that baseline cardiovascular risk may have been a confounding factor in the patients who had a standard MACE on prucalopride.

In addition to the events of MACE and non-MACE reviewed by the adjudication committee, FDA considered other cardiovascular events of interest using the pooled safety data from phase 2 through 4 double-blind, placebo-controlled trials of at least 4 weeks duration in patients with CIC (Pool D). Adverse events of interest are related to the concerns with the drug class and pharmacovigilance plans that stem from the original authorization in the EU. For our review, a focused review of AEs of special interest included palpitations, QT prolongation, ventricular arrhythmias, syncope, electrocardiogram abnormalities, unadjudicated cardiovascular events, and psychiatric events.

In addition to the risk factors identified by the Applicant, the FDA considered the recommendations in the recent FDA draft guidance: *Assessment of Pressor Effects of Drugs* (May 2018). FDA acknowledges that the trials submitted in this NDA were designed and completed prior to the issuance of this draft guidance. As described in the guidance, there is evidence to demonstrate the relationship of increases in elevated blood pressure with increases in rates of stroke, heart attack, and death. Further, data show that elevated blood pressure leads to increases in cardiovascular events in populations of all levels of risk. The blood pressure parameters evaluated in the Pool D trials (phase 2 through 4, double-blind, placebo-controlled trials of ≥4 weeks in adults with CIC) did not reveal any meaningful increases in blood pressure when prucalopride 2 mg is compared to placebo. Despite this limitation, the shifts in blood pressure were generally small and comparable to those observed in the placebo group.

7.3.2. Palpitations

In Pool D (phase 2 through 4, double-blind, placebo-controlled trials in adults with CIC), 43 of 3305 patients (1.3%) reported palpitations in the overall prucalopride group (0.5 mg, 1 mg, 2 mg, 4 mg) and 14 of 1973 patients (0.7%) in placebo group. There was a higher percentage of patients reporting palpations in the 4 mg group (1.9%), which appears to drive the overall number. The other doses of prucalopride, including the 2 mg dose (proposed dose), had 0.9% of patients with palpitations. The onset of palpitations occurred primarily on the first 1 to 2 days of prucalopride administration, were most often associated with a constellation of symptoms associated with first exposure and including nausea, vomiting, abdominal pain and sometimes headache. These symptoms were generally transient in nature. The majority of the patients experiencing palpitations recovered while on treatment. Only one event of palpitations was reported as serious in the prucalopride 2 mg dose group. There were no deaths attributed to these adverse events.

The only serious case in the prucalopride 2 mg group involved a 44-year old female with a medical history of mitral valve prolapse and supraventricular tachycardia who intermittently used atenolol. The subject was hospitalized on day 3 of prucalopride treatment due to tachycardia supraventricular, heart valve disorders, hypokalemia (potassium 2.9 mEq), and palpitations and permanently discontinued the study medication. The investigator considered the TEAE of palpitations as very likely related to the study medication; however, the history of supraventricular tachycardia confounds the ability to definitively attribute the palpitations to

prucalopride. No other cases of palpitations in the prucalopride ≤2 mg group led to permanent discontinuation of the study medication.

There were 17 patients in the ≤2 mg prucalopride group that reported one or more palpitation event. Seven subjects in the prucalopride ≤2 mg group had a history of predisposing cardiovascular or pulmonary disease. Two of these subjects also took concomitant medication with known associated palpitations, tachycardia or arrhythmic events. An additional three subjects used concomitant medication with known associated to cardiovascular side effects and had no history of predisposing cardiovascular or pulmonary disease.

Additional, extensive information is obtained from a frail elderly cardiovascular study: Study PRU-USA-26 was a 4-week double-blind placebo-controlled study designed to evaluate the safety and tolerability of daily prucalopride oral solution (up to 2 mg) in three cohorts (89 subjects) of elderly subjects with constipation living in a nursing facility. Extensive Holter evaluations, ECG monitoring and assessment for arrhythmia, ischemia and other cardiac parameters were performed. The subjects had a mean age of 83 years and more than 80% had a history of cardiovascular disease. No episodes of palpitations were reported, and no increase in arrhythmogenicity was observed on ECGs and continuous Holter monitoring.

7.3.3. QT Prolongation, Related Ventricular Arrhythmias, and Syncope

Overall in Pool D, treatment-emergent events related to QT prolongation, related ventricular arrhythmias, and syncope were reported in 13 of 1349 patients (1.0%) in the prucalopride 4 mg group, 6 of 1516 (0.4%) in prucalopride 2 mg, 2 of 330 (0.6%) in prucalopride 1 mg, 1 of 110 (0.9%) in prucalopride 0.5 mg compared to 11 of 1973 (0.6%) in the placebo group. When prucalopride 2 mg (proposed dose) is compared to placebo, these events were reported more frequently in the placebo group. The table below (Table 23) shows the specific types of events.

Table 23. Individual TEAEs Related to QT Prolongation, Related Ventricular Arrhythmias, or Syncope—Phase 2 through 4 Double-blind Trials in Adult Patients with CIC (Pool D)

	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 TEAE	11 (0.6)	1 (0.9)	2 (0.6)	6 (0.4)	13 (1.0)	22 (0.7)
Cardiac disorders	1 (0.1)	1 (0.9)	1 (0.3)	1 (0.1)	1 (0.1)	4 (0.1)
Ventricular extrasystoles	1 (0.1)	0	0	1 (0.1)	1 (0.1)	2 (0.1)
Ventricular tachycardia	0	1 (0.9)	1 (0.3)	0	0	2 (0.1)
Investigations	3 (0.2)	0	0	3 (0.2)	5 (0.4)	8 (0.2)
Electrocardiogram QT prolonged	2 (0.1)	0	0	3 (0.2)	4 (0.3)	7 (0.2)
Electrocardiogram repolarization abnormality	1 (0.1)	0	0	0	1 (0.1)	1 (0.0)
Nervous system disorders	7 (0.4)	0	1 (0.3)	2 (0.1)	7 (0.5)	10 (0.3)
Syncope	5 (0.3)	0	1 (0.3)	1 (0.1)	6 (0.4)	8 (0.2)
Presyncope	2 (0.1)	0	0	1 (0.1)	1 (0.1)	2 (0.1)

ADR = adverse drug reaction; AE = adverse event; n = number of subjects with TEAE; PLA = placebo; PRU = prucalopride; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event
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.
Note 3: AEs were classified into SOC and PT using Version 19.1 of MedDRA.

Source: Applicant's submission, Integrated Summary of Safety, Table 52, page 193

Overall, the number of events and percentage of patients experiencing these events was small. The 4 mg dose is not being proposed for labeling. There does not appear to be a clear imbalance between the prucalopride 2 mg dose (proposed dose) and placebo. Although, three (0.2%) patients in the prucalopride 2 mg group compared to two (0.1%) patients in placebo reported QT prolongation on ECG, the number of events is small and as noted in the Clinical Pharmacology section above in this document, the QT study was found to be acceptable and supports excluding small mean increases (i.e., 10 ms) in the QTc interval for prucalopride. Note that there were no deaths associated with QT prolongations or ventricular arrhythmias, and no TEAEs of sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes.

There was one serious TEAE, ECG QT prolonged and decreased blood pressure after 119 days of prucalopride, a 59-year-old female subject treated with prucalopride 2 mg. The patient had a history of an asymptomatic prolonged QT interval, atrial hypertension, and hemorrhoids who was reported to have a premature ventricular contraction and QTcB/F duration of 470 ms and 461 ms, respectively, at screening. The study medication was temporarily discontinued due to these events. Both events were reported as mild in intensity. The event of ECG QT prolonged was assessed as possibly related to the study medication and the event of decreased blood pressure was assessed as unlikely related to the study medication. Both events were reported as resolved after 35 days. The patient's history of an asymptomatic prolonged QT interval confounds the ability to conclude that there is a causal relationship between the ECG findings of QT prolongation and treatment with prucalopride.

Two patients experienced ventricular tachycardia (one patient in the 0.5 mg prucalopride group and one in the 1 mg prucalopride group). One patient who permanently discontinued the study drug was a 93-year-old treated with prucalopride 0.5 mg who had an extensive history of

cardiovascular disease who was using concomitant medication with a known association to arrhythmias. The ventricular tachycardia occurred on day 1 of treatment and resolved the same day despite continued treatment for 2 weeks. The event was considered possibly related to the study medication by the investigator. The other patient with ventricular tachycardia was a 69-year-old male treated with prucalopride 1 mg. The event was deemed to be mild (non-sustained) on day 1 of treatment. His medical history includes an extensive cardiovascular history, including use of concomitant medication with an association to arrhythmias. The event did not lead to the discontinuation of the study medication and resolved in 1 day.

Extensive ECG assessments (cardiologists performed central reads of ECGs) and Holter monitoring was performed in a randomized, double-blind, dose-escalation trial frail, geriatric patients living in a nursing home (Study PRU-USA-26). The patients were treated with prucalopride 0.5 mg, 1 mg, or 2 mg or placebo for 4 weeks. An increase in median heart rate was observed 3 hours after dosing in both the placebo and the prucalopride groups. No relevant differences between treatment groups were noted for systolic and diastolic blood pressure. No QT-related adverse events or ventricular arrhythmias were reported, except for two cases of ventricular tachycardia in patients with an extensive history of cardiovascular disease and use of concomitant medications with known associations to arrhythmias.

As shown in Table 23 above, syncope was more frequent in the placebo group than in the prucalopride 2 mg group.

7.3.4. Electrocardiogram Abnormalities

FDA evaluated other ECG abnormalities, in addition to QT prolongation. A summary of the most common ECG-related TEAEs observed in more than 2 patients in the total prucalopride group reported in Pool D (all phase 2 or 3 double-blind, placebo-controlled studies of ≥4 weeks duration in adult patients with CIC) is provided in the table below (Table 24).

Table 24. Treatment-Emergent Adverse Reactions Related to Electrocardiogram Abnormalities Observed in More than Two Patients (Pool D)

	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
Heart rate increased	1 (<1)	1 (<1)	1 (<1)	3 (<1)	5 (<1)	10 (<1)
Tachycardia	1 (<1)	0	2 (<1)	1 (<1)	4 (<1)	7 (<1)
ECG QT prolonged	2 (<1)	0	0	3 (<1)	4 (<1)	7 (<1)
Atrial fibrillation	1 (<1)	0	0	3 (<1)	2 (<1)	5 (<1)
Bradycardia	4 (<1)	0	0	2 (<1)	3 (<1)	5 (<1)
ECG T wave abnormal	0	1 (<1)	0	2 (<1)	0	3 (<1)
Extrasystoles	0	0	1 (<1)	0	2 (<1)	3 (<1)
Heart rate irregular	0	0	0	2 (<1)	1 (<1)	3 (<1)
Supraventricular extrasystoles	1 (<1)	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with TEAE; PLA = placebo; PRU = prucalopride; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event
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
Note 3: AEs were classified into SOC and PT using Version 16.0 of MedDRA.
Note 4: TEAEs were ordered by decreasing frequency in the total PRU group.

Source: Applicant Integrated Summary of Safety, page 257
** Data from phase 2 to 4 double-blind studies in adults with chronic idiopathic constipation (Pool D)

The TEAEs related to various reported electrocardiogram abnormalities were comparable across the prucalopride doses, and all occurred in <1% of patients in the prucalopride and placebo groups.

The subjects that had clinically meaningful cardiac conditions have already been discussed save for those with atrial fibrillation. There were several subjects in the total prucalopride group that had a history of atrial fibrillation; however, according the subject narrative information, there were not cases of atrial fibrillation that were attributed to study drug.

The safety data from the controlled trials (12 weeks duration) did not reveal clear imbalances in cardiovascular events, including MACE. However, the CV safety risk may not have been adequately characterized as there are no controlled trial data of 12 months duration. In order to address this issue, the results from study SPD555-802, a post-marketing retrospective cohort (observational) study to measure the incidence of MACE in European patients with exposure to prucalopride (PRU) compared to that of polyethylene glycol 3350 (PEG) were submitted and are reviewed below.

7.4. Division of Epidemiology Review of Observational Study SPD555-802

To support the CV safety of prucalopride, Shire submitted results from SPD555-802, *A Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort*.

7.4.1. SPD555-802 Overview

SPD555-802 followed a protocol for a post-marketing retrospective cohort (observational) study to measure the incidence of Major Adverse Cardiovascular Events (MACE) in European patients with exposure to prucalopride (PRU) or polyethylene glycol 3350 (PEG). (In October 2009, the European Commission granted prucalopride (Resolor®) marketing authorization valid throughout the European Union). Designed to exclude a three-fold risk from prucalopride, the primary analysis pooled results from studies separately conducted in four European data sources. This primary analysis estimated MACE incidence in PRU versus PEG with a standardized incidence rate ratio (SIRR) of 0.64, 95% confidence interval (CI) 0.36 to 1.13. Subgroup analysis in ≥55-year-old men estimated risk from prucalopride at a SIRR 2.57, 95% CI 0.71 to 9.29. Declaring results otherwise consistent across pre-specified primary, secondary, subgroup, and sensitivity analyses, the investigators for SPD555-802 concluded by finding "no evidence of an increased risk of MACE in patients with chronic constipation using prucalopride as compared with PEG."

7.4.2. SPD555-802 Methods Summary

SPD555-802 initially planned to combine results generated with data from Germany and the United Kingdom. For reasons discussed below, the primary analysis for SPD555-802 replaced German data with data from Sweden.

SPD555-802 used a common protocol and a retrospective cohort design to measure MACE incidence in five data sources,

- Swedish National Registers (SNR)
- Clinical Practice Research Datalink (CPRD)
- The Health Improvement Network (THIN)
- Information Services Division (ISD) of Scotland
- German Pharmacoepidemiological Research Database (GePaRD)

Table 25 compares these five data sources.

Table 25. SPD555-802 Data Sources Compared

Data source feature	Data Source				
	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
Population-based	Yes	Yes	No	No	No
Data type[1]	Claims	Claims	GP EHR	GP EHR	Claims
Exposure	Prescriptions dispensed	Prescriptions dispensed	Prescriptions written	Prescriptions written	Prescriptions dispensed
Outpatient data used for baseline covariates	Yes	No	Yes	Yes	Yes
Lifestyle risk factors (i.e., smoking and BMI)	No	No	Yes	Yes	No
Data source linked to death certificates	Complete	Complete	Partial	None	None
MACE adjudication procedure	Not applicable	Medical chart review	Profile with questionnaire	Profile with EHR free text	Reason hospitalized

Abbreviations: SNR, Swedish National Registers; ISD, Information Services Division of Scotland; CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network; GePaRD, German Pharmacoepidemiological Research Database; BMI, body mass index; MACE, Major Adverse Cardiovascular Event; GP, general practitioner; EHR; electronic health record
[1] Claims, a reference to databases used to manage healthcare systems.

SPD555-802 defined two populations, separately identified by the first (index) PRU or PEG prescription written or dispensed during study periods specified differently in each data source (Table 25). SPD555-802 excluded from these populations,

- Patients with <12 months data available before an index date defined by the dispensing date for the index prescription

- Patients <18 years of age on the index date
- PEG patients with an index prescription supplying ≤4 days of treatment
- PRU patients, filling before the study period (Table 25), a prucalopride prescription
- PEG patients filling, before the study period (Table 25), a PEG prescription supplying >4 days of treatment
- PRU or PEG patients filling, within 12 months + 10 days before the index date, a PEG prescription supplying ≤4 days of treatment
- Patients filling, on a PRU index date, a prescription for PEG
- Patients filling, on a PEG index date, a prescription for prucalopride
- PRU patients with prucalopride-exposed time completely covered by treatment with PEG
- PEG patients with PEG-exposed time completely covered by treatment with prucalopride

For the primary analysis, SPD555-802 defined prucalopride exposure by treatment time (in days) covered uniquely by prucalopride prescriptions (written or dispensed, depending on data source; Table 25), with 7-day gaps allowed between a sequence of prescriptions, 7-day extension added to the last prescription in a sequence, and follow-up terminated on first switch to PEG, as indicated by first post-PRU-index PEG prescription supplying >4 days of treatment.

Likewise, SPD555-802 defined PEG exposure by treatment time (in days) covered uniquely by PEG prescriptions (written or dispensed, depending on data source; Table 25) that supplied >4 days of treatment, with 7-day gaps allowed between a sequence of prescriptions, 7-day extension added to the last prescription in a sequence, and follow-up terminated on first switch to prucalopride, as indicated by first post-PEG-index prucalopride prescription.

Patient exposure ended on death, second switch, prescription filled for PRU and PEG on the same date or end of study period. Event-specific analysis terminated all follow-up upon first event.

SPD555-802 specified one primary outcome, MACE, conceived as a composite of non-fatal acute myocardial infarction (AMI), non-fatal stroke, and in-hospital cardiovascular death. Depending on electronic data source, SPD555-802 used diagnosis codes in electronic health records, diagnosis codes on hospital discharge summaries, or cause-of-death codes on death certificates to ascertain events. The five data sources validated these events as MACE with variable rigor (Table 25). One data source (SNR) relied on codes only. On August 31, 2018, the Applicant informed FDA about a recently discovered programming error in the SNR case

identification algorithm. Additional information on the nature of the programing error is currently pending. Any relevant updates will be provided at the AC. One data source (ISD) adjudicated information rigorously abstracted from patient charts. Three data sources (CPRD, THIN, and GePaRD) adjudicated lower quality clinical information. Adjudication procedures permitted distinction between definite and probable MACE.

Data analysis entailed five steps.

Step 1. Use sex, calendar year of index date, and year of birth to find five PEG matches for every PRU patient. (SNR additionally matched on recent hospitalization and provider specialty.)

Step 2. Use logistic regression and other variables available for analysis to calculate, for every patient from Step 1, a propensity score.

Step 3. Trim Step 1 cohorts by excluding patients with extreme propensity scores.

Step 4. Calculate MACE incidence (Incidence Rate, IR) as the number of events per 1000 patient-years, with 95% CI estimated per Dobson, et al. (Dobson et al. 1991)

Step 5. For controlled comparison,

- Separately in PRU and PEG (after trimming), calculate MACE IR in each of ten strata defined by trimmed propensity-score decile cut-points in PRU.

- Calculate a Standardized Incidence Rate (SIR), separately in PRU and PEG, by averaging the stratum-specific IRs, weighted by patient-years in PRU.

- Calculate a Standardized Incidence Rate Ratio (SIRR) as the ratio between the SIRs for PRU and PEG, with 95% CI estimated per equation 15-11 in Rothman, et al. (Rothman et al. 2008).

7.4.3. SPD555-802 Results Summary

The number of patients available in the five data sources varied over a 10-fold range (Table 26).

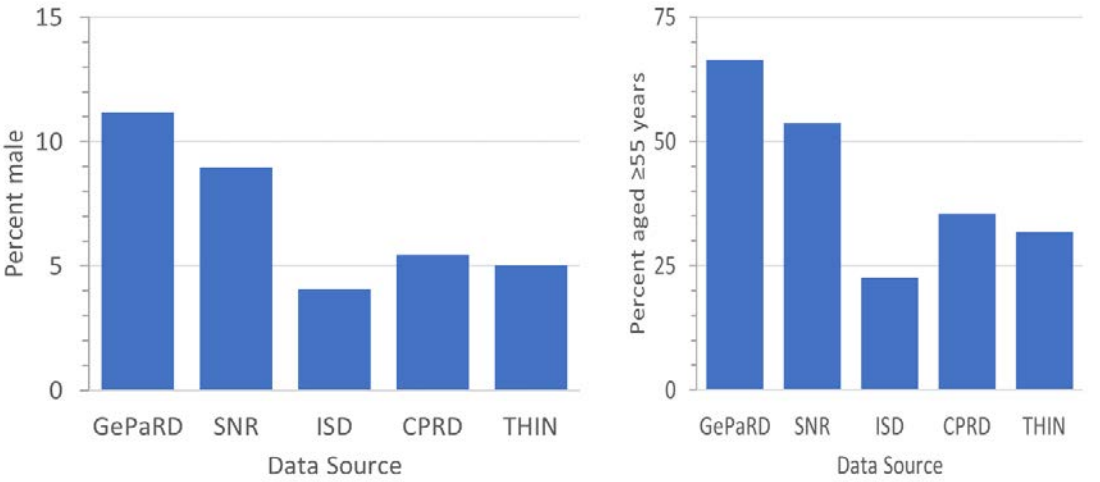
Table 26. Number of Patients in Matched Prucalopride and Polyethylene Glycol 3350 Cohorts, Before and After Trimming, by Data Source

Data Source	Before trimming		After trimming		% Trimmed	
	PRU	PEG	PRU	PEG	PRU	PEG
GePaRD	5,636	28,017	5,326	25,388	5.5	9.4
SNR	3,656	18,280	3,194	16,769	12.6	8.3
ISD	1,249	6,245	1,154	5,806	7.6	7.0
CPRD	952	4,758	866	4,254	9.0	10.6
THIN	537	2,685	501	2,543	6.7	5.3

Source: Final Study Report, Table 6, page 66.
Abbreviations: GePaRD, German Pharmacoepidemiological Research Database; SNR, Swedish National Registers; ISD, Information Services Division of Scotland; CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network

As shown in Figure 4, men and older patients (≥55-years) comprised a greater fraction of the prucalopride-exposed populations in Germany and Sweden (GePaRD and SNR) than the United Kingdom (ISD, CPRD, and THIN).

Figure 4. Percent Male and Percent Aged ≥55 Years in Matched Prucalopride Cohorts, Before Trimming, by Data Source



Source: Plots constructed from Table 13 in Supplemental Full Results File.
Abbreviations: GePaRD, German Pharmacoepidemiological Research Database; SNR, Swedish National Registers; ISD, Information Services Division of Scotland; CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network

Table 27 shows worrisome baseline differences in GePaRD between PEG and PRU. Despite matching on age, a prescription for PEG identified a study population distinctly characterized by history of cancer, recent opioid prescription, and recent hospitalization, confounding factors plausibly associated with MACE.

At the pre-NDA meeting with FDA, the Applicant proposed to exclude GePaRD from primary analysis. The Applicant learned that Germany restricted prescription coverage for laxatives, such as prucalopride. Classifying PEG as a medical device, Germany regulated PEG even more strictly. Because of these policies, SPD555-802 investigators concluded that a prescription in GePaRD selected a distinctly sicker and older study population, especially for PEG. This disparate clinical profile precluded combining the study population of GePaRD with those of the United Kingdom and Sweden. FDA agreed to the Applicant's proposal to exclude GePaRD from primary analysis.

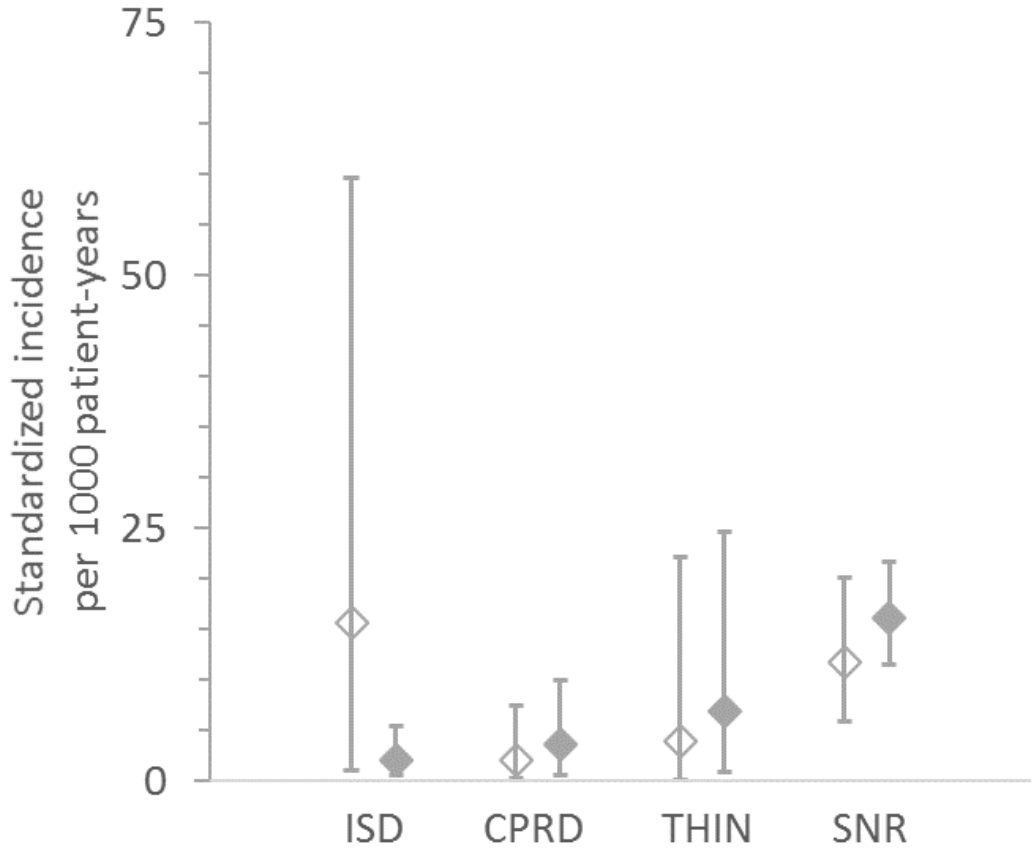
Table 27. Frequency of Three Selected Baseline Attributes in Matched PRU and PEG Cohorts[1]

Baseline attribute	PRU (%)	PEG (%)	Diff. (%)	Std. Diff.[2]
Recent opioid[3]				
GePaRD	20.8	44.0	-23.2	0.51
SNR	25.3	31.3	-5.9	0.13
ISD	39.9	41.9	-2.0	0.04
CPRD	31.6	30.2	1.4	0.03
THIN	37.1	33.3	3.9	0.08
Recent hospitalization[4]				
GePaRD	5.9	15.9	-10.1	0.33
SNR	2.7	2.5	0.2	0.01
ISD	8.1	8.5	-0.3	0.01
CPRD	5.2	6.3	-1.1	0.05
THIN	4.6	7.5	-2.9	0.12
History of cancer				
GePaRD	27.3	40.9	-13.6	0.29
SNR	9.1	10.5	-1.4	0.05
ISD	4.6	4.7	-0.1	0.00
CPRD	7.6	9.1	-1.5	0.05
THIN	5.8	7.0	-1.2	0.05

Source: Table assembled from Table 13 in Supplemental Full Results File.
Abbreviations: CPRD, Clinical Practice Research Datalink; Diff., differences; GePaRD, German Pharmacoepidemiological Research Database; ISD, Information Services Division of Scotland; PEG, polyethylene glycol 3350; PRU, prucalopride; SNR, Swedish National Registers; Std. Diff., standardized differences; THIN, The Health Improvement Network
[1].Data after trimming of cohorts, shown by data source with differences and standardized differences between PRU and PEG.
[2] Standardized difference calculated using an equation on page 412 in Austin PC (Austin 2011).
[3] Any opioid prescription within 6 months before index date.
[4] Hospitalization within 14 days before index date.

Descriptive comparisons suggested higher baseline MACE incidence in Swedish than U.K. data sources, even after adjustments for sex and age (Figure 5).

Figure 5. MACE Incidence (Per 1000 Patient-Years) in Matched and Trimmed Cohorts*



Source: Table 10a in Supplemental Full Results File.
Abbreviations: ISD, Information Services Division of Scotland; CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network; SNR, Swedish National Registers
*Prucalopride group shown with solid diamond symbol and polyethylene glycol 3350 group shown with open diamond symbol. Data are sex-, age-, and calendar-time-standardized against patient-years summed across both cohorts and all four data sources.

Table 28 summarizes results from the primary analysis, three secondary analyses, and one selected subgroup analysis. Pooling results from SNR, ISD, CPRD, and THIN, SPD555-802 reported results from the primary analysis for MACE (nonfatal AMI, nonfatal stroke, or in-hospital cardiovascular death) in PRU versus PEG as SIRR 0.64, 95% CI 0.36 to 1.13.

Table 28. Results Integrating Four Data Sources

Result	Events, N PRU	Events, N PEG	SIRR	95% CI
MACE				
U.K. and SNR (Primary)	18	74	0.64	0.36-1.13
United Kingdom (U.K.[1)]	4	9	0.68	0.19-2.38
Sweden (SNR)	14	65	0.63	0.33-1.19
Secondary Analyses				
nonfatal AMI	8	22	1.06	0.44-2.57
nonfatal stroke	9	39	0.58	0.25-1.31
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	54	0.70	0.36-1.36
18-54 year-old men	0	1		
≥55 year-old men	4	11	2.57	0.71-9.27

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).

Pooling results from Swedish and U.K. data sources, one sensitivity analysis evaluated the effect of adding out-of-hospital cardiovascular death to the outcome definition. With 18 PRU and 120 PEG events, this sensitivity analysis estimated MACE risk (including out-of-hospital cardiovascular death) in PRU versus PEG at SIRR 0.43, 95% CI 0.25 to 0.73.

Two additional sensitivity analyses pooled results from U.K. data sources only.

- The first sensitivity analysis evaluated the effect of adding probable AMI or stroke to the outcome definition. With 6 PRU and 15 PEG events, this sensitivity analysis estimated MACE risk (including probable AMI or stroke) in PRU versus PEG at SIRR 0.75, 95% CI 0.27 to 2.05.

- The second sensitivity analysis evaluated the effect of considering past use as time at risk. With 6 PRU and 75 PEG events, this sensitivity analysis estimated risk for MACE during current or past use in PRU versus PEG at SIRR 0.51, 95% CI 0.22 to 1.20.

7.4.4. FDA Synthesis

FDA's assessment of SPD555-802 reached two main conclusions.

- SPD555-802 satisfies a pre-NDA expectation for a European post-marketing observational study that reasonably excluded, with 95% statistical confidence, three-fold MACE risk from prucalopride.

- SPD555-802 does not definitively exclude possibly unacceptable MACE risk from prucalopride.

Primarily because of a concern about serious risk of bias due to confounding, FDA placed low confidence in the quantitative result, i.e., SIRR 0.64, from the SPD555-802 primary analysis. Interpreting this quantitative result as causally valid, a patient starting treatment might expect to suffer a 36% lower incidence of a subsequent major cardiovascular event, if started on prucalopride instead of PEG. However, the serious risk of bias due to confounding demanded more cautious interpretation.

Findings determining FDA's assessment of serious risk of bias due to confounding included,

- Generalized potential for channeling profoundly different patients to treatment with prucalopride or PEG, as demonstrated overtly in Germany.

- Patient-years in PRU and PEG distributed differently on age and other baseline factors, despite stratification by propensity-score decile. Though procedures tightly matched patients on age, patient-years distributed differently on age because of age-related differences between PRU and PEG with respect to treatment durations.

In summary, FDA accepted the findings from SPD555-802 as evidence that reasonably excludes a greater than three-fold MACE risk from prucalopride use. Because of the serious potential for bias due to confounding, FDA could not use SPD555-802 to reliably bound MACE risk at levels lower than three-fold.

7.5. Clinical Safety: Psychiatric Events

Given the concern for potential psychiatric risks with the 5-HT_4 receptor agonist class, including suicide, an analysis of such events was conducted. Following the receipt of three post-marketing spontaneous reports of suicidal ideation, the Applicant conducted a cumulative review and analysis of all worldwide safety data relating to anxiety, depression and suicide/self-injury in patients treated with prucalopride through September 14, 2012. Two additional safety evaluations were completed by the Applicant relating to other psychiatric disorders, suicide related events (SRE), and psychiatric reactions. At that time, it was concluded that the Applicant planned to continue routine pharmacovigilance. No changes to the Applicant's reference safety information were recommended based on any of the post-marketing safety evaluations by the Applicant. The table below summarizes the Applicant's triggers and findings.

Table 29. Summary of Applicant Inquiries into Psychiatric Symptoms/ Suicides and Prucalopride

Topic	Trigger	Conclusion
Suicide-related events (SRE)	A draft publication from the Uppsala (safety) Monitoring Centre regarding SRE and prucalopride	There is insufficient evidence of an association of SRE with prucalopride therapy. There was no change in risk profile for prucalopride. Routine pharmacovigilance will be used to monitor any further cases reporting SRE.
Psychiatric reactions	Request from MHRA following submission of PSUR 009 (15 Oct 2014 to 14 Oct 2015). The MHRA noted a potential signal raised by the WHO (April 2015) in relation to prucalopride and suicidal ideation and requested a cumulative review of psychiatric reactions.	There is insufficient evidence of an association of psychiatric reactions with prucalopride therapy. There was no change in the benefit-risk profile for prucalopride. Routine pharmacovigilance will be used to monitor any further cases reporting psychiatric reactions. No change in the labelling for prucalopride is required at this time.
Anxiety, depression, and suicide/self-injury	Receipt of 3 spontaneous reports of suicidal ideation	There was no evidence to indicate that prucalopride is associated with anxiety, depression or suicide/self-injury. This safety topic will be subject to routine pharmacovigilance procedures, and will be discussed again only if further reports require re-evaluation of the topic.

Source: Adapted from Applicant's submission, Integrated Summary of Safety, Table 93, pages 277-278

Overall, the numbers of patients in the total safety database (4476 subjects receiving prucalopride in the double-blind and open label studies as described in the MACE analysis) who experienced any type of psychiatric symptom were low. Overall, the most common psychiatric events reported across the entire safety database were insomnia, depression, and anxiety (each approximately <3% in the prucalopride treatment groups). The other reported psychiatric events were less than one percent. In the double-blind study pool (Pool D), percentages were comparable between placebo and prucalopride 2 mg patients (approximately 1% or less).

There were two completed suicides (discussed previously in the Deaths Section) from the safety database and four cases of the suicide attempts. None of these events were directly attributable to the study drug.

There was one patient with a reported suicide attempt from the double-blind studies. The subject was a 29-year-old female enrolled in Study INT-6 and treated with prucalopride 2 mg. The patient had a history of depression and was admitted to the hospital with an anxiety crisis 42 days after initiation of prucalopride ((b) (6)). The patient recovered from this event, and it was considered not drug related. On (b) (6), 7 days after the end of treatment, the patient attempted suicide by ingesting cocaine and rivotril (clonazepam intoxication). This event was also not considered to be drug related. The patient's medical history of depression and illicit drug use confound the ability to conclude that the event was related to prucalopride. Additionally, the event occurred 7 days after the end of prucalopride treatment (half-life is about 24 hours).

There were three other cases of suicide attempt that occurred in the open label studies. In each case, the subject had completed a double-blind study prior to entering an open label study.

- The patient was a 38-year-old female with no documented past medical history who was hospitalized due to a suicide attempt due to "personal problems". Trial medication was initiated on February 28, 1996. Treatment was discontinued on November 23, 1996. The subject prematurely discontinued the trial on December 5, 1996. The only other documented medication taken by this subject prior to the event was Bisacodyl. At follow-up on (b) (6), this subject had repeated suicide attempts and was still hospitalized. This event was deemed as severe and not related to the study drug by the Investigator.

- The patient was a 37-year-old male who was hospitalized for a suicide attempt after 142 days of treatment (total treatment duration 579 days with 455 days off treatment). Other relevant reported adverse events for this subject included anxiety, multiple pain diagnoses including back pain, skeletal pain. Relevant concomitant medications included nefazodone hydrochloride, Vicodin, pentazocine, hydrocodone compound, fluoxetine, benztropine, oxazepam, zolpidem tartrate, amfebutamone hydrochloride, risperidone, and valproate semisodium. The subject did recover, and the event was deemed severe and not drug related by the Investigator.

- The patient was a 24-year-old male who was hospitalized for psychosis (psychotic episode) and a suicide attempt (homicidal thoughts) after 452 days of treatment (total treatment duration was 548 days including 11 days off treatment). Other relevant reported adverse events for this subject included insomnia, hallucination, and depression. Relevant concomitant medications included nefazodone hydrochloride, risperidone, and venlafaxine hydrochloride. The subject did recover, and these events were considered severe and doubtfully related to the study medication by the Investigator.

One additional event of interest, serotonin syndrome, occurred in a patient who was treated with prucalopride 2 mg. The patient had a history of depression and concomitant medications use with obetrol, sertraline hydrochloride, sibutramine hydrochloride, and developed severe abdominal pain, moderate flushing, and serotonin syndrome, all believed to be probably due to the trial medication. These symptoms resolved after drug discontinuation. The concomitant medication use, including sertraline hydrochloride, confound the ability to definitively attribute this event to prucalopride.

8. APPENDIX

8.1. Study Overview and Patient Narratives

Table 30. Overview of Studies and Sample Size for Pool E: Phase 2 through 3 Open Label Studies

	PRU **N = 2759**
	n (%)
All Studies	2759
PRU-BEL-08	44 (1.6)
PRU-FRA-1B	34 (1.2)
PRU-INT-3	142 (5.1)
PRU-INT-4	72 (2.6)
PRU-INT-10	693 (25.1)
PRU-NED-4	17 (<1)

	PRU **N = 2759**
PRU-USA-22	1757 (63.7)

PRU = prucalopride

Note: Percentages were based on all subjects in the safety set for Phase 2-3 open-label studies

Source: Applicant's Submission, Integrated Summary of Safety, pages 108-109
Abbreviations: PRU, prucalopride

Table 31. Narratives of CIC Patients Treated with Prucalopride with Standard MACE

#	Event	Narrative
1	Nonfatal Stroke	77-year-old male subject with a medical history of hypertension started treatment with prucalopride 2 mg daily in a study investigating the efficacy of prucalopride in subjects with chronic idiopathic constipation on (b) (6). On (b) (6), the dose of study medication/placebo was increased to 2 mg once daily in accordance with the protocol. On (b) (6) (22 days of treatment), the subject went to the emergency department due to inability to get out of bed at night in an attempt to use the restroom related to decreased strength in his left arm and leg. During the physical examination, the subject showed marked dysarthria and slowed speech, generalized muscle stiffness (predominantly of the left side), latent to mild left hemiparesis (predominantly in the lower extremity), and slowed performance on coordination tests, paresis and ataxia on the left side. A brain computed tomography scan performed the same day revealed circumscribed hypodense lesions visible in the region of both basal ganglions and a hypodense area of 20mm in the border zone on the right side. The subject was diagnosed with a stroke and admitted to the hospital. Cerebrovascular accident was reported as TEAE. No action was taken toward the study medication/placebo. Additional examinations were performed on (b) (6): a duplex ultrasound of the cervical arteries revealed atherosclerotic lesions in the carotid arteries with normal vertebral arteries and an ECG examination showed a normal sinus rhythm and right bundle branch block. The impression was infarction in the right posterior border zone, and multiple lacunar infarctions. Treatment with acetylsalicylic acid, perindopril erbumine, benserazide, levodopa, amlodipine, and vinpocetine was started. In addition, physical therapy was started. Ropinirole was added to the medications upon discharge. Cerebrovascular accident was considered moderate in intensity and unlikely to be related to the study medication/placebo by the investigator. The subject's condition improved, and he was discharged from the hospital on (b) (6). The event was considered resolved with sequelae, i.e., on discharge, the subject still had not regained full functionality of his left extremities (i.e., movement remained "clumsy") but was able to walk without aids and had no paresis or speech impairments. The adjudication committee classified this event as: nonfatal stroke.
2	Cardiovascular Death	81-year-old Caucasian male, with a history of ischemic heart disease and TIA (1998), started prucalopride (unknown dose) in an open-label study on (b) (6). Note that this subject rolled over from a 4-week double-blind study, where he was randomized to placebo. Total duration of treatment 272 days. On (b) (6), the subject discontinued intake of the study medication. On (b) (6), the subject died due to myocardial infarction (MI) (67 days after discontinuing prucalopride). The subject was not hospitalized prior to his death. No other TEAEs were reported for this subject during the open-label study. No additional information is available. The investigator considered the MI as not related to the study medication. He considered the event to be related to the subject's prior ischemic heart disease. The adjudication committee classified this event as: cardiovascular death.

#	Event	Narrative
3	Nonfatal Stroke	70-year-old Caucasian female started prucalopride at a dose of 2 mg twice daily in an open-label study on (b) (6) Note that this subject rolled over from a 12-week double-blind study, where she was randomized to prucalopride. Total duration of treatment 190 days. During the study, the subject had the AEs of hypertension and blood cholesterol increased reported after 61 days of treatment. Her screening cholesterol and triglycerides levels were elevated at 286 (0-220) and 212 (50-190), respectively, and her blood pressure was 140/90 mm Hg. The subject was treated with pravastatin and propranolol. Her blood pressure at the month 3 (day 100) visit was 168/92 mm Hg and at the month 6 (day 183) visit was 162/90 mm Hg. After 190 days of treatment with prucalopride, cerebrovascular accident (verbatim: small stroke shown on a computed tomography image) was reported as a TEAE. This event was considered moderate in intensity. No concomitant treatment was administered for the TEAE and no action was taken towards the study medication. The TEAE was considered resolved the same day. No further details are available. The investigator considered the TEAE not related to the study medication. The adjudication committee classified this event as: nonfatal stroke.
4	Nonfatal MI	71-year-old Caucasian female started prucalopride (unknown dose) treatment in an open label study on (b) (6) (per clinical study report). Note that this subject rolled over from a 12-week double-blind study, where she was randomized to placebo. In December 1998, the subject was diagnosed with a torn rotator cuff. On (b) (6) (112 days of treatment), the subject was hospitalized and had the cuff repaired. The intake of study medication was temporarily interrupted. While in the hospital, the subject started experiencing chest pain. She also experienced shortness of breath, palpitations, and diaphoresis. An ECG was performed and revealed anterior T-wave inversions. The subject was diagnosed with a MI. Troponin and myoglobin levels were elevated. The subject was started on intravenous heparin and topical nitrates. This event was reported as a serious TEAE, considered severe in intensity. On (b) (6), the subject underwent a diagnostic cardiac catheterization that showed the circumflex coronary artery was 85% stenosed. The subject was treated with heparin sodium and on (b) (6), a stent was inserted. The subject recovered with sequelae. The investigator considered MI as unrelated to the study medication. The adjudication committee classified this event as: nonfatal MI.
5	Nonfatal MI	70-year-old Caucasian female with a history of hypertension and angina was randomized to prucalopride 4 mg in a 12-week double-blind study in subjects with chronic idiopathic constipation and started treatment on 10 Nov 1998. On 05 Feb 1999, after 12 weeks of treatment, the subject completed the study. Baseline ECG and Visit 4 ECG were reported as within normal limits. ECG performed at the final visit showed a (recent) subacute infarction. The TEAE of MI was considered moderate in intensity. No concomitant medication was administered, and the event was considered resolved 18 days after their onset. The investigator considered MI to be not related to the study medication. The adjudication committee classified this event as: nonfatal MI.

#	Event	Narrative
6	Nonfatal Stroke	64-year-old Caucasian male, with a history of hypercholesterolemia, also being treated with flecainide and atenolol for unreported conditions, started prucalopride at a dose of 2 mg in an open-label study on (b) (6). Note that this subject rolled over from a 4-week double-blind study, where he was randomized to prucalopride. In 1998 (per case report form), 860 days after the first intake of study medication, the subject was hospitalized with retinal artery thrombosis, resulting in 80% blindness. This TEAE was considered severe in intensity. He was treated with acetylsalicylic acid and dipyridamole. The TEAE was still ongoing at the end of the study. The event was not yet resolved at the end of the study. The investigator considered retinal artery thrombosis to be unrelated to the study medication. The adjudication committee classified this event as: nonfatal stroke.
7	Nonfatal Stroke	78-year-old female started treatment with prucalopride in this open-label study on (b) (6). Note that this subject rolled over from a 12-week double-blind study, where she was randomized to prucalopride. The subject had a BMI of 34.7kg/m² at screening and was being treated with conjugated estrogens which had been initiated prior to study entry. On (b) (6), 21 days after the first intake of prucalopride in this open-label study, the subject experienced a right-sided stroke and was hospitalized. Cerebrovascular accident was reported as a serious TEAE, considered moderate in intensity. After the event, the subject had vision problems (diplopia) and was treated in a rehabilitation center. No action was taken towards the study medication, and the event was considered resolved 33 days after onset. The investigator considered cerebrovascular accident as unrelated to the study medication. The adjudication committee classified this event as: nonfatal stroke.

#	Event	Narrative
8	Nonfatal Stroke	61-year-old Caucasian male, with a history of bypass surgery for coronary artery disease, atrial fibrillation (inactive at study entry) and hypertension started treatment with prucalopride in an open-label study on (b) (6). Note that this subject rolled over from a 4-week plus 4-week retreatment double-blind study, where he was randomized to placebo. On (b) (6), 76 days after the first intake of prucalopride in the open-label study, the subject experienced a headache and loss of peripheral vision in his right eye along with severe pain and diaphoresis. An ECG taken that day showed atrial fibrillation with a rapid ventricular response of 144 beats per minute. A computed tomography scan revealed a 1.3 cm decreased density in the right parieto-occipital area which appears to represent an ischemic infarction and slight diffuse decreased density in the left occipital lobe, which may represent an early infarction. There was no evidence of hemorrhage or mass effect. The magnetic resonance angiography results revealed 70% occlusion of the right internal carotid and 70 to 75% occlusion of the left internal carotid. A magnetic resonance image showed an acute left posterior cerebral distribution stroke with regional edema and mass effect. ECG on (b) (6) revealed sinus rhythm and a ventricular rate of 90 beats per minute. The subject was treated with anticoagulation medication (enoxaparin sodium) and digoxin; atorvastatin and diltiazem were also initiated. The investigator considered cerebrovascular accident, atrial fibrillation, ECG change, carotid artery stenosis, visual field defect, and hyperhidrosis to be doubtfully related to the study medication. Chest pain was considered unrelated. The adjudication committee classified this event as: nonfatal stroke.
9	Cardiovascular Death	56-year-old Caucasian male, with a history of cardiomyopathy, atrial fibrillation, cerebrovascular accident, hypertension, and hypercholesterolemia, started treatment with prucalopride in an open-label study on (b) (6). Note that this subject rolled over from a 4-week double-blind study, where he was randomized to prucalopride. On (b) (6), the subject was hospitalized with a MI. The subject died due to the MI (day 48 of the open-label study; 75 days total treatment). The investigator considered the MI as unrelated to the study medication. The adjudication committee classified this event as: cardiovascular death.

Source: Applicant's submission, MACE Report, Appendix 5, pages 480-505, and adapted based on Applicant's response to an Information Request, dated September 11, 2018, and individual clinical study reports and case report forms.
Abbreviations: AE, adverse event; BMI, body mass index; ECG, electrocardiogram; MI, myocardial infarction; QD, daily; TEAE, treatment-emergent adverse event

8.2. Statistical Appendix

Calculation of the Weekly Frequencies (BM, SBM, CBM, SCBM) and Strategies for Missing Data Handling

Calculations of Weekly Frequencies:
For all periods, weekly frequency is calculated for events (BM, SBM, CBM, and SCBM) as follows: (# of events in interval)*7 / (# of evaluable days in interval).

Evaluable day: Each e-diary entry with at least a date recorded in the Treatment Period will be considered an evaluable day and will be used in the calculation of weekly averages.

Baseline weekly frequencies were calculated only if data were available for 7 or more days, otherwise the weekly frequency was set to 'missing' and no changes from baseline was calculated.

For each of the 12 consecutive 7-day periods, weekly frequencies were calculated if data were available for 4 or more days in the 7-day period. If data were available for only 3 days or less, the weekly frequency was set to 'missing'.

For the 4-week and 12-week period analyses, weekly frequencies were calculated if data were available for 14 or more days in the 4-week or 12-week periods. If data were available for only 13 days or less, the weekly frequency was set to 'missing' for that period.

Strategies for Missing Data Handling

Several sensitivity analyses, including generalized linear mixed model for repeated measures, generalized estimating equation model, logistic regression with multiple imputation, worst case imputation, non-responder imputation, were conducted to assess the impact of the missing data. LOCF imputed data was used for primary efficacy analyses.

Table 32. Summary of Demographics for Study 302 in mITT Population

	PLA N=181	PRU ≤2 mg N=177	Total N=358
Age, years			
Mean (SD)	58.6 (16.46)	58.8 (17.44)	58.7 (16.93)
Median (min, max)	62.0 (20; 89)	62.0 (18; 91)	62.0 (18; 91)
Age category, n (%)			
<65 years	110 (60.8)	98 (55.4)	208 (58.1)
65-<75 years	39 (21.5)	43 (24.3)	82 (22.9)
75 years	32 (17.7)	36 (20.3)	68 (19.0)
Sex, n (%)			
Male	181 (100.0)	177 (100.0)	358 (100.0)
BMI, kg/m²			
Mean (SD)	26.9 (3.87)	26.9 (4.13)	26.9 (4.00)
Race, n (%)			
White	174 (96.1)	172 (97.2)	346 (96.6)
Asian	1 (0.6)	0	1 (0.3)
Black	3 (1.7)	5 (2.8)	8 (2.2)
Other	3 (1.7)	0	3 (0.8)

Source: Applicant's Table 11 on Page 70 of integrated-summary-of-efficacy.pdf, verified by the reviewer
Abbreviations: BMI, body mass index; mITT, modified intent-to-treat; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with characteristic; PLA, placebo; PRU, prucalopride; SD, standard deviation
In Study SPD555-302, for subjects at sites in Germany, the code 01-01-yyyy was used for completion of the date of birth, except for subjects aged 64 at randomization and turning age 65 later that year then the code 31-12-yyyy was used.

Table 33. Summary of Demographics for Study 3001 in ITT Population

	PLA N=252	PRU 2 mg N=249	Total N=501
Age, years			
Mean (SD)	41.8 (12.88)	41.4 (12.92)	41.6 (12.89)
Median (min, max)	43.0 (18; 65)	43.0 (18; 65)	43.0 (18; 65)
Age category*, n(%)			
<65 years	252 (100.0)	249 (100.0)	501 (100.0)
Sex, n(%)			
Female	223 (88.5)	227 (91.2)	450 (89.8)
Male	29 (11.5)	22 (8.8)	51 (10.2)
BMI, kg/m²			
Mean (SD)	22.3 (3.13)	22.6 (3.44)	22.5 (3.29)
Race, n (%)			
White	19 (7.5)	12 (4.8)	31 (6.2)
Asian	231 (91.7)	232 (93.2)	463 (92.4)
Black	0	0	0
Other	2 (0.8)	5 (2.0)	7 (1.4)

Source: Applicant's Table 11 on Page 70 of integrated-summary-of-efficacy.pdf, verified by the reviewer
Abbreviations: BMI, body mass index; ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with characteristic; PLA, placebo; PRU, prucalopride; SD, standard deviation

Table 34. Summary of Demographics for Studies INT-6, USA 11 and 13 in ITT Population

	PRU-INT-6		PRU-USA-11		PRU-USA-13	
	PLA N=240	PRU 2 mg N=238	PLA N=209	PRU 2 mg N=207	PLA N=212	PRU 2 mg N=214
Age, years						
Mean (SE)	43.7 (0.99)	42.7 (0.98)	48.9 (0.9)	48.2 (0.98)	46.2 (0.89)	48.6 (0.97)
Median	43	40	48	48	45	46.5
(min, max)	(18, 80)	(17, 83)	(18, 81)	(20, 83)	(18-82)	(20-95)
Age category, n (%)						
<65	216 (90)	211 (89.7)	178 (85.2)	180 (87.0)	189 (89.2)	180 (85.1)
≥65	24 (10.0)	27 (11.3)	31 (14.8)	27 (13.0)	23 (10.8)	34 (15.9)
Sex, n (%)						
Female	222 (92.5)	213 (89.5)	183 (87.6)	188 (90.8)	189 (89.2)	181 (84.6)
Male	18 (7.5)	25 (10.5)	26 (12.4)	19 (9.2)	23 (10.8)	33 (15.4)
Race, n (%)						
White	226 (94.2)	223 (93.7)	182 (87.1)	188 (90.8)	197 (92.9)	183 (85.5)
Black	2 (0.8)	3 (1.3)	18 (8.6)	13 (6.3)	9 (4.2)	24 (11.2)
Hispanic	2 (0.8)	0	4 (1.9)	5 (2.4)	5 (2.4)	3 (1.4)
Asian	2 (0.8)	5 (2.1)	2 (1.0)	1 (0.5)	0	3 (1.4)
Other	8 (3.3)	7 (2.9)	3 (1.4)	0	1 (0.5)	1 (0.5)
Weight, kg						
Mean (SE)	66.7 (0.84)	68.8 (0.93)	68.4 (1.02)	69.3 (0.96)	70.7 (0.99)	71.1 (1.04)

Source: Applicant's Table 12 on Page 72 of integrated-summary-of-efficacy.pdf, verified by the reviewer
Abbreviations: ITT, intent-to-treat; Max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with characteristic; PLA, placebo; PRU, prucalopride; SE, standard error

Table 35. Summary of Demographics for Study 401 in ITT Population.

	Placebo	PRU ≤2 mg	Total
	N=169	N=171	N=340
Age (years)			
Mean (SD)	48.5 (16.46)	48.5 (15.70)	48.5 (16.06)
Age category (n [%])			
<65 years	138 (81.7)	141 (82.5)	279 (82.1)
≥65 to <75 years	20 (11.8)	22 (12.9)	42 (12.4)
≥75 years	11 (6.5)	8 (4.7)	19 (5.6)
Sex (n [%])			
Female	144 (85.2)	147 (86.0)	291 (85.6)
Male	25 (14.8)	24 (14.0)	49 (14.4)
Race (n [%])			
White	158 (93.5)	158 (92.4)	316 (92.9)
Not allowed to ask[a]	9 (5.3)	9 (5.3)	18 (5.3)
Other [b]	1 (0.6)	3 (1.8)	4 (1.2)
Asian	1 (0.6)	0	1 (0.3)
Black	0	1 (0.6)	1 (0.3)
Body mass index (kg/m^2)			
Mean (SD)	24.8 (4.34)	25.4 (4.80)	25.1 (4.58)

Source: Applicant's Table 4 on Page 7 of Applicant's IR response dated July 23, 2018, verified by the reviewer
Abbreviations: ITT, intent-to-treat; PRU, prucalopride; SD, standard deviation
[a] Not allowed to ask per local regulations.
[b] All four subjects indicated "Other: Caucasian."

Table 36. Summary of Baseline Disease Characteristics for Study 302 in mITT Population

	PLA N=181	PRU ≤2 mg N=177	Total N=358
History of constipation, years			
Mean (SD)	9.36 (11.456)	9.33 (12.131)	9.34 (11.780)
Median (Min; Max)	10.00 (0.5; 45.5)	10.00 (0.7; 60.0)	10.00 (0.5; 60.0)
Main complaint, n (%)			
Infrequent defecation	42 (23.2)	29 (16.5)	71 (19.9)
Straining	44 (24.3)	38 (21.6)	82 (23.0)
Feeling not completely empty*	33 (18.2)	54 (30.7)	87 (24.4)
Hard stools	21 (11.6)	23 (13.1)	44 (12.3)
Abdominal bloating	22 (12.2)	14 (8.0)	36 (10.1)
Abdominal pain	19 (10.5)	18 (10.2)	37 (10.4)
Previous use of diet adjustments as constipation treatment, n (%)			
Yes	108 (59.7)	120 (67.8)	228 (63.7)
No	73 (40.3)	57 (32.2)	130 (36.3)
Previous use of laxatives, n (%)			
Yes	110 (60.8)	113 (63.8)	223 (62.3)
No	71 (39.2)	64 (36.2)	135 (37.7)
Previous use of bulk-forming laxatives, n (%)			
Yes	52 (28.7)	44 (24.9)	96 (26.8)
No	129 (71.3)	133 (75.1)	262 (73.2)
Number of SBMs during the last 6 months, n (%)			
0	14 (7.7)	22 (12.4)	36 (10.1)
>0 - ≤1	48 (26.5)	54 (30.5)	102 (28.5)
>1 - ≤3	107 (59.1)	93 (52.5)	200 (55.9)
>3	12 (6.6)	8 (4.5)	20 (5.6)
Percentage of BMs that are hard/very hard, n (%)			

	PLA N=181	PRU ≤2 mg N=177	Total N=358
0-25	23 (9.1)	16 (6.4)	39 (7.8)
26-50	44 (17.5)	43 (17.3)	87 (17.4)
51-75	51 (20.2)	58 (23.3)	109 (21.8)
76-100	134 (53.2)	132 (53.0)	266 (53.1)
Overall therapeutic effect, n (%)			
Adequate	8 (4.4)	7 (4.0)	15 (4.2)
Inadequate	159 (87.8)	154 (87.0)	313 (87.4)
NA	14 (7.7)	16 (9.0)	30 (8.4)

Source: Applicant's Table 14 on Pages 74-75 of integrated-summary-of-efficacy.pdf, verified by the reviewer
Abbreviations: BM, bowel movement; max, maximum; min, minimum; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with characteristic; PLA, placebo; PRU, prucalopride; SBM, spontaneous bowel movement SD, standard deviation
* There was significant difference in main complaint on feeling not completely empty between the two treatment arms with p-value of 0.01 based on chi-squared test.

Table 37. Summary of Baseline Disease Characteristics for Study 3001 in ITT Population

	PLA N=252	PRU 2 mg N=249	Total N=501
History of constipation, years			
Mean (SD)	12.83 (9.967)	12.89 (9.747)	12.86 (9.849)
Median (Min; Max)	10.00 (0.5; 45.5)	10.00 (0.7; 60.0)	10.00 (0.5; 60.0)
Main complaint, n (%)			
Infrequent defecation	45 (17.9)	55 (22.1)	100 (20.0)
Straining	58 (23.0)	47 (18.9)	105 (21.0)
Feeling not completely empty	35 (13.9)	33 (13.3)	68 (13.6)
Hard stools	49 (19.4)	49 (19.7)	98 (19.6)
Abdominal bloating	53 (21.0)	50 (20.1)	103 (20.6)
Abdominal pain	12 (4.8)	15 (6.0)	27 (5.4)
Previous use of diet adjustments as constipation treatment, n (%)			
Yes	147 (58.3)	126 (50.6)	273 (54.5)
No	105 (41.7)	123 (49.4)	228 (45.5)
Previous use of laxatives, n (%)			
Yes	177 (70.2)	183 (73.5)	360 (71.9)
No	75 (29.8)	66 (26.5)	141 (28.1)
Previous use of bulk-forming laxatives, n (%)			
Yes	69 (27.4)	62 (24.9)	131 (26.1)
No	183 (72.6)	187 (75.1)	370 (73.9)
Number of SBMs during the last 6 months, n (%)			
0	57 (22.6)	57 (22.9)	114 (22.8)
>0 - ≤1	63 (25.0)	73 (29.3)	136 (27.1)
>1 - ≤3	132 (52.4)	119 (47.8)	251 (50.1)
>3	0	0	0
Percentage of BMs that are hard/very hard, n (%)			
0-25	23 (9.1)	16 (6.4)	39 (7.8)
26-50	44 (17.5)	43 (17.3)	87 (17.4)
51-75	51 (20.2)	58 (23.3)	109 (21.8)
76-100	134 (53.2)	132 (53.0)	266 (53.1)
Overall therapeutic effect, n (%)			
Adequate	8 (4.4)	7 (4.0)	15 (4.2)
Inadequate	159 (87.8)	154 (87.0)	313 (87.4)
NA	14 (7.7)	16 (9.0)	30 (8.4)
Number of SBMs per week at baseline			

	PLA N=252	PRU 2 mg N=249	Total N=501
<1	111 (44.0)	111 (44.6)	222 (44.3)
1-2	134 (53.2)	127 (51.0)	261 (52.1)
>2	7 (2.8)	11 (4.4)	18 (3.6)

Source: Applicant's Table 14 on Pages 74-75 of integrated-summary-of-efficacy.pdf and Table 5 on Page 49 of the Study 3001 CSR, verified by the reviewer
Abbreviations: BM, bowel movement; ITT, intent-to-treat; max, maximum; min, minimum; NA, not applicable; N, number of subjects in treatment group; n, number of subjects with characteristic; PLA, placebo; PRU, prucalopride; SBM, spontaneous bowel movement; SD, standard deviation

Table 38. Summary of Baseline Disease Characteristics for Studies INT-6, USA-11 and USA-13 in ITT Population

	PRU-INT-6		PRU-USA-11		PRU-USA-13	
	PLA N=240	PRU 2 mg N=238	PLA N=209	PRU 2 mg N=207	PLA N=212	PRU2 mg N=214
History of constipation, years						
Mean (SD)	18.5 (0.9)	15.9 (0.97)	21.6 (1.19)	21.1 (1.10)	21.4 (1.06)	22.7 (1.08)
Median (Min; Max)	18 (1; 68)	10 (1; 70)	20 (1; 77)	20 (1; 78)	20 (1; 71)	20 (1; 63)
History of constipation category, years						
<1	8 (3.3)	9 (3.8)	5 (2.4)	4 (1.9)	3 (1.4)	2 (0.9)
1-<10	66 (27.5)	83 (34.9)	59 (28.2)	51 (24.6)	54 (25.5)	52 (24.3)
10-<20	51 (21.3)	69 (29.0)	37 (17.7)	47 (22.7)	42 (19.8)	41 (19.2)
20-<30	63 (26.3)	36 (15.1)	40 (19.1)	40 (19.3)	46 (21.7)	40 (18.7)
30-<40	25 (10.4)	18 (7.6)	30 (14.4)	32 (15.5)	33 (15.6)	38 (17.8)
40-<50	17 (7.1)	12 (5.0)	21 (10.0)	18 (8.7)	22 (10.4)	24 (11.2)
≥50	10 (4.2)	11 (4.6)	17 (8.1)	15 (7.2)	12 (5.7)	17 (7.9)
Main complaint, n (%)						
Infrequent defecation	59 (24.6)	57 (23.9)	71 (34.0)	86 (41.5)	61 (28.8)	66 (30.8)
Abdominal bloating	64 (26.7)	73 (30.7)	45 (21.5)	30 (14.5)	58 (27.4)	53 (24.8)
Abdominal pain	61 (25.4)	58 (24.4)	19 (9.1)	18 (8.7)	19 (9.0)	27 (12.6)
Feeling not completely empty	29 (12.1)	26 (10.9)	38 (18.2)	30 (14.5)	30 (14.2)	29 (13.6)
Straining	17 (7.1)	18 (7.6)	24 (11.5)	28 (13.5)	30 (14.2)	22 (10.3)
Hard stools	10 (4.2)	6 (2.5)	12 (5.7)	15 (7.2)	14 (6.6)	17 (7.9)
Previous use of diet adjustments as constipation treatment, n (%)						
Yes	140 (58.3)	154 (64.7)	137 (65.6)	150 (72.5)	144 (67.9)	139 (65.0)
No	100 (41.7)	84 (35.3)	72 (34.4)	57 (27.5)	68 (32.1)	75 (35.0)
Previous use of laxatives, n (%)						
Yes	198 (82.5)	191 (80.3)	183 (87.6)	185 (89.4)	189 (89.2)	189 (88.3)
No	42 (17.5)	47 (19.7)	26 (12.4)	22 (10.6)	23 (10.8)	25 (11.7)
Previous use of bulk-forming laxatives, n (%)						
Yes	141 (58.8)	143 (60.1)	138 (66.0)	136 (65.7)	122 (57.5)	123 (57.5)
No	99 (41.3)	95 (39.9)	71 (34.0)	71 (34.3)	90 (42.5)	91 (42.5)
Number of SBMs during the last 6 months n (%)						
0	99 (41.3)	86 (36.1)	79 (37.8)	77 (37.2)	85 (40.1)	96 (44.9)
>0 - ≤1	84 (35.0)	78 (32.8)	78 (37.3)	79 (38.2)	65 (30.7)	73 (34.1)
>1 - ≤3	51 (21.3)	65 (27.3)	49 (23.4)	50 (24.2)	60 (28.3)	43 (20.1)
>3	6 (2.5)	9 (3.8)	3 (1.4)	1 (0.5)	2 (0.9)	2 (0.9)
Percentage of BMs that are hard/very hard, n (%)						

	PRU-INT-6		PRU-USA-11		PRU-USA-13	
	PLA N=240	PRU 2 mg N=238	PLA N=209	PRU 2 mg N=207	PLA N=212	PRU2 mg N=214
0-25	36 (15.0)	45 (18.9)	30 (14.4)	31 (15.0)	28 (13.2)	30 (14.0)
26-50	31 (12.9)	35 (14.7)	24 (11.5)	21 (10.1)	38 (17.9)	33 (15.4)
51-75	56 (23.3)	39 (16.4)	50 (23.9)	45 (21.7)	49 (23.1)	52 (24.3)
76-100	117 (48.8)	119 (50.0)	105 (50.2)	110 (53.1)	97 (45.8)	99 (46.3)
Overall therapeutic effect, n (%)						
Adequate	32 (14.0)	48 (21.1)	32 (15.8)	34 (16.9)	46 (22.1)	39 (18.6)
Inadequate	196 (86.0)	180 (78.9)	170 (84.2)	167 (83.1)	162 (77.9)	171 (81.4)

Source: Applicant's Table 15 on Pages 77 of integrated-summary-of-efficacy.pdf, verified by the reviewer
Abbreviations: BM, bowel movement; ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with characteristic; PLA, placebo; PRU, prucalopride; SBM, spontaneous bowel movement; SD, standard deviation

Table 39. Summary of Baseline Disease Characteristics for Study 401 in ITT Population

	Placebo N=169	PRU ≤2 mg N=171	Total N=340
Duration of constipation (years)			
Subjects with available data	135	135	270
Mean (SD)	14.1 (13.33)	16.3 (16.00)	15.2 (14.74)
Number of baseline SCBMs per week			
Subjects with available data	169	171	340
0 (n [%])	97 (57.4)	107 (62.6)	204 (60.0)
>0 to <1 (n [%])	41 (24.3)	34 (19.9)	75 (22.1)
≥1 to <2 (n [%])	25 (14.8)	24 (14.0)	49 (14.4)
≥2 to <3 (n [%])	4 (2.4)	4 (2.3)	8 (2.4)
≥3 (n [%])	2 (1.2)	2 (1.2)	4 (1.2)
Subject's main complaint (n [%])			
Feeling of not completely emptying bowels	42 (24.9)	42 (24.6)	84 (24.7)
Infrequent defecation	43 (25.4)	41 (24.0)	84 (24.7)
Abdominal pain	32 (18.9)	27 (15.8)	59 (17.4)
Abdominal bloating	25 (14.8)	23 (13.5)	48 (14.1)
Straining	15 (8.9)	24 (14.0)	39 (11.5)
Hard stools	12 (7.1)	14 (8.2)	26 (7.6)

Source: Applicant's Table 5 on Page 8 of Applicant's IR response dated July 23, 2018, verified by the reviewer
Abbreviations: ITT, intent-to-treat; PRU, prucalopride; SCBM, spontaneous complete bowel movement; SD, standard deviation

Table 40. Sex Subgroup Analyses Results for Primary Efficacy Endpoint in Phase 3/4 Studies

	Female			Male		
Study	PLA n/N (%)	PRU 2 mg n/N (%)	Percent Difference PRU–PLA (95% CI)	PLA n/N (%)	PRU 2 mg n/N (%)	Percent Difference PRU–PLA (95% CI)
PRU-CRC-3001	24/223 (10.8)	77/227 (33.9)	23 (16;31)	2/29 (6.9)	6/22 (27.3)	20 (-0.4;41)
SPD555-302	NA	NA	NA	32/181 (17.7)	67/177 (37.9)	20 (11;29)
PRU-INT-6	21/222 (9.5)	43/211 (20.4)	11 (4;18)	2/18 (11.1)	3/25 (12.0)	0.9 (-18;20)
PRU-USA-11	21/169 (12.4)	52/174 (29.9)	17 (9;26)	4/24 (16.7)	3/16 (18.8)	2 (-22;26)
PRU-USA-13	20/189 (10.6)	43/181 (23.8)	13 (6;21)	5/23 (21.7)	7/33 (21.2)	-0.5 (-22;21)
SPD-555-401	29/144 (20.1)	35/147 (23.8)	4 (-6;13)	5/25 (20.0)	8/24 (33.3)	13 (-11;38)

Source: Adapted from Table 1-6 of Applicant's IR response dated 6/26/2018
Abbreviations: CI, confidence interval; PLA, placebo; PRU, prucalopride

Table 41. Age Subgroup Analyses Results for Primary Efficacy Endpoint in Phase 3/4 Studies

	Age <65 years			Age ≥65 years		
Study	PLA n/N (%)	PRU 2 mg n/N (%)	Percent Difference PRU–PLA 95% CI	PLA n/N (%)	PRU 2 mg n/N (%)	Percent Difference PRU–PLA 95% CI
PRU-CRC-3001	26/252 (10.3)	83/249 (33.3)	23.02 (16.06;29.97)	NA		
SPD555-302	16/110 (14.5)	39/98 (39.8)	25.25 (13.53;36.97)	16/71 (22.5)	28.79 (35.4)	12.91 (-1.43;27.25)
PRU-INT-6	20/216 (9.3)	40/209 (19.1)	9.88 (3.29;16.47)	3/24 (12.5)	6/27 (22.2)	9.72 (-10.8;30.24)
PRU-USA-11	20/165 (12.1)	49/165 (29.7)	17.58 (9.01;26.14)	5/28 (17.9)	6/25 (24.0)	6.14 (-15.8;28.09)
PRU-USA-13	23/189 (12.2)	42/180 (23.3)	11.16 (3.42;18.90)	2/23 (8.7)	8/34 (23.5)	14.83 (-3.49;33.16)
SPD-555-401	30/138 (21.7)	36/141 (25.5)	3.79 (-6.17;13.75)	4/31 (12.9)	7/30 (23.3)	10.4 (-8.8;29.6)

Source: Adapted from Table 1-6 of Applicant's IR response dated 6/26/2018
Abbreviations: CI, confidence interval; PLA, placebo; PRU, prucalopride

Table 42. Race Subgroup Analyses Results for Primary Efficacy Endpoint in Phase 3/4 Studies

Study	White			Non-White		
	PLA n/N (%)	PRU 2 mg n/N (%)	Percent Difference PRU–PLA 95% CI	PLA n/N (%)	PRU 2 mg n/N (%)	Percent Difference PRU–PLA 95% CI
PRU-CRC-3001	NA			26/252 (10.3)	83/249 (33.3)	23 (16; 30)
SPD555-302	32/181 (17.7)	67/177 (37.9)	20 (11;29)	NA		
PRU-INT-6	22/226 (9.7)	45/221 (20.4)	11 (4; 17)	1/14 (7.1)	1/15 (6.7)	-0.5 (-19; 18)
PRU-USA-11	22/166 (13.3)	53/171 (31.0)	18 (9; 26)	3/27 (11.1)	2/19 (10.5)	-0.6 (-19; 18)
PRU-USA-13	25/197 (12.7)	43/183 (23.5)	11 (3; 19)	0/15 (0.0)	7/31 (22.6)	23 (8; 37)
SPD-555-401	32/158 (20.3)	41/158 (25.9)	6 (-4; 15)	2/11 (18.2)	2/13 (15.4)	-3 (-33; 27)

Source: Adapted from Table 1-6 of Applicant's IR response dated 6/2/2018
Abbreviations: CI, confidence interval; PLA, placebo; PRU, prucalopride

9. GLOSSARY

AC	advisory committee
AE	adverse event
AMI	acute myocardial infarction
AUC	area under the curve
BID	twice daily
BM	bowel movement
BMI	body mass index
CBM	complete bowel movement
CEC	Cardiovascular Endpoint Committee
CI	confidence interval

CIC	chronic idiopathic constipation
CMH	Cochran–Mantel–Haenszel
CPRD	Clinical Practice Research Datalink
CV	cardiovascular
ECG	electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
GePaRD	German Pharmacoepidemiological Research Database
GI	gastrointestinal
GIDAC	Gastrointestinal Drugs Advisory Committee
5-HT_4	5-hydroxytryptamine (serotonin) receptor type 4
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IND	investigational new drug application
IR	incidence rate
IRR	incidence rate ratio
ISD	Information Services Division of Scotland
ITT	intent-to-treat
LOCF	last observation carry forward
MACE	major adverse cardiac event
MI	myocardial infarction
mITT	modified intent-to-treat
NDA	New Drug Application
OIC	opioid-induced constipation
PEG	polyethylene glycol
PK	pharmacokinetics
PLA	placebo
SAE	serious adverse event
SBM	spontaneous bowel movement
SCBM	spontaneous complete bowel movement
SD	standard deviation
SIRR	standardized incidence rate ratio
SNR	Swedish National Registers
TEAE	treatment-emergent adverse event
THIN	The Health Improvement Network
TQT	thorough QT
y/o	year-old

10. REFERENCE LIST

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