CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210166Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	210166
Priority or Standard	Standard
Submit Date(s)	12/20/2017
Received Date(s)	12/21/2017
PDUFA Goal Date	12/19/2018
Division/Office	DGIEP/ODE III
Review Completion Date	12/13/2018
Established/Proper Name	Prucalopride
(Proposed) Trade Name	Motegrity
Pharmacologic Class	Serotonin (5-HT_4) receptor agonist
Applicant	Shire Development LLC
Dosage form	Oral tablets
Applicant proposed Dosing Regimen	2 mg daily (b) (4) 1 mg daily for patients with severe renal impairment (creatinine clearance (CrCL) less than 30 mL/min)
Applicant Proposed Indication(s)/Population(s)	Treatment of chronic idiopathic constipation in adults
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of chronic idiopathic constipation in adults
Recommended Dosing Regimen	2 mg daily 1 mg daily for patients with severe renal impairment (creatinine clearance (CrCL) less than 30 mL/min)

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OPQ = Office of Pharmaceutical Quality, OPDP = Office of Prescription Drug Promotion, OSI = Office of Scientific Investigations OSE = Office of Surveillance and Epidemiology, DEPI = Division of Epidemiology, DMEPA = Division of Medication Error Prevention and Analysis, DRISK = Division of Risk Management, DMPP = Division of Medical Policy Programs

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
AUC	area under the curve
BID	twice daily
BLA	biologics license application
BM	bowel movement
BMI	body mass index
BRF	Benefit Risk Framework
BCRP	breast cancer resistance protein
CBM	complete bowel movement
CEC	Cardiovascular Endpoint Committee
CI	confidence interval
CIC	chronic idiopathic constipation
CRCL	creatinine clearance
CV	cardiovascular
CYP	cytochrome P450
ECG	electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	good clinical practice
GI	gastrointestinal
GIDAC	Gastrointestinal Drugs Advisory Committee
HEK	human embryonic kidney
HPLC	high-performance liquid chromatography
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
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LC-MS/MS	liquid chromatography-tandem mass spectrometry
MACE	major adverse cardiac event
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent to treat
NDA	new drug application
PBPK	physiologically based pharmacokinetic
PEG	polyethylene glycol
PK	pharmacokinetics

PLA	placebo
PO	oral
PP	per protocol
PRU	prucalopride
QD	once daily
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBM	spontaneous bowel movement
SCBM	spontaneous complete bowel movement
StdDev	standard deviation
SD	single dose
TCTT	total colon transit time
TEAE	treatment emergent adverse event
TQT	thorough QT

1. Executive Summary

The currently available treatment options do not completely meet the needs of patients with chronic idiopathic constipation (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 (PRU), a selective 5-hydroxytryptamine (serotonin) type 4 receptor ($5\text{-}HT_4$) 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 male patients. Prucalopride is approved in 82 countries and marketed in 59 countries. Due to the concern for cardiovascular (CV) risks potentially associated with the $5\text{-}HT_4$ 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 United States.

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 Food and Drug Administration (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]).

Five of the six the trials achieved statistical significance for the primary efficacy endpoint; study 401 did not achieve statistical significance at week 12 or 24. The primary endpoint was the response rate, defined by a mean of ≥3 spontaneous complete bowel movements (SCBMs) per week over the 12-week treatment period. In study 3001 and study 302, prucalopride demonstrated statistically significant response rates that were 23% and 20.2% higher in the treatment arm compared to the placebo arm, respectively, and p-values <0.001 for both trials. Three out of the four supportive efficacy trials, studies INT-6, USA-11, and USA-13, also demonstrated statistically significant treatment differences of 10%, 16%, and 12%, respectively, and p-values of <0.01. Study 401, a phase 4 trial conducted in Europe to evaluate prucalopride for 24 weeks, reported a response rate at week 12 in the prucalopride arm (25%) as compared to the placebo arm (20%) with a difference in response rate of 5% and a p-value of 0.34. At week 24, the response rates in the prucalopride (25%) and placebo (21%) arms were similar to the week 12 results. Therefore, 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.

Additional efficacy analyses were conducted using the FDA's currently recommended efficacy endpoint for trials evaluating treatment of CIC (i.e., "Alternative Endpoint A"). Using this endpoint, treatment response rates ranged from 8 to 18% higher in the treatment arm (compared to the placebo arm). Alternative Endpoint A defines an overall 12-week SCBM responder as a patient who is a SCBM weekly responder for ≥9 out of the 12-week treatment period. A SCBM weekly responder is a patient who has a SCBM weekly frequency rate of ≥3 and increased by ≥1 from baseline. The treatment effect demonstrated in these trials are generally consistent with what has been demonstrated for other products approved for CIC using similar efficacy endpoints (response rates approximatly range 8 to 17% higher for treatment arms compared to placebo arms).

Additional sensitivity analyses of the primary endpoint (Section 8.11 Efficacy Results – Primary Endpoint) confirmed the efficacy of prucalopride as compared to the placebo arm. Subgroup analyses (8.14 Additional Analyses Conducted on the Individual Trials) demonstrated consistent efficacy trends by age, sex, and race across all trials with reasonable subgroup sizes.

In six clinical trials submitted to support product approval (studies 3001, 302, USA-11, USA-12, INT-6, and 401), the most commonly identified treatment-emergent adverse events (TEAEs) among prucalopride treated patients included headache, abdominal pain, nausea, diarrhea, abdominal distention, dizziness, vomiting, flatulence, and fatigue. The serious TEAEs and discontinuations due to adverse events (AEs) occurred in small numbers. There were no deaths in the six clinical trials submitted to support product approval.

In the safety database of completed phase 2 through 4 trials of at least 4 weeks in duration in adult patients with CIC treated with prucalopride at multiple doses (MDs) (0.5 mg, 1 mg, 2 mg, and 4 mg), there were seven deaths out of 6064 patients verses one death out of 1973 placebo treated patients. In the double-blind trials, there were two deaths in the prucalopride group and one death in the placebo group. None of those deaths occurred in the in the six double-blind clinical trials submitted to support product approval (Studies 3001, 302, USA-11, USA-12, INT-6, and 401). There were 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.

AEs of special interest were evaluated from 28 completed trials; 19 double-blind and 9 open-label trials. There were four cases of standard major adverse cardiac events (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 CV risk factors, 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). The Division has been recommending applicants submitting NDAs for 5-HT_4 agonists to treat GI disorders provide controlled data for at least 12 months duration due to potential 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 CV 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, hospitalization for stroke, and in-hospital CV death, was submitted in lieu of a premarket safety study. Therefore, the safety database includes data from study SPD555-802 conducted to estimate the adjusted incidence rate ratio and 95% confidence interval (CI) for MACE in prucalopride compared to polyethylene glycol (PEG), a drug commonly used to treat constipation with no evidence of a cardiovascular safety concern. The findings from this study reasonably exclude a greater than three-fold MACE risk from prucalopride use.

The additional information relevant to the evaluation of CV safety in this review include nonclinical data, a thorough QT (TQT) study, platelet aggregation studies, additional data from completed comparative trials, and an analysis of postmarket observational data. The nonclinical 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 TQT study. In one platelet aggregation study, prucalopride did not significantly potentiate platelet aggregation inducted by a range of physiologically relevant platelet activators.

Finally, a review of the safety database revealed suicidal ideation and behavior (SIB) events which are also reviewed as a potential class issue. Description of the SIB events will be included under the Warnings and Precautions section of labeling. In general, the safety data submitted for patients treated with prucalopride at multiple doses of 0.5 mg, 1 mg, 2 mg, and 4 mg resulted in small numbers of patients with psychiatric AEs.

1.1. Product Introduction

The Applicant submitted 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 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 (GI) prokinetic agent that stimulates colonic peristalsis by increasing bowel motility. There are safety concerns regarding the potential for CV and psychiatric risk with this class of 5-HT_4 agonists being developed to treat GI motility disorders.

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

- Adults: 2 mg once daily (QD)

(b) (4)

- Patients with severe renal impairment (glomerular filtration rate less than 30 ml/min/1.73 m^3): 1 mg QD.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Five of the six the trials achieved statistical significance for the primary efficacy endpoint; study 401 did not achieve statistical significance at week 12 or 24. The primary endpoint was the response rate, defined by a mean of ≥3 SCBMs per week over the 12-week treatment period. In study 3001 and study 302, prucalopride demonstrated statistically significant response rates that were 23% and 20.2% higher in the treatment arm compared to the placebo arm, respectively, and p-values <0.001 for both trials. Three out of the four supportive efficacy trials, studies INT-6, USA-11, and USA-13, also demonstrated statistically significant treatment differences of 10%, 16%, and 12%, respectively, and p-values of <0.01. Study 401 reported a response rate at week 12 in the prucalopride arm (25%) as compared to the placebo arm (20%) with a difference in response rate 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. Using the efficacy analyses conducted using the Division's currently recommended efficacy endpoint for trials evaluating treatment of CIC, treatment response rates ranged from8 to 18% in the treatment arm as compared to the placebo arm. This treatment difference is generally consistent with what has been demonstrated for other approved products using similar efficacy endpoints. While the reasons for the smaller treatment effect in study 401 remain unclear, the substantial evidence of effectiveness of prucalopride as a treatment of CIC is established.

Because the two trials submitted as the primary basis to support approval (studies 3001 and 302) each enrolled non-U.S. patient populations, we requested that the data from three other clinical trials (studies INT-6, USA-11 and USA-13) be submitted to support that the results from studies 3001 and 302 are generalizable to the U.S. patient population with CIC. Studies USA-11 and USA-13 were conducted in the United States. Although study INT-6 enrolled primarily a European patient population, the demographic and baseline disease characteristics of the patients enrolled in INT-6 were generally similar to the two U.S. trials. The demographics and disease history of the patient population for the individual trials differ from one another but are complimentary when considered together.

The overall mean body mass index (BMI) for study 3001 was slightly lower (approximately 23 kg/m^2) compared to the mean BMI reported for the other trials (approximately 25 to 27 kg/m^2). Study 302 enrolled male patients and the other trials enrolled a primarily female population. The median age in study 302 was 62 years, with 42% of patients ≥65 years of age. Other trials

enrolled patients with a younger median age (range 43 to 48) and smaller proportion of patients ≥65 years of age (10 to 14%). In subgroup analysis by age (<65 versus ≥65 years), the treatment benefit over placebo was numerically greater for prucalopride in both older and younger patients. CIC occurs more commonly in females and increases with age; therefore, the age distribution of the trials and primarily female patient population are reflective of the patient population likely to develop CIC.

With the exception of study 3001 that enrolled a predominantly Asian population, the patient population of the clinical trials was primarily Caucasian. Subgroup efficacy analysis by race did not provide clinically meaningful information because of the small numbers in each non-Caucasian category. The relationship between race and constipation remains uncertain as there are conflicting results in published studies (Sanchez and Bercik 2011).

There were several differences in the characteristics of the disease history between the patient population in the two U.S. trials and the other four trials. Compared to patients enrolled in studies 3001 and 302, patients in the trials conducted in the United States reported a longer history of constipation, and a higher percentage of patients reported prior laxative use and ≤1 spontaneous bowel movement (SBM)/week over the past 6 months as compared to patients enrolled in studies 3001 and 302. Despite these differences, the proportion of patients with ≤2 SCBMs/week at baseline was similar across all the trials, supporting that the patient populations enrolled in the U.S. and non-U.S. trials had similar disease characteristics at trial entry. However, the longer history of constipation and increased use of prior (possibly ineffective) laxative therapy may have contributed to slightly lower treatment response observed in the U.S. trials compared to the non-U.S. trials. A prucalopride treatment benefit over placebo was demonstrated in the U.S. and non-U.S. trials, with the exception of study 401. The efficacy results from all six trials, U.S. and non-U.S., are recommended for inclusion in the product label.

There did not appear to be differences in demographic or disease characteristics that would preclude approval in the United States patient population with CIC. In addition, study 3001 (Asian population) and study 302 (male population) provide data on prucalopride in populations who were underrepresented in the trials conducted in the United States. Furthermore, the clinical trials that were conducted outside of the United States were conducted according to good clinical practice (GCP), were adequate and well-controlled, and used a control group, diagnostic criteria, and assessments that are generally appropriate for CIC.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Chronic idiopathic constipation, also known as functional constipation, is a considerable healthcare issue and can profoundly impact patient quality of life of those affected. The prevalence of CIC in North America is estimated to vary between 2 to 27 percent (average of approximately 15 percent), occurring more commonly in women and increases in prevalence with age. There are three approved and marketed therapies for CIC (lubiprostone, linaclotide, and plecanatide). Unapproved products patients often use for treatment of chronic constipation include probiotics, osmotic and stimulant laxatives, stool softeners, and fiber. At times, patients also use dietary and lifestyle modifications to treat their chronic constipation. Not all patients will have an adequate response to available therapy; therefore, additional treatment options are needed.

Motegrity (prucalopride), a 5-HT_4 receptor agonist, is a new molecular entity proposed for oral treatment of CIC in adults. The proposed dose is 2 mg daily for adults. The dose for patients with severe renal impairment (creatinine clearance (CRCL) less than 30 mL/min) regardless of age is 1 mg daily.

The Applicant evaluated the efficacy of Motegrity (prucalopride) in six adequate and well-controlled trials; five 12-week phase 3 trials (studies 302, 3001, INT-6, USA-11, USA-13) and one 24-week phase 4 trial (study 401). Five of the six trials achieved statistical significance for the primary efficacy endpoint; study 401 did not achieve statistical significance at week 12 or 24. The primary endpoint was the response rate, defined by a mean of ≥3 SCBMs per week over the 12-week treatment period. In study 3001 and study 302, prucalopride demonstrated statistically significant response rates that were 23% and 20.2% higher in the treatment arm compared to the placebo arm, respectively, and p-values <0.001 for both trials. Three out of the four supportive efficacy trials, Studies INT-6, USA-11, and USA-13, also demonstrated statistically significant treatment differences of 10%, 16%, and 12%, respectively, and p-values of <0.01; and study 401 reported a response rate at week 12 in the prucalopride arm (25%) as compared to the placebo arm (20%) with a difference in response rate 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. Using the efficacy analyses conducted using the Division's currently recommended efficacy endpoint for trials evaluating treatment of CIC (i.e., "Alternative Endpoint A"), treatment response rates ranged from 8 to 18% higher in the treatment arm compared to the placebo arm for the five successful trials. Alternative Endpoint A defines an overall 12-week SCBM responder as a patient who is a SCBM weekly responder for ≥9 out of the 12-week 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 effect is

generally consistent with what has been demonstrated for other products approved for CIC using similar efficacy endpoints (approximate range 8 to 17% treatment effect over placebo).

In six clinical trials submitted to support product approval (studies 3001, 302, USA-11, USA-12, INT-6, and 401), the most commonly identified treatment-emergent adverse events (TEAEs) reported in ≥2% of patients treated with prucalopride 2 mg and greater than placebo included headache, abdominal pain, nausea, diarrhea, abdominal distention, dizziness, vomiting, flatulence, and fatigue. Severe diarrhea occurred in 1.8% of prucalopride-treated patients compared to 1% of patients in the placebo group. There was a dose-dependent increase in headache, diarrhea, and abdominal pain. The serious TEAEs and discontinuations due to AEs occurred in few patients.

There were no deaths in the six clinical trials submitted to support product approval. In the safety database of completed phase 2 through four trials of at least 4 weeks in duration in adult patients with CIC treated with prucalopride at multiple doses of 0.5 mg, 1 mg, 2 mg, and 4 mg, there were seven deaths out of 6064 patients 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. There were 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. None of these deaths appear to be related to prucalopride.

Adverse events of special interest were evaluated from 28 completed trials; 19 double-blind and 9 open-label trials. 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 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 Extended MACE in the overall safety database, and the majority of the patients with events had baseline CV risk factors, possibly confounding the causality determination.

Additionally, a review of the safety database revealed a number of suicidal ideation and behavior events. Completed suicide was reported in two patients, previously treated with prucalopride 2 mg or 4 mg; both discontinued prucalopride for at least one month prior to the event. One patient reported a suicide attempt 7 days after the end of treatment with prucalopride 2 mg in a double-blind trial; none were reported in patients in the placebo group. Two patients reported suicide attempts and one patient reported suicidal ideation in the open-label trials. These patients had comorbid psychiatric conditions except for a 38-year old patient with no documented psychiatric history who reported “personal problems.” The WHO Global Individual Case Safety Report (ICSR)

database, VigiBase® as of December 2014, reported suicidal ideation in three patients hours to days after taking the first dose of prucalopride. The patients did not appear to have a documented psychiatric history and symptoms were reported to have resolved after discontinuation of prucalopride (Gasparotto and Chandler 2015; Lindholm 2015). The information on suicidal ideation and behavior will be included under the Warning and Precautions section of labeling.

The safety database was limited because there were no controlled trial data beyond 12 weeks (except for one 24-week trial). The Division has been recommending applicants submitting NDAs for 5-HT_4 agonists to treat GI disorders provide controlled data for at least 12 months duration due to potential 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 CV 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, hospitalization for stroke, and in-hospital CV death, was submitted in lieu of a premarket safety study. The findings from this study exclude a greater than three-fold MACE risk from prucalopride use.

The additional information relevant to the evaluation of CV safety in this review include nonclinical data, a TQT study, platelet aggregation studies, additional data from completed comparative trials, and an analysis of postmarket observational data. The nonclinical 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 TQT study. In one platelet aggregation study, prucalopride did not significantly potentiate platelet aggregation inducted by a range of physiologically relevant platelet activators.

The adequacy of the safety database was discussed during a public Gastrointestinal Advisory Committee (GIDAC) meeting on October 18, 2018. The GIDAC voted 10 to 0 that the efficacy and safety of the clinical trial data, nonclinical findings, including the selectivity of prucalopride for the 5-HT_4 receptor, and the results of the pharmacoepidemiology study included in the NDA are sufficient to support approval.

Based on the above findings, we conclude that the benefits of Motegrity (prucalopride) outweigh its risks for treatment of adults with CIC, when used in accordance with the proposed labeling. In addition to routine pharmacovigilance, postmarketing activities will include pediatric trials under PREA, two studies to assess infant outcomes when as administered to pregnant women, and one milk-only lactation trial to obtain data on the drug concentration in mature milk production.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	CIC, also known as functional constipation, is characterized according to the Rome diagnostic criteria. The prevalence of CIC in North America is estimated to vary between 2 to 27 percent (average of approximately 15 percent). CIC is more common in women and the prevalence rises with age.	CIC remains a considerable health issue and can profoundly impact patient quality of life.
Current Treatment Options	The general goal of CIC treatment is to increase the frequency of bowel movements (BMs), improve stool consistency, and reduce straining associated with BMs. There are three approved and marketed therapies for CIC, lubiprostone (an apical chloride-2 channel activator), and linaclotide and plecanatide (guanylate cyclase-C agonists). In addition to these therapies, unapproved products often used for chronic constipation are probiotics, osmotic and stimulant laxatives, stool softeners, and fiber. At times, patients also use dietary and lifestyle modifications to treat their chronic constipation.	Not all patients will have an adequate response to available therapy; therefore, additional treatment options are needed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Five of the six clinical trials in the prucalopride development program achieved statistical significance for the primary efficacy endpoint with response rates ranging from 10 to 23 percent higher in the treatment arm compared to placebo. The sixth trial was not statistically significant and reported a response rate at week 12 in the prucalopride arm (25%) as compared to the placebo arm (20%) with a difference in response rate of 5%. Using the efficacy analyses conducted using the FDA's currently recommended efficacy endpoint, treatment response rates ranged from 8 to 18% higher in the treatment arm compared to placebo.	The applicant established substantial evidence of effectiveness of prucalopride for the treatment of CIC in adults. Prucalopride offers a different mechanism of action from the currently available and marketed therapies for the treatment of CIC. Five of the six trials achieved statistical significance for the primary efficacy endpoint. In the same five trials, additional 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; therefore, showing that the results of the primary endpoint are comparable to the current standards for approved therapies for CIC. The treatment effect over placebo is generally consistent with what has been demonstrated for other approved products using similar efficacy endpoints (approximate range 8 to 17% higher in treatment arms compared to placebo). Overall, the variety of demographic characteristics across the six clinical trials are complimentary and the results of the trials are generalizable to the U.S. patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management (continued below)	The safety population of the five 12-week phase 3 and one 24-week phase 4 trial submitted to support approval includes 2530 patients (1251 received prucalopride 2 mg and 1279 received placebo) with a duration of exposure of approximately 80 days for the five 12-week trials. The most commonly identified treatment-emergent adverse events (TEAEs) among prucalopride treated patients included headache, abdominal pain, nausea, diarrhea, abdominal distension, dizziness, vomiting, flatulence, and fatigue. The serious TEAEs and discontinuations due to AEs occurred in small numbers. 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 occurred in the prucalopride group and one death in the placebo group among double-blind trials; five deaths occurred in the 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. None of these deaths appear to be related to prucalopride. 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 28 completed trials (19 double-blind and 9 open-label) in adult patients with CIC resulted in small numbers of patients 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). Additionally, there were small numbers of patients with psychiatric AEs. One patient reported a suicide attempt 7 days after the end of treatment with prucalopride 2 mg in a double-blind trial; none were reported in patients in the placebo group. Two patients reported suicide attempts and one patient reported suicidal ideation in the open-label trials. Completed suicide was reported in two patients, previously treated with prucalopride 2 mg or 4 mg; both discontinued prucalopride for at least one month prior to the event. These patients had comorbid psychiatric conditions except for the 38-year old patient with no documented psychiatric history who reported “personal problems”. The WHO Global Individual Case Safety Report (ICSR) database, VigiBase® as of December 2014, reported suicidal ideation in four patients hours to days after taking the first dose of prucalopride. The patients did not appear to have a documented psychiatric history and symptoms were reported to have resolved after discontinuation of prucalopride.	Product labeling will describe the common adverse reactions (ARs) reported in the six clinical trials submitted to support approval. Because of the concern for CV events in the 5-HT_4 receptor agonist class of drugs, the labeling will describe the MACE events reported in the broader safety database. Overall, it does not appear that prucalopride presents a CV risk. Suicide ideation, suicidal attempts and completed suicides occurred in a number of patients, some of whom had comorbid psychiatric conditions. The two patients with completed suicides had discontinued prucalopride for at least one month prior to the event. Again, because of the class concern and our inability to exclude the contribution of prucalopride, the Warnings and Precautions section of labeling will include a statement on suicidal ideation and behavior to communicate the potential risk and address the concerns expressed during the Advisory Committee (AC) meeting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management (continued)	In a 2-year mouse carcinogenicity study, the incidences of mammary gland adenocarcinoma in females at the high dose (80 mg/kg) were significantly higher than the controls. The 80 mg/kg dose provides a 219-fold exposure margin for the clinical dose of 2 mg/day. There were no significant tumor incidences at 10 and 20 mg/kg (24x the therapeutic exposure at 20 mg/kg) doses. In a 2-year carcinogenicity study in rats, the incidences of tumors were significant only at the high dose which provides 556- and 495-fold exposure margins for the therapeutic exposure. The doses of 5 and 20 mg/kg (6x and 63x the therapeutic exposure) in males and 5 and 10 mg/kg (7x and 40x the therapeutic exposure) in females did not cause a significant increase in the tumor incidences. A neonatal mouse carcinogenicity study in Swiss mice was negative. The Applicant conducted a pediatric trial in Europe that failed to demonstrate a treatment benefit of prucalopride over placebo in pediatric patients with functional constipation who were 6 months to 17 years of age. However, the design (e.g., endpoint selection, behavioral modification, presence/history of fecal mass) or suboptimal dose selection may have contributed to the failure to detect a treatment benefit compared to placebo. There is also limited data in pregnant and lactating women. Prucalopride is a new molecular entity that is systemically absorbed and has potential for chronic use in females of reproductive age. The Applicant submitted data from an open-label lactation study; however, the data were collected during the weaning phase and there is insufficient information on the drug concentration in mature milk production.	The increased incidences of tumors in 2-year carcinogenicity studies in mice and rats were only seen at very high exposure ratios. The lack of significant tumor occurrence at 24-times the therapeutic exposure suggests lack of risks in humans at the therapeutic dose. The standard labeling and postmarketing safety monitoring are recommended. No safety concerns or signals were identified that would require a REMS at this time. Post-marketing trials will be required under the Pediatric Research Equity Act to collect information on the safety and efficacy of prucalopride in pediatric patients with functional constipation. The modifications to the trial design and dose selection that were described at a high-level in the agreed PSP and additional protocol elements that are currently being negotiated for the PPSR will help to address challenges that may have contributed to the lack of treatment benefit over placebo in the completed pediatric trial. Additionally, we are requiring postmarketing studies to assess infant outcomes when prucalopride is administered to pregnant women, and a milk-only lactation trial to obtain data on the drug concentration in mature milk production.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Efficacy
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
X	Patient experience data that were not submitted in the application, but were considered in this review:			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	X	Other: (Please specify):		Advisory Committee Meeting
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

CIC, also known as functional constipation, is characterized according to the Rome diagnostic criteria, and is 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 SBMs per week

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

(3) Insufficient criteria for irritable bowel syndrome.

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). 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, CIC 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.

2.2. Analysis of Current Treatment Options

The general goal of CIC treatment is to increase the frequency of BMs, improve stool consistency, and reduce straining associated with BMs. The currently approved therapies for CIC are summarized in the table below. Unapproved products patients often use for treatment of chronic constipation include probiotics, osmotic and stimulant laxatives, stool softeners, and fiber. At times, patients also use dietary and lifestyle modifications to treat their chronic constipation. Not all patients will have an adequate response to available therapy; therefore, additional treatment options are needed.

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

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
Source: Reviewer's Table

3. Relevant Prucalopride Regulatory History

3.1. U.S. Regulatory Actions and Marketing History

Prucalopride is not currently marketed in the United States. See regulatory activity below.

3.2. Summary of Presubmission/Submission Regulatory Activity

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 investigational new drug application (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 authorization 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 rare CV safety signal associated with the 5-HT4 receptor agonist class of drugs.
  - FDA informed the Applicant that on November 17, 2011, the 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, irritable bowel syndrome with constipation, 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. The Division suggested that a possible path forward would be to include data from completed and ongoing trials as well as available postmarket 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 patients 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 complete response to the partial hold (due to genotoxicity and carcinogenicity concerns which were completely resolved); 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 postapproval 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 The Health Improvement Network pharmacoepidemiology study preapproval 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 (postmarketing pharmacoepidemiology safety study), designed to rule out an incidence rate ratio of 3, appeared reasonable. Depending on the results of SPD555-802, a postmarketing observational study to rule out an incidence rate ratio 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 CV safety concerns.
- September 26, 2017: The FDA notified Shire of agreement on the iPSP.
- December 21, 2017: Shire submitted NDA 210166.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

For additional details, see Clinical Inspection Summary by Dr. S. Leibenhaut, dated August 24, 2018, and amended November 8, 2018. The overall assessment from the Clinical Inspection Summary is provided below.

Inspections for this NDA consisted of inspections of five clinical investigator sites and the Applicant. All the clinical sites have the final or preliminary classification of No Action Indicated. The sponsor inspection has the classification of Voluntary Action Indicated. No significant regulatory findings or data integrity issues were noted.

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, Shire stated that source data from only 29% of sites in USA-11 and 22% of sites in USA-13

would be available for inspection and data verification due to the long period of time since the trials had been conducted. More importantly, source data from only one site in each of the top ten enrolling sites would be available for review. For Studies 302 and 3001 data from 88% and 87% of the sites respectively were available. Data for three of the top ten enrolling sites in Study 302 and all of the top ten enrolling sites for Study 3001 were available for inspection. FDA stated that the ability to verify data for these trials would be assessed in the overall review of the application. There was a lack of source data at most clinical sites from Studies USA-11 and USA-13.

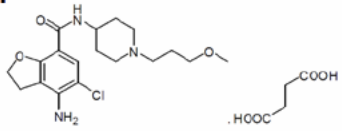
However, the results of the inspections at the sites where source data were available, the results of the sponsor inspection including review of monitoring reports, and the history of the monitoring from Janssen Research Foundation indicate that these trials were adequately conducted at the sites inspected and can be used in support of the application.

The data from Studies 302 and 3001 are considered reliable. The reliability of the data from Studies USA-11 and USA-13 could not be determined by inspection because most of the original study records were not available for inspection due to age of the trials.

4.2. Product Quality

The active pharmaceutical ingredient in prucalopride tablets is prucalopride succinate. It is an achiral, nonhygroscopic, water soluble and white to almost white powder. (b) (4) The chemical structure of prucalopride succinate was confirmed by elemental analysis, proton (^{1}H) and carbon (^{13}C) NMR spectroscopy; mass spectroscopy, IR spectroscopy, polymorph screening and X-ray powder diffraction. Prucalopride succinate has the following chemical structure:

Figure 1. Chemical Structure of Prucalopride



Prucalopride succinate
Molecular Formula: C18H26ClN3O3.C4H6O4
Molecular Weight: 485.96

Prucalopride succinate is manufactured (b) (4) The API manufacturer has provided sufficient information to ensure consistent manufacturing of prucalopride succinate with respect to identity, strength, purity and quality for drug product formulation of prucalopride tablets. The overall quality of the API is controlled by its specification. Based on the stability studies of multiple batches of the API a re-test period of (b) (4) months was granted when stored at room temperature.

Prucalopride immediate release tablets are supplied in 1-mg and 2-mg strengths. Each 1-mg tablet is a white to off-white, round, biconvex film-coated tablet debossed with "PRU 1" on one side. Each 2-mg tablet is a pink, round, biconvex film-coated tablet debossed with "PRU 2" on one side. Prucalopride tables also contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, silicone dioxide colloidal, magnesium stearate and (b) (4) film-coating. Prucalopride tablets are packaged in high density polyethylene bottle with child-resistant polypropylene closure (b) (4) Each bottle contains 30 tablets.

Prucalopride tablets are manufactured (b) (4)
The tablet manufacturing process involves (b) (4) The overall control strategy for the drug product is deemed adequate based on raw material controls, drug product specification including appearance, identity, assay, impurities, uniformity of dosage units and dissolution.

The drug product dissolution methods development, dissolution data, dissolution specification and in vitro bridging studies were reviewed and were deemed adequate from biopharmaceutical perspective.

Based on the stability studies of the drug product, 18 months of expiration dating period is granted when stored at room temperature.

A claim of a categorical exclusion from the requirements of an environmental assessment in accordance with 21 Code of Federal Regulations Part 25.31 was deemed acceptable.

The Office of Process and Facilities has made an "Adequate" recommendation for all manufacturing and testing facilities involved in this NDA.

The information provided in the label/labeling is deemed satisfactory from the chemistry, manufacturing, and controls perspective.

Therefore, from the Office of Pharmaceutical Quality perspective, this NDA is recommended for approval.

4.3. Clinical Microbiology

N/A

4.4. Devices and Companion Diagnostic Issues

N/A

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

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 GI 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 of prucalopride 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 GI motility and induce contractions of the colon at oral doses ≥0.04 mg/kg.

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 ≥9.6 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 electrocardiogram (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 (SD) of 1.25 mg/kg IV did not affect systolic and diastolic pulmonary artery pressure, CV pressure parameters, pulmonary vascular resistance, or ECG parameters (i.e., PQ interval duration, QRS complex duration, 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.

Prucalopride tested positive in the Ames bacterial mutation assay in the *S. typhimurium* TA100 strain, at concentrations ≥500 mcg/plate, both in the presence and absence of metabolic activation. However, prucalopride was negative in other assays evaluating mutagenesis,

including in vitro mammalian-based assays (e.g., mouse lymphoma assay, chromosomal aberration assays in human lymphocytes) and in vivo tests (e.g., micronucleus test in mice, a UDS test, a gene mutation assay in Big Blue transgenic rats, and a ^{32}P-postlabeling study in target tissues identified in the carcinogenicity studies, including; liver, mammary gland, thyroid and adrenal tissues). Based on the weight of evidence, prucalopride does not appear to have a mutagenic potential.

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 80 mg/kg dose provides a 219-fold exposure margin for the clinical dose of 2 mg/day. There were no significant tumor incidences, including mammary tumors at 10 and 20 mg/kg (24x the therapeutic exposure at 20 mg/kg) doses.

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 for these tumors were significant only at the high dose which provides 556 and 495-fold exposure margins for the therapeutic exposure. The doses of 5 and 20 mg/kg (6x and 63x the therapeutic exposure) in males and 5 and 10 mg/kg (7x and 40x the therapeutic exposure) in females did not cause a significant increase in the tumor incidences. A neonatal mouse carcinogenicity study in Swiss mice was negative.

Thus, the significantly increased incidences of tumors in 2-year carcinogenicity studies in mice and rats were only seen at very high exposure ratios. Mechanistic studies indicated that 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.

Prucalopride was studied in segment I, segment II and segment III reproductive and developmental toxicity studies following oral administration in rats and rabbits. Prucalopride had no adverse effects on fertility and early embryonic development in rats at oral doses up to 20 mg/kg/day. However, at a dose of 80 mg/kg (390x the therapeutic dose of 2 mg/day, based on body surface area), there was an increase in precoital interval and preimplantation loss. These effects were considered related to the pharmacological effects of prucalopride, secondary to increased prolactin levels in females. Increased precoital interval was also observed at the 20 mg/kg/day subcutaneous dose. In the oral embryofetal developmental studies in rats and rabbits (at up to 80 mg/kg/day; 390x in rats and 780x in rabbits, based on body surface area), had no adverse effect on embryofetal development when administered during the period of organogenesis. In a pre- and post-natal developmental toxicity study with oral prucalopride in rats at doses up to 80 mg/kg/day (390 times the therapeutic dose, based on body surface area),

there were no treatment-related effects on the fertility, gestation rate, duration of gestation and the number of implantations. Prucalopride had no effect on the development of the F1 pups.

There are [redacted] impurities [redacted] identified in the prucalopride succinate drug substanc [redacted] qualified by the chronic toxicity study in rats, and the proposed levels are acceptable. The level of the residual solvent, [redacted] which is not ICH classified, was qualified from the permissible daily exposure (PDE) calculated from the NOAEL in a 13-week oral toxicity in rats. There are no safety concerns for the elemental impurities at the specified levels.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

The assessment of pharmacologic activity of prucalopride was assessed in vitro and in vivo to determine its affinity and selectivity for 5-HT_4 receptors in GI and non-GI tissues to understand its mechanism of action in affecting GI motility. Prucalopride was shown to have a high affinity and selectivity for the human 5-HT_4 receptors expressed in HEK293 cells with an inhibition constant [Ki] of 2.5 to 8nM. Its interaction with the 5-HT_4 receptor leads to the elevation of cyclic adenosine monophosphate (cAMP) levels in HEK293 cells with a median effective concentration (EC_{50}) of 5nM. The affinity of prucalopride for other receptors, channels or transporters was only detected at concentrations exceeding its affinity for the 5-HT_4 receptor by at least 150X.

In vitro studies on isolated GI tissues from various animal species including humans, show that prucalopride facilitated acetylcholine release from the myenteric neurons to enhance the amplitude of contractions, enhance acetylcholine release from intrinsic sensory neurons to stimulate peristalsis, enhance nitric oxide release from myenteric neurons to improve relaxation, or act directly on 5-HT_4 receptors on smooth muscle cells to relax the smooth muscle layer and reduce resistance to aboral propulsion. The sum of these actions leads to improved GI propulsion and fecal pellet expulsion as demonstrated in the guinea pig colon. The EC_{50} values 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 in vivo studies in rats and dogs, prucalopride was shown to stimulate GI motility, inducing contractions starting from the proximal colon, and all the way to the anal sphincter at oral doses $\geq$0.04 mg/kg. Prucalopride was also shown to stimulate gastric and small intestinal motility to accelerate gastric emptying, and these effects were sensitive to the 5-HT_4 receptor antagonist.

Prucalopride was evaluated in in vitro CV safety pharmacology studies in isolated cells, including HEK293 cells transfected with hERG, ventricular myocytes from guinea pig hearts, Purkinje fibers from rabbit and canine hearts, papillary muscles of guinea pig heart, porcine, canine and human isolated coronary arteries, and isolated human atrial muscle strips. Prucalopride had no effect on the delayed rectifier current (I_{Kr}) at concentrations up to 1µM (400 ng/ml), and only attenuated I_{Kr} in hERG-transfected HEK cells and in guinea pig ventricular myocytes at high micromolar concentrations. The half maximal inhibitory concentration for blockade of hERG current in transfected HEK293 cells was 22µM. In isolated guinea pig papillary muscles, canine and rabbit Purkinje fibers and isolated rabbit hearts, prucalopride prolonged the action potential duration (at 90% repolarization, +14% to +22%) at high concentrations of ≥3µM (1110 ng/ml). In isolated human atrial muscle strips, prucalopride caused only minor increases in contractile force at concentrations starting at 100nM. Prucalopride had no contractile effect on porcine, canine and human isolated left anterior descending coronary arteries over a concentration range of 1nM to 10µM. In an in vitro platelet aggregation study, prucalopride at up to 200nM, had no significant effect on platelet aggregation in human blood.

In conscious or anesthetized dogs, prucalopride had no relevant effect on ECG intervals or on the duration of the action potential of the right ventricle. In conscious dogs, after IV dosing or at high oral doses (≥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. In guinea pigs and rabbits, only high IV doses (guinea pigs ≥1.5 mg/kg; rabbits ≥9.6 mg/kg) of prucalopride prolonged the duration of the QTc interval. There were no apparent effects of prucalopride on ECG characteristics in conscious dogs following oral dosing at 30 mg/kg/day for 12 months. In the anesthetized methoxamine-challenged rabbit model of arrhythmia, IV doses of prucalopride at up to 18.6 mg/kg (4812 ng/ml or 12µM) did not cause ventricular tachycardia, torsades de pointes or other cardiac arrhythmias. In anesthetized dogs and juvenile pigs, prucalopride had no effects on respiratory parameters at up to the highest doses administered (dogs, plasma levels of 3793 ng/ml; pigs, plasma levels of 757 ng/ml).

In single dose toxicity studies in rats and mice, CNS related findings including palpebral ptosis, tremors, ataxia, clonic convulsions, hypothermia, sedation (≥160 mg/kg in mice) and salivation were noted at PO (oral) doses ≥320 mg/kg. In addition, tachypnea and spasms were noted at IV doses of 80 mg/kg and 40 mg/kg in mice and rats, respectively. Ptosis was also observed in rats after repeated oral administration at ≥80 mg/kg/day. In dogs, prucalopride induced pedaling movements, sedation, ptosis, decubitus and salivation in repeat dose toxicity studies at doses ≥20 mg/kg/day.

5.4. ADME/PK

5.4.1. Absorption

Pharmacokinetics (PK), absolute bioavailability and tissue distribution of R093877 in the male SPF Wistar rat after single IV and oral administration of R093877 at 0.63 mg (base-eq.)/kg (Report number N111732/1)

Male SPF Wistar rats (4/dose/time point) were dosed with oral formulation of ^{14}C-R093877 specific activity 74.2 µCi/mg base eq./kg) dissolved in demineralized water at a final concentration of 0.063 mg (base-eq.)/ml by gastric intubation. Male rats (4/dose/time-point) were also dosed IV through the tail vein with ^{14}C-R093877 dissolved in an aqueous 50-mg glucose/ml solution at a final concentration of 0.315 mg (base-eq.)/ml. Groups of four rats were sacrificed at 8 and 15 min after IV administration and at 0.5, 1, 2, 4, 8, 24, 48 and 96 h after both IV and oral administration. Blood (6 to 8 ml) was collected at the time points above for PK parameters and total radioactivity (TR) were measured in plasma/blood/tissue by liquid scintillation spectrometry. Concentrations of unchanged drug (R093877) were measured by high-performance liquid chromatography (HPLC) method with the limits of quantification of 2 ng/ml for plasma, and 10 ng/g for tissue.

After IV administration, the mean half-life was 0.34 h, the volume of distribution at steady state (V_{dss}) was 4.9 l/kg, and total plasma clearance was high (CL =11.4 l/h/kg). Following oral administration, R093877 was rapidly absorbed. The highest mean concentrations were seen at 0.5 hr, and were 6.7 ng/ml.

Table 2. Pharmacokinetic Parameters of Unchanged R093877 in Plasma of Male SPF Wistar Rats After Single IV and Oral Administration at 0.63 mg (base-eq.)/kg

	Pharmacokinetic parameters	
	Intravenous	Oral
Vc (l/kg)	3.38	-
Vd_{ss} (l/kg)	4.90	-
Vd_{β} (l/kg)	5.65	-
Cl (l/h/kg)	11.4	-
$t_{1/2\ (0.5\ -\ 1\ h)}$ (h)	0.34	-
$AUC_{0-\infty}$ (ng.h/ml)	55.1	≤ 4.4
T_{max} (h)	-	0.5
C_{max} (ng/ml)	-	6.7 ± 3.1
F_{abs} (%)	(100)	≤ 8

Abbreviations: V_c, volume of distribution of the central compartment; V_{dss}, volume of distribution at steady state; $V_{d\beta}$, volume of distribution; CI, confidence interval; AUC, area under the curve; $t_{1/2}$, mean elimination half-life; T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration
Note: F_{abs} = The absolute oral bioavailability was calculated as the $AUC_{0\text{-infinite}}$ ratio of unchanged drug after oral administration to that after IV administration

Pharmacokinetics and absolute bioavailability of R093877 in the female rabbit after single intravenous (IV) and oral administration of an aqueous solution of R093877 at 0.31 mg (base-eq.)/kg (Report number N111684/1)

Four female rabbits were dosed orally by gastric intubation (phase 1) or by IV injection in an ear vein (phase 2) with ^{14C}-R093877 (specific activity 74.2 µCi/mg base eq), dissolved in 50 mg glucose/ml solution) at a final concentration of 0.31 mg (base-eq.)/kg. Blood (5 to 6 ml) was collected at 0 (predose), 0.5, 1, 3, 8, 24, 48 and 96 h after oral administration and at 0 (predose), 0.167, 0.5, 1, 3, 8, 24, 48, and 96 h after IV administration, for measurement of PK parameters. Total radioactivity (TR) was measured in plasma/blood/tissue by liquid scintillation spectrometry. Concentrations of unchanged drug (R093877) were measured by HPLC method with the limits of quantification of 2 ng/ml for plasma, and 10 ng/g for tissue.

The plasma concentrations of unchanged drug (UD) declined biphasically with a half-life of 0.7 h, at least till 3 h after IV administration. At 8 h after injection, plasma levels of UD were below the limit of quantitation (≤2.0 ng/ml). An average volume of distribution at steady state VD_{ss} was estimated at 4.3 l/kg, and average total plasma clearance (CL) was estimated at 4.4 l/h/kg. Following oral administration, plasma levels of R093877 were slightly higher than the limit of quantification only in two rabbits (No. 2 at 0.5 and 1 h, and in rabbit No. 3 at 0.5 h). The absolute oral bioavailability for R093877 in the female rabbit is ≤5%.

Table 3. Pharmacokinetic Parameters of Unchanged R093877 in Plasma of the Female Albino Rabbit After Single IV and Oral Administration at 0.31 mg (base-eq.)/kg

	Pharmacokinetic parameters	
	Intravenous	Oral
Vc (l/kg)	3.55 ± 0.89	-
Vd_{ss} (l/kg)	4.30 ± 0.45	-
Vd_{β} (l/kg)	4.50 ± 0.62	-
Cl (l/h/kg)	4.40 ± 0.40	-
$t_{1/2,\alpha}$ (h)	0.25 ± 0.10	-
$t_{1/2,\beta}$ (h)	0.71 ± 0.04	-
$AUC_{0-\infty}$ (ng.h/ml)	70.8 ± 6.0	≤ 3.5[1)]
T_{max} (h)	-	0.5 - 1[2)]
C_{max} (ng/ml)	-	≤ 2.0[1)]
F_{abs} (%)	-	≤ 5[1)]

1) median value

2) n = 2

Abbreviations: V_c, volume of distribution of the central compartment; V_{dss}, volume of distribution at steady state; $V_{d\beta}$, volume of distribution; CI, confidence interval; AUC, area under the curve; $t_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration
Note: F_{abs} = The absolute oral bioavailability was calculated as the $AUC_{0\text{-infinite}}$ ratio of unchanged drug after oral administration to that after IV administration

Pilot study on the pharmacokinetics and absolute bioavailability of R093877 in the male Beagle dog after single IV and oral administration of an aqueous solution of R093877 at 1.25 mg (Base-eq.)/kg (Report # N111720/1)

Male Beagle dogs were dosed with R093877 intravenously and orally (PO) at 1.25 mg (base-eq.)/kg (1.0 ml/kg) following a cross-over design. R093877 was administered IV as a bolus injection in the jugular vein, and orally using a stomach tube. Blood (4.5 ml) was collected at 0, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h after each route of administration. PK parameters were determined from plasma by HPLC.

After IV administration in dogs, the plasma concentration of R093877 decreased in a mono- or biphasic manner, with a mean elimination half-life of 7 h. The volume of distribution was 3.4 l/kg, and total plasma clearance (CL) was 338 ml/h/kg. After oral administration, R093877 was rapidly absorbed with average peak plasma concentration of 279 ng/ml reached within 1 or 2 h after dosing. The absolute oral bioavailability in dogs was 77%.

Table 4. Pharmacokinetic Parameters of R093877 in Male Beagle Dogs After Single IV and Oral Dosing

Parameters	IV (mean)	Oral (mean)
$V_d\beta$ (1/kg)	3.44	--
Cl (ml/kg/h)	338	--
$AUC_{0\text{-}24\ h}$ (ng.h/ml)	3630	2696
$AUC_{0\text{-}\alpha}$ (ng.h/ml)	3957	3011
$t_{1/2}\beta$ (h)	7.01	7.20
T_{max} (h)	--	1.5
C_{max} (ng/ml)	--	279
Fabs (%)	--	77

Abbreviations: $V_{d\beta}$, volume of distribution; CI, confidence interval; AUC, area under the curve; $t_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration
Note: Fabs = The absolute oral bioavailability was calculated as the $AUC_{0\text{-}infinite}$ ratio of unchanged drug after oral administration to that after IV administration

Plasma levels of R093877 after single oral administration of a solution of R093877 by gavage at 0.31 mg/kg to awake Beagle dogs (Report # N111747/1)

Seven male Beagle dogs (±13 kg) surgically instrumented for chronic studies were dosed by single oral gavage with R093877 at 0.31 mg/kg. Blood was collected prior to dosing at time 0 and at 1, 2, 4 h after dosing and plasma drug concentrations determined using HPLC. PK parameters were measured using HPLC with a quantification limit of 4 ng/ml.

After single oral administration in dogs, the maximum plasma levels of R093877 was 66.1 ng/ml, and was reached after 1 h in six out of seven dogs, and after 4 h in the remaining dog. The $AUC_{0\text{-}4\ h}$ was 172 ng.h/ml with the absolute oral bioavailability of R093877 in dogs at 76.7%.

Table 5. Pharmacokinetic Parameters in Instrumented Awake Male Beagle Dogs After Single Oral Dose of R093877 at 0.31 mg/kg

Parameters	Mean ± StdDev
$AUC_{0\text{-}4\ h}$ (ng.h/ml)	172±81
T_{max} (h)	1.4±1.1
C_{max} (ng/ml)	66.1±29.3

Abbreviations: AUC, area under the curve; T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; StdDev, standard deviation

5.4.2. Distribution

The plasma protein binding and the distribution of R093877 in blood (Report # N111726/1)

Blood was obtained from healthy male volunteers, Wistar rats, Swiss mice, female Albino rabbits and male Beagle dogs. Ten ng base-eq./ml and 500 ng base-eq./ml of 3H R093877 were added to human blood and to animal (dogs, rats, rabbits and mice) blood, respectively, for distribution study. For protein binding study, 10 ng base-eq./ml and 500 ng base-eq./ml of 3H R093877 were added to human plasma and to animal (dogs, rats, rabbits and mice) plasma, respectively. A pool of blank plasma from five male adults was fortified with ^{3}H-R093877 at concentrations of 2, 10, 25, 100 and 250 ng base-eq./ml. Pools of blank plasma from five male dogs, from five male rats, five female rats, five female rabbits or 50 mice were fortified with ^{3}H-R093877 at concentrations of 25, 100, 500, 1,000 and 2,000 ng base-eq./ml. Radioactivity levels were measured in human and animal blood and plasma.

In human plasma, the binding of R093877 increased at higher pH values. In the pH-range 7.1 to 7.7, the percentage bound increased from 23.3% to 35.5%. R093877 showed a low extent of protein binding, and the species differences were small: at 28.9±1.4% (man), 26.8±1.5% (dog), 29.5±1.1% (male rat), 30.7±0.5% (female rat), 30.7±0.4% (male mouse) and 36.6±0.8% (female rabbit). The blood to plasma concentration ratio (C_b/C) of R093877 at 10 ng base-eq./ml is 1.60 in human blood. The C_b/C at 500 ng/ml averaged 1.69 in dog blood, 1.52 in male rat blood, 1.44 in female rat blood, 1.41 in rabbit blood, and 1.39 in mouse blood.

The fractions of R093877 distributed to plasma water, plasma proteins and to blood cells were comparable in the five species. In whole blood, more than half of the drug was distributed to blood cells (53.7 to 70.6%). The fraction present in plasma water (21.6 to 32.1%) was about twice the fraction bound to plasma proteins (7.9 to 16.1%).

The tissue distribution of ^{14}C-R108512 in the male SPF Wistar rat after single oral administration at 5 mg base-eq./kg, as studied by whole-body autoradiography (Report # N125384/1)

Male SPF Wistar rats (average weight 238±8 g) were dosed orally by gastric intubation of 1 ml of ^{14}C-R108512/100 g body weight to provide a dose of 5 mg base-eq./kg. The average amount of radioactivity administered was 1.9 MBq per rat. At 0.5, 2, 4, 8 and 24 h after dosing, one rat was sacrificed/time point, and exposed to whole body autoradiography.

In most tissues, the maximum concentrations of total radioactivity were observed at 0.5 h after gavage, indicating a rapid distribution of R108512 and initial metabolites. TR levels did not decrease very much up to 8 h after administration. Highest concentrations were observed in GI

contents (36 to 100 µg-eq./g from 0.5 till 8 h after gavage), bile (41 µg-eq./g at 0.5 h after gavage) and urine (32 µg-eq./g at 8 h after gavage). Highest tissue concentrations were observed in liver, small intestinal tissue and pancreas, reaching $AUC_{0\text{-}8\ h}$-values of 11 to 12 times that in blood. TR levels in the male Wistar rat rapidly declined from 8 h after administration, and at 24 h, TR levels were at least in the order of 10 times lower than their peak values in most tissues, with exception of testicle.

The tissue distribution of ^{14}C-R093877 in the male SPF Wistar rat after single IV and Oral administration at 0.63 mg base-eq./kg, as studied by whole-body autoradiography (Report # N111732/1)

Tissue distribution of ^{14}C-R093877 was studied in male SPF Wistar rats, as indicated above.

The distribution of radioactivity in various tissues after IV and oral administration was rapid as previously reproduced. The tissue levels of total radioactivity (TR) and unchanged drug (UD) were rapidly in equilibrium with corresponding plasma levels. The maximum concentration of total radioactivity (TR), in most tissues were observed at 8 or 15 min after IV, and at 30 min after oral dose. These were generally similar (or slightly later) to peak times of TR in plasma. The highest concentration after IV or oral were found in liver (16 to 19%, small intestine (5 to 8%), kidney (0.8 to 3%), and large intestine (0.5 to 0.9%). Brain had very low conc. (0.02 to 0.09%). The amounts of TR were much higher in the stomach contents after oral, than after IV doses. The tissue to plasma $AUC_{0\text{-}8\ h}$ ratios of TR, after IV dosing were 42 in liver, 16 in small intestine, 13 in kidney, and 10 in the large intestine. These values after oral dosing were 60 in liver, 29 in small intestine, 11 in kidney, and 12 in the large intestine. Maximal TR levels in small intestinal contents were ~40% of the dose at 2 h, whereas the maximal TR in small intestinal tissues were 8% and 6%, after oral and IV dosing, respectively. In GI tissues, UD to TR concentration ratios after oral dosing were generally higher than in other tissues. The TR and UD, in tissues initially declined rapidly, at later time points it was more gradual, but no retention was noted. In GI, the concentration versus time profiles were influenced by the amounts in their GI contents, especially after oral doses.

5.4.3. Metabolism

The metabolism of ^{14}C-R093877 was studied in male rats (0.63 mg/kg, batch No 1055), 96 hrs. after single oral (by gavage, 1 ml/100 g) or IV dose (0.2 ml/100 g, into tail vein). The metabolic patterns in urine, feces and plasma were determined by HPLC with on-line radiometric and fluorescence methods. The results of excretion studies are presented under that section.

The drug was extensively metabolized in rats. Both in urine and feces, mostly similar metabolites were present after oral or IV doses. The major metabolites accounted for 31.8% and 37.7% after an oral and IV doses respectively, in urine + feces. The major metabolite (#7), was identified as R106569 (results from acyclic oxidation, at the 3 position of the 2, 3-dihydrobenzofuran ring). The second major metabolite (#2) made up 20.1% and 16.5% after an oral and IV dose respectively. Several other metabolites (#1, 3, 4, 5, and 6) accounted for 0.7 to 5.9%. In plasma, these same metabolites (#7 and #2), along with unchanged drug (UD) were present after oral or

IV doses, up to 8 hrs. after dosing. The UD/TR ratio was much more abundant after IV, than after oral administration, at 1 hr.

The metabolism of R093877 after a single oral intravenous dose of 0.31 mg (base-eq.)/kg in female rabbits (Report # 111728/1)

The metabolism of ^{14}C-R093877 was studied in female rabbits (0.31 mg/kg, batch No 1055), 96 hrs. after single oral (by gavage, 1 ml/100 g) or IV dose (1 ml/100 g, into the tail vein). The metabolic patterns in urine, feces, and plasma were determined by HPLC with on-line radiometric and fluorescence methods. The results of excretion studies are presented under that section.

In rabbits, the major metabolite in urine was a glucuronide of R093877 (the aromatic amine on the 2, 3-dihydrobenzofuran ring). This accounted for 45.8% of an oral, and 50.3% of IV doses. The unchanged drug (UD) accounted for 23.5% of the oral and 17.3% of the IV dose in feces. Several other metabolites #1 (R107504), #2 (R106569), and #3 (R103451) accounted for 0.3 to 1.1% in urine/feces. In plasma, same metabolites were present after oral or IV doses, the glucuronide was the major product, along with UD, up to 24 hrs. dosing. The unchanged drug (UD) was much more abundant in plasma during first hrs. after IV dosing than after oral, however the $AUC_{0\text{-}8hr}$ was similar after oral or IV doses (182 and 195 ng/h/ml).

In Vitro Metabolism of R093877 in Hepatocytes and Liver Subcellular fractions of Mouse, Rat, Dog and Human (Report # 1113041/1)

The in vitro metabolism of ^{14}C-R093877 was examined in cell cultures and subcellular fractions of mouse, rat, dog and human hepatocytes. Hepatocytes were prepared from the livers of male mice (SPF albino), male rats (SPF Wistar), Beagle dogs, and liver piece from an organ transplant donor. Liver preparations were incubated with ^{14}C-R093877, and various substrates (7-ethoxycoumarin, scoparone, cyclosporine A, and dextromethorphan) to further determine the biotransformation of the drug in hepatocytes. The major metabolites were characterized by radio-HPLC methods.

In both rat and mouse hepatocyte suspensions and primary cell cultures, extensive metabolism was noted, with a total of 11 to 12 metabolites. The metabolite #7 (alicyclic hydroxylated metabolite R106569) was the major metabolite in both species (40% and 33 to 61% of the incubated dose, in 107 cells/ml, in mouse and rat, respectively). The second major metabolite in rat hepatocytes was #10 (acid metabolite, R107504), and in the mouse, it was #17 (dehydrated derivative, R104068). Several other metabolites were detected both in rat (2, 3 ,4, 6, 12, 13, 14, 16, and 17) and mouse (9, 2, 3, 4, 10, 11, 6, 12, 14, and 16). Metabolite #12 was identified as R084536, and #13 as R104065. Less extensive metabolism of the drug was noted in the dog. Total of five metabolites (10, 12, 6, 7, and 15) were found in the 2-hr incubates of dog subcellular fractions/hepatocyte, but 88 to 94% of the drug was found in the unchanged form, Figure 2. Very little and slow metabolism of the drug was noted in the human hepatocytes/liver subcellular fractions. A total of three metabolites (10, 13, and 7), which were found in the 51-hr incubates of the human liver hepatocytes/subcellular fractions. Most (84 to 98%) of the drug was in the unchanged form, and the major metabolite #7, was observed only in trace amounts. The

comparative conversion of R093877 to these three metabolites was higher in rats and mice (48-hr incubates). Metabolite #6 (accounting for 0.8% of the incubated dose) in human hepatocytes was detected after 6.5 hrs. of incubation. This metabolite was later identified as a degradation product of R093877. Treatment of incubates with β-glucuronidase/arylsulphatase indicated that metabolite #2 in dog in dog incubates was conjugated, but in rat/mouse hepatocytes, no conjugation was detected. In a pilot in vitro study of rat, dog, and human liver subcellular fraction with unlabeled drug (study # 111730/1), additional metabolites (M2, M3, and M4) were characterized. M2 (R84536) was found in human, rat, and dog. It was an N-dealkylation product of metabolite #7. Thus, extensive metabolism of the drug was noted in rat and mouse, and much less in dog, with #7 being the major metabolite. Very little metabolism, with trace amounts was observed in humans.

Figure 2. Mass Balance of R093877 and Metabolites in Mouse, Rat, Dog, and Human

TABLE 7: Mass balance of R093877 and its metabolites in 2-h incubates of R093877 (2 µM) with liver subcellular fractions (microsomes and 12000 x *g* supernatant fractions) of mouse, rat, dog and human. The protein concentration of the microsomes amounted to 1 mg/ml. The incubations with the 12000 x *g* supernatants were performed at a cytochrome P-450 concentration equivalent to that of the microsomes of the respective species. The samples were analysed for unchanged R093877 (UD) and its metabolites by reversed-phase radio-HPLC. The figures represent the percentage of the sample radioactivity accounted for by UD and by the various metabolites.

	Mouse		Rat		Dog		Human	
	12000 x g SN	Microsomes	12000 x g SN	Microsomes	12000 x g SN	Microsomes	12000 x g SN	Microsomes
Metabolite								
4'	0.6	- (1)	1.5	-	-	-	-	-
10	1.4	0.7	2.3	-	1.9	-	-	-
11'	-	-	1.4	-	-	-	-	-
12	1.0	3.2	3.2	2.4	1.3	1.9	-	-
6	1.1	2.3	2.5	1.8	1.9	1.1	0.8	-
13	-	0.9	3.0	0.7	-	-	0.6	-
7	45.0	34.8	57.9	32.9	1.3	0.6	T (2)	-
15'	-	-	-	-	5.6	2.3	-	-
17	3.9	3.5	3.4	2.8	-	-	-	-
UD	46.7	54.6	24.8	59.1	88.0	94.1	98.2	100.0

(1): not detected (detection limit: 200 dpm)

T (2): trace amount

5.4.4. Excretion

The excretion of R093877 after a single oral or IV dose of ^{14}C-R093877 at 0.63 mg base-eq./kg in male SPF rats (Report # 111650/1)

R093877 was labeled with ^{14C} at the carboxamide carbon atom with a specific activity of 1.01 GBq/mmole (27.3 mCi/mmole) or 2.75 MBq/mg base-equivalent (74.3 µCi/mg base-equivalent). Five male rats (average weight 241 g) were dosed by gastric intubation with 1 ml/100 g body

weight of R093877 at 12 µCi/rat. Five male rats (average weight 243 g) were also dosed by IV injection into the tail vein with 0.2 ml/100 g body weight at 11 µCi/rat. Urine samples were collected from 0 to 4 h, 4 to 8 h, 8 to 24 h, 48 to 72 h, and 72 to 96 h; and feces from 0 to 24 h, 24 to 48 h, 48 to 72 h, and 72 to 96 h after dosing. Total radioactivity (TR) was counted in samples by liquid scintillation counter.

In male rats (after IV or oral) dosing with ^{14C}-R093877, 61 to 64% of the administered dose was recovered in feces, and 32 to 35% in the urine, at 96 hours. The unchanged drug (UD) in feces was 2.4% of oral and IV dose.

In summary, after single oral administration, prucalopride was rapidly absorbed in all animal species examined, with peak plasma concentrations between 0.3 and 1.5 hours. The absolute oral bioavailability was very low in rabbits (≤5%), intermediate in rats (≤8 to 53%; dose and sex dependent), and high in dogs (77%). The exposures (C_{max} and AUC_{0-24}) to prucalopride after oral administration of the succinate and hydrochloride salts in rats and dogs were similar.

The plasma protein binding of prucalopride was low in all species (mice, rats, rabbits, dogs, man) ranging from 27% to 37%, and the blood-plasma concentration ratio ranged from 1.39 to 1.69 across species, indicating a preferential distribution to the blood cells. In dogs, after 6 months of PO dosing, residual concentrations of prucalopride were highest in the colon tissue and lowest in brain and fat tissue.

In vitro metabolism studies in liver microsomes and hepatocytes indicated that the metabolism in mice and rats was more extensive than in dogs and man. In mice, prucalopride was less extensively metabolized than rats, with unchanged prucalopride accounting for 44.3%-49.3% of the total radioactivity in plasma after oral administration of 10 mg/kg to male and female mice.

5.5. Toxicology

5.5.1. General Toxicology

In acute oral and IV toxicity studies of R093877 in mice and rats (Reports # M4476M, N112651/1); M4478M, N112649/1, R4480M (N112650/1, R4482M (N112648/1), R093877 (batch # ZR093877PFA021) was administered to male and female albino Swiss mice at 160, 320 and 640 mg/kg, by oral gavage. A single IV dose of R093877 at 40 mg/kg; and doses of 0 (control), 40 and 80 mg/kg were also administered to two males and two female mice. Male and female Wistar rats (five per sex) were administered oral R093877 (batch # ZR093877PFA021) at 0 (control), and 640 mg/kg; and single IV doses of R093877 at 0 (control), 40 and 80 mg/kg were also administered to rats (two per sex per group).

After oral administration in mice, one male and three female mice died after receiving 640 mg/kg dose, and one female mouse died from the 320 mg/kg dose. No mortality was observed in rats. In both mice and rats, the oral dosing of R093877 (at all doses) induced ataxia, palpebral ptosis, tremors, salivation and hypothermia. In addition, in mice, it induced loss of righting reflex, tonic and clonic convulsions, prostration, sedation, and wet urogenital region, and in rats, it induced hypotonia.

In another study, single subcutaneous doses of prucalopride (R108512) at 20, 40, 80, 160, 320, 640 or 1,280 mg/kg were administered to male and female Wistar rats. Rats dosed at 1,280 mg/kg had 100% mortality in males and 60% mortality in female rats within 6 hours after

dosing. In animals dosed at 640 mg/kg, sedation and ptosis were observed up to 24 hours after dosing. Sedation, ptosis and salivation were observed in animals dosed at 1,280 mg/kg before death, and the surviving animals showed sedation up to 24 hours postdosing

SD escalation subcutaneous toxicity study in the Beagle dog (Report # D4486M or N151691), no animal mortality occurred, and animal body weight or body weight gain was normal during the dosing or post dosing periods. Prucalopride administration at 5 mg/kg led to salivation, deep-set eyes, congested conjunctiva, appearance of the third eyelid and photophobia. There were no adverse effects on ECG, blood chemistry or urine parameters measured. At 20 mg/kg, salivation, deep-set eyes, congested conjunctiva, appearance of the third eyelid and photophobia were observed, in addition to slight sedation. ECG analysis at this dose showed a shortened PQ-interval. After a single SC dose of 50 mg/kg prucalopride to dogs, convulsions, ataxia, tremors, sedation and coughing were observed in addition to the effects seen with the lower doses. Hematological, serum or urinalysis parameters were not adversely affected. However, full clinical recovery occurred in the animals within 24 hours of dosing.

5.5.1.1. Repeat-Dose Toxicity

One-Month Pilot Oral Toxicity Study of R093877 in SPF Wistar Rats (Report # 4498M or 99959/1)

Testing Laboratories: Janssen Research Foundation,
2340 Beerse, Belgium.

Study Start Date: March 22, 1993

Study Completion Date: June 21, 1993

GLP Requirement: A non-GLP study.

Animals: SPF Wistar rats (6 weeks old), mean body weight, males 154 g, females 130 g.

Drug Batch No.: MCDL-0161-009-1

Methods: Four groups of Wistar rats (5/sex/group) were administered IV injections of R093877, at 0 (vehicle, control), 0.63, 2.5, and 10 mg/kg/day for 1 month, at volumes of 1 ml/100 g body weight/day. Additional three groups of five rats per sex were used for toxicokinetic (TK) studies (report # R4490M or study # N111680/1). These rats similarly received the aqueous solution. Mortality, clinical signs, body weights, food consumptions, hematology, clinical chemistry, and urinalysis were conducted. Organ weights and gross pathological examinations were carried out on all animals. In male rats, histopathological examinations were carried out on lymph nodes and spleens of control and high dose animals. For TK, blood was collected from the rats at autopsy.

Results:

Observed Effects: No treatment related effects were observed.

Mortality: None.

Body Weight/Food Consumption/Water Consumption: The initial and final (week 4) mean body weight of male rats were 154 g and 375 g, and of female rats were 130 g and 229 g, respectively. In the 10 mg/kg/day males, there was a slight decrease in the body weight (349 g versus 375 g in controls) and weight gain (221 g versus 193 g). The initial and final food consumptions of control male rats were 27.3 g/animal/day and 30.4 g/animal/day, and of female rats were 21 g/animal/day and 21.4 g/animal/day, respectively. In the 10 mg/kg/day male rats, there were slightly lower food consumptions (28.1 g versus 30.4 g/animal/day).

Hematology: In the 10 mg/kg/day male rats, there was a slight decrease in mean cell volume (59 versus 62 fl in controls).

Blood Chemistry/Urinalysis: No treatment related changes in serum or urinalysis were observed.

Organ Weights: In the 10 mg/kg/day males, decreases ion the spleen weights were noted (absolute: 574 versus 805 mg, relative: 1643 versus 2147 mg/kg).

Gross Pathology: No treatment related effects were observed.

Histopathology: No treatment related effects were observed.

Toxicokinetics: The data are shown in the Table below. At low dose, serum concentrations were undetectable. The peak serum concentration at 2.5 or 10 mg/kg dose, and AUC values (between 1 and 8 hours after dosing), were 2-fold higher in females than in males, and increased proportionally with increases in doses.

Table 6. Mean Plasma Toxicokinetic Parameter Values of R093877 Following Oral Gavage in 1 Month Rat Toxicity Study

Doses (mg/kg/day)	C_{max} (ng/ml) males	C_{max} (ng/ml) females	AUC ng·hour/ml) males	AUC ng·hour/ml females
2.5 mg/kg/day	94.4	245	275	352
10 mg/kg/day	349	701	950	2,346

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration

Six-Month Oral Toxicity Study of R093877 in Rats (Report # R4493M or N106682/2)

Testing Laboratories: Janssen Research Foundation, 2340 Beerse, Belgium.

Study Start Date: April 11, 1994

Study Completion Date: May 19, 1995

GLP Requirement: A statement of compliance with the GLP regulations and quality assurance unit was included.

Animals: SPF Wistar rats (4 to 5 weeks old).

Drug Batch No.: ZR093877PFA011

Methods: Four groups of Wistar rats (5/sex/group) were administered R093877 by oral gavage at, 0 (vehicle control), 1.25, 5, and 20 mg (base eq.)/kg/day for 6 months at volumes of 1 ml/100 g body weight/day. Additional three groups of (four per sex per group) rats were used for toxicokinetic (TK) studies (report # R4494M or study # 111723/1). Also, an in vitro study of R093877 on induction or inhibition of liver enzymes was carried out, in liver tissues of rats, at the end of 6-month period (report # FK1857 or study # 111649/1). R093877 was prepared in aqueous solution at conc. of 0.125, 0.5, and 2 mg/ml, pH 5 to 6.2. Mortality and clinical signs were observed QD. Body weights and food consumptions were noted once weekly. Ophthalmological examinations were carried out on 10 rats from control and high dose group, both before and at the end of 3 and 6 month period. Hematology, clinical chemistry and urinalysis (following deprivation of food and water) were carried out at the end of 3 and 6 months. Physical examinations and body weights recorded prior to sacrifice, and all animals were necropsied. Gross pathology and complete histopathological examinations were carried out on all animals. For toxicokinetics (TK), blood was collected from the orbital venous plexus of the satellite rats at the following times:

- On day 1, 7, 28, and 119, 1 hr after treatment, from the first two males and females of every group
- On days 4, 14, and 56, from the next two males and females of every group
- On day 183, at 1, 4, and 12 hours from the first two males and females
- On day 183, at 2, 8, and 24 hours, from the next two male and female rats

Additionally, in this study, liver pieces of four males and females were collected and frozen at the end of the treatment from all groups. Liver microsomes (at 110,000 x g) were later prepared from these frozen tissues to examine if R093877 induced or inhibited the hepatic drug metabolizing enzymes. Protein cytochrome P-450 contents (determined by the method of (Imai et al. 1966)), and several monooxygenases were measured by established methods. These monooxygenases were ethanol inducible aniline hydroxylase 9CYP2E1), dexamethasone-inducible (CYP3A1 and CYP3A2), phenobarbital-inducible (CYP2B subfamily), polycyclic aromatic compound-inducible (CYP1A1 and CYP1A2), and clofibrate induced (or hydroxylation of lauric acid, CYP4A1) cytochromes.

Results:

Observed Effects: No treatment related effects were observed.

Mortality: Two male rats in the control group were sacrificed due to poor physical health (one had cachexia and dehydration, and the other had various lesions). One female from the control group died due to an accident in week 13. One male from the high dose group died in week 18, due to severe prostitis. None of these deaths were drug related.

Body Weight/Food consumption/Water consumption: The initial and final (week 26) mean body weight of male rats were 204 g and 512 g, and of female rats were 153 g and 296 g, respectively. In females from the 20 mg/kg/day group, there was slight to moderate increases body weight and weight gain (17% to 38%) throughout the study. The initial and final mean food consumptions of control male rats were 28.7 g/animal/day and 50.6

g/animal/day, and of female rats were 20 g/animal/day and 39 g/animal/day, respectively. At 20 mg/kg/day in females, there was a significant increase in weekly (7%), total food consumption (548.4 versus 518.3 g/animal/day).

Hematology: At 20 mg/kg/day dose in both sexes, there were significant increases in mean hematocrit (males 46.4 versus 44.6, females 44.3 versus 41.7%), hemoglobin (males 16.0 versus 15.1, females 15.5 versus 14.4 g/dl) and red blood cells (males 9.2 versus 8.6, females 8.1 versus 7.6 106 /mm3) at 6 months. Similar changes were also observed at 3 months.

Blood Chemistry/Urinalysis: No treatment related changes in serum chemistry or urinalysis were observed.

Ophthalmology: No treatment related effects were observed.

Organ Weights: No treatment related effects were observed.

Gross Pathology: No treatment related effects were observed.

Histopathology: No treatment related effects were observed.

Toxicokinetics: Mean steady state plasma concentrations for the dose groups in rats were: males (1.25 mg/kg) were 9.7, (5 mg/kg) 198, and (20 mg/kg) 1,501 ng/ml; females (1.25 mg/kg) 17.5, (5 mg/kg) 475, and (20 mg/kg) 2,622 ng/ml, respectively. The drug concentrations were 2-fold higher in females, and increased in more than a dose proportional manner. The peak plasma concentrations and AUC values were similar between the sexes at 1.25 mg/kg dose, as shown in the table below. At higher doses, these were 2- to 5-fold higher in females than in males. Both AUC values and peak plasma levels increased in more than a dose proportional manner over the three doses.

Table 7. Mean Plasma Toxicokinetic Parameter Values for R093877 Following Oral Gavage in the Six Month Rat Toxicity Study

Doses (mg/kg/day)	C_{max} (ng/ml) males	C_{max} (ng/ml) females	T_{max} (hours) males	T_{max} (hours) females	AUC_{0-24h} ng·h/ml males	AUC_{0-24h} ng·h/ml females
1.25 mg/kg/day	11.8	12.7	2	4	30.1*	37.6*
5 mg/kg/day	229	655	2	2	785	4,148
20 mg/kg/day	1,979	4,224	1	2	7,914	26,532

Abbreviations: AUC, area under the curve; T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration
*AUC_{0-4h}

Studies in liver microsomes: No treatment related effects were noted on the hepatic protein or on the cytochrome P-450 contents at any drug concentration, except in females, at 5 mg/kg/day, where small inhibitory effects on microsomal protein, and lauric acid hydroxylase activity were observed. Since these were not affected at higher doses, they were not considered drug related. These studies indicate that R093877 had no pertinent inhibitory or stimulatory effects on hepatic cytochrome P-450 isoenzyme in rats.

These studies indicate that oral gavage administration of R093877 for 6 months at 1.25, 5 and 20 mg/kg/day, did not produce any toxicity in rats. The no effect dose in rats was 20 mg/kg/day.

Six-Month Oral Gavage Toxicity Study of R093877 in Beagle Dogs (Report # R4505M or N106683/2)

Testing Laboratories: Janssen Research Foundation, Beerse, Belgium.
Study Start Date: April 19, 1994
Study Completion Date: May 19, 1995
GLP Requirement: A statement of compliance with the GLP regulations and quality assurance unit was included.
Animals: Beagle dogs (~6 to 8 months old), mean body weight, 8.5 kg.
Drug Batch No.: ZR093877PFA011

Methods: Four groups of Beagle dogs (4/sex/group) were administered R093877 by oral gavage at 0 (vehicle, control), 0.63, 2.5, and 10 mg/kg/day for 6 months, at volumes of 5 ml/kg body weight/day. Three additional groups of dogs (4/sex/group) were used for toxicokinetics (TK), and tissue distribution studies (report # D4506M or study # 111724/1). Mortality and clinical signs were observed QD. Body weights and food consumptions were noted once weekly. Ophthalmological examinations were carried out on all dogs, both before and at the end of 3 and 6 month periods. Blood pressures, ECG and heart rates were measured on all dogs, at baseline, and at the end of 1, 3 and 6 months. Hematology and clinical chemistry were carried out twice in the baseline period, after 2 and 4 weeks, and every 4 weeks from there onwards. Urinalysis was carried out at baseline, at 1 and 3 months and at the end of the study. Physical examinations were performed prior to sacrifice, and all animals were necropsied. Gross pathology and complete histopathological examinations were carried out on all animals. For toxicokinetics (TK), blood was collected from the jugular veins of the satellite dogs at the following times: on day 0 and 168, at 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 hrs. After treatment, an additional sample was taken at autopsy. Blood was also collected on days 2, 3, 4, 7, 14, 28, 56, and 119 of the study, just prior to treatment. For tissue distribution studies, the following tissue samples were collected from dogs at autopsy (24 hrs. after treatment): liver, lung, brain, heart, kidney adrenal, pancreas, fat, muscle, stomach, duodenum and colon. The drug concentrations in plasma and tissues were measured by HPLC, with a limit of quantification of 2 ng (base-eq)/ml for plasma, and 10 ng/g for tissues.

Results:

Observed Effects: No treatment related effects were observed.

Mortality: None
Blood Pressure/ECG/Heart Rate: No treatment related effects were observed
Body Weight/Food Consumption/Water Consumption: The initial and final (week 24) mean body weight of control dogs were 8.5 kg and 10.5 kg, respectively. The initial and final mean food consumptions of control dogs were 0.35 kg/animal/day and 0.34 kg/animal/day, respectively. No treatment related effects on body weights or food consumptions were observed.
Hematology: No treatment related effects were observed.
Blood Chemistry/Urinalysis: No treatment related changes in serum or urine analysis were observed.
Ophthalmology: No treatment related effects were observed.

Organ Weights: No treatment related effects were observed.
Gross Pathology: No treatment related effects were observed.
Histopathology: At 10 mg/kg, in the urinary bladder, bleeding (mucosa) was noted in two of eight dogs, and round cells (mucosa) in four of eight dogs versus none of the above findings were seen in controls.

Toxicokinetics: Mean steady state plasma concentrations were reached from the 2nd to 3rd day onwards. The peak plasma concentrations were similar after single (day 0) and repeated treatment (day 168) and were reached within 2 hours. There were increases in peak concentration and AUC values in proportion to the dose. The half-lives were 4.2 to 5.6 hrs. after SD, and 6.7 to 7.5 hrs. after repeated dosing. The measured TK parameters are shown in the table below.

Table 8. Mean Plasma Toxicokinetic Parameter Values for R093877 Following Oral Gavage in the Six Month Dog Toxicity Study

Doses (mg/kg/day)	C_{max} (µg/ml) Day 0	C_{max} (µg/ml) Day 168	T_{max} (hours) Day 0	T_{max} (hours) Day 168	$T_{1/2}$ Hours Day 0	$T_{1/2}$ Hours Day 168	AUC µg·h/ml Day 0	AUC µg·h/ml Day 168
0.63 mg/kg/day	0.137	0.140	1	1.8	4.2	6.7	0.894	1.36
2.5 mg/kg/day	0.595	0.695	2	1.1	4.2	7.1	3.5	6.8
10 mg/kg/day	2.6	2.9	1	1.1	5.6	7.5	17.7	27.4

Abbreviations: AUC, area under the curve; $T_{1/2}$, mean elimination half-life; T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration
Note: $AUC_{0-\alpha}$ on day 0, and AUC_{0-24} hr on day 168

Tissue concentrations of R093877 were measured in various tissues. The concentrations of R093877 were higher in the tissues than in the plasma. The T/P ratios were highest in colon (42 to 97) and lowest in brain and fat (1.8 to 3.2). In all tissues, the tissue concentrations increased in a dose proportional manner, and T/P concentrations remained fairly constant over the three doses. No accumulation was observed in any tissue.

Table 9. Twelve-Month Repeated Dose Oral Toxicity Study in the Beagle Dog

Study no.:	N 134120/2
Study report location:	E-report pages 1-783
Conducting laboratory and location:	Department of Toxicology Janssen Research Foundation 2340 Beerse, Belgium
Date of study initiation:	November 13, 1996
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Prucalopride, lot # ZR108512PFA061, purity not given.

Key Study Findings

Administration of prucalopride to dogs at 0 (control), 2.5, 10 and 30 mg/kg/day for 12 months, was associated with three mortalities in the male dogs dosed at 30 mg/kg/day. Dosing at 30 mg/kg/day resulted in adverse CNS effects such as decubitus, pedaling movements, salivation and sedation. Ocular changes observed consisted of ptosis, protrusion of the third eyelid and

photophobia. Additional changes observed in the high dose group were decreases in body weight and weight gain, alterations in hematological (increased thrombocytes and monocytes, and decreased lymphocytes) and serum chemistry parameters (decreased cholesterol, phospholipids, and increased total bilirubin, AST and ALT). Post-mortem evaluation showed increased liver weight as well as slight focal necrosis, a retardation in cyclic activity in female dogs and a slight acceleration in thymic involution that was considered related to the decreased body weight.

Table 10. Methods of Twelve-Month Repeated Dose Oral Toxicity Study in the Beagle Dog

Doses:	**0 (control), 2.5, 10 and 30 mg/kg/day**
Frequency of dosing:	Daily (7days/week)
Route of administration:	Oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	0.5, 2 and 6 mg/ml / demineralized water.
Species/Strain:	Beagle dog
Number/Sex/Group:	4/sex/group
Age:	6 to 7 months old.
Weight:	4.8 to 13.5 kg.
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	Hematological examinations of two dogs were omitted predosing, therefore, the values were not recorded but was replaced by values recorded for two replacement dogs two weeks later. The deviations from study protocol had no effect on study results or outcome.

5.5.2. Observations and Results

5.5.2.1. Mortality

All animals were observed daily for signs of waning health, moribund state and mortality.

Three male dogs from the 30 mg/kg dose group were found dead (No. 61 at day 33, No. 63 at day 134, No. 64 at day 163). All the three dogs were observed with prucalopride-related CNS effects before dying including decubitus, sedation, pedaling movements and salivation. In addition, dog No. 64 was moribund the day before sacrifice.

5.5.2.2. Clinical Signs

All animals were observed daily for clinical signs of ill health, abnormal behavior or unusual appearance, untoward clinical effects.

At 30 mg/kg, test article-related observations seen in all males and most females include, decubitus, slight pedaling movements, moderate salivation, slight to moderate sedation. In addition, no vaginal discharge was seen in three of the four female dogs in the high dose group. Three of four male dogs receiving the 30 mg/kg dose, died or were sacrificed during the dosing period. One female dog (No. 162) was slightly dehydrated and had cachexia towards the end of the dosing period.

5.5.2.3. Body Weights

Body weight of all dogs were recorded prior to the dosing period and at weekly intervals during the dosing period. Body weight and body weight gain in animals dosed with 30 mg/kg prucalopride were marginally to moderately decreased (-8.2%) but were not statistically significant when compared to controls.

5.5.2.4. Feed Consumption

Food consumption was recorded in all dogs at weekly intervals during the dosing period, and was not adversely affected in any group dosed with prucalopride.

5.5.2.5. Ophthalmoscopy

Ophthalmological examination was performed on all dogs prior to the administration of the first dose, after 24 weeks and towards the end of the study.

After 12 months of dosing, the changes observed in dogs dosed at 30 mg/kg include, slight bilateral ptosis in the lone surviving male dog and in three females (Nos. 161, 162, 164). Slight protrusion of the third eyelid was seen bilaterally in female dog No. 161. Slight photophobia was bilaterally observed in two female dogs (Nos. 162 and 164).

5.5.2.6. ECG

ECG and heart rate measurements were conducted prior to administration of the first dose and after 4, 12, 24, 40 and 52 weeks of dosing.

The ECG and heart rate changes in treated dogs were small, transient and/or not dose-related, when compared to that of control animals, and therefore the changes were not considered relevant. There were no test article-induced arrhythmias observed, and there were no effects on systolic and diastolic blood pressure.

5.5.2.7. Hematology

Hematological examinations were performed in all the animals twice before administering the first dose, after 2 and 4 weeks of dosing and further every 4 weeks, with the exception of week 22 (where additional blood samples were taken from male dog No. 64 of the 30 mg/kg dose group, which was in bad condition).

In dogs dosed at 30 mg/kg, the increases in thrombocytes (17% - 26.9%) and monocytes (22% - 31%) and decreases in lymphocytes (-16.4% to -33.9%) were considered test article-related.

5.5.2.8. Clinical Chemistry

In dogs dosed at 30 mg/kg, decreases in cholesterol and phospholipids and marginal increases in total bilirubin as well as increases in AST (54%) and ALT (81%) were considered to be test article-related.

5.5.2.9. Urinalysis

Urinalysis was performed in all dogs prior to administration of the first dose and after 4, 12, 24, 40 and 52 weeks of dosing.

The urinary parameters were not affected in dogs dosed with prucalopride at 2.5, 10 and 30 mg/kg/day.

5.5.2.10. Gross Pathology

At the end of dosing, the dogs were weighed, anesthetized, and exsanguinated via the carotid artery. A full necropsy was performed, and all macroscopic changes were recorded.

There were no gross pathological changes observed that were considered treatment-related in all groups.

5.5.2.11. Organ Weights

Increased liver weights (23.2%) were observed in male and female dogs at the 30 mg/kg/day dose. The increased liver weight was considered test article-related since histological examinations showed changes such as slight centrilobular and focal necrosis in the 30 mg/kg dose groups. The observed increase in relative weights of the adrenals and thyroids in dogs dosed at 30 mg/kg were considered related to the decreased body weight seen at 30 mg/kg, and since there were no histological changes, they were not considered treatment-related.

5.5.2.12. Histopathology

There were slight hepatic changes (disturbance of centrilobular architecture, moderate chronic hepatitis, focal necrosis, pigmentation and prominent presence of Kupffer cells) observed in the liver of two of eight dogs treated with 30 mg/kg/day prucalopride.

In conclusion, the oral administration of R108512 at 0, 2.5, 10 and 30 mg/kg to male and female dogs for 12 months did not show any clinical signs of toxicity and did not result in any significant changes up to the dose of 10 mg/kg/day. Three R108512-related mortalities occurred in male dogs at the 30 mg/kg/day dose. All the three dogs were observed with signs of decubitus, sedation, pedaling movements and salivation prior to death.

5.5.3. Genetic Toxicology

Salmonella Typhimurium Gene Reverse Mutation Test: Ames test (Report # V4523M or Study # N 92911/1)

Testing Laboratories: Janssen Research Foundation, 2340 Beerse, Belgium.

Salmonella typhimurium strains TA97, TA98, TA100, TA1535, and TA1538 bacterial strains were exposed to final concentrations of 250, 500, 1000, 2000, 4000, and 5000 µg/plate. Distilled water was used as the solvent control, and the positive controls were 2-aminoanthracene (1 µg/ml), sodium azide (1 µg/ml), 2-nitrofluorene (5 µg/ml). Drug Batch No.: MDCL-0161-009-1.

R093877 was not mutagenic in tester strains TA97, TA98, TA1535, and TA1538 at doses ranging from 25 to 5000 µg/plate, in the presence or absence of metabolic activation (S9 mix). However, a significant increase in the number of revertant colonies was observed with the strain TA100 at conc. ≥3000 µg/plate (these concentrations were not cytotoxic to the cells), both in the presence (347 to 726 versus 172 in solvent control) and absence (455 to 680 versus 141 in solvent control) of metabolic activation system. This increase in the number of revertant colonies with R093877 was higher, than observed in the microbial strains employed with positive controls (with or without S9 mix) as shown in the table below.

Table 11. Effects of R093877 in the Tester Strain TA100 in the Ames Assay

Concentration of R093877 (µg/plate)	Number of Revertant Colonies without S9	Number of Revertant Colonies with S9
Solvent Control	141	172
250	134	150
500	148	160
1000	173	186
2000	250	225
3000	455*	347*
4000	466*	495*
5000	680*	726*
Positive Control	423	427

*a significant 2- to 5-fold increase was observed in a dose-dependent manner

Salmonella Typhimurium Gene Reverse Mutation Test: Ames test (Report # V4524M or Study # N 111745/1)

Testing Laboratories: Janssen Research Foundation, 2340 Beerse, Belgium.

Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to prucalopride (R093877) at concentrations of 250, 500, 1000, 2000, 4000, and 5000 µg/plate.

Solvent Control: Water

Positive Controls: 2-aminoanthracene (1 to 2.5 µg/ml), sodium azide (1 µg/ml), 2-nitrofluorene (5 µg/ml), 9-aminoacridine (50 µg/ml).

Drug Batch No. ZR093877PFA021.

R093877 was not mutagenic in tester strains TA98, TA1535, TA1537, and TA1538 at doses ranging from 25 to 5000 µg/plate, in the presence and absence of metabolic activation (S9 mix). However, a significant increase in the number of revertant colonies was observed with the strain TA100 at concentrations ≥2000 µg/plate, both in the presence (301 to 640 versus 144 with the solvent control) and absence (336 to 566 versus 141 with the solvent control) of metabolic activation system. A significant increase in the number of revertant colonies was also observed in all the microbial strains employed with positive controls (with or without S9 mix). See table below.

Table 12. Effects of R093877 in the Tester Strain TA100 in the Ames Assay

Concentration of R093877 (µg/plate)	Number of Revertant Colonies without S9	Number of Revertant Colonies with S9
Solvent Control	141	144
250	162	162
500	212	180
1000	203	216
2000	336*	301*
3000	528*	585*
4000	543*	685*
5000	566*	640*
Positive Control	508	1315

In Vitro Chromosomal Aberration Assays in Mammalian Cells

Evaluation of DNA Repair Inducing Ability of R093877 in a Primary Culture of Rat Hepatocytes (Report # V4831M or Study # 109001/1)

Rat Hepatocytes, isolated from male Wistar rats were used in the study, and the concentrations of R093877 used were 1.0, 3.3, 10, 33, 100, 100, and 333 µg/ml. The positive control used was 7, 12-Dimethylbenz anthracene, 0.05mM. Drug Batch No.: ZR093877PFA011.

R093877 did not increase the number of grains/cytoplasm at any concentration tested, but the nuclear grain count, corrected for cytoplasm, significantly increased at 100 and/or 333 µg/ml. The data from two experiments are shown in the tables below. A significant increase in the number of mean nuclear grain counts were observed with the positive controls (dimethylbenz anthracene).

Effects of R093877 in 'In Vitro' unscheduled DNA synthesis (UDS) in Primary Culture of Rat Hepatocytes

Table 13. Experiment 1 Results: 'In Vitro' Unscheduled DNA Synthesis (UDS) in Primary Culture of Rat Hepatocytes

Concentration of R093877 (µg/ml)	Main Nuclear Grain Count, corrected for Cytoplasm	Mean Percentage of Viable Cells, relative to Blank
Solvent Control	-3, -4	100
1	1, 0	90
3.3	1, -1	86
10	1, 0	77
33	-1, 0	76
100	2, 0	58
333	1, 16*	11
Positive Control	52, 52	38

Table 14. Experiment 2 Results: 'In Vitro' Unscheduled DNA Synthesis (UDS) in Primary Culture of Rat Hepatocytes

Concentration of R093877 (µg/ml)	Main Nuclear Grain Count, corrected for Cytoplasm	Mean Percentage of Viable Cells, relative to Blank
Solvent Control	-2, 0	100
1	0, 2	98
3.3	1, 1	87
10	4, 1	71
33	2, 2	74
100	27*, 5	57
333	6, 9*	9
Positive Control	53, 47	20

*significant differences were observed at this concentration

This study suggests that R093877 was positive in this assay at concentrations of 100 µg/ml or higher, which were found to be cytotoxic. Thus, the positive findings were observed only at the cytotoxic concentrations. In addition, a repeated UDS assay was negative. Overall, the rat hepatocyte UDS assay was not considered positive.

Ex Vivo Rat Hepatocyte DNA Repair Assay, Evaluation of DNA Repair Inducing Ability of R093877 in Male Rat Hepatocytes (Report # 4866 or Study # N111721/3)

Testing Laboratories: (b) (4)

Test Strain: Male Wistar rats, ~12 weeks old, 259 to 388 g.

No. of Animals: 3 animals/group/sacrifice time.

Route of Administration: Oral intubation (20 ml/kg body weight).

Doses Employed: 40, 160, and 548 mg/kg body weight (formulated as 2, 8, and 27.4 mg/ml).

Cells Employed: Rat hepatocytes, isolated from male Wistar rats by the method of Ashby et al and Butterwoorth et al (Mutation Res 156:(1); 1985, and 189 (123), 1987)

Basis of Dose Selection: The dose selection was based on the maximum concentration of the drug, that could be formulated, which was 27.4 mg/ml in the vehicle.

Solvent Control: Water containing 30% hydroxypropyl-β-cyclodextrin.

Positive Controls: Dimethylnitrosamine (DMN 10 mg/kg), for 4-hr treatment time, 2-acetylaminofluorene (2-AAF, 50 mg/kg), for 12-hr treatment time.

Drug Batch No.: ZR093877PFA011.

The objective of this test is to determine the in vivo hepatocyte DNA-repairing ability of the drug as unscheduled DNA synthesis (UDS). Rats were given a single oral dose of 40, 160, or 548 mg/kg of R093877 (20 ml/kg). A group of rats were similarly treated with the vehicle (distilled water containing 30% hydroxypropyl-β-cyclodextrin) or DMN/2-AFF (the positive controls). Additional four groups of satellite animals were used for toxicokinetic (TK) studies (study # FK1832). These rats (N=6) similarly received the three doses of the drug, and the vehicle (N=3). UDS was determined by counting the number of silver grains resulting from 3HTdR incorporation in the hepatocyte nucleus. The slides are scored by counting the grain counts over nuclei of 50 cells. Grain counts over nuclear areas were compared to grain counts over a single adjacent cytoplasm area of the same size, in the same cell (net nuclear grain counts). For every cell, the number of grains/cytoplasm, grains/nucleus, and the net nuclear grain counts are determined, and comparisons are made between the drug versus control.

No effects on the body weight were noted, but at 548 mg/kg, one animal died. Cell viability was not different between treated (55 to 81%) versus negative controls (60 to 80%). R093877 did not increase the net nuclear grain count (N-C) in any animal, or the percentage of cells in repair/group average in animals, at 4 or 12 hrs sampling time. A significant increase in the net nuclear grain count, and the percentage of cells in repair/group average was observed with the positive controls (DMN, 2-AAF).

Mouse Lymphoma Forward Gene Mutation (At the TK Locus) Test of R093877 (Report # V4529M or Study # N109250/1)

Testing Laboratories: (b) (4)

Mouse lymphoma L5178Y cell line, heterozygous at the tyrosine kinase (TK) locus, originally derived from the Fischer L5178Y line, isolated by Clive (Mutation Res. 31: 17, 1975). These cells are resistant to the cytotoxic effects of the pyrimidine analogue trifluorothymidine (TFT). By applying the TFT-selection procedure, it is possible to discriminate between the two different classes of the TFT-resistant mutants (small and large colonies) which are believed to represent the different types of lesions induced in the DNA by the test substance.

Concentration Employed: Without metabolic activation 330, 560, 1000, 1780, and 2380 µg/ml. With metabolic activation 330, 1000, 1780, 2360, and 3340 µg/ml.

Solvent Control: F10 medium, buffered with 20mM HEPES

Positive Control: Ethylmethanesulfonate (EMS, 2mM) was used in the absence of metabolic activation, and 3-dimethyl nitrosamine (DMN 0.5mM) was used, in the presence of metabolic activation.

Drug Batch No.: ZR093877PFA011

Cells (8 to 16 x 10^6) with or without S9 activation mixture were incubated in HEPES buffer for 3 hours, with the indicated concentrations of R093877, along with the positive and negative controls. At the end of the experiment, the mutagenic response of the small and large colonies was separated, and the mutant frequency (after 3 days), and the cloning efficiency (after 9 days) of the cells (as % of control) was determined. The small colonies result from chromosomal damage to the TK and adjacent genes, whereas large colonies result from mutants with single gene mutations (substitutions, deletions of base-pairs) affecting the TK gene. A total of three independent experiments were carried out.

In the first two experiments, in the presence of metabolic activation, R093877 up to 3340 µg/ml, showed no significant differences in mutant frequencies, between vehicle control and the treated samples, although, a significant increase in the number of mutant frequency was observed in all the positive controls. However, without metabolic activation, significant differences (3- to 4-fold) in mutant frequency, at the TK- locus were observed, only at one concentration, i.e. at 1000 µg/ml, in both experiments. Since there was no dose related trend, a third experiment was conducted in the absence of metabolic activation (using 650 to 1541 µg/ml concentrations of the drug). The third experiment was negative and did not confirm the results of the first two experiments.

Effects of R093877 on Chromosome Aberration in Human Peripheral Blood Lymphocytes (Report # V4530M or Study # 109219/1)

Testing Laboratories: Janssen Research Foundation, Beerse, Belgium.

Cells employed: Cultured peripheral human lymphocytes were prepared from two healthy male donors.

Concentration Employed: Without metabolic activation, 35, 117, and 395 µg/ml, and with metabolic activation, 23, 117, and 2000 µg/ml were used.

Solvent Control: Dimethylsulphoxide, 2% v/v.

Positive Control: Mitomycin C (0.2 µg/ml) was used in the absence of metabolic activation, and cyclophosphamide (20 µg/ml). in the presence of metabolic activation.

Drug Batch No.: ZR093877PFA011

Triplicate human lymphocyte cell cultures were exposed to various concentrations of R093877, in the presence or absence of metabolic activation. In the first experiment (with cells from the first donor), the cultures were harvested at 69 hours after the initiation of treatment. In the second experiment (with cells from the second donor), the cultures were harvested at 69 and 93 hours. Positive and negative controls were similarly treated. At the end of the study, at least 100

metaphases/duplicate cultures were examined for sister chromatid- and chromosome-type aberrations. Mitotic index was determined by examining 1000 cells/culture.

R093877 did not show any increase in structural chromosome aberrations at any concentration tested, which ranged from 23 to 2000 µg/ml, with or without metabolic activation. The concentration of the drug analyzed, was within ±3% of the dose at 2000 µg/ml. Also, the drug did not affect the pH, or the osmolality, and it was stable up to 48 hours after preparation. The positive controls showed a highly significant increase in chromosome aberrations. Therefore, R093877 was not mutagenic in this assay.

In Vivo Micronucleus Test of Oral R093877 in Mice: (Report # M4865M or Study # N 111746/1)

Testing Laboratories: Janssen Research Foundation, Beerse, Belgium.

Test Strain: Adult male and female Albino Swiss SPF mice, 8 weeks old. Males 30 to 40 g, females 26 to 37 g.

No of Animals: 5 animals/sex/group/sacrifice time.

Route of Administration: Oral intubation (suspension, 0.1 ml/10 g body weight).

Doses Employed: 40, 160, and 640 mg/kg body weight.

Solvent Control: Tween 20 + Avicel RC 591 + distilled water.

Positive Controls: Cyclophosphamide (CP), 40 mg/kg.

Drug Batch No.: ZR093877PFA021

Mice were given a single oral (suspension) dose of 40, 160, or 640 mg/kg of R093877. A group of mice were similarly treated with the vehicle (tween 20 + Avicel + water) or CP (positive control). Mortality, clinical signs, and body weights were observed at 24 and 48 hours prior to sacrifice. Animals were sacrificed at 24 and 48 hours after dosing, and bone marrow cells were prepared from the surviving animals. Cells were stained, and 1000 polychromatic and normochromatic erythrocytes (NCE) per animal were examined for the presence of micronuclei, and number of NCE, PCE and the ratio of PCE to NCE were recorded. The statistical significance in the treated groups was determined, using Mann-Whitney U test.

R093877 did not cause any changes in the body weights, in male or female mice at any dose. At 640 mg/kg, three mice died (two males and one female) at 24 hours, and seven died (four males and three females) at 48 hours. At 160 and 640 mg/kg, animals had slight and strong sedation, respectively. No marked reduction in the number of PCE to PCE + NCE was observed at any of the doses, except at 160 mg/kg, in females only at 24 hours (47.5% versus 57% in vehicle controls). R093877 did not induce an increase in micronucleated PCE and NCE, in either male or female mice bone marrow, at any dose level, including at 640 mg/kg. In contrast, CP induced a significant increase in the micronucleated PCE in both male and female mice, compared to the vehicle control.

5.5.4. Carcinogenicity

Prucalopride was tested in the 2-year oral gavage carcinogenicity studies in mice at dose levels of 0, 10, 20 and 80 mg/kg/day, and in rats (0, 5, 20 and 80 mg/kg/day in males and 0,5, 10 and 40 mg/kg/day in females). Carcinogenic potential of prucalopride was also assessed in a 12-month neonatal mouse carcinogenicity study at dose levels of 0, 75, 150, and 300 mg/kg/day.

In the 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 fatal epithelial mammary tumors, particularly mammary adenocarcinoma in female mice. The incidence of mammary gland adenocarcinoma was significant only at the high dose of 80 mg/kg which provides a 200-fold exposure margin for the clinical dose of 2 mg/day. There were no significant tumor incidences at 10 and 20 mg/kg (24x the therapeutic exposure at 20 mg/kg) doses. The tumor incidences and the toxicology data are summarized in the Tables below.

Table 15. Significant Neoplastic Changes in Male and Female Mice Receiving Oral Prucalopride for 24 Months

Tumors	Control	10 mg/kg	20 mg/kg	80 mg/kg	P (1-sided) for trend (a)
Males					
Testis					
Benign Leydig cell tumors	0/60	1/60	2/60	2/60	(c) 0.0488*
Females					
Mammary gland					
Adenocarcinoma	2/60	1/60	1/60	7/60	(b) 0.0061**
Uterus-cervix-vagina					
Endometrial stromal sarcoma	0/60	0/60	1/60	2/60	(c) 0.0332*

Toxicokinetics: The plasma exposure levels in mice were compared with that in humans receiving repeated oral dosing of 2 mg twice a day for 6 days ($AUC_{0\text{-}24h}$, 210 ng.h/ml). The AUC ratios (mouse to human) indicate that the exposure in mice was higher than in humans. The exposure ratios in the males after 10, 20 and 80 mg/kg doses were approximately 6, 15 and 114, and in the females, the ratios were 3.2, 13 and 101 respectively.

The preliminary data summarizing the C_{max}, AUC and AUC ratios in the male and female mice receiving different doses of prucalopride is summarized in the table below.

Table 16. Pharmacokinetic Parameters in Male and Female Mice

	Male Mice			Female Mice		
Dose(mg/kg/day)	**10**	**20**	**80**	**10**	**20**	**80**
Day 180						
C_{max} (ng/ml)	730	1207	5859	494	1491	6692
C_{max} ratio	97	161	781	66	199	892
AUC_{0-24h} (ng.h/ml)	1273	3194	23900	673	2633	21135
AUC_{0-48h} (ng.h/ml)	804*	2010*	12443*	456*	1707*	12089*
AUC_{0-24h} ratio	12	29	219	6.2	24	194
AUC_{0-48h} ratio	n.d	n.d	n.d	n.d	n.d	n.d
Day 731						
C_{max} (ng/ml)	376	1140	3647	322	1110	6543
C_{max} ratio	50	152	486	43	148	872
AUC_{0-24h} (µg.h/ml)	748*	1519*	7090*	n.d	n.d	n.d
AUC_{0-48h} (ng.h/ml)	n.d	n.d	n.d	662*	1899*	10153*
AUC_{0-24h} ratio	n.d	n.d	n.d	n.d	n.d	n.d
AUC_{0-48h} ratio	n.d	n.d	n.d	n.d	n.d	n.d

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; n.d, not determined

In the rat carcinogenicity study, there were significantly increased incidences of benign pheochromocytoma, hepatocytic tumors, mammary gland glandular tumors, pancreatic islet cell tumors, pituitary adenomas, and thyroid follicular tumors in the male rats. In the females, there were increased incidences of mammary gland glandular tumors, thyroid follicular tumors and hepatocellular adenomas. The incidences for these tumors were significant only at the highest dose which provides 556- and 495-fold margins for the therapeutic exposure. The doses of 5 and 20 mg/kg (6x and 63x the therapeutic exposure) in males and 5 and 10 mg/kg (7x and 40x the therapeutic exposure) in females did not cause a significant increase in the tumor incidences.

The tumor incidences in male and female mice and the toxicokinetic data for male and female rats are shown in the Tables below.

Table 17. Tumor Incidence in Male Mice

Male Tumors	Control	5 mg/kg	20 mg/kg	80 mg/kg	P (1-sided) for trend (a)
Liver					
Hepatocytic tumors	3/60	6/60	9/60	15/59	(b) 0.0001***
Hepatocellular adenoma	2/60	6/60	8/60	13/59	(b) 0.0002***
Hepatocarcinoma	1/60	0/60	1/60	2/59	(b) 0.1159
Thyroid					
Follicular tumors	14/60	9/60	11/60	23/59	(b) 0.0158*
Adenoma, follicular	13/60	9/60	11/60	20/59	(b) 0.0344*
Adenocarcinoma, follicular	2/60	1/60	0/60	3/59	(b) 0.3321
Pituitary					
Adenoma	19/60	25/59	23/58	29/59	(b) 0.0095**
Mammary gland					
Glandular tumors	0/56	0/59	1/59	2/58	(c) 0.0397*
Adenoma, fibroadenoma	0/56	0/59	0/59	2/58	(c) 0.0400*
Adenocarcinoma	0/56	0/59	1/59	0/58	(b) 0.2846
Pancreas					
Islet cell tumors	5/60	6/60	5/60	17/59	(b) 0.0010**
Adenoma, islet cell	5/60	6/60	5/60	15/59	(b) 0.0026**
Adenocarcinoma, islet cell	0/60	0/60	0/60	2/59	(c) 0.1234
Adrenal glands					
Medullary tumors	1/60	5/60	0/60	8/59	(b) 0.0208*
Pheochromocytoma, benign	1/60	3/60	0/60	8/59	(b) 0.0074**
Pheochromocytoma, malignant	0/60	2/60	0/60	0/59	(b) 0.6982

Table 18. Tumor Incidence in Female Mice

Female Tumors	Control	5 mg/kg	10 mg/kg	40 mg/kg	P (1-sided) for trend (a)
Liver					
Hepatocellular adenoma	0/60	0/60	2/60	3/60	(c) 0.0147*
Thyroid					
Follicular tumors	2/59	4/60	3/60	9/60	(b) 0.0121*
Adenoma, follicular	2/59	4/60	3/60	8/60	(b) 0.0255*
Adenocarcinoma, follicular	0/59	1/60	0/60	1/60	(b) 0.2223
Mammary gland					
Glandular tumors	25/60	19/60	28/60	33/60	(c) 0.0310*
Adenoma, fibroadenoma	17/60	13/60	16/60	28/60	(c) 0.0092**
Adenocarcinoma	14/60	8/60	13/60	7/60	(b) 0.9058

Note: (a):age-adjusted analysis taking into account the context of observation
(Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426); dose levels 0, 1, 2, 3, 4
p-values are either asymptotic (b) or "exact" (c)
*: statistically significant for positive trend; p<0.05
**: statistically significant for positive trend; p<0.01
***: statistically significant for positive trend; p<0.001

Toxicokinetics: The C_{max} and $AUC_{0\text{-}24h}$ values increased dose dependently in both males and females on day 189 and day 372 of dosing of oral prucalopride. The C_{max} and $AUC_{0\text{-}24h}$ values for different doses in male and female rats on day 189 and day 372 are shown in the table below.

Table 19. Toxicokinetic Parameters of Prucalopride in the Two-Year Carcinogenicity Study in Rats

	Male Rat			Female Rat		
Dose(mg/kg)	5	20	80	5	10	40
Day 189						
C_{max} (µg/ml)	0.227	1.43	6.15	0.286	0.808	3.62
AUC_{0-24h} (µg.h/ml)	0.637	6.28	48.0	0.869	3.62	41.2
Day 372						
C_{max} (µg/ml)	0.269	1.60	7.35	0.217	0.962	4.61
AUC_{0-24h} (µg.h/ml)	0.669	6.83	66.0	0.772	4.32	57.4

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration

A neonatal mouse carcinogenicity study in Swiss mice was negative.

5.5.5. Reproductive and Developmental Toxicology

Key Findings

Prucalopride was studied in segment I, segment II and segment III reproductive and developmental toxicity studies following oral administration in rats and rabbits. Prucalopride had no adverse effects on fertility and early embryonic development in rats at oral doses up to 20 mg/kg/day. However, at a dose of 80 mg/kg, there was an increase in precoital interval and preimplantation loss. These effects were considered related to the pharmacological effects of prucalopride, secondary to increased prolactin levels in females. Increased precoital interval was also observed at the 20 mg/kg/day subcutaneous dose.

In the oral embryofetal developmental studies in rats and rabbits (at up to 80 mg/kg/day; 938x therapeutic exposure in rats and 162x in rabbits), had no adverse effect on embryofetal development when administered during the period of organogenesis. In a pre- and post-natal developmental toxicity study with oral prucalopride in rats at doses up to 80 mg/kg/day, there were no treatment-related effects on the fertility, gestation rate, duration of gestation and the number of implantations. Prucalopride had no effect on the development of the F1 pups.

Individual studies are summarized below.

Oral Male and Female Fertility Study in the Wistar Rat (Report # R4901M or Study # 136372/1)

Four groups of 24 males and 24 females were administered R108512 by oral gavage at doses of 0, 5, 20 and 80 mg/kg/day. Males were dosed QD for 4 weeks prior to mating and during mating. The females were dosed 2 weeks prior to mating, during mating and up to day 7 of pregnancy. After 2 weeks of dosing, females were mated on a one-to-one basis with the corresponding 4-week dosed males of the same dosage group. All animals were observed once a day for any manifestation of pharmacological or toxicological response. Individual body weights and food consumption were determined weekly. The time elapsing between initial pairing and mating was recorded. Female rats were sacrificed for examination of their uterine contents on day 14 of pregnancy. Male rats were sacrificed after successful mating. The female genital tract was dissected followed by recording of weight of gravid uterus, number of corpora lutea, number of implantation sites, number of live and dead fetuses, and the number of resorption sites. Uteri of

apparently nonpregnant animals and animals with maximum three live fetuses were examined for evidence of implantation using ammonium sulfide staining.

No drug-related mortalities were observed in male and female animals in any of the dose groups. There were no adverse clinical observations in male rats of any dose group, and there were no adverse effects on body weight or body weight gain in any of the male rats from any dose group.

While the copulation and fertility rates were normal and comparable between the dose groups, the precoital interval was increased only in rats dosed at 80 mg/kg.

The following parameters were normal and comparable between groups: weight of gravid uterus; number of implantations and corpora lutea; number of live fetuses and resorptions. There were no adverse effects on postimplantation loss in any of the dose groups, or in preimplantation loss in rats dosed at 5 or 20 mg/kg, however, preimplantation loss was slightly increased in female rats dosed at 80 mg/kg.

Oral Embryotoxicity and Teratogenicity study (Segment II) with R093877 in SPF Wistar Rats (Caesarian section) (Report # R4920M or Study # N109245/1)

Four groups of 24 mated female rats were administered R093877 by oral gavage at doses of 0, 1.25, 5, and 20 mg/kg/day from day 6 to day 16 of pregnancy. A satellite group consisting of eight female SPF Wistar rats was used for toxicokinetic (TK) assessment (Report # R4921M or N 111681/1). Females were sacrificed on day 22 of pregnancy, necropsied, and all macroscopic pathological changes noted. The female genital tracts were removed, dissected, and the following parameters were recorded: weight of gravid uterus, number of corpora lutea, number of live and dead fetuses, and number of early and late resorptions. Uteri of animals with maximum three live fetuses were examined for evidence of implantation using ammonium sulfide staining. All live fetuses were individually weighed, sex was determined and all live fetuses were examined for anomalies. Half of the fetuses in each litter were processed for skeletal examination and the remaining ones were placed in Bouin's fixative for visceral examination.

No mortality was noted in any of the dosage groups. No relevant effects on body weight and corrected mean maternal weight gain were noted in any of the dosage groups. The following parameters were comparable between groups: weight of the gravid uterus, the mean litter size and number of live, dead and resorbed fetuses, number of implantations and number of corpora lutea; body weight and sex ratio of live fetuses, and pre- and postimplantation loss. The number of malformations in the fetuses was comparable between groups.

The TK of R093877 was examined in female Wistar rats on day 16 of pregnancy. Animals received 1.25, 5 or 20 mg/kg/day oral aqueous dose of R093877 from day 6 until day 16 of pregnancy. On day 16 of pregnancy, blood was collected at 1, 2, 4, and 8 hours after dosing. At 1 hour after dosing, the mean plasma concentrations (C_{1h}) amounted to 0.035 µg/ml (1.25 mg/kg), 0.427 µg/ml (5 mg/kg) and to 2.43 µg/ml (20 mg/kg). The increased was more than dose-proportional (i.e. 12 times between the 1.25- and 5-mg/kg dose levels and 5.7 times between the

5- and 20-mg/kg dose levels. The same tendency was observed for the mean plasma concentrations measured at 8 hours after dosing.

Conclusion: Oral gavage administration of R093877 to rats did not produce embryofetal developmental abnormalities at doses up to 20 mg/kg/day.

Oral Developmental toxicity study in the Wistar rats (Experiment # 5023).

In this study (conducted by Janssen Pharmaceutica N.V, Beerse, Belgium), pregnant rats (body weight 161 to 204 g; 24 animals/group) were administered (oral gavage) prucalopride (R108512; batch No. ZR108512PUA031) at doses of 5, 20 and 80 mg/kg/day from day 6 through 16 of pregnancy. The drug was dissolved in water and administered at a dosing volume of 1 mL/100 g bogy weight. Clinical signs were observed daily and the body weights and food consumption were recorded at predetermined time intervals. The dams were sacrificed on day 22 of pregnancy, and a complete necropsy performed. The uterine weights were recorded, and the number of corpora lutea, live and dead fetuses, number of implantation sites, and the late and early resorptions were determined. Live fetuses were individually weighed, sex determined, and examined for external malformations. Half of the fetuses were examined for skeletal abnormalities and remaining fetuses were examined for visceral malformations. A satellite group of eight rats were used for toxicokinetic assessment.

There were no mortality or adverse effects on body weight, food consumption, and gross pathology in the maternal animals at doses up to 20 mg/kg. At 80 mg/kg, there was an increase in food consumption.

There were no adverse effects on the number of corpora lutea of pregnancy, live and dead fetuses, sex ratio of the pups, mean body weight of the live fetuses, and pre- and postimplantation loss at any doses. The number of early resorptions was slightly increased at the 20 mg/kg dose and was not considered treatment related because of the lack of a dose response. No treatment related visceral, or skeletal malformations were observed in the fetuses at any dose.

Thus, oral administration of R-108512 to pregnant rats at doses up to 80 mg/kg/day from gestation day 6 through 16 did not cause any embryofetal developmental toxicity.

Toxicokinetic parameters at 5, 20 and 80 mg/kg/day doses in pregnant Wistar rats are shown in the Table below (Sponsor’s submission).

Table 20. Toxicokinetic Parameters at 5, 20 and 80 mg/kg/day Doses in Pregnant Wistar Rats

Dose[1] / Time after dosing (h)	5 mg/kg	20 mg/kg	80 mg/kg
1	259	1924	6716
2	-[2]	2184[3]	-
4	116[3]	1301	6986
8	-	989[3]	-
C_{max} (ng/ml)	259	2184	6986
T_{max} (h)	1	2	4
$AUC_{1-8\,h}$ (ng.h/ml)		11081	

1) Doses expressed as mg R108512 base-eq./kg/day.
2) No samples were taken.
3) n=1

Source: Sponsor's submission
Abbreviations: AUC, area under the curve; T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration
Mean (n=2) plasma concentrations (ng/ml) and some basic pharmacokinetic parameters of R108512 in pregnant SPF Wistar rats measured on day 16 of an oral segment II reproduction toxicity study (Exp. No. 5023) on aqueous solutions of R108512 at 5, 20, and 80 mg/kg/day.

Oral Embryotoxicity and Teratogenicity study (Segment II) with R093877 in Cunistar Rabbits (Report # L4929M or Study # N111687/1)

Four groups of 18 artificially inseminated female rabbits were administered R093877 by oral gavage at doses of 0, 5, 20 or 80 mg/kg/day from day 6 through day 18 of pregnancy. Eight animals were assigned to a concurrently performed toxicokinetic study.

All animals were observed once a day for any manifestation of pharmacological or toxicological response. Body weights were recorded on days 0, 6, 19, and 27, and food consumption was recorded on days 0, 6, 19 and 28 of pregnancy. Females were sacrificed on day 28 of the pregnancy, and an autopsy was performed on dead or sacrificed animals, with all macroscopic pathological changes noted. The uterus was removed and the weight of the gravid uterus was determined. Dams were examined for number of corpora lutea, live and dead fetuses, early and late resorptions. All live fetuses were individually weighed and carefully examined for external anomalies. After sacrifice, the neck and thoracic and abdominal cavities of all fetuses from each litter were dissected and examined for visceral anomalies using a modified Staples technique. Bouin's fixed heads were examined using a modified Wilson technique. Clearing and staining of skeletons was done with Alzarin red S.

Two rabbits from the 5 mg/kg dose groups (Nos. 19 and 30) died on days 17 and 26, respectively. The death of rabbit No. 19 was due to gavage dosing accident, while rabbit No. 30 died due to shock after abortion of its entire litter. Two rabbits from the 20 mg/kg dose group (Nos. 44 and 48) were sacrificed during the postdosing period because of abortion of their litter. The mortalities were considered coincidental and not drug related since no abortion occurred in the 80 mg/kg dose group. Body weights and corrected mean maternal weight gain were comparable between control and the 5 and 20 mg/kg/day dose groups. At 80 mg/kg/day, there is a decrease in corrected mean maternal weight gain.

The fertility rate and the weight of the gravid uterus were comparable between the control and the dosed groups. For fetal data, the following parameters were comparable between the control group and the dosed groups: the numbers of live, dead and resorbed fetuses as well as the weight of live fetuses were normal and comparable; number of implantations and corpora lutea were normal and comparable; no differences were observed in the sex ratio. There was no significant increase in the incidence of major or minor visceral and skeletal abnormalities and variations in any of the R093877-dosed groups.

Conclusion: R093877 did not produce adverse embryofetal developmental effects in Albino rabbits after oral administration at doses up to 80 mg/kg/day.

Segment III Pre- and Postnatal Developmental Toxicity Study with Prucalopride in rats by the Oral Route (Report # R4933M or Study # 126894/2)

To investigate the effects of prucalopride on pre- and postnatal development in rats. female Wistar rats, after confirmed mating, (24/group) received the vehicle or prucalopride at doses of 5, 20 and 80 mg/kg/day (by oral gavage) from day 6 of pregnancy through week 3 of lactation. The F0 dams were observed daily for clinical signs, and the body weight, and food consumptions were measured once every 6 days during the gestation period and once every 4 days during the lactation period. The animals were allowed to deliver normally and the duration of gestation for each animal was recorded. After parturition, the number of live and dead pups was counted and the mean litter size per pregnant female was recorded. During the lactation period, all F1 pups were observed at least once a day for any abnormal signs. The weights of the pups were recorded on the day of parturition and on days 4, 7, 14 and 21 postpartum. The pups were examined for the following physical development at different times: Pinna detachment- day 4 to day 10, surface righting- day 4 to10, incisor eruption- day 11 to 13, eye opening- day 14 to 17, air righting- day 14 to 17. On day 21, the pups (except two animals/sex/litter) were sacrificed and examined macroscopically. The surviving pups were observed for the following behavioral and sexual development: vaginal opening- day 35 to 42, preputial separation- day 42 to 50 and locomotor activity- days 29±6 and 50±6. After an approximate 3-month growth period, one F1 male and one F1 female of each litter were randomly selected and were paired on a one to one basis, within the same dose group. Females that had failed to mate within 14 days were mated with a male of proven mating ability. The F1 females were sacrificed on day 15 of gestation and examined macroscopically. The weight of the gravid uterus, number of corpora lutea, number of fetuses and the number of resorptions were recorded. Copulation and fertility rates and pre- and post- implantation losses were also calculated to assess the potential effects of prucalopride on the litter parameters.

One animal in the 80 mg/kg/day dose group showed abnormal nursing behavior and all pups delivered by this dam died. There was no treatment-related mortality in any groups. Seven F0 animals in the control group, four F0 animals in the 5 mg/kg group, three F0 animals in the 20 mg/kg group, and five F0 animals in the 80 mg/kg group failed to deliver pups on day 26 and were sacrificed. One animal in the control group had two implantations and another animal in the 20 mg/kg group had three implantations. The other animals were not pregnant. There were slight decreases in the body weights of the animals in the 80 mg/kg dose group on lactation days 7

(4%) and 14 (5%). The number of corpora lutea of lactation was significantly reduced in the 20 (27%) and 80 (28%) mg/kg dose groups.

F1 Generation: Eight F1 pups from one dam receiving the 20 mg/kg dose had irregular hair coat and another dam receiving the 80 mg/kg dose had seven pups with alopecia. These changes were considered not related to treatment with prucalopride. The body weight of the pups in the 80 mg/kg dose group were lower than controls on day 14 (not significant) and day 21 (11% in males and 10% in females). Incisor eruption and eye opening was earlier than controls in F1 pups in the 20 mg/kg group. Surface righting was slightly slower in few pups in the 20 mg/kg and 80 mg/kg groups. The weights of both males and females of the 80 mg/kg dose group were significantly lower than controls during the 3-month period. There were no treatment-related changes in the sexual and behavioral development of the F1 pups.

The body weights of the F1 females, used for reproductive performance, were significantly lower in the 80 mg/kg dose group throughout the pregnancy period (on gestation day 15, all animals were sacrificed). Food consumption was also lower in the 20 mg/kg and 80 mg/kg groups during the gestation period. The copulation and fertility rates of the F1 dams from the prucalopride groups were not different from the controls. The weight of the gravid uterus was lower than that of the control in the 80 mg/kg dose group (14.4%).

F2 fetuses: The number of fetuses and mean litter size was higher than controls in the 5 mg/kg dose group. There were no other differences in the number of fetuses, mean litter size, the number of implantations or the number of pre- and post- implantation losses between the control and the treatment groups. The number of corpora lutea of pregnancy was slightly lower than control in the 80 mg/kg dose group. The pregnancy data for F1 dams and F2 litters are summarized in the table below.

Table 21. Pregnancy Data From Developmental Toxicity Study With Prucalopride in Rats

Data type	Control	5 mg/kg	20 mg/kg	80 mg/kg
Adult Data				
Deaths	0/16	0/19	0/20	0/18
Copulation rate	16/16	19/19	20/20	18/18
Fertility rate	16/16	18/19	20/20	18/18
Mean body weight on day 1 of pregnancy(g)	226.9	217.1*	215.7	205.0***
Mean body weight on day 9 of pregnancy(g)	247.9	244.5	236.8	227.9***
Mean body weight on day 15 of pregnancy (g)	273.6	269.1	262.9	250.1***
Mean weight of gravid uterus (g)	9	9.5	8.2	7.7*
Litter Data				
Number of live fetuses	10.5	11.7*	9.8	8.8
Number of dead fetuses	0	0	0	0
Mean litter size	10.5	11.7*	9.8	8.8
Number of resorptions	1.06	0.61	0.65	1.28
Number of implantations	11.6	12.3	10.5	10.1
Number of corpora lutea	13.6	14.1	13.1	12.3

*p<0.05; **p<0.01; ***p<0.001

In summary, Segment III pre- and postnatal development study with oral prucalopride was conducted in rats that received 0, 5, 20 and 80 mg/kg/day of the drug, there were no treatment-related effects on the fertility, gestation rate, duration of gestation and the number of implantations. Treatment with prucalopride also had no effect on the development of the F1 pups.

5.5.6. Other Toxicology Studies

Single Dosage Phototoxicity Study to Determine the Effects of Oral (Gavage) Administration of Prucalopride on Eyes and Skin in Pigmented Rats (Study No. BOV00030)

The purpose of this study was to determine the phototoxicity of oral prucalopride to the skin and eyes following exposure to sunlight in Long-Evans pigmented male rats.

Male Long-Evans pigmented rats were randomized (3 to 5/group) to main study groups or (3/group) TK groups to receive a single oral dose of prucalopride at 0 (control), 2.5, 5, 10 mg/kg or 8-Methoxypsolaren (8-MOP), the comparator molecule at 50 mg/kg. One hour after dosing with the test article or the comparator, an UVR exposure dose equivalent to 0.5 minimal erythema dose was delivered to each rat over a period of 30±5 minutes. Rats were individually examined 30 minutes and 4 hours 30 minutes after the completion of UVR exposure for general appearance and signs of skin responses at the UVR exposure site, as well as 1, 2, and 3 days after exposure. Animals were also subjected to ophthalmological examinations three days after UVR exposure. Rats were sacrificed on day 4 of study and, eye and skin samples were collected from phototoxicity animals. Blood was collected from toxicokinetic (TK) animals.

Results: One control rat and one rat in the 10 mg/kg dose group were found dead on observation day 1 (OD 1) after UVR exposure. One rat in the 5 mg/kg dose group was sacrificed prior to scheduled termination on OD 1 due to a severe ocular injury. These mortalities were attributed to procedural errors and not treatment related. All the other animals survived till scheduled sacrifice.

There were no skin reactions in the lightly or darkly pigmented skin sites of the control animals or animals administered prucalopride at 2.5, 5 or 10 mg/kg, followed by a single exposure to UVR. Two of the three rats dosed with 8-MOP had skin reactions indicative of phototoxicity in the lightly or darkly pigmented skin sites, including erythema grade 1, erythema grade 2, edema grade 1 and/or flaking grade 1. All the rats administered the 8-MOP formulation had periorbital edema which was interrelated with the induction of cutaneous phototoxicity.

Ophthalmological examinations did not show any findings related to the oral administration of the vehicle or prucalopride. Most of the study animals, including control had focal retinopathy. Following 8-MOP administration, bilateral diffuse superficial corneal edema occurred in all the rats dosed with the comparator article and simulated sunlight exposure. This finding was considered an indication of ocular phototoxicity.

There were no treatment-related microscopic changes observed in any of the ocular structures specified for examination in any of the rats dosed with vehicle or prucalopride at 2.5, 5 or 10 mg/kg, with subsequent UVR exposure.

In summary, a single oral administration of prucalopride at doses of 0 (vehicle), 2.5, 5 and 10 mg/kg, followed by a single exposure to simulated sunlight (UVR exposure) did not elicit any cutaneous or ocular reactions indicative of phototoxicity in Long-Evans pigmented rats. There were no treatment-related microscopic changes observed in the ocular structures in any of the rats administered the control or the test article.

6. Clinical Pharmacology

6.1. Executive Summary

Prucalopride is a serotonin 5-HT_4 receptor agonist with a proposed indication for the treatment of CIC in adults. It is a new molecular entity that acts as a GI prokinetic agent that stimulates peristalsis and accelerates colonic transit. Prucalopride has been approved outside the U.S., but not in the U.S.

In support of this application, the Applicant submitted clinical data from 46 phase 1 studies, 14 phase 2 studies, and 16 phase 3/4 studies, including efficacy analyses based on the data from two proposed "pivotal" (studies 3001 and 302) and four supportive (studies INT-6, USA-11, USA-13, and 401) clinical trials. In addition, population PK analysis and physiologically-based PK (PBPK) modeling and simulations were also performed.

The key clinical pharmacology review questions focused on the appropriateness of the general dosing instructions, dosage for specific patient populations, e.g., renal impairment, hepatic impairment, patients aged 65 years or older, and drug-drug interactions.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed this submission and found it acceptable for approval from a clinical pharmacology standpoint. Key review issues with specific recommendations and comments are summarized below:

Table 22. Review Issues and Recommendations

Review Issues	Recommendations and Comments
Pivotal evidence of effectiveness	The effectiveness of prucalopride was supported by the efficacy results from five well-controlled efficacy trials. Prucalopride 2 mg given once daily (QD) significantly increased the proportion of patients with an average of ≥3 spontaneous complete bowel movements (SCBMs) per week over 12-week treatment period, the primary efficacy endpoint, compared to placebo.

Review Issues	Recommendations and Comments
General dosing instructions	The proposed oral dosage at 2 mg QD for adult patients with chronic idiopathic constipation (CIC) is acceptable. Prucalopride at 2 mg and 4 mg QD were studied in three phase 3 studies (studies PRU-INT-6, PRU-USA-11, and PRU-USA-13) in patients with chronic idiopathic constipation for 12 weeks. The 4 mg QD dose provided no additional clinical benefit over the 2 mg QD dose based on evaluation of the proportion of patients with an average of ≥3 SCBMs per week over the 12-week treatment period compared to placebo.
Dosing in patient subgroups (intrinsic and extrinsic factors) (continued below)	Prucalopride can be taken with or without food. <u>Renal impairment</u> No dosage adjustment is recommended for patients with mild to moderate renal impairment. For patients with severe renal impairment (creatinine clearance (CRCL) 15-29 mL/min), a dose reduction to 1 mg QD is recommended. The PK in individuals with end stage renal disease have not been adequately studied. <u>Hepatic impairment</u> No dosage adjustment is recommended for patients with any degree of hepatic impairment. <u>Geriatric patients</u> No dosage adjustment for patients aged 65 years or older is necessary. The Applicant proposed a dose reduction to 1 mg QD in patients aged 65 years or older with an option of a dose increase to 2 mg QD to be consistent with the phase 3 trial design (studies SPD555-302 and SPD555-401). However, we do not agree that the dose reduction is necessary for patients aged ≥65 years. Among patients aged 65 years and older who started at a prucalopride dose of 1 mg QD, 81% (88 out of 109) of the patients had their dose increased from 1 mg to 2 mg QD based on insufficient clinical response at week 2 or week 4. Furthermore, steady-state C_{max} and AUC in patients aged 65 to 81 years were not significantly different when decreased renal function in elderly subjects was taken into account. Therefore, we do not recommend further dose reduction for patients aged 65 years or older from a clinical pharmacology standpoint, because a dose reduction is already recommended for patients with severe renal impairment. <u>Drug-drug interactions</u> *Effects of other drugs on prucalopride* No dosage adjustment for prucalopride is recommended when co-administered with ketoconazole, erythromycin, probenecid, cimetidine, and paroxetine. *Effects of prucalopride on other drugs* No clinically relevant effects on the PK of erythromycin, warfarin, digoxin, alcohol, paroxetine, and oral contraceptives (ethinyl estradiol and norethisterone) was identified to warrant dose adjustment when co-administered with prucalopride.
Bridge between the "to-be-marketed" and clinical trial formulations	The to-be-marketed formulation (1 mg and 2 mg immediate-release tablets) was used in the two pivotal phase 3 clinical trials (studies PRU-CRC-3001 and SPD555-302). The formulations (2 mg and 4 mg immediate-release tablets) used in supportive clinical trials were different from the to-be-marketed formulation and were adequately bridged to the to-be-marketed formulation.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacology

Prucalopride is a serotonin type 4 (5-HT_4) receptor agonist. It acts as a GI prokinetic agent that stimulates peristalsis and accelerates colonic transit.

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 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 SD or MDs 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 SD of 2 mg prucalopride was administered with a high fat meal. Mean C_{max} was 6% higher and mean AUC_{0-inf} was 4% lower in the fed state compared to the fasted state.

Distribution

Prucalopride is 28.9% bound to human plasma proteins.

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. Population PK analysis showed that creatinine clearance is 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.

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.

PK in Patients with Chronic Idiopathic Constipation:

PK of prucalopride in patients with CIC were characterized using sparse PK sampling schemes in phase 2 and phase 3 studies, while intensive PK samples were collected at steady-state in a 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 (Table 23). Moreover, mean (±standard deviation(StdDev)) trough concentrations at steady state were 1.53 (±1.09), 2.97 (±1.29), and 5.6 (±1.5) ng/mL following 1 mg, 2 mg, and 4 mg QD dosing in patients with CIC, respectively (studies PRU-NED-2 and PRU-NED-13) and within the ranges observed in healthy subjects (Table 23). Additionally, there is no significant difference in prucalopride PK between patients with CIC and healthy subjects based on the population PK analysis.

Table 23. 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

Abbreviations: AUC_{tau}, area under the plasma concentration over time curve during a dosing interval; CIC, chronic idiopathic constipation; C_{min}, minimum plasma concentration; C_{max}, maximum plasma concentration; PK, pharmacokinetic; QD, once daily; StdDev, standard deviation
Note: For healthy subjects, range of mean values from multiple studies are presented
[1] Data presented as mean ± StdDev
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

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant has proposed a dosage of 2 mg QD, taken orally with or without food, in adult patients with CIC.

Although both 2 and 4 mg QD were studied, the 2 mg QD dosage for the general patient population is recommended based on the statistically significant increase in the proportion of patients with an average of ≥3 SCBMs per week over the 12-week treatment period as compared to placebo treatment in five of the six efficacy trials. No additional benefit was observed with the 4 mg QD dose.

See Sections 7 Sources of Clinical Data and Review Strategy, Section 8 Statistical and Clinical and Evaluation, and Section 9 Review of Safety of this multi-discipline review for the related efficacy and safety data.

Therapeutic Individualization

Renal impairment

No dosage adjustment is recommended for patients with mild to moderate renal impairment. For patients with severe renal impairment (creatinine clearance 15 to <30 mL/min), the dose reduction to 1 mg QD is recommended. In patients with severe renal impairment, $AUC_{0\text{-}inf}$ was 2.4-fold higher as compared to healthy subjects. The PK in patients with end stage renal disease have not been adequately studied.

Hepatic impairment

No dosage adjustment is deemed necessary for patients with any degree of hepatic impairment.

Drug-drug interactions

Effect of Other Drugs on Prucalopride

In vitro, prucalopride is a substrate of 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 5.8-fold higher C_{max} than 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, 2D6, 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. Prucalopride is not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, BSEP, and MRP2 at in vitro concentrations up to 300μM.

No significant effect (no more than 10% change in C_{max} and AUC) on the PK of warfarin, digoxin, alcohol, paroxetine, and oral contraceptives (ethinyl estradiol and norethisterone) was identified when 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.

Summary of in vivo drug-drug interaction study results are presented in the table below.

Table 24. Summary of In Vivo Drug-Drug Interactions

	Geometric Mean Ratio for C_{max}	**Geometric Mean Ratio for AUC**
Effect of Prucalopride on Other Drugs		
Erythromycin (CYP3A4 substrate)	↑40%	↑28%
Warfarin (CYP2C9 substrate)	R-Warfarin ↑8% S-Warfarin ↑12%	R-Warfarin ↑2% S-Warfarin ↓1%
Digoxin (P-gp substrate)	↓3.4%	↓10%
Paroxetine (CYP2D6 substrate)	↓1.5%	↔
Oral contraceptives (ethinyl estradiol and norethisterone) on day 5	Ethinyl estradiol ↓1% Norethisterone ↓1%	Ethinyl estradiol ↓2% Norethisterone ↓4%
Effect of Other Drugs on Prucalopride		
Ketoconazole (strong CYP3A4 inhibitor, P-gp/BCRP inhibitor)	↑38%	↑37%
Erythromycin (moderate CYP3A4 inhibitor, inhibitor for P-gp, OATP1B1/1B3)	↑5%	↑2%
Probenecid (OAT1/OAT3 inhibitor)	↓1%	↔
Cimetidine (H2-receptor antagonist, inhibitor of CYP1A2, CYP2D6, CYP3A4, MATE1, MATE-2K, and OCT2)	↑3%	↑8%
Paroxetine (strong CYP2D6 inhibitor)	↑6%	↑5%

Outstanding Issues

There are no outstanding issues that would preclude the approval of Motegrity from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

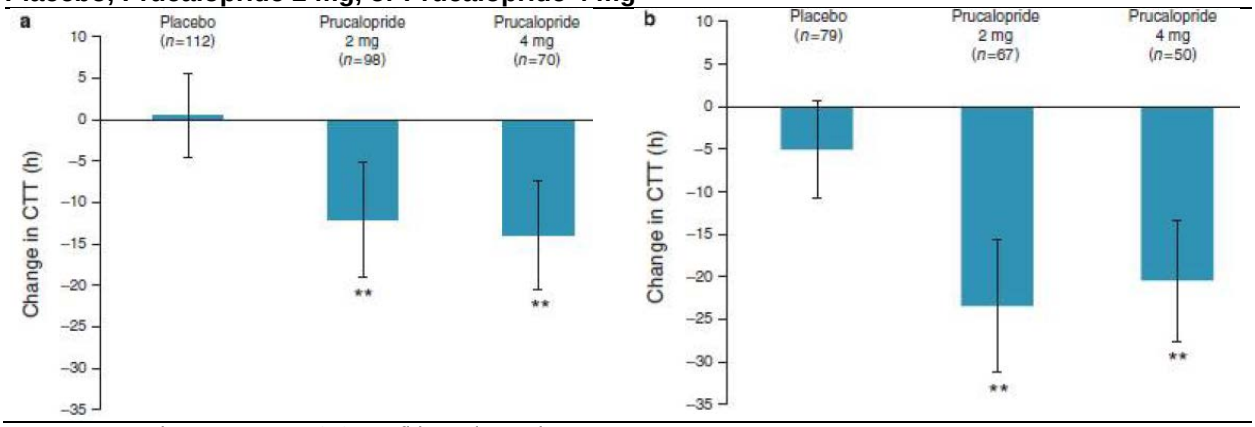
6.3.1.1. Pharmacology

The effects of prucalopride on human 5-HT_4 receptors were studied in HEK293 cells with an inhibition constant [Ki] of 2.5 to 8nM. The affinity of prucalopride for other 5-HT receptor subtypes was low and only detected at concentrations exceeding the affinity for the 5-HT_4 receptor by 150- to 10,000-fold.

Effect on colonic transit time

An integrated analysis of three phase 2 dose-finding studies (studies PRU-INT-1, PRU-INT-2, and PRU-USA-3) in 280 patients with CIC was conducted by the applicant. Treatment with prucalopride at doses of 2 mg and 4 mg QD reduced the mean colonic transit time by 12 hours and 13.9 hours, respectively, compared to an increase of 0.5 hour in the placebo group. In the subgroup analysis in patients with mean colonic transit time >48 hours at baseline, prucalopride at doses of 2 mg and 4 mg QD reduced the mean colonic transit time by 23.4 and 20.4 hours, respectively, compared to a 5-hour reduction in the placebo group.

Figure 3. Change in Colonic Transit Time From Before Treatment to the End of Treatment With Placebo, Prucalopride 2 mg, or Prucalopride 4 mg



Note: Data are shown as mean ±95% confidence interval
Figure a represents the all patients group; Figure b represents the subgroup of patients with slow or very slow colonic transit (>48 h) at baseline
CTT is colonic transit time (calculated based on abdominal X-ray following the ingestion of radio-opaque markers)
Source: Module 2.5 of the Applicant's submission, Clinical Overview, Figure 4

Of note, prucalopride was administered for 4 weeks in two of these phase 2 trials (PRU-INT-1 and PRU-USA-3) and for 12 weeks in phase 2 trial PRU-INT-2. It should also be noted that the relationship between the decrease in colonic transit time by prucalopride and the clinical benefit, i.e., increase in BMs over 12-week treatment period, have not been established in the phase 3 trials.

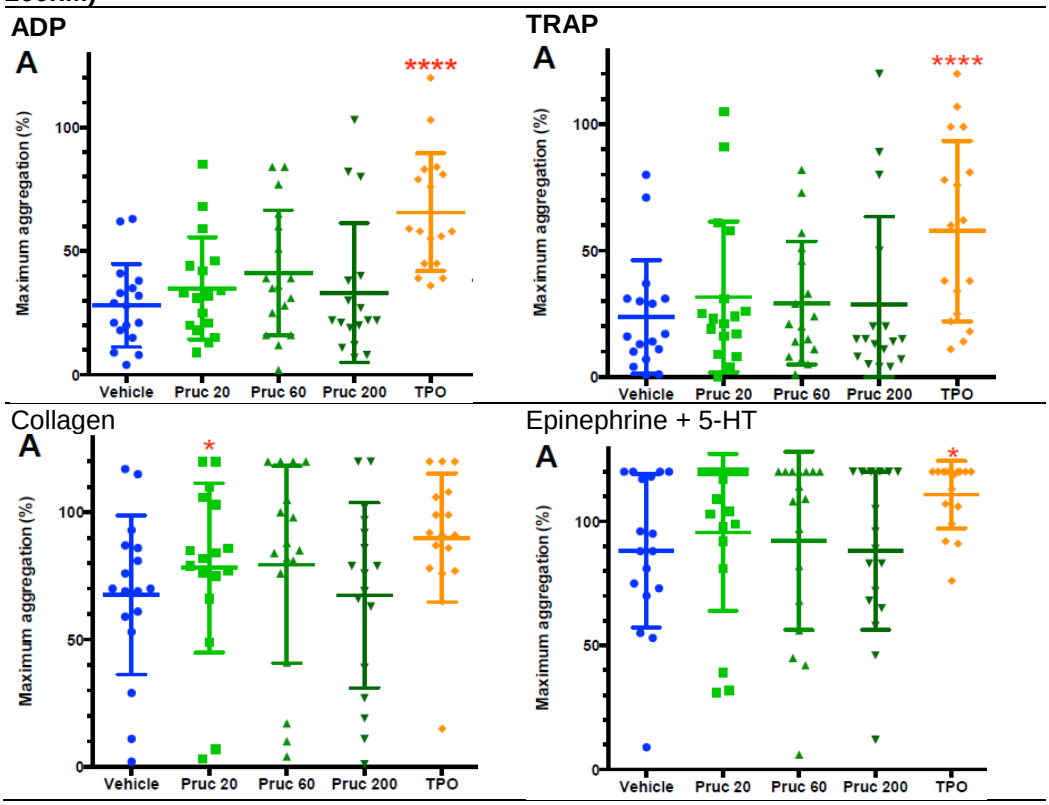
In addition, the pharmacodynamic effects of prucalopride was evaluated in 12 female patients with CIC using manometry sensor investigating the effect of a SD of prucalopride at 2 mg and an osmotic laxative (PEG3350) on colon motility as determined by the number of colonic high amplitude propagating contractions (HAPCs). The applicant reported that prucalopride increased the number and amplitude of high amplitude propagating contraction (HAPCs) during the 12 hours following treatment initiation as compared with PEG3350. However, due to the limited sample size of the study and the relationship between the increase in HAPCs and the clinical benefit has not been established in the phase 3 trials, the results are not discussed in detail in this review.

Effect on human platelet aggregation

As part of the supportive information for the CV safety profile, 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 (study V6002M-SPD555). Platelet aggregation responses were monitored using an 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 (TRAP), 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, TRAP, 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 4. Platelet Aggregation by Agonists and by Prucalopride (Concentrations of 20, 60, and 200nM)



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

6.3.1.2. Pharmacokinetics

PK of prucalopride were characterized in healthy adult subjects and in patients with CIC. A summary of the general PK of prucalopride is provided in the table below.

Table 25. Pharmacokinetic Information

General Information	
Bioanalysis	PK assay Two different assays were used for the measurement of plasma prucalopride concentrations, radioimmunoassay (RIA) method and liquid chromatography-tandem mass spectrometry (LC-MS/MS). Both the RIA and the LC-MS/MS assays have been adequately validated. In addition, prucalopride concentrations in human urine samples were measured by a validated high-performance liquid chromatography (HPLC) method.
Healthy subjects vs. patients with CIC	The PK of prucalopride in patients with CIC and healthy subjects are similar.
Drug exposure at steady state following the proposed dosing regimen	In adult subjects, mean trough and peak concentrations at steady state ranged 2.4 to 2.79 ng/mL and 6.32 to 7.76 ng/mL, respectively, following 2 mg QD dosing. Mean AUC_{tau} at steady state ranged 95.3 to 109 ng·h/mL.

General Information	
Dose Proportionality	Approximate dose-proportional increase in the systemic exposure (C_{max} and AUC) was observed over the dose range of 1 mg to 20 mg following single dose and once daily oral dosing across studies in healthy subjects.
Accumulation	Following 2 mg once daily dosing, steady state was achieved within 3 to 4 days and the accumulation ratio averaged 1.9 to 2.3.
Hepatic Impairment	The C_{max} and AUC of prucalopride in subjects with moderate or severe hepatic impairment were 10 to 20% higher than in healthy subjects.
Renal Impairment	The C_{max} of prucalopride was in the same range in subjects with normal and impaired renal function following a single 2-mg dose. The mean AUC0-inf values in subjects with mild, moderate, and severe renal impairment were increased by 23%, 40%, and 138%, respectively, compared to healthy subjects.
Absorption	
T_{max}	The mean time to peak plasma concentration is generally within 2 to 3 hours after oral dosing.
Bioavailability	The absolute bioavailability of prucalopride is 93.2% following a single oral administration of 2 mg in healthy subjects.
Food effect	No significant food effect on the PK of prucalopride was observed when a single dose of 2 mg prucalopride was administered in the fasted state and with a high fat meal. Mean C_{max} was 6% higher and mean AUC0-inf was 4% lower in the fed state compared to the fasted state.
Distribution	
Volume of Distribution	The mean (StdDev) volume of distribution at steady state was 567±107 L following a single IV infusion of 2 mg prucalopride.
Plasma Protein Binding	Prucalopride is approximately 28.9% bound to human plasma proteins.
Elimination	
Terminal Elimination half-life and Clearance	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. Mean elimination half-life ($t_{1/2}$) of prucalopride ranged 13.5 to 24.6 hours following a single IV administration of 0.125 to 5 mg prucalopride. Prucalopride is primarily eliminated via renal excretion. The population PK analysis showed that creatinine clearance was a significant covariate on the apparent clearance (CL/F) of prucalopride. Once creatinine clearance was added to the population PK model, no other covariates (e.g., sex, race, and age) showed impact on the CL/F of prucalopride.
Metabolism	In vitro, prucalopride is a substrate of cytochrome CYP3A. 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. R107504 is formed by CYP3A4 according to the in vitro study using recombinant CYP3A4 (study V5993M-SPD555). None of the other metabolites accounted for more than 3% of the dose.
Excretion	On average, 97.5% of the administered radioactive dose was recovered by the end of sample collection (240 hours): 84.2% of 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. In a bile-cannulated dog (study D4471M-SPD555) suggests that biliary excretion may also potentially contribute to elimination of prucalopride and metabolites.

In healthy subjects:

Following a SD of 2 mg in healthy adult subjects, the absolute oral bioavailability of prucalopride is 93.2%.

Table 26. Mean Pharmacokinetic Parameters Following Single Dosing of 2 mg Oral Tablet and 10-Minute IV Dosing in Healthy Subjects

Parameter (Unit)	10-minute IV Infusion Mean ± SD	Tablet Fasting Mean ± SD
t_{max} (h)	-	2.1 ± 0.9
$C_{end\ infusion}/C_{max}$ (ng/mL)	9.21 ± 5.96	4.34 ± 0.82
$AUC_{0-\infty}$ (ng·h/mL)	108 ± 21	99.2 ± 17.2
$t_{1/2}$ (h)	22.5 ± 3.8	21.2 ± 3.7
F_{abs} (%)	-	93.2 ± 11.6

Abbreviations: AUC, area under the curve; T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; $t_{1/2}$, mean elimination half-life; $C_{end\ infusion}$, concentration at end of infusion
Note: F_{abs} = The absolute oral bioavailability was calculated as the $AUC_{0-infinite}$ ratio of unchanged drug after oral administration to that after IV administration
Note: Data presented as mean ± StdDev
Source: Clinical study report for study PRU-BEL-32, synopsis table

Dose proportionality

A dose-dependent increase in the systemic exposure to prucalopride was observed over the dose range of 1 mg to 6 mg following SD and QD oral dosing in healthy subjects (study PRU-BEL-15). Following a single oral dose of 1, 2, 4, and 6 mg to healthy adults, mean C_{max} increased 7.8-fold and AUC0-inf increased 6.5-fold over this dose range. Following repeated dosing at 1, 2, 4, and 6 mg QD, mean C_{max} increased 7.3-fold and AUC_{tau} increased 7.4-fold over this dose range.

Table 27. Mean (StdDev) Prucalopride Pharmacokinetic Parameters After Single Oral Dosing in Healthy Subjects

PK Parameter	1 mg (N=12)	2 mg (N=12)	4 mg (N=12)	6 mg (N=12)
T_{max} (h)	2.3±1.1	2.6±1.5	1.8±0.7	2.4±2.1
C_{max} (ng/mL)	1.75±0.40	3.93±0.73	8.75±1.21	13.6±3.1
AUC_{0-24h} (ng·h/mL)	24.6±3.1	57.3±8.2	112±13	183±28
AUC_{0-inf} (ng·h/mL)	46.3±6.1	104±21	190±26	302±52
$t_{1/2}$ (h)	25.2±4.5	24.0±3.6	23.5±3.2	22.3±2.6

Abbreviations: AUC, area under the curve; T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; $t_{1/2}$, mean elimination half-life
Note: Data presented as mean ± StdDev
Source: Clinical study report for study PRU-BEL-15, Table 4-1

Table 28. Mean (StdDev) Prucalopride Pharmacokinetic Parameters After Once Daily Oral Dosing in Healthy Subjects

PK Parameter	1 mg QD (N=12)	2 mg QD (N=12)	4 mg QD (N=12)	6 mg QD (N=12)
C_{min} (ng/mL)	1.17±0.22	2.49±0.68	5.02±1.19	7.84±1.86
T_{max} (h)	2.3±1.1	1.7±1.3	1.8±1.2	1.8±1.2
C_{max} (ng/mL)	3.19±0.55	7.45±1.48	15.2±2.6	23.3±4.0
AUC_{tau} (ng·h/mL)	47.3±8.0	109±23	219±38	352±65
$t_{1/2}$ (h)	33.6±8.0	30.5±4.6	29.5±4.0	28.3±3.6

Abbreviations: AUC, area under the curve; T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; $t_{1/2}$, mean elimination half-life
Note: Data presented as mean ± StdDev
Source: Clinical study report for study PRU-BEL-15, Table 4-2

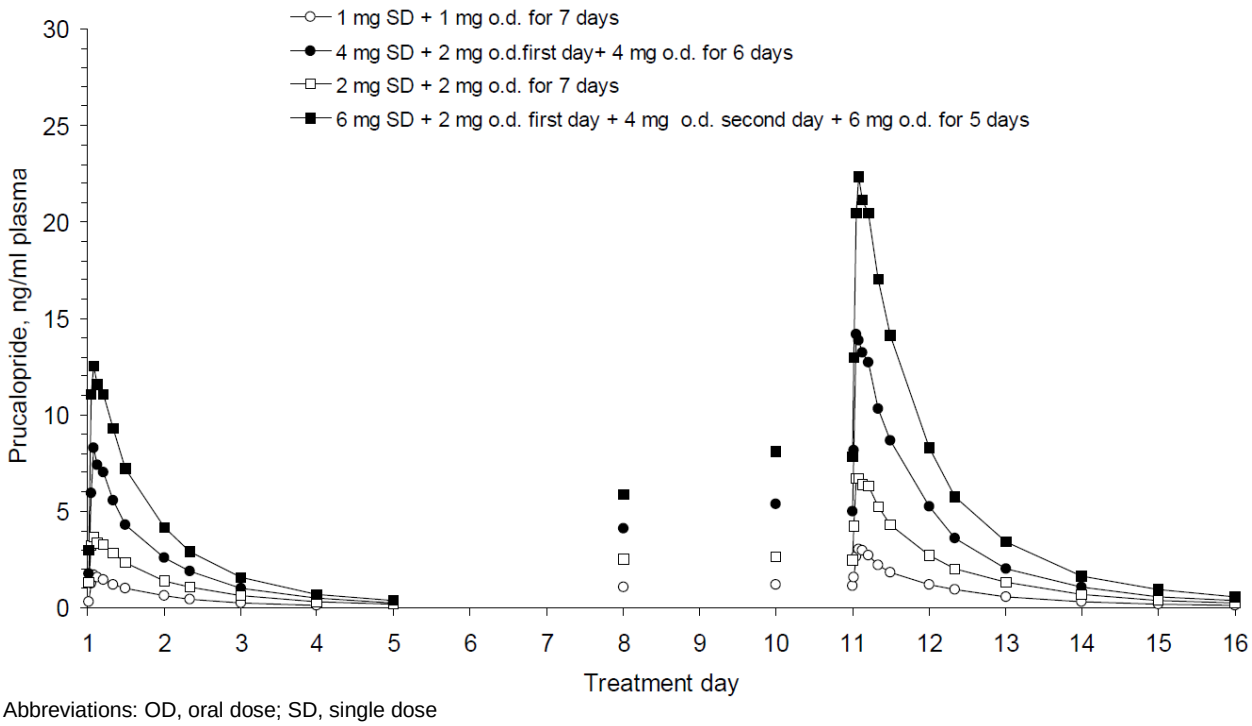
Approximate dose-proportional increase in the systemic exposure was observed at doses up to 10 mg. In a TQT study M0001-C102, prucalopride 10 mg QD dosing was studied as a supratherapeutic dose. Mean C_{max} increased 5.8-fold and AUC_{tau} increased 5.5-fold with a dose increased from 2 mg to 10 mg QD.

Table 29. Mean (StdDev) Prucalopride Pharmacokinetic Parameters After Once Daily Oral Dosing at 2 mg From Days 1 to 5 and 10 mg From Days 11 to 13 in Healthy Subjects

PK Parameter	2 mg QD on Day 5 (N=60)	10 mg QD on Day 13 (N=60)
C_{min} (ng/mL)	2.48±0.62	12.8±2.39
T_{max} (h)	1.85±0.96	1.69±0.76
C_{max} (ng/mL)	7.37±1.38	42.7±7.06
AUC_{tau} (ng·h/mL)	108±18.7	590±82.0

Abbreviations: AUC, area under the curve; T_{max}, time to maximum plasma concentration; C_{max}, C_{min}, maximum and minimum plasma concentration
Note: Data presented as mean ± StdDev.
Prucalopride 2 mg QD was administered on days 1 to 5, prucalopride up-titration occurred on days 6 to 9, then prucalopride 10 mg QD was administered on days 10 to 13
Source: Clinical study report for study M0001-C102, Post-text Table 3.2

Figure 5. Mean Plasma Prucalopride Concentration-Time Profile Following Single Dose and Once Daily Oral Dosing in Healthy Subjects



Abbreviations: OD, oral dose; SD, single dose
Note: Patients were stratified into two PK sampling groups during the first 3 hours postdose: at 0.75 and 2.0 hours and at 1.5 and 3.0 hours postdose, respectively
Source: Clinical study report for study PRU-BEL-15, Display 7

Lactation study

The excretion of prucalopride in breast milk was studied in eight healthy lactating female subjects no longer breastfeeding their baby or agreeing to stop breastfeeding in an open label study (study PRU-RSA-1). Prucalopride was administered orally at 2 mg QD for 4 days. Plasma and breast milk concentrations of prucalopride were assessed on day 4.

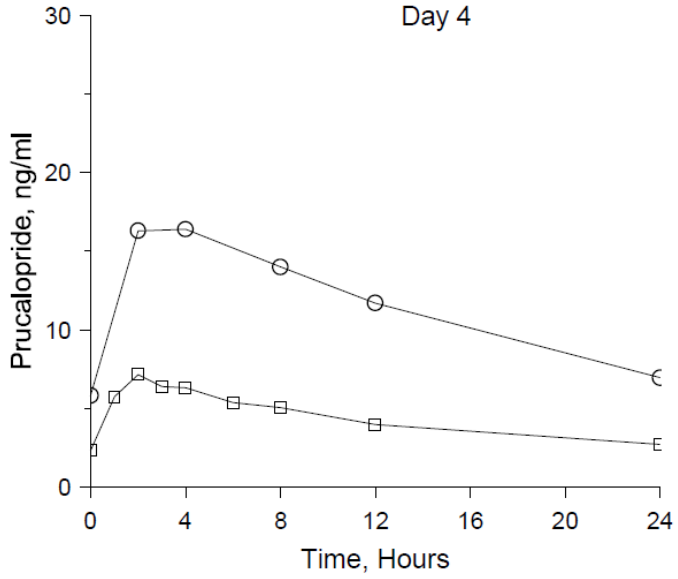
Overall mean breast milk to plasma ratio for prucalopride AUC was 2.65:1. Of note, the applicant estimated that the prucalopride dose passed on to the infant would have been 1.74±0.35 µg/kg/day, based on the average steady-state milk concentration in the mother, and assuming a milk intake by the infant of 150 mL/kg/day. The estimated prucalopride dose consumed in breast milk over 24 hours was about 6% of the maternal dose, adjusted for body weight. The potential clinical impact of this dose to infants is unknown.

Table 30. Prucalopride Pharmacokinetic Parameters in Plasma and Breast Milk on Day 4 and Extrapolated Exposure Via Breast Milk After Repeated Oral Dosing With 2 mg QD in Healthy Lactating Subjects

Parameter	Plasma	Breast Milk
	Mean ± SD	Mean ± SD
t_{max} (h)	2.4 ± 1.1	3.7 ± 2.0
C_{min} (ng/mL)	2.33 ± 0.35	5.82 ± 1.08
C_{max} (ng/mL)	7.57 ± 0.96	18.0 ± 5.0
$AUC_{0-\tau}$ (ng·h/mL)	104 ± 13	277 ± 56
C_{ss} (ng/mL)	4.35 ± 0.53	11.6 ± 2.4
AUC ratio milk/plasma	-	2.65 ± 0.37
Dose in infant (µg/kg)	1.74 ± 0.35	
Relative exposure (%) (infant/mother)	6.13 ± 1.55	

Abbreviations: AUC, area under the curve; T_{max}, time to maximum plasma concentration; C_{max}, C_{min}, maximum and minimum plasma concentration; C_{ss}, concentration at steady state; QD, once daily; SD, standard deviation
Note: Data presented as mean ± StdDev
Dose in infant was calculated as $C_{ss,av}$ (breast milk) * 150 mL/kg/day
Relative dose in infant/mother (%) was calculated [Css,av (breast milk) * 150 mL/kg/day] / [2 mg/BW mother]
Source: Clinical study report for study PRU-RSA-1, Table 11.4-1

Figure 6. Mean Plasma Prucalopride Concentration-Time Profile in Plasma (□) and Breast Milk (○) After Repeated Oral Dosing of Prucalopride 2 mg QD in Healthy Lactating Subjects



Source: Clinical study report for study PRU-RSA-1, Display 5

Of note, prucalopride concentrations in breast milk were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, while prucalopride in plasma was measured by RIA method. No formal cross-validation has been conducted by the Applicant.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The primary evidence of effectiveness of 2 mg prucalopride QD was supported by a significantly higher proportion of patients with an average of ≥3 SCBMs/week compared to placebo treatment over 12-week treatment in five of the six efficacy trials. The proportion of responders in the prucalopride treatment group was 33.3% and 37.9% in two pivotal trials, PRU-CRC-3001 and SPD555-302, respectively, compared with 10.3% and 17.7% in the placebo treatment group, respectively. See Section 8 of this multi-discipline review for the related efficacy data.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed oral dosage at 2 mg QD for the general adult patient population is appropriate.

In the main phase 2 dose ranging study, PRU-USA-3, prucalopride at 0.5 mg, 1 mg, 2 mg, and 4 mg QD or placebo were administered for 4 weeks in patients with CIC. Efficacy results from this study suggested a dose-related increase in the proportion of patients with an average of ≥3 SCBMs/week, while the 2 mg and 4 mg dosage showing statistically significant improvements compared to placebo (Table 31).

Table 31. Proportion of Patients 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%**

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

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 patients with CIC for 12 weeks. 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 patients with an average of ≥3 SCBMs/week over 12-week treatment period compared to placebo (Table 32). As such, the 4 mg dosage was not further evaluated by the applicant in additional clinical studies (SPD555-302, PRU-CRC-3001, SPD555-401).

Table 32. Proportion of Patients 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)

Abbreviations: QD, once daily; SCBM, spontaneous complete bowel movement
Note: Data presented are based on applicant's ITT population
Source: Clinical study reports for studies PRU-INT-6 (Table 11.3-1), PRU-USA-11 (Table 11.3-1), and PRU-USA-13 (Table 11.3-1)

The most common TEAEs in the prucalopride group included GI disorders (diarrhea, nausea, and abdominal pain) and nervous system disorders (headache). An apparent 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. See Section 8 of this multi-discipline review for the related efficacy and safety data.

Effect on QT interval

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 TQT study in healthy subjects (study M0001-C102). The largest upper bounds of the two-sided 90% CI for the mean difference between prucalopride (2 mg and 10 mg) and placebo were below 10 ms (Table 33). At 10 mg QD, mean C_{max} was 5.8-fold higher than that at the proposed 2 mg QD dose.

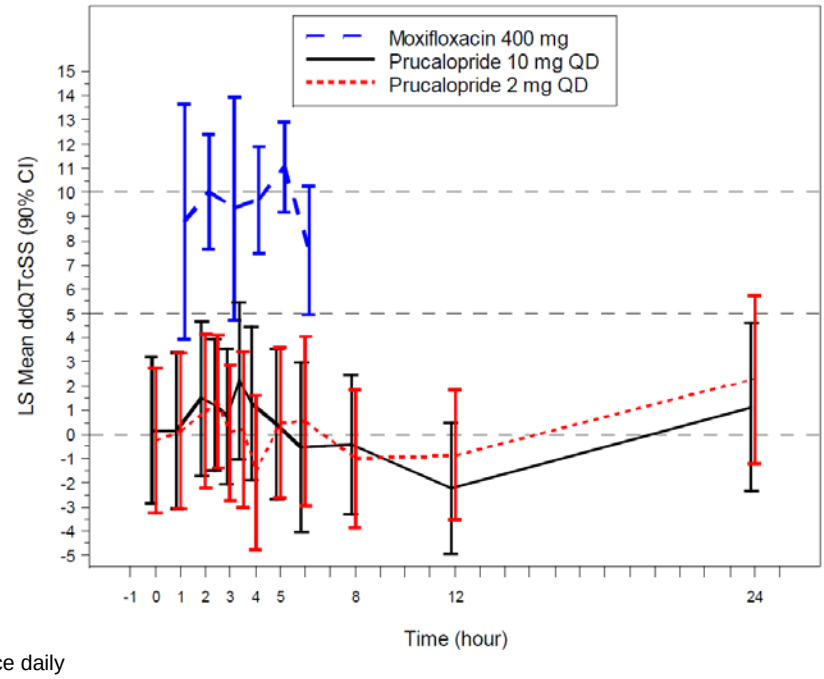
Table 33. Point Estimates and 90% CIs Corresponding to the Largest Upper Bounds for Prucalopride (2 mg and 10 mg) and the Largest Lower Bound for Moxifloxacin

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)

Abbreviation: CI, confidence interval
[1] Multiple endpoint adjustment of three time points was applied
Source: FDA QT-IRT review for IND 055078 (DARRTS 12/27/2013), Table 1

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 7. Mean and 90% CI for ΔΔQTcSS Time Profile

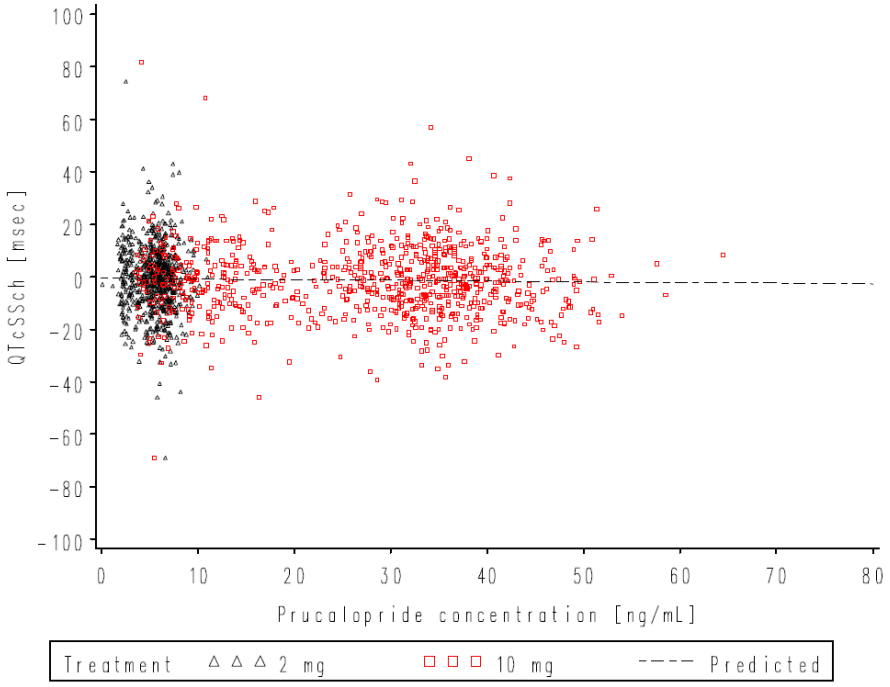


Abbreviation: QD, once daily
Source: FDA QT-IRT review for IND 055078, Figure 4

Of note, a total of 120 subjects were enrolled in this TQT 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 8).

Figure 8. Plasma Prucalopride Concentrations vs. ΔQTcSS



Source: Clinical study report for study M0001-C102, Post-Text Figure 4.2

Given data for moxifloxacin were available only between 1 and 6 hours postdose, there were concerns about assay sensitivity of this TQT 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. Refer to the QT-IRT review for prucalopride in Document Archiving, Reporting and Regulatory Tracking System dated 12/27/2013 (under IND 055078) and the QT-IRT review memo in Document Archiving, Reporting and Regulatory Tracking System dated 4/17/2018 (under NDA 210166).

Overall, the proposed dosage of 2 mg QD is considered appropriate for the treatment of CIC in adult patients based on the efficacy data in the pivotal and supportive clinical studies.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

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

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 (StdDev) PK parameters of prucalopride from this study are presented in Table 34.

Table 34. 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	CRCL ≥90 mL/min	CRCL 60-89 mL/min	CRCL 30-59 mL/min	CRCL 15-29 mL/min	CRCL <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

Abbreviations: AUC, area under the curve; CRCL, creatinine clearance; C_{max}, maximum plasma concentration; ESRD, end-stage renal disease; PK, pharmacokinetic; RI, renal impairment; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration
Note: Data presented as mean ± StdDev
Source: FDA reviewer's analysis based on the data submitted for study PRU-USA-6

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.

Hepatic impairment

No dosage adjustment is deemed necessary for patients with any degree of 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 (Table 35).

Table 35. Prucalopride Pharmacokinetic Parameters After a Single Oral Dose of 2 mg in Subjects With Hepatic Impairment and in Healthy Subjects

PK Parameter	Healthy Subjects (N=8)	Moderate Hepatic Impairment (N=8)	Severe Hepatic Impairment (N=8)
T_{max} (h)	2.00 (1.00-4.00)	2.00 (1.00-3.00)	1.50 (0.50-3.00)
C_{max} (ng/mL)	3.77±0.91	4.17±0.75	4.43±1.56
AUC_{last} (ng·h/mL)	86.7±24.3	101±32.9	99.8±39.3
$AUC_{0\text{-}inf}$ (ng·h/mL)	96.2±25.5	115±36.5	111±42.2
$T_{1/2}$ (h)	27.4±5.56	29.8±10.3	27.4±8.96

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; PK, pharmacokinetic; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration
Note: Data presented as mean ± StdDev, except for T_{max} presented as median (range)
Source: Clinical study report for study M0001-C103, Table 5

Patients ≥65 years of age

The effect of age on the PK of prucalopride was studied in a dedicated study (PRU-NED-5). A SD 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 young subjects (aged 20 to 32 years). Single-dose and repeated-dose PK parameters of prucalopride are presented in the table below.

Table 36. Prucalopride Pharmacokinetic Parameters After Single 1 mg and Repeated (1 mg QD) Oral Dosing to Healthy Subjects Aged 65 Years or Older and to 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_{min} (ng/mL)	2.18±0.45	1.55±0.50
C_{max} (ng/mL)	4.57±0.96	3.63±1.12
AUC_{tau} (ng·h/mL)	72.2±12.5	56.2±12.5
CL_{renal} (mL/min)	156±29	190±40
CRCL (mL/min)	78.6±10.6	132±26

Abbreviations: AUC, area under the curve; CRCL, creatinine clearance; CL_{renal}, renal clearance; C_{max}, maximum plasma concentration; PK, pharmacokinetic; QD, once daily; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration
Note: Data presented as mean ± StdDev
Source: Clinical study report for study PRU-NED-5, display 12

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 (intent-to-treat (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. In a phase 2 trial, efficacy results suggested there was no statistically significant improvements for the 1 mg QD dosage as compared to placebo. Thus, the dose reduction for patients aged 65 years and older is deemed not necessary, unless they have severe renal impairment as discussed above.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No. The proposed dosing instruction to administer prucalopride with or without food is appropriate.

Food-drug interaction

No significant food effect on the PK of prucalopride was observed when a SD of 2 mg prucalopride was administered in the fasted state and 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 (Table 37). Mean T_{max} values for prucalopride were similar in the fed (2.4 h) and fasted (2.1 h) states.

Table 37. Pharmacokinetic Parameters and Statistical Evaluation Following Single Oral Dose of 2-mg Tablet in the Fasted and Fed States

PK Parameter	2 mg Fasted (N=14)	2 mg Fed (N=14)	Geometric Mean Ratio Fed/Fasted (90% Confidence Interval)
T_{max} (h)	2.1±0.9	2.4±0.9	NA
C_{max} (ng/mL)	4.34±0.82	4.58±0.78	106% (98%-115%)
AUC_{last} (ng·h/mL)	93.7±15.9	90.3±20.0	96% (91%-101%)
$AUC_{0\text{-}inf}$ (ng·h/mL)	99.2±17.2	95.9±22.3	96% (91%-101%)

Abbreviations: AUC, area under the curve; PK, pharmacokinetic; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration
Source: Clinical study report for study PRU-BEL-32, Table 4-1 and synopsis table

Drug-drug interactions

In vitro, prucalopride is a substrate of CYP3A4, P-gp, and BCRP. Based on in vitro study results, the potential for prucalopride to inhibit major CYP enzymes (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) and transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, BSEP, and MRP2), or induce CYP enzymes (1A2, 2B6, and 3A4) is low at the clinical concentrations.

Details of the in vivo drug-drug interaction study results are as follows.

Effects of Prucalopride on Other Drugs

Effects of prucalopride on warfarin

Warfarin is a sensitive CYP2C9 substrate with a narrow therapeutic index. Prucalopride 2 mg QD or placebo QD were administered for 10 days in 12 healthy subjects. A SD of 25 mg warfarin was co-administered on day 5. No significant effect of prucalopride on the C_{max} and $AUC_{0\text{-}inf}$ of R-warfarin and S-warfarin was observed.

In addition, no statistically significant differences were observed in peak prothrombin times (PT_{max}) or total area under the prothrombin-time-time curve ($AUC_{PT\ 144h}$) following repeated dosing of prucalopride at 2 mg QD.

Table 38. Warfarin Pharmacokinetic Parameters and Prothrombin Time Parameters After a Single Oral Dose of 25 mg Administered With Placebo or Prucalopride 2 mg QD in Healthy Subjects

Parameter (Unit)	Warfarin + Placebo Mean ±SD	Warfarin + Prucalopride Mean ± SD	Prucalopride *vs* Placebo Co-Treatment Ratio 90% CI [a]
Pharmacokinetic parameters of R-Warfarin			
t_{max} (h)	4.3 ± 2.9	3.3 ± 2.4	-
C_{max} (µg/mL)	1.41 ± 0.15	1.52 ± 0.14	108 (103-113)
$AUC_{0\text{-}t}$ (µg·h/mL)	74.6 ± 13.1	75.8 ± 12.6	101 (98-106)
$AUC_{0\text{-}\infty}$ (µg·h/mL)	84.1 ± 16.7	85.8 ± 16.3	102 (98-107)
$t_{1/2}$ (h)	44.8 ± 4.8	45.5 ± 7.0	-
Pharmacokinetic parameters of S-Warfarin			
t_{max} (h)	3.3 ± 2.0	2.0 ± 0.9	-
C_{max} (µg/mL)	1.36 ± 0.17	1.51 ± 0.15	112 (104-119)
$AUC_{0\text{-}t}$ (µg·h/mL)	53.5 ± 13.4	53.3 ± 12.0	100 (97-103)
$AUC_{0\text{-}\infty}$ (µg·h/mL)	57.8 ± 16.1	57.2 ± 15.0	99 (96-102)
$t_{1/2}$ (h)	37.9 ± 6.0	35.0 ± 8.4	-
Warfarin Plasma Protein Binding [b]			
PPB (%)	99.05 ± 0.06	99.06 ± 0.07	-
Prothrombin Times			
t_{PTmax} (h)	27.3 ± 19.0	30.7 ± 15.8	-
PT_{max} (s)	18.6 ± 2.8	18.7 ± 2.9	101 (95-105)
$AUC_{PT\ 144h}$ (s·h)	2169 ± 215	2224 ± 204	102 (101-104)

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; PK, pharmacokinetic; QD, once daily; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration
Source: Clinical study report for study PRU-BEL-20, Display 8, 9, 12, 13, 14, and 18

Effects of prucalopride on digoxin

Digoxin is a P-gp substrate with a narrow therapeutic index. Prucalopride 4 mg QD or placebo QD were administered for 11 days in 16 healthy subjects. Digoxin was administered at 0.25 mg three times a day on day 1, 0.25 mg twice daily (BID) on day 2, and 0.25 mg QD on days 3 to 8. No significant effect of prucalopride on the PK of digoxin was observed. Co-administration of prucalopride decreased mean C_{min}, C_{max}, and AUC_{tau} of digoxin by about 9%, 3%, and 10%, respectively. However, the 90% CIs for the geometric mean treatment ratios of C_{min}, C_{max}, and AUC_{tau} were all contained within the range of 80 to 125%. Mean T_{max} and $t_{1/2}$ values of digoxin were similar between the two treatments when digoxin was administered with placebo and with prucalopride 4 mg QD.

Table 39. Digoxin Pharmacokinetic Parameters After the Last Dose When Administered With Placebo or Prucalopride 4 mg QD in Healthy Subjects

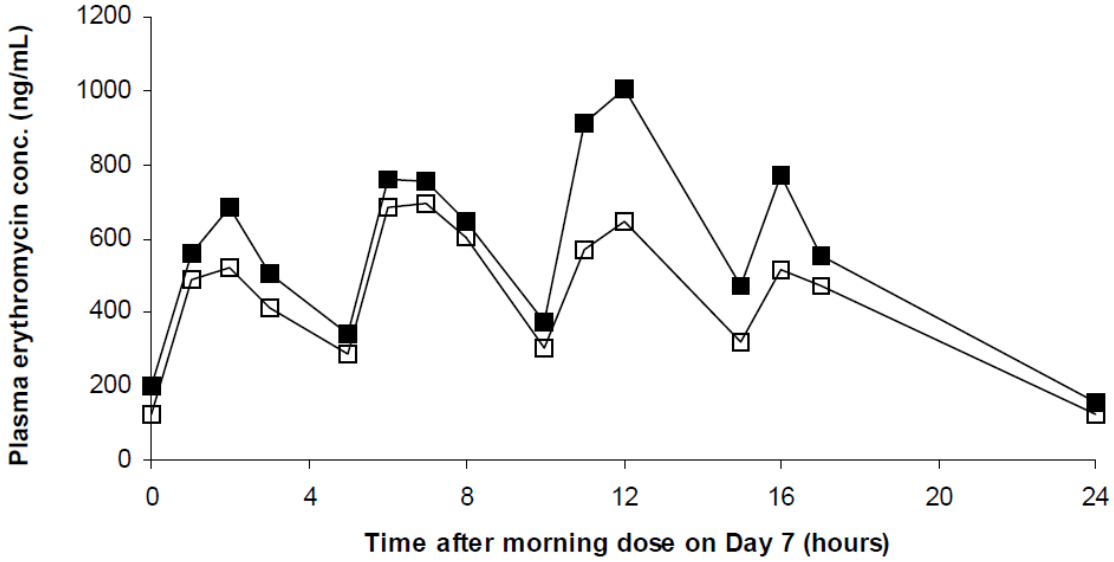
Parameter (Unit)	Digoxin + Placebo (N = 15) Mean ± SD	Digoxin + Prucalopride (N = 16) Mean ± SD	Prucalopride *vs* Placebo Co-Treatment Ratio 90% CI [a]
t_{max} (h)	1.1 ± 0.4	1.2 ± 0.6	-
C_{min} (µg/mL)	0.57 ± 0.20	0.52 ± 0.17	90.6 (82.8-99.1)
C_{max} (µg/mL)	1.87 ± 0.47	1.79 ± 0.42	96.6 (88.1-106)
$AUC_{0-\tau}$ (µg·h/mL)	19.4 ± 5.2	17.7 ± 5.2	89.8 (84.4-95.7)
$t_{1/2}$ (h)	41.6 ±8.3	43.0 ± 8.9	-

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; PK, pharmacokinetic; QD, once daily; $t_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration
Source: Clinical study report for study PRU-NED-11, Display 12, 14

Effects of prucalopride on erythromycin

Erythromycin 500 mg QID was administered orally for 7 days alone or in combination with prucalopride 2 mg QD in 18 healthy subjects. Co-administration of prucalopride increased the C_{max} and AUC_{tau} of erythromycin at steady state by 40% and 28%, respectively.

Figure 9. Plasma Concentration-Time Profile of Erythromycin at Steady-State When Administered Alone or in Combination With Prucalopride 2 mg QD in Healthy Subjects



Abbreviation: QD, once daily
Note: Erythromycin at 500 mg QID alone (□) or in combination with prucalopride 2 mg QD (■).
Source: Clinical study report for study PRU-NED-14, Display 13

Table 40. Erythromycin Steady-State Pharmacokinetic Parameters Administered Alone or With Prucalopride 2 mg QD in Healthy Subjects

Parameter (Unit)	Erythromycin Alone Mean ± SD	Erythromycin + Prucalopride Mean ± SD	Prucalopride *vs* No co-treatment Ratio 90% CI [a]
t_{max} (h)	7.6 ± 4.0	9.8 ± 4.2	-
C_{min} (ng/mL)	115 ± 111	149 ± 144	121 (91.1-161)
C_{max} (ng/mL)	920 ± 536	1230 ± 643	140 (109-181)
AUC_{0-24h}(µg·h/mL)	10.2 ± 6.8	13.1 ± 9.2	128 (101-162)
$f_{e\ 24h}$ (% of dose)	1.5 ± 1.7	1.40 ± 0.88	119 (96.2-147)
CL_{renal} (mL/min)	44.9 ± 21.3	39.9 ± 14.4	93.4 (75.8-115)

Abbreviations: AUC, area under the curve; CI, confidence interval; CL_{renal}, renal clearance; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; fe, fraction excreted; QD, once daily; T_{max}, time to maximum plasma concentration
Source: Clinical study report for study PRU-NED-14, Display 14, 15

The mechanism for the increased exposure to erythromycin is not well understood (Hospira and Food and Drug Adminstration 2018; U.S. National Library of Medicine 2018). Given that erythromycin is intended as a short-term antibiotic treatment, the increase of 30 to 40% in systemic exposure does not appear to warrant dose adjustment. In addition, the Applicant's PK data showed that %CV for C_{max} and AUC of erythromycin was 58% and 67%, respectively.

Of note, the effect of erythromycin as a moderate CYP3A4 inhibitor and an inhibitor for P-gp, OATP1B1, and OATP1B3 on the PK of prucalopride was evaluated in this study (see section below under Effect of Other Drugs on Prucalopride).

Effects of prucalopride on paroxetine

Prucalopride 4 mg QD was administered alone for 7 days or in combination with paroxetine 10 mg BID on days 1 to 3 and 20 mg QD on days 4 to 7 in 18 healthy subjects. No significant effect of prucalopride on the PK of paroxetine was observed. Mean C_{max} and AUC_{tau} of paroxetine at steady state were similar when administered alone and with prucalopride 4 mg QD (mean ratios: 98.5% - 99.8%).

Effects of prucalopride on oral contraceptives ethinyl estradiol and norethisterone

Oral contraceptive (0.035 mg ethinyl estradiol and 1 mg norethisterone) was administered QD on days 1 to 5 alone or with prucalopride 2 mg QD administered on days 1 to 6 in 16 healthy female subjects. No clinically meaningful effects of prucalopride on the PK of ethinyl estradiol and norethisterone were observed when co-administered with prucalopride 2 mg QD.

Table 41. Ethinyl Estradiol and Norethisterone Steady-State Pharmacokinetic Parameters and Summary of the Equivalence Analysis After Repeated Oral Dosing of 0.035/1 mg for 5 days With or Without Prucalopride 2 mg QD in Healthy Subjects

Parameter (Unit)	OC Treatment A Mean ± SD [a]	OC + Prucalopride Treatment B Mean ± SD [a]	OC versus Prucalopride PE [b]	90% CI [b]
Ethinylestradiol Day 1 (N = 13)				
t_{max} (h)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0	(-0.50-0.00)
C_{max} (pg/mL)	90.5 ± 21.8	103 ± 32.0	110.37	(99.74-122.13)
AUC_{0-24h} (pg·h/mL)	727 ± 156	720 ± 204	95.52	(90.70-100.61)
Ethinylestradiol Day 5 (N = 13)				
t_{max} (h)	1.0 (1.0-3.0)	1.0 (1.0-3.0)		
C_{min} (pg/mL)	18.6 ± 7.4	17.8 ± 8.1	83.00	(65.43-105.29)
C_{max} (pg/mL)	130 ± 34	123 ± 27	96.07	(89.37-103.28)
$AUC_{0-\tau}$ (pg·h/mL)	1153 ± 323	1090 ± 296	92.54	(85.07-100.66)
$t_{1/2}$ (h)	17.1 ± 2.4	51.0 ± 3.2		
Ethinylestradiol Day 5 (N = 12) [c]				
t_{max} (h)	1.0 (1.0-3.0)	1.0 (1.0-3.0)	-0.25	(-0.50-0.00)
C_{min} (pg/mL)	19.4 ± 7.0	19.3 ± 6.3	97.10	(86.83-108.59)
C_{max} (pg/mL)	132 ± 35	126 ± 27	99.12	(92.80-105.88)
$AUC_{0-\tau}$ (pg·h/mL)	1135 ± 331	1119 ± 288	97.65	(93.36-102.14)
$t_{1/2}$ (h)	17.4 ± 2.2	15.3 ± 3.1		
Norethisterone Day 1 (N = 13)				
t_{max} (h)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0	(-0.03-0.00)
C_{max} (pg/mL)	12.6 ± 5.0	12.4 ± 4.4	94.14	(81.02-109.37)
AUC_{0-24h} (pg·h/mL)	61.1 ± 30.7	58.2 ± 26.2	90.29	(79.12-103.02)
Norethisterone Day 5 (N = 13)				
t_{max} (h)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0	(0.00-0.00)
C_{min} (pg/mL)	0.929 ± 0.450	0.921 ± 0.504	73.92	(49.05-111.39)
C_{max} (pg/mL)	17.1 ± 4.6	17.0 ± 4.7	98.07	(88.37-108.84)
$AUC_{0-\tau}$ (pg·h/mL)	105 ± 39	98.9 ± 33.7	91.36	(82.58-101.09)
$t_{1/2}$,(h)	10.2 ± 2.0	9.8 ± 1.8		
Norethisterone Day 5 (N = 12) [c]				
t_{max} (h)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0	(-0.50-0.00)
C_{min} (pg/mL)	0.965 ± 0.451	0.998 ± 0.440	97.94	(84.37-113.70)
C_{max} (pg/mL)	17.0 ± 4.8	17.1 ± 4.9	99.00	(88.02-111.35)
$AUC_{0-\tau}$ (pg·h/mL)	99.8 ± 37.0	100.3 ± 34.8	96.04	(88.28-104.47)
$t_{1/2}$ (h)	10.3 ± 2.0	9.9 ± 1.9		

Abbreviations: AUC, area under the curve; CI, confidence interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; OC, oral contraceptive; QD, once daily; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration
Note: Point estimate and 90% CI on day 5 are based on all data (N=13) and on N=12, after exclusion of Subject A0110024 as evidence indicated that this subject did not take the study medication on days 3 and/or 4.
Source: Clinical study report for study M0001-C101, synopsis table

Of note, the applicant stated that because of the likelihood that C_{min} at day 5 was biased by the noncompliance of Subject A011024 on days 3 and/or 4, the statistical comparison on day 5 was performed with and without this subject. On the other hand, the 90% CIs for the geometric mean

treatment ratios of C_{max} and AUC_{tau} on day 5 for ethinyl estradiol and norethisterone were all contained within the range of 80 to 125% with and without Subject A011024.

Effects of prucalopride on alcohol

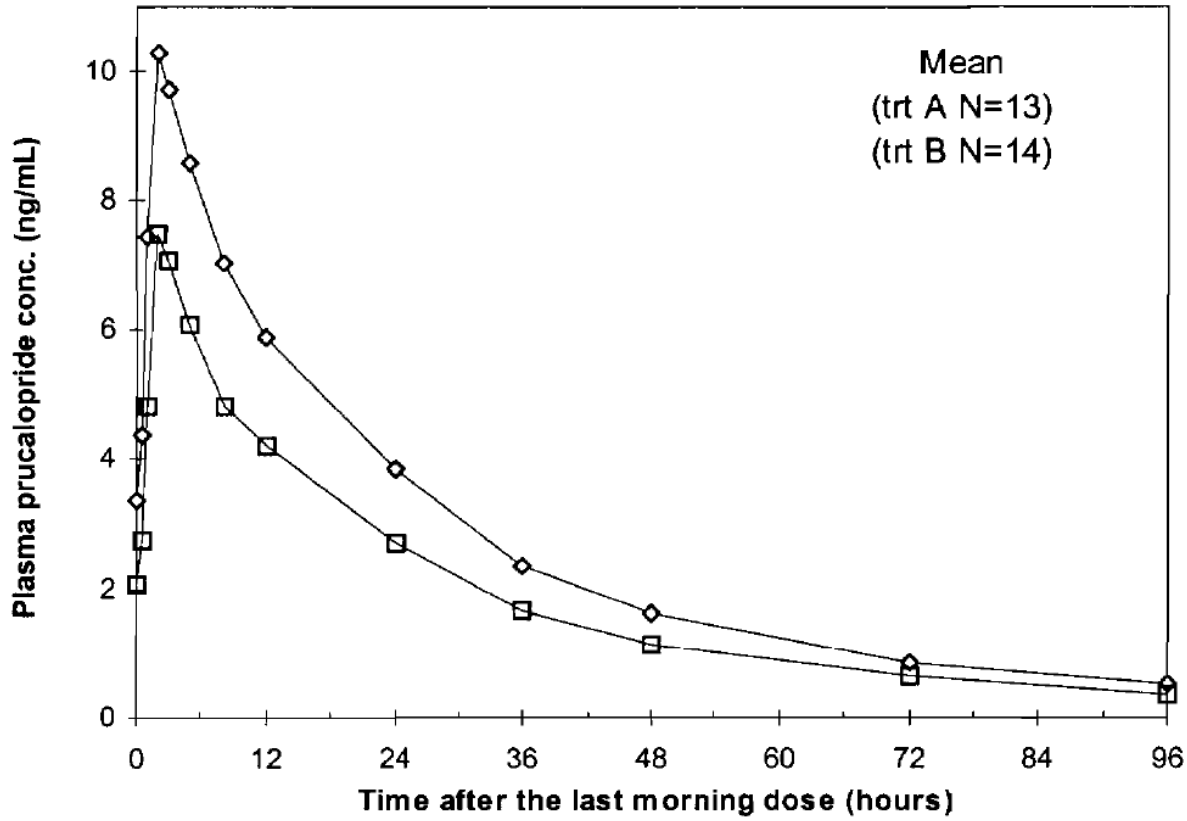
Since prucalopride may potentially accelerate alcohol absorption through its effect on the intestinal transit time, the effects of prucalopride on alcohol PK was evaluated. Prucalopride 4 mg QD or placebo was administered for 4 days in 16 healthy subjects. On day 4 of each treatment, a beverage containing 0.7 g/kg of alcohol was drunk at 30 min after the prucalopride or placebo administrations. No significant effect of prucalopride on the PK of alcohol was observed when co-administered with prucalopride 4 mg QD. Mean C_{max} and AUC_{0-8h} of alcohol increased by about 4% and 1%, respectively. (b) (4)

Effect of Other Drugs on Prucalopride

Effects of ketoconazole on prucalopride

Ketoconazole is a strong CYP3A4 inhibitor and an inhibitor of P-gp and BCRP. Prucalopride 2 mg QD was administered for 7 days alone (placebo) or with ketoconazole 200 mg BID in 14 healthy subjects. Co-administration of ketoconazole increased the C_{max} and AUC_{tau} of prucalopride at steady state by 38% and 37%, respectively.

Figure 10. Plasma Concentration-Time Profile of Prucalopride at Steady-State When Administered Alone or in Combination With Ketoconazole in Healthy Subjects



Note: Prucalopride 2 mg QD was administered for 7 days alone (trt B; □) or with ketoconazole 200 mg BID (trt A; ◊)
Source: Clinical study report for study PRU-NED-6, Display 6

Table 42. Prucalopride Pharmacokinetic Parameters at Steady State When Administered Alone or With Ketoconazole in Healthy Subjects

Parameter (Unit)	Prucalopride + Placebo n = 14	Prucalopride + Ketoconazole N = 13	Ketoconazole *vs* Placebo Co-treatment
	Mean ± SD	Mean ± SD	Ratio 90% CI [a]
t_{max} (h)	2.3 ± 0.5	2.3 ± 1.0	-
C_{min} (ng/mL)	2.51 ± 0.82	3.67 ± 1.05	141 (129-155)
C_{max} (ng/mL)	7.76 ± 2.12	10.8 ± 2.2	138 (128-149)
$AUC_{0-\tau}$ (ng·h/mL)	106 ± 25	149 ± 36	137 (131-144)
$t_{1/2}$ (h)	26.3 ± 3.9	27.1 ± 7.0	-

Abbreviations: AUC, area under the curve; CI, confidence interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; SD, standard deviation; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration
Source: Clinical study report for study PRU-NED-6, Display 10, 11

The increase in prucalopride exposure is likely due to the inhibition of CYP3A but not P-gp. In another DDI study, co-administration of erythromycin (a moderate CYP3A4 inhibitor and also an inhibitor for P-gp) did not have a significant effect on the PK of prucalopride.

Effects of probenecid and cimetidine on prucalopride

Probenecid is an inhibitor for OAT1 and OAT3. Cimetidine is a H_2-receptor antagonist and also an inhibitor of CYP1A2, CYP2D6, CYP3A4, as well as an inhibitor of MATE1, MATE-2K, and OCT2 transporters. Prucalopride 2 mg QD was administered for 7 days alone, with cimetidine 800 mg BID, or with probenecid 500 mg BID in 18 healthy subjects. Administration of therapeutic doses of cimetidine or probenecid did not have a significant effect on the PK of prucalopride.

Table 43. Prucalopride Pharmacokinetic Parameters at Steady State When Administered Alone, With Cimetidine, or Probenecid in Healthy Subjects

Parameter (Unit)	Prucalopride Alone	Prucalopride + Cimetidine	Prucalopride + Probenecid
	Mean ± SD	Mean ± SD	Mean ± SD
t_{max} (h)	2.7 ± 1.0	2.9 ± 1.0	2.7 ± 0.8
C_{min} (ng/mL)	2.41 ± 0.57	2.49 ± 0.74	2.16 ± 0.40
C_{max} (ng/mL)	7.02 ± 1.46	7.23 ± 1.45	6.93 ± 1.34
$AUC_{0-\tau}$ (ng·h/mL)	103 ± 21	111 ± 22	101 ± 15
$A_{e\ 24h}$ (µg)	1.21 ± 0.13 [a]	1.24 ± 0.13	1.15 ± 0.13 [b]
$f_{e\ 24h}$ (% of dose)	60.7 ± 6.3 [a]	62.1 ± 6.3	57.7 ± 6.4 [b]
CL_{renal} (mL/min)	205 ± 38	194 ± 38	194 ± 40 [a]
CL_{CR} (mL/min)	129 ± 28	114 ± 18	122 ± 30
	Geometric Mean Treatment Ratio (%) and Associated 90% CI		
	Cimetidine *vs* No Co-treatment		Probenecid *vs* No Co-treatment
C_{min}	102 (94.1-110)		90.3 (83.4-97.7)
C_{max}	103 (97.0-110)		99.0 (93.1-105)
$AUC_{0-\tau}$	108 (103-113)		99.7 (95.5-104)
$A_{e\ 24h}$	102 (97.5-107)		94.7 (90.4-99.2)

Abbreviations: AUC, area under the curve; CI, confidence interval; CL_{CR}, creatinine clearance; CL_{renal}, renal clearance; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; fe, fraction excreted; SD, standard deviation; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration
Source: Clinical study report for study PRU-NED-7, Display 12, 13

Effects of erythromycin on prucalopride

Erythromycin is a moderate CYP3A4 inhibitor and also an inhibitor for P-gp, OATP1B1, and OATP1B3. Co-administration of erythromycin does not have a significant effect on the PK of prucalopride.

Table 44. Prucalopride Pharmacokinetic Parameters at Steady State When Administered Alone or With Erythromycin in Healthy Subjects

Parameter (Unit)	Prucalopride Alone	Prucalopride + Erythromycin	Erythromycin *vs* No co-treatment
	Mean ± SD	Mean ± SD	Ratio 90% CI [a]
t_{max} (h)	3.4 ± 2.6	2.7 ± 1.5	-
C_{min} (ng/mL)	2.79 ± 0.56	2.75 ± 0.79	97.2 (89.3-106)
C_{max} (ng/mL)	7.14 ± 1.26	7.50 ± 1.61	105 (98.2-111)
$AUC_{0-\tau}$ (ng·h/mL)	108 ± 18	111 ± 27	102 (97.3-106)
$f_{e\ 24h}$ (% of dose)	57.8 ± 7.8	65.5 ± 9.3	113 (107-121)
CL_{renal} (mL/min)	184 ± 40	207 ± 56	-
CL_{CR} (mL/min)	111 ± 17	110 ± 17	-

Abbreviations: AUC, area under the curve; CI, confidence interval; CL_{CR}, creatinine clearance; CL_{renal}, renal clearance; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; fe, fraction excreted; SD, standard deviation; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration
Note: Prucalopride 2 mg QD for 7 days and erythromycin 500 mg QID for 7 days were administered alone and in combination to 18 healthy subjects
Source: Clinical study report for study PRU-NED-14, Display 8, 9

Effects of paroxetine on prucalopride

Paroxetine is a strong CYP2D6 inhibitor. Co-administration of paroxetine does not have a significant effect on the PK of prucalopride.

Table 45. Prucalopride Pharmacokinetic Parameters at Steady State When Administered Alone or With Paroxetine in Healthy Subjects

Parameter (Unit)	Prucalopride Alone (n = 17)	Prucalopride + Paroxetine (n = 18)	Prucalopride *vs* No co-treatment
	Mean ± SD	Mean ± SD	Ratio 90% CI [a]
t_{max} (h)	2.5 ± 0.7	2.2 ± 0.9	-
C_{min} (ng/mL)	4.87 ± 0.89	5.12 ± 0.93	105 (95.5-115)
C_{max} (ng/mL)	14.1 ± 2.6	15.1 ± 3.1	106 (98.4-115)
$AUC_{0-\tau}$ (ng·h/mL)	197 ± 31	208 ± 39	105 (98.9-111)
$t_{1/2}$ (h)	23.8 ± 3.3	23.3 ± 3.8	-

Abbreviations: AUC, area under the curve; CI, confidence interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; SD, standard deviation; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration
Note: Prucalopride 4 mg QD was administered alone for 7 days or in combination with paroxetine 10 mg BID on days 1 to 3 and 20 mg QD on days 4 to 7 to 18 healthy subjects
Source: Clinical study report for study PRU-NED-12, Display 12, 14

Bridge Between the To-Be-Marketed and Clinical Trial Formulations?

The formulations used in the two proposed pivotal phase 3 trials (studies PRU-CRC-3001 and SPD555-302) and clinical study SPD555-401 are the same as the to-be-marketed formulations.

Since the formulations used in the supportive phase 3 trials for studies PRU-INT-6, PRU-USA-11, and PRU-USA-13 are different from the to-be-marketed formulation as shown in the following table, relative bioavailability studies were conducted to bridge the clinical trial

formulations to the to-be-marketed formulation. Bioequivalence was demonstrated between the formulations used in the phase 3 trials for studies PRU-INT-6, PRU-USA-11, and PRU-USA-13 and the to-be-marketed formulations.

Table 46. Summary of Clinical Formulations and Relative Bioavailability Studies to the To-Be-Marketed Formulations

Study	Dose	Clinical Trial Formulation	Relative Bioavailability Study	Clinical Information
PRU-CRC-3001	2 mg	To-be-marketed formulation (b) (4)	NA	Pivotal efficacy trial
SPD555-302	1 mg, 2 mg	To-be-marketed formulation (b) (4)	NA	Pivotal efficacy trial
PRU-INT-6	2 mg 4 mg[1]		PRU-USA-29 PRU-USA-31	Supportive efficacy trial
PRU-USA-11	2 mg 4 mg[1]		PRU-USA-29 PRU-USA-31	Supportive efficacy trial
PRU-USA-13	2 mg 4 mg[1]		PRU-USA-29 PRU-USA-31	Supportive efficacy trial
SPD555-401	1 mg, 2 mg	To-be-marketed formulation (b) (4)	NA	Supportive efficacy trial
SPD555-802	1 mg, 2 mg	To-be-marketed formulation (b) (4)	NA	Post-marketing epidemiology (observational) study

[1] The 4-mg dose strength is not proposed for clinical use in the current submission

A request to conduct an inspection of the clinical and bioanalytical sites for the BE studies PRU-USA-29 and PRU-USA-31 was submitted to the Office of Study Integrity and Surveillance (OSIS). OSIS declined to conduct the inspection due to the reasons including the permanently closed site, age of the study (i.e., both studies were conducted in 1999), and uncertainty of the availability of the study records that present impediments to OSIS for conducting an inspection. However, because no concerns were identified in the consult, OSIS recommends accepting the data for review. Of note, the to-be-marketed 1 mg and 2 mg formulations were both used in the two pivotal phase 3 clinical trials.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

For this NDA, the Applicant submitted data from five phase 3 trials and one phase 4 trial and labeling for prucalopride 2 mg (Table 1). The two trials considered to be the primary basis for demonstration of efficacy (Studies 3001 and 302) were conducted outside of the U.S. and primarily enrolled female Asian or male Caucasian patients and were completed in 2011 and 2013, respectively. The submission contains data from three phase 3 trials (Studies INT-6, USA-

11, and USA-13) to support the generalizability of results of non-U.S. pivotal trials to the U.S. patient population. The NDA also contains a sixth trial, a phase 4, 24-week trial (study 401).

Table 47. 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 trial 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 trial 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 trial 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 trial 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

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
Source: Reviewer's analyses

7.2. Review Strategy

The efficacy evaluation in this review is based on efficacy results from five controlled phase 3 trials and one controlled phase 4 trial, shown in Table 47 above.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used To Support Efficacy

Trial Design

Except for the duration of study 401 (24 weeks), the study design was generally similar for all efficacy trials: a 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 BM was considered to be "spontaneous" if the BM was not preceded by the intake of a laxative agent or enema within a period of 24 hours. A SBM was considered complete if the patient responded "yes" to the e-diary question about completely emptying his/her bowels.

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 SBMs, whereas study 302 relied on a history of SCBMs. In both trials, a BM 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 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 two 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.

8.2. Study Endpoints

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

Each efficacy study protocol listed multiple exploratory secondary endpoints. This review included one of the secondary endpoints which the Applicant proposed to label: proportion of patients with an average increase of ≥1 SCBM/week from baseline over a 12-week treatment period. 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.

The prespecified primary endpoint in the six phase 3/4 trials differed from the Division's currently recommended primary efficacy endpoint for the CIC indication. Therefore, at a meeting on July 15, 2014, we requested an additional post hoc efficacy analysis using the recommended overall responder endpoint (referred to as Alternative Endpoint A). 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. Patients who did not have at least 4 days of evaluable response were considered weekly nonresponders.

8.3. Statistical Analysis Plan

The six efficacy trials were completed between 1999 and 2011, and none of the statistical analysis plans (SAPs) were submitted to the Agency prior to this NDA submission in December 2017.

Study populations:

The primary analysis population was defined differently for each study including the ITT population for Studies 3001, USA-11, USA-13 and INT-6, and modified ITT (mITT) population for study 302.

- Study 3001 (ITT population): all randomized subjects received at least one dose of study drug.
- Studies USA-11, USA-13 and INT-6 (ITT population): all randomized subjects received at least one dose of study drug and provided at least one record for at least one key efficacy endpoint.
- Study 302 (mITT population): all randomized subjects received at least one dose of study drug excluding subjects enrolled at Site 350012 for a violation of GCP.
- Study 401 (ITT population): all randomized subjects received at least one dose of study drug excluding 21 subjects who were potentially unblinded due to an error in the interactive web/voice response system report sent to the investigators

Per-protocol (PP) Population for all studies was a subset of the ITT Population, including subjects with no major protocol violations. The PP population was used for a sensitivity analysis on the primary endpoint and the key secondary endpoint.

Completer population was not included in the study reports or SAPs. It was defined post hoc as response to the Agency's information request. This population is a subset of the ITT/mITT population, excluding subjects whose status at study termination is early withdrawal or whose duration in the study (from day 1 to the disposition day) was less than 81 days.

Calculations of Weekly Frequencies

For all intervals (week, month, 12 weeks, etc.), weekly frequency is calculated for events (BM, SBM, complete bowel movement (CBM) and SCBM) as follows: (# of events in interval) ×7 / (# of evaluable days in interval).

An evaluable day was defined as an e-diary entry with at least a date recorded in the treatment period.

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 week, weekly frequency was calculated if data were available for 4 or more days in the 7-day period, otherwise, the weekly frequency was set to "missing".

For the 4-week interval, weekly frequency was calculated if data were available for 14 or more days in the 4-week period, otherwise the weekly frequency was set to "missing" for that period.

For the 12-week period, Studies 302 and 401 set weekly frequency to "missing" for a patient with less than 14 days of data and Studies 3001, INT-6, USA-11 and USA-13 set weekly frequency to "missing" for a patient with less than 37 days of data.

Strategies for Missing Data Handling

1. Non-responder imputation: Different cutoffs were used for nonresponder imputation based on number of evaluable diary days for the week 1 to 12 evaluation period (including study days beyond day 84).
    a. For Studies INT-6, USA-11, USA-13 and 3001, subjects with less than 37 diary days, were considered as nonresponder.
    b. For Study 302, a subject with less than 14 days was considered as nonresponder for the week 1 to 12 period.
    c. For Study 401, subjects with less than 37 diary days in a 12-week period (i.e. weeks 1 to 12 or weeks 13 to 24) were considered as nonresponder for that 12-week period.
2. Last observation carry forward method:
    a. Subjects with less than 14 days of e-diary data were assumed to be nonresponders and no further imputation was performed.
    b. For subjects with at least 7 nonmissing e-diary days after the first week of treatment but with less than 84 days of e-diary data, the information from the last 7 nonmissing e-diary days was compressed into a block of 7 days and was repeatedly copied to all missing days after the last available e-diary day up to day 84.
3. Other imputation methods and sensitivity analyses used:
    a. Studies 302 and 401: generalized linear mixed model for repeated measures based on nonimputed data and multiple imputation and logistic regression.
    b. Study 3001: The generalized estimating equation model was applied to the nonmissing responders' data to assess the consistency in treatment effects over time to support the primary analysis.
    c. Studies INT-6, USA-11 and USA-13: Three imputation methods for the missing values of the last observation carry forward imputation:
        i. subjects with less than 7 nonmissing diary days (during any week, including week 1) were considered nonresponders.
        ii. subjects with less than 7 nonmissing diary days (during any week, including week 1) were considered responders.
        iii. subjects with less than 7 nonmissing diary days after week 1 were considered responders.

Primary Analysis Method

Cochran-Mantel-Haenszel test was used to test the treatment difference in the primary efficacy endpoint during weeks 1 to 12 between the placebo and prucalopride arms in the primary analysis population, controlling for the randomization stratification factors in each study, based on the last observation carry forward imputed dataset.

The randomization stratification factors were (1) study 302: baseline number of CBMs/week (0 or >0 CBM) and country; (2) study 3001: country and the baseline weekly SBM (<1 or ≥1 and ≤2); (3) study INT-6: country; (4) Studies USA-11 and USA-13: investigator and (5) study 401: baseline number of CBMs/week (0 or >0 CBM), country and sex.

For study 302, as prespecified in the SAP, countries with <12 subjects in the mITT Population were pooled according to geographical region for analyses where country was a factor in the model. As a result, Netherlands with 10 subjects was grouped with Belgium, the country with the next smallest number of randomized subjects (n=20) in Western Europe.

Secondary Analyses

Each efficacy study protocol listed multiple exploratory secondary endpoints. There was no multiplicity control prespecified for the secondary endpoints.

This review also included efficacy analysis results for one of the secondary endpoints which was considered clinically relevant, proportion of patients with an average increase of ≥1 SCBM/week from baseline over a 12-week treatment period. The same analyses method as was used for the primary endpoint was utilized (stratified CMH test based on nonimputed data). Other secondary analyses were not included in the review.

Subgroup Analyses of the Primary Endpoint

The prespecified sub-group analyses for the primary endpoint were by randomization stratification factors for each study, which did not include age, race and country. During the review process, we requested subgroup analyses by demographics and baseline characteristics in the primary analysis population using the primary analyses method.

Post hoc Analyses for the Alternative Endpoint A:

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

The alternative endpoint A was derived as follows:

1. This endpoint was based on nonimputed data. Weekly frequencies of SCBM were calculated by week as, 7×(the number of SCBM / the number of evaluable days). If the

number of evaluable days in a given week was less than 4, the weekly frequency of SCBM was set to missing for that week.

2. A responder was any subject who meets both criteria a and b below:
    a. Between weeks 1 to 12, there were at least 9 weeks with both a weekly frequency of at least three SCBMs and an increase of at least one SCBM versus baseline.
    b. Between weeks 9 to 12, there were 3 weeks with a weekly frequency of at least three SCBMs and an increase of at least one SCBM versus baseline.

The alternative endpoint A was analyzed using the CMH test stratified by number of CBMs/week at baseline (0 or >0), region, and sex, based on the integrated summary of efficacy SAP dated September 27, 2013 (Section 12.1). There was no prespecified sensitivity analysis for the alternative endpoint A.

8.4. Protocol Amendments

The amendments to the protocols were incorporated into the final protocol for each trial.

8.5. Compliance With Good Clinical Practices

The Applicant stated that the trials were conducted in accordance with International Conference on Harmonization of GCP, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements. The study protocol, any protocol amendments, the final approved informed consent document, relevant supporting information, and all types of patient recruitment information were submitted by the investigator to the Ethics Committee and approved by the Ethics Committee and relevant regulatory agency (as appropriate) prior to study initiation. Informed consent was mandatory for participation in the trials.

During a for cause audit for study 401, one study site was found to have no medical history documentation, including verification of a medical history of CIC contained in the clinical study files, and an advertisement for male patients with constipation on the investigator's web page that contained wording that was not compliant with International Conference on Harmonization GCP requirements. The Applicant stated that the well-being and safety of the patients were not compromised during the study. Because of these findings, for study 401 a post hoc efficacy analysis was performed excluding the results of 21 patients who were potentially unblinded due an error in the interactive web/voice response system. This study center was also involved in study 302 and the results from 12 patients enrolled at the site were excluded from the efficacy prior to database lock and unblinding. In addition, 50 patients were excluded from the efficacy analyses for USA-11 due to data quality issues.

8.6. Financial Disclosure

See Appendix for details.

8.7. Patient Disposition

Patient disposition was summarized for the six efficacy studies in the Table 48 below.

Table 48. Summary of Patient Disposition by Efficacy Study

	Study ID					
Population	**3001**	**302**	**INT-6**	**USA-11**	**USA-13**	**401**
Randomized	501	374	478	411	426	364
ITT/mITT Population*	501	358	476	383	426	340
PP population	446	291	386	309	371	271
Completer**	462	318	414	354	382	261
Withdrawn	29	56	64	62	44	103

Abbreviations: ITT, intention to treat; mITT, modified intent to treat; PP, per protocol
* ITT for studies 3001, INT-6, USA-11, USA-13 and 401, and mITT for study 302
**This completer terminology was used by the Applicant in the CSRs for each study, which had no specific definition. The results for number of post hoc defined completer (a subject with at least 81 days of records) are not included in this review
Source: Sponsor's Table 8, 9 and 10 of the ISE, and study CSRs for the six efficacy studies, verified by the reviewer

Overall, the majority of patients completed the six trials; study 401 had a slightly lower completion rate compared to the other five trials. The specifics reasons for trial withdrawal were generally balanced between the treatment arm(s) and the placebo group in each of the six trials. Refer to the Appendix for details on patient disposition by treatment arm, distribution for withdrawn, and reason for withdrawn.

8.8. Protocol Violations/Deviations

The number and type of protocol deviations varied across the six trials; however, the deviations were generally balanced between the prucalopride and placebo groups in each of the six trials. The reasons for protocol deviations generally included missing efficacy assessments, taking prohibited medication, study medication noncompliance, or investigator mistake. We noted that the proportion of protocol deviations in Studies USA-11 and USA-13 were high compared to Studies 3001 and 302; therefore, we requested additional information from the Applicant on protocol deviations related to violations of the permitted rescue medication ("rescue rule"). The number of patients with violations of the rescue rule on more than 1 or 2 days was small. There did not appear to be imbalances between the prucalopride 2 mg and placebo groups that raised concerns. Since the primary efficacy endpoint accounted for laxative use and missing diary data, these protocol deviations were unlikely to have influenced the results of the trials.

8.9. 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 49):

- 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 patients 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 49. 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
Black	0	8	5	31	33	1
Age groups						
≥65 years	2 (0.4)	150 (41.9)	51 (10.7)	53 (13.8)	57 (13.4)	61 (17.9)
≥75 years	0 (0)	68 (19.0)	13 (2.7)	18 (4.7)	15 (3.5)	19 (5.6)
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 of 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

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

Of note, there were 31 self-identified African American subjects in study USA-11 and 33 in study USA-13. Ethnicity information was not collected for the two U.S. studies. A few (less than ten) Hispanic subjects were enrolled in studies 302, INT-6 and 401.

8.10. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance, measured by mean number of tablets taken per day, was generally similar between the treatment and placebo groups within each trial.

Dulcolax® was the protocol-specified rescue medication used in each of the clinical trials. The primary endpoint accounted for laxative use in that a SBM could not have been preceded by the use of a laxative within 24 hours. In general, number of days with laxative use at baseline was similar between the prucalopride and placebo groups in each of the six trials. At the end of the 12-week trials, the mean number of days with laxatives was smaller in the prucalopride group compared with the placebo group for each trial.

8.11. Efficacy Results – Primary Endpoint

The primary efficacy analysis results are presented in Table 50. In Study 3001 and Study 302, prucalopride demonstrated statistically significant response rates that were 23% and 20.2% higher in the treatment arm compared to the placebo arm, respectively, and p-values <0.001 for both trials. Three out of the four supportive efficacy studies, studies INT-6, USA-11, and USA-13, also demonstrated statistically significant treatment differences of 9.9%, 16%, and 11.6%, respectively, and p-values of <0.01. Study 401, a phase 4 trial conducted in Europe to evaluate prucalopride for 24 weeks, reported a 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. The primary efficacy endpoint of Study 401 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 50. Primary Efficacy Analysis Results for Phase 3/4 Studies (ITT/mITT Population)

	PLA		PRU ≤2 mg		Percent Difference	
Study	N	n (%)	N	n (%)	PRU–PLA (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

Abbreviations: CI, confidence interval; PLA, placebo; PRU, prucalopride
[1] P-value based on primary analyses method for each study. Note that the proportions of patients on PRU <2 mg were 46% (79 of 177) for study 302 and 15% (30 of 171) for study 401
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

Results of sensitivity analyses for missing data and additional supportive analyses (PP and completer analyses) were consistent with the primary efficacy findings on the comparison between the prucalopride and the placebo arm. Completer analysis was conducted in subjects with at least 81 days of diary records in each study. The results for sensitivity analyses and supportive analyses are not included in this review.

Since weekly diary data was used as the basis for the primary endpoint, we examined the missing pattern by summarizing percentages of subjects without a single evaluable diary day entry per week (during weeks 1 to 12). There were 9 to 17% of missing weekly diary data across the six efficacy studies and the missing pattern was balanced between two treatment arms (Refers to the Figure in the Appendix).

We conducted primary analyses using observed case data for subjects with at least 37 days of data and nonresponder imputation for <37 days of data, shown below in Table 51. The Agency's primary analyses results were similar to the applicant's efficacy results.

Table 51. Agency's Primary Results for Phase 3/4 Studies (ITT/mITT Population)

	Placebo		PRU ≤2 mg		Percent Difference PRU–PLA	
Study	N	n (%)	N	n (%)	(95% CI)	P-value[1]
PRU-CRC-3001	252	25 (9.9)	249	81 (32.5)	22.6 (15, 30)	<0.0001
SPD555-302	181	32 (17.7)	177	67 (37.9)	20.2 (11, 29.2)	<0.001
PRU-INT-6	240	23 (9.6)	236	45 (19.1)	9.5 (3, 16)	0.003
PRU-USA-11	193	23 (11.9)	190	52 (27.4)	15.5 (8, 23)	<0.0001
PRU-USA-13	212	25 (11.8)	214	48 (22.4)	10.6 (4, 18)	0.003
SPD-555-401	169	33 (19.5)	171	43 (25.1)	5.6 (-3.2, 14.5)	0.261

Abbreviations: CI, confidence interval; PLA, placebo; PRU, prucalopride; ITT, intention to treat; mITT, modified intent to treat
[1] P-value based on primary analyses method for each study
Source: Reviewer's analyses results using observed case data (nonimputed data) for subjects with at least 37 days of evaluable diary days and nonresponder imputation for those who had less than 37 days of diary in ITT/mITT population

8.12. Efficacy Results of the Alternative Endpoint A

While these treatment effects for Alternative endpoint A were relatively smaller than those for the primary endpoint, the results for the Alternative endpoint A are statistically significant (p-values <0.005) in five of the six efficacy trials; and the p-value equals 0.52 for study 401 (Table 52).

Table 52. 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

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 nonimputed data (based on Section 12.1 of the ISE SAP)
Source: Applicant's Table 2 of the IR response dated June 8, 2018, verified by the reviewer

8.13. 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 53).

Table 53. Summary of Missing Source Documentation for Phase 3/4 Studies in the ITT/mITT Population

Study	Sites/Total number of Sites (%)	Patients/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)

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

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. 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. At sites where source data were available, results indicated that that these studies were adequately conducted and can be used in support of the application. Inspections included review of monitoring reports and review of history of monitoring from Janssen Research Foundation.

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, assuming data with no source documentation occurred completely at random.

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). We conducted subgroup analyses to compared the efficacy in patients with versus without source data. Generally, there were no major numerical inconsistencies between the efficacy data from study sites without source documentation and the rest of the efficacy data in these studies.

Efficacy Results – Secondary and Other Relevant Endpoints

Overall, the secondary endpoint results were consistent with the primary endpoint in favor of prucalopride over placebo.

Table 54 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 302 and 401.

Table 54. Secondary Analyses Result on Proportion of Patients 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	
Study	N	n (%)	N	n (%)	PRU–PLA (95% CI)	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

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 prespecified CMH test for the primary analysis for each study using nonresponder imputation
Source: Table 7 on Page 9 of the Applicant's IR response dated June 26, 2018, verified by the reviewer

Dose/Dose Response

See clinical pharmacology section.

Durability of Response

The controlled clinical trials included in this submission were 12 weeks in duration and one trial was 24 weeks. The 24 week trial failed to achieve statistical significance; the treatment difference from placebo was similar at week 12 and week 24. Although the magnitude of the treatment difference from placebo fluctuated at each week, overall the improvements in the frequency of SCBMs/week were greater in the prucalopride-treated patients compared to placebo through week 12. Longer-term controlled trial data are not available to determine durability of response.

Persistence of Effect

Available data did not permit a robust analysis of persistence of effect (i.e., treatment benefit after the drug was stopped).

8.14. Additional Analyses Conducted on the Individual Trials

The primary efficacy endpoint is summarized in subgroups by age (<65 versus ≥65 years), sex (male versus female), race (white versus non-white) and country (U.S. versus non-U.S.) in Table 55, Table 56, and Table 57. The results for country refer to Table 50 (primary efficacy results) that show the results for studies USA-11 and USA-13, which represent the U.S. region and the studies representing the non-U.S. regions. Subgroup analyses results demonstrated consistent

efficacy trend by age, sex, race, and country across all studies when subgroup sizes were reasonable.

Table 55. 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 (11)	77/227 (34)	23 (16,31)	2/29 (7)	6/22 (27)	20 (-0.4,41)
SPD555-302	NA	NA	NA	32/181 (18)	67/177 (38)	20 (11,29)
PRU-INT-6	21/222 (10)	43/211 (20)	11 (4,18)	2/18 (11)	3/25 (12)	0.9 (-18,20)
PRU-USA-11	21/169 (12)	52/174 (30)	17 (9,26)	4/24 (17)	3/16 (19)	2 (-22,26)
PRU-USA-13	20/189 (11)	43/181 (24)	13 (6,21)	5/23 (22)	7/33 (21)	-0.5 (-22,21)
SPD-555-401	29/144 (20)	35/147 (24)	4 (-6,13)	5/25 (20)	8/24 (33)	13 (-11,38)

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

Table 56. 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)	83/249 (33)	23 (16,30)	NA		
SPD555-302	16/110 (15)	39/98 (40)	25 (14,37)	16/71 (23)	28/79 (35)	13 (-1,27)
PRU-INT-6	20/216 (9)	40/209 (19)	10 (3,17)	3/24 (13)	6/27 (22)	10(-11,30)
PRU-USA-11	20/165 (12)	49/165 (30)	18 (9,26)	5/28 (18)	6/25 (24)	6(-16,28)
PRU-USA-13	23/189 (12)	42/180 (23)	11.16 (3,19)	2/23 (9)	8/34 (24)	15 (-3,33)
SPD-555-401	30/138 (22)	36/141 (26)	3.79 (-6,14)	4/31 (13)	7/30 (23)	10 (-.8,30)

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

Table 57. Race Subgroup Analyses Results for Primary Efficacy Endpoint in Phase 3/4 Studies

	White			Non-White		
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	NA			26/252 (10.3)	83/249 (33.3)	23 (16; 30)
SPD555-302	32/181 (18)	67/177 (38)	20 (11,29)	NA		
PRU-INT-6	22/226 (10)	45/221 (20)	11 (4, 17)	1/14 (7)	1/15 (7)	-0.5 (-19, 18)
PRU-USA-11	22/166 (13)	53/171 (31)	18 (9, 26)	3/27 (11)	2/19 (11)	-0.6 (-19, 18)
PRU-USA-13	25/197 (13)	43/183 (24)	11 (3, 19)	0/15 (0)	7/31 (23)	23 (8, 37)
SPD-555-401	32/158 (20)	41/158 (26)	6 (-4, 15)	2/11 (18)	2/13 (15)	-3 (-33, 27)

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

8.15. Integrated Assessment of Effectiveness

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 percentage of responders than that in the placebo arm; one study, study 401, did not have statistically significant findings. The treatment effect, at week 12 and 24, was lower in study 401 compared to the other trials. The exact reasons for failure of study 401 remain unclear; however, efficacy of prucalopride compared with placebo was demonstrated in five other trials submitted to support product approval. The findings of sensitivity analyses for missing data using different imputation approaches, PP, and completer analyses 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 of prucalopride for the treatment of CIC in adults.

9. Review of Safety

9.1. Safety Review Approach and Methodology

Data from five phase 3 trials and one phase 4 trial to support product approval and labeling for prucalopride 2 mg as described in Section 7.1 were reviewed for the routine analysis of safety. Studies 301 and 3001 were considered separately from the other four studies to assess comparability of AEs.

The safety review also includes focused safety analyses of AEs of special interest, including CV 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 (Pools D and E) 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 safety review for AEs of special interest 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 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 105).

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 poststudy.

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 (five phase 3 trials and one phase 4 trial) were reviewed individually and the overall type and frequency of AEs were generally aligned with the safety findings from the broader safety database (Pool D). The results from the six studies are reported below. 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 58).

Table 58. 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

Abbreviations: CIC, chronic idiopathic constipation
Source: Applicant table, Integrated Summary of Safety, Table 12, page 106/504

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 CV events of interest (excluding Standard and Extended MACE), and psychiatric AEs, discussed later in this document.

Additional analyses of AEs of special interest (CV and psychiatric) were performed. CV AEs reviewed included MACE (standard and extended), palpitations, QT prolongation, ventricular arrhythmias, syncope, CV and cerebrovascular ischemic events, and ECG abnormalities. The review of psychiatric AEs emphasized completed suicide, suicide attempts, and suicidal ideation. 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 postmarketing retrospective cohort (observational) study to measure the incidence of MACE in European patients with exposure to PRU or PEG 3350. The study was designed to exclude a three-fold risk of MACE attributable to prucalopride; a primary analysis pooled results from studies separately conducted in four European data sources. This study is reviewed below in section 10.7 Review of Observational Study SPD555-802.

9.2. Review of the Safety Database

9.3. Overall 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 postmarketing CV safety data were reviewed to address long-term exposure.

For Pool D (phase 2 through 4 double-blind, placebo-controlled trials), Table 59 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 four patients [<1%] for at least 180 days), there were no patients with at least 12 months duration of use in the controlled trials.

Table 59. 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

Abbreviations: CIC, chronic idiopathic constipation; PRU, prucalopride; StdDev, standard deviation; Min, minimum; Max, maximum
Source: Reviewer's table adapted from Applicant submission, Integrated Summary of Safety, Table 7, page 98/504

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.

9.4. Relevant Characteristics of the Safety Population

Patient demographics and baseline characteristics are summarized in Table 49 and Table 68 in this review.

9.5. Adequacy of Applicant's Clinical Safety Assessments

The applicant provided adequate numbers of patients across several controlled and uncontrolled studies in patients with CIC. While there were no randomized studies of one year in duration, prucalopride has been approved in many countries including the EU since 2009. In addition, study SPD555-802 provided additional safety information from healthcare databases. For purposes of this review, the safety database appears adequate the assessment of MACE and suicidal ideation and behavior.

9.6. Categorization of Adverse Events

The Applicant maps verbatim terms on case report forms to Preferred Terms (PTs) and System-Organ Classes from the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA versions for each of the studies are as follows:

- PRU-INT-6, PRU-USA-11, PRU-USA-13 – MedDRA 12.1
- PRU-CRC-3001 – MedDRA 13.1
- SPD555-302 – MedDRA 16.1
- SPD555-401 - MedDRA 12.1
- All AEs in the Integrated Summary of Safety (ISS) ADAE dataset were recoded to MedDRA version 16.0 for consistency.

9.7. Routine Clinical Tests

Routine clinical evaluations in the trials are comprehensive and include the following tests: vital signs, ECG, hematology and serum chemistry.

9.8. Review of Clinical Safety Results (Six Efficacy Trials)

9.8.1. Deaths

There were no deaths reported during the double-blind period in any of the six studies; studies 302, 3001, USA-11, USA-13, INT 6, and study 401. For deaths that occurred in the broader safety database, refer to the Integrated Summary of Safety Analyses located in the Appendix.

9.8.2. Serious Treatment-Emergent Adverse Events

Serious Adverse Events Studies 302 and 3001:

Studies 302 and 3001 were the primary studies used for the purposes of demonstrating safety and efficacy for the CIC indication, and are grouped here for comparison. Serious adverse events (SAEs) occurred in infrequently these trials. There was no more than one of each of the clinically relevant SAEs occurring in the prucalopride arms. Several of the events occurred in the placebo

group including chest pain, chest discomfort, dizziness, myocardial ischemia, and palpitations. The SAEs are summarized in Table 60.

Table 60. Relevant Serious Adverse Events for Studies 302 and 3001

	Study 302		Study 3001	
Event	Placebo n =186	Prucalopride n =184	Placebo n=252	Prucalopride 2 mg n=249
Atrial Fibrillation	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Dizziness	1 (0.5%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
ECG Signs of Myocardial Ischemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Myocardial Ischemia	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Palpitations	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)

Abbreviation: ECG, electrocardiogram
Source: Reviewer's Table created in J-Review

In study 302, one case of atrial fibrillation occurred in an 80-year-old male with a history of atrial fibrillation, ischemic cardiomyopathy, Wolff-Parkinson-White syndrome, hypertension, and arteriosclerosis. He was started on 1 mg prucalopride daily on (b) (6) Three days later, he developed moderate atrial fibrillation which was successfully treated in the emergency department. The investigator considered the atrial fibrillation to be unrelated to prucalopride. His prucalopride dose was increased to 2 mg due to lack of efficacy on (b) (6) and he completed the study on (b) (6) Given the patient's medical history of atrial fibrillation, the recurrence of atrial fibrillation was probably not related to prucalopride.

In study 3001, ECG signs of myocardial ischemia were reported in a 63-year-old South Korean male after 15 days of prucalopride exposure, who was asymptomatic at the time of the ECG findings. The severity was deemed mild, but the investigator felt there was a possible relationship between these clinical findings and the study drug, so the drug was discontinued. The patient was considered to have recovered from this event. The available information in the study report and datasets do not suggest that the ECG findings reflected true ischemic cardiac pathology; this case was not adjudicated as MACE.

Studies USA-11, USA-13, and INT-6:

These three studies were grouped for the purposes of this safety analysis since they were completed around the same time (1999) and submitted as supportive studies. In general, there were low numbers of SAEs in these trials. There were no more than one of each of the clinically relevant SAEs occurring in the prucalopride arms. The relevant SAEs are summarized in the Table 61.

Table 61. Relevant Serious Adverse Events for Studies USA-11, USA-13, and INT-6

	Study USA-11 (All Treated Population)			Study USA-13 (All Treated Population)			Study INT-6 (All Treated Population)		
Preferred Term	PLACEBO (n=209)	PRUCALOPRIDE SUCCINATE 2.0 MG (n=207)	PRUCALOPRIDE SUCCINATE 4.0 MG (n=204)	PLACEBO (n=212)	PRUCALOPRIDE SUCCINATE 2.0 MG (n=214)	PRUCALOPRIDE SUCCINATE 4.0 MG (n=215)	PLACEBO (n=240)	PRUCALOPRIDE SUCCINATE 2.0 MG (n=238)	PRUCALOPRIDE SUCCINATE 4.0 MG (n=238)
ABDOMINAL PAIN	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
ANGINA UNSTABLE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ANXIETY	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
ATRIAL FIBRILLATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CARDIAC FAILURE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CHEST PAIN	1 (0.5%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CIRCULATORY COLLAPSE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
DIZZINESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
GASTRITIS	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GASTROENTERITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
HYPERHIDROSIS	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERTENSION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
HYPOKALAEMIA	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MITRAL VALVE PROLAPSE	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NARCOTIC INTOXICATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
NON-HODGKINS LYMPHOMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PALPITATIONS	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PARAESTHESIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PARATHYROID TUMOUR BENIGN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
PROLACTINOMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
PULMONARY OEDEMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PYREXIA	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SHOCK	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SUPRAVENTRICULAR TACHYCARDIA	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VERTIGO	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Reviewer's Table created in J-Review

The following selected events are described in more detail.

- A 44-year-old male with a history of mitral valve prolapse, supraventricular tachycardia, and the intermittent use of atenolol developed severe palpitations 2 days after being started on prucalopride 2 mg in study USA-11. On the third day of treatment, he was hospitalized with chest pain and diagnosed with supraventricular tachycardia, multifocal premature ventricular contractions, and severe hypokalemia (potassium 2.9 mEq/L). His potassium during the run-in period was 4.4 mEq/L (reference range 3.4 to 5.4). There was no documentation of severe diarrhea or diuretic use. Despite the history of SVT, the investigator considered these events to be very likely to prucalopride, and the drug was discontinued. These events ultimately resolved. Given the patient's medical history, the event is difficult to attribute causality to prucalopride.
- An 80-year-old male with a history of angina and nitroglycerine patch use, deep vein thrombosis, elevated cholesterol, and decreased blood pressure was hospitalized with decreased blood flow to heart (blood pressure fluctuation, shock) 29 days after starting prucalopride 2 mg in study USA-11. The patient was treated with atenolol and underwent a pacemaker implant. Four days prior to the onset of this SAE, the patient had a blood pressure that was 20 mmHg below his baseline with an increase in heart rate; however, both measurements were within a normal range (118/80 mmHg, 84 beats per minute). The investigator considered this event to be doubtfully related to the study drug, and the prucalopride was discontinued.
- A patient with a history of coronary artery disease and myocardial infarction was hospitalized for unstable angina after 75 days of treatment with prucalopride 4 mg in study USA-13. The symptoms resolved, and the patient completed study treatment. The event was considered not related to the study medication; nonetheless, the event was

adjudicated as Extended MACE in the Applicant's MACE analysis (See Section 10.2 Summary of Results of MACE Analysis).

- An 89-year-old female with a history of atrial fibrillation and occasional palpitations was hospitalized with uncontrolled cardiac failure, atrial fibrillation, and pulmonary edema after 53 days of treatment with prucalopride 4 mg in study INT- 6. The patient discontinued therapy; however, the investigator listed these events as having a doubtful relationship to the study drug.
- A 29-year-old female with a history of depression was admitted to the hospital with an anxiety crisis (b) (6) after being treated with prucalopride 2 mg for 42 days in study INT-6. The patient recovered from this event, and the event was considered not drug related. (b) (6) 7 days after the end of treatment, the patient attempted suicide (ingestion of cocaine and rivotril [clonazepam intoxication]).
- A 44-year-old Caucasian female was hospitalized for 'prolactinoma' (b) (6) 39 days after the start of double-blind treatment with prucalopride 2 mg. The investigator considered the event to be mild and not related to study medication. Blood results of a hormonal profile done prior to entry into the study revealed a raised prolactin concentration (>200 μg/mL).

Study 401:

Study 401 was unique compared to the other 5 studies from a safety perspective due to the longer duration of treatment, 24 weeks. For this reason, it was considered separately. There were seven SAEs that occurred in the prucalopride groups (six in the 2 mg group, and one patient started on 1 mg and increased to 2 mg) versus 5 in the placebo group. The SAEs from the prucalopride groups (preferred terms) included abnormal behavior, anal abscess, blood pressure decreased, cerebrovascular accident, ECG QT Prolonged, hemorrhoidal hemorrhage, and obstruction gastric. Three of these events are described below. The other events were reviewed by analyzing the submitted datasets and study report and were not felt to be related to prucalopride administration.

- A 31-year-old female with a history of a psychiatric disorder was hospitalized and diagnosed with abnormal behavior (adaptation adult personality and behavior disorder) on day 134 of treatment with prucalopride 2 mg. A neurologic examination and head CT scan were negative. She was ultimately discharged from the hospital on duloxetine hydrochloride and valproic acid while continuing on prucalopride. The investigator considered this event to be possibly related to the study drug. The clinical information is insufficient to determine a relationship between the drug and this event.
- A 59-year-old female with a history of asymptomatic prolonged QT interval and hypertension developed a prolonged QT interval on day 119 of treatment with prucalopride 2 mg. Though essentially unchanged from baseline, her blood pressure was also documented as low. The prucalopride was stopped on day 123 and restarted on day 127. The prolonged QT interval and low blood pressure were considered resolved on day 153. This patient had concomitant use of lidocaine. The investigator considered the prolonged QT interval to be possibly related and the decreased blood pressure to be unlikely related to the study drug. Given that the patient's blood pressure and QT interval improved while on prucalopride with only 4 days of treatment interruption, a relationship between study drug and these events cannot be definitively established.

- A 77-year-old male with a history of hypertension presented to the emergency department on day 22 of study treatment with stroke symptoms. This patient was started on prucalopride 1 mg (b) (6) and the dose was increased to 2 mg (b) (6) (b) (6) (day 15). A CT scan revealed bilateral ischemic lesions in the supply region of the middle cerebral arteries and a hypodense area of 20 mm in the border zone on the right side. The prucalopride was continued. A duplex ultrasound of the "cervical arteries" revealed atherosclerotic lesions of the carotid arteries with normal vertebral arteries. An ECG revealed normal sinus rhythm with a right bundle branch block. The patient was ultimately diagnosed with a cerebrovascular accident. His symptoms did improve. The investigator considered this event to be unlikely related to the study drug. Given the bilateral nature of the carotid disease and lesions seen of the CT scan, it is likely that this patient was at high risk for having a stroke prior to entering this study. Thus, the investigator's conclusion is reasonable; nonetheless, this case was adjudicated as Standard MACE in the Applicant's MACE analysis (See Section 10.2 Summary of Results of MACE Analysis).

9.8.3. Discontinuation due to Adverse Events

Studies 302 and 3001:

In study 302, 7 (3.8%) of patients permanently discontinued due to a treatment emergent adverse event (TEAE) in the placebo group versus 6 (3.3%) in the prucalopride group. All of the patients that discontinued prucalopride received the 2 mg dose except for one patient who was started on the 1 mg dose and discontinued due to cholelithiasis and biliary colic. The percentages of events leading to discontinuation were higher for headache, diarrhea, dizziness, nausea, anxiety disorder, biliary colic, cholelithiasis, fatigue, and nightmare in the prucalopride group versus the placebo group. The percentages of each event leading to discontinuation were low (Table 62).

In study 3001, 3 (1.2%) of patients permanently discontinued due to a TEAE in the placebo group versus 6 (3.3%) in the prucalopride group. The percentages of events leading to discontinuation were higher for diarrhea, nausea, abdominal distention, vomiting, ECG signs of myocardial ischemia, ECG T wave abnormal, lichen planus, pain, and urticaria in the prucalopride group versus the placebo group. The percentages of each event leading to discontinuation were low (Table 62).

In general, the total percentages of TEAEs leading to permanent discontinuation were comparable between Studies 302 and 3001. This is summarized below in Table 62. Discontinuation due to headache, diarrhea, dizziness, nausea and vomiting occurred in both studies. Beyond these common TEAEs, no additional pattern of events leading to discontinuation is apparent when comparing these two studies.

Table 62. Treatment Emergent Adverse Events Leading to Permanent Discontinuation for Studies 302 and 3001

	Study 302		Study 3001	
PREFERRED TERM	PLACEBO (n = 186)	PRUCALOPRIDE (n = 184)	PLACEBO (n=252)	PRUCALOPRIDE 2mg (n=249)
HEADACHE	2 (1.1%)	3 (1.6%)	1 (0.4%)	1 (0.4%)
DIARRHOEA	0 (0.0%)	3 (1.6%)	0 (0.0%)	4 (1.6%)
DIZZINESS	0 (0.0%)	2 (1.1%)	1 (0.4%)	1 (0.4%)
NAUSEA	0 (0.0%)	2 (1.1%)	0 (0.0%)	2 (0.8%)
ABDOMINAL DISTENTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
ABDOMINAL PAIN UPPER	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
VOMITING	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)
ANXIETY	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ANXIETY DISORDER	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
BLOOD PRESSURE INCREASED	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CHOLELITHIASIS	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
BILIARY COLIC	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
CONSTIPATION	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ECG SIGNS OF MYOCARDIAL ISCHAEMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
ELECTROCARDIOGRAM T WAVE ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
LICHEN PLANUS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
URTICARIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
FATIGUE	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
FLATULENCE	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NIGHTMARE	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
PALPITATIONS	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PROLACTINOMA	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Reviewer's Table created in J-Review

Of note, the subject who discontinued due ECG signs of myocardial ischemia was discussed in the Serious Adverse Events section above.

Studies USA-11, USA-13, and INT-6:

For study USA-11, 4 (1.9%) patients in the placebo group permanently discontinued due to a TEAE versus 18 (8.7%) in the prucalopride 2 mg group and 16 (7.9%) in the prucalopride 4 mg group. For study USA-13, 5 (2.4%) patients in the placebo group permanently discontinued due to a TEAE versus 8 (3.7%) in the prucalopride 2 mg group and 13 (6.0%) in the prucalopride 4 mg group. For study INT-6, 15 (6.3%) patients in the placebo group permanently discontinued due to a TEAE versus 14 (5.9%) in the prucalopride 2 mg group and 36 (15.1%) in the prucalopride 4 mg group. In general, there was higher percentage of events leading to discontinuation in the prucalopride 4 mg group in study INT-6 (conducted primarily in Europe) compared to studies USA-11 and USA-13 which were conducted in the United States. It is interesting to note that the placebo withdrawal rate was also 2 to 3 times higher than the other studies. The percentages of withdrawals in the prucalopride 2 mg groups were small in these three studies.

Studies 3001, 302 and USA-13 (2 mg treatment group) had a similar percentages of TEAEs leading to permanent discontinuation. There were higher percentages in the studies USA-11 and INT-6 compared to studies 3001 and 3001. Discontinuation due to abdominal pain, diarrhea, nausea, headache, and vomiting occurred in all three studies in the prucalopride 2 mg treatment

groups. Beyond these common TEAEs, no additional pattern of events leading to discontinuation is apparent when comparing these three studies.

The TEAEs leading to discontinuation for studies USA-11, USA-13, and INT-6 are summarized in Table 63.

Table 63. Treatment Emergent Adverse Events Leading to Permanent Discontinuation Studies USA-11, USA-13, and INT-6

	Study USA-11			Study USA-13			Study INT-6		
PREFERRED TERM	PLACEBO (n=209)	PRUCALOPRIDE SUCCINATE 2.0 MG (n=207)	PRUCALOPRIDE SUCCINATE 4.0 MG (n=204)	PLACEBO (n=212)	PRUCALOPRIDE SUCCINATE 2.0 MG (n=214)	PRUCALOPRIDE SUCCINATE 4.0 MG (n=215)	PLACEBO (n=240)	PRUCALOPRIDE SUCCINATE 2.0 MG (n=238)	PRUCALOPRIDE SUCCINATE 4.0 MG (n=238)
ABDOMINAL PAIN	1 (0.5%)	8 (3.9%)	6 (2.9%)	0 (0.0%)	1 (0.5%)	6 (2.8%)	6 (2.5%)	3 (1.3%)	11 (4.6%)
DIARRHOEA	0 (0.0%)	4 (1.9%)	9 (4.4%)	0 (0.0%)	3 (1.4%)	4 (1.9%)	1 (0.4%)	1 (0.4%)	9 (3.8%)
NAUSEA	0 (0.0%)	8 (3.9%)	5 (2.5%)	1 (0.5%)	1 (0.5%)	6 (2.8%)	5 (2.1%)	3 (1.3%)	11 (4.6%)
HEADACHE	0 (0.0%)	4 (1.9%)	7 (3.4%)	1 (0.5%)	2 (0.9%)	4 (1.9%)	2 (0.8%)	5 (2.1%)	13 (5.5%)
DIZZINESS	0 (0.0%)	1 (0.5%)	4 (2.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.7%)
DYSPEPSIA	0 (0.0%)	2 (1.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
MYALGIA	1 (0.5%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.8%)	0 (0.0%)
TREMOR	0 (0.0%)	1 (0.5%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VOMITING	0 (0.0%)	0 (0.0%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	2 (0.9%)	1 (0.4%)	1 (0.4%)	6 (2.5%)
ANOREXIA	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)
ASTHENIA	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)
CONSTIPATION	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PALPITATION	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
VISION ABNORMAL	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CRAMPS LEGS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INFLUENZA-LIKE SYMPTOMS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
FATIGUE	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)	0 (0.0%)	2 (0.8%)
MIGRAINE	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.3%)
ANXIETY	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)
CHEST PAIN	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)
FEVER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)
FLATULENCE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)	0 (0.0%)	0 (0.0%)
HAEMORRHAGE RECTUM	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)
HYPERTENSION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)	0 (0.0%)	0 (0.0%)
MALAISE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)
PAIN	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)	0 (0.0%)

Source: Reviewer's Table created in J-Review

There were several events that lead to discontinuation that are not shown in the above table that require further comment. From study USA-11, a patient treated with prucalopride 2 mg had a history of depression (concomitant medications included obetrol (amphetamine that can precipitate serotonin syndrome when co-administered with a SSRI), sertraline hydrochloride (labeled for serotonin syndrome), sibutramine hydrochloride (labeled for serotonin syndrome)) 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. Another patient developed supraventricular tachycardia, and an additional patient developed shock in the 2 mg prucalopride group. Both cases were discussed in the previous Serious Adverse Events section. A 59-year-old male with a history of hypertension treated with 2 mg prucalopride developed "arrhythmia supraventricular" and dizziness 26 days after the start of study treatment. Both events were determined to be moderate in intensity and probably related to study medication. Both events resolved after study drug discontinuation. From study INT-6, a 21-year-old female treated with prucalopride 4 mg developed abdominal pain and syncope (collapse), both considered severe and very likely related to the study drug. There was no change in this patient's ECG or laboratory tests compared to baseline. Another patient (4 mg group) who

developed uncontrolled cardiac failure, atrial fibrillation, and pulmonary edema was discussed in Serious Adverse Events Section.

Study 401:

For study 401, 9 (5.0%) patients in the placebo group permanently discontinued due to a TEAE versus 14 (7.7%) in the prucalopride group. There was a higher percentage of patients who permanently discontinued in the treatment group for diarrhea, nausea, headache, abdominal pain, and dizziness in the prucalopride group compared to the placebo group. All these patients discontinued in the 2 mg dose group except for one patient in the 1 mg group who experienced dizziness, headache and hypotension.

The percentages of TEAEs leading to permanent discontinuation were higher in study 401 compared to studies 3001 and 302. Beyond these common AEs, no additional pattern of AEs leading to discontinuation is apparent when comparing this study to the previous ones.

The TEAEs leading to discontinuation for study 401 are summarized in Table 64.

Table 64. Treatment Emergent Adverse Events Leading to Discontinuation Study 401

PREFERRED TERM	PLACEBO (N=180)	PRUCALOPRIDE (N=181)
DIARRHOEA	1 (0.6%)	4 (2.2%)
NAUSEA	2 (1.1%)	3 (1.7%)
HEADACHE	1 (0.6%)	3 (1.7%)
ABDOMINAL PAIN	1 (0.6%)	2 (1.1%)
DIZZINESS	0 (0.0%)	2 (1.1%)

Note: The preferred terms Abdominal Pain and Upper Abdominal Pain were combined for this table
Source: Reviewer's Table created in J-Review

In general, the common TEAEs leading to discontinuation were seen across all six studies. The percentages of total events leading to discontinuation were low, and comparable between U.S. and non-U.S. studies. Study INT-6 had a higher placebo rate compared to the other trials, and a higher percentage of withdrawals in the 4 mg prucalopride group as compared to the other trials that evaluated the 4 mg dose.

9.8.4. Common Treatment- Emergent Adverse Events and Severity

Studies 302 and 3001:

For both studies, the most common TEAEs were headache, abdominal pain, nausea, diarrhea, and dizziness. Note that the percentages of these events were higher in study 3001 compared to study 302. It should also be noted that even though abdominal pain is a common TEAE for study 302, the percentage of abdominal pain was higher in the placebo group (14 (7.5%)) versus the prucalopride group (11 (6.0%)). The other events (headache, nausea, diarrhea and dizziness) were higher in the prucalopride group for both studies. The percentages of the common TEAEs for studies 302 and study 3001 are summarized in Table 65.

Table 65. Common Treatment Emergent Adverse Events for Studies 302 and 3001

	Study 302		Study 3001	
PREFERRED TERM	PLACEBO (n=186)	PRUCALOPRIDE (n=184)	PLACEBO (n=252)	PRUCALOPRIDE (n=249)
HEADACHE	7 (3.8%)	17 (9.2%)	5 (2.0%)	31 (12.5%)
ABDOMINAL PAIN	14 (7.5%)	12 (6.5%)	14 (5.6%)	29 (11.7%)
NAUSEA	4 (2.2%)	11 (6.0%)	8 (3.0%)	29 (11.7%)
DIARRHOEA	3 (1.6%)	12 (6.5%)	20 (8.0%)	55 (22.0%)
DIZZINESS	3 (1.6%)	4 (2.2%)	4 (1.6%)	5 (2.0%)
VOMITING	3 (1.6%)	1 (0.5%)	2 (0.8%)	4 (1.6%)
FATIGUE	0 (0.0%)	2 (1.1%)	2 (0.8%)	2 (0.8%)

Note: For study 302, the preferred terms Abdominal Pain, Abdominal Pain Upper, Abdominal Discomfort, and Gastrointestinal Pain were combined. For study 3001, the preferred terms Abdominal Pain, Abdominal Pain Upper, Abdominal Discomfort, Abdominal Pain Lower, and Epigastric Discomfort were combined
Source: Reviewer's Table created in J-Review

In both studies, the numbers of the common TEAEs that were regarded as severe (characterized as TEAE associated with inability to perform normal daily activities) were low. When the percentages of the common TEAEs reported as severe were compared between the placebo and treatment groups, no consistent pattern emerged.

In study 302, there were no reported severe headaches. The percentage of cases of abdominal pain that were reported as severe were 1 (7.1%) in the placebo group versus 2 (16.7%) in the prucalopride group. For nausea, the percentages of events regarded as severe were 1 (25%) in the placebo group versus 1 (9.1%) in the prucalopride group. For diarrhea, the percentages of events regarded as severe were 1 (33.3%) versus 1 (8.3%) in the prucalopride group. For dizziness, the percentages of events regarded as severe were 1 (33.3%) in the placebo group versus 1 (25.0%) in the prucalopride group.

For study 3001, the percentage of headache cases that were reported as severe were 0 in the placebo group verses 5 (16.1%) in the prucalopride group. For abdominal pain, the percentage of events regarded as severe were 1 (7.1%) versus 0 in the prucalopride group. For nausea, the percentage of events reported as severe were 0 in the placebo group versus 2 (6.9%) in the prucalopride group. For diarrhea, the percentages of events considered severe were 3 (15.0%) in the placebo group versus 12 (21.8%) in the prucalopride group. For dizziness, the percentages of events regarded as severe were 1 (25.0%) in the placebo group versus 1 (20.0%) in the prucalopride group.

Studies USA-11, USA-13, and INT-6:

Studies USA-11, USA-13, and INT-6 demonstrated the same common TEAEs as studies 302 and 3001: abdominal pain, headache, nausea, diarrhea and dizziness. There were higher numbers and percentages of these events in studies USA-11, USA-13, and INT-6 (2 mg dose) compared to study 302. In general, abdominal pain, headache and nausea occurred in higher percentages in studies USA-11, USA-13, and INT-6 (2 mg dose) compared to study 3001. Of note, diarrhea

occurred in a higher percentage compared to the 2 mg dose in studies USA-11, USA-13, and INT-6 (study 3001 22% versus studies USA-11, USA-13, and INT-6 roughly 12 to 13%). The common TEAEs for studies USA-11, USA-13, and INT-6 are summarized in Table 66.

Table 66. Common Treatment Emergent Adverse Events for Studies USA-11, USA-13, and INT-6

	Study USA-11			Study USA-13			Study INT-6		
PREFERRED TERM	PLACEBO (n=209)	PRUCALOPRIDE SUCCINATE 2.0 MG (n=207)	PRUCALOPRIDE SUCCINATE 4.0 MG (n=204)	PLACEBO (n=212)	PRUCALOPRIDE SUCCINATE 2.0 MG (n=214)	PRUCALOPRIDE SUCCINATE 4.0 MG (n=215)	PLACEBO (n=240)	PRUCALOPRIDE SUCCINATE 2.0 MG (n=238)	PRUCALOPRIDE SUCCINATE 4.0 MG (n=238)
ABDOMINAL PAIN	47 (22.9%)	49 (23.7%)	55 (27.0%)	25 (11.8%)	40 (18.7%)	37 (17.2%)	47 (19.6%)	62 (26.1%)	52 (21.8%)
HEADACHE	24 (11.5%)	54 (26.1%)	61 (29.9%)	32 (15.1%)	54 (25.2%)	54 (25.1%)	40 (16.7%)	61 (25.6%)	71 (29.8%)
NAUSEA	17 (8.1%)	46 (22.2%)	44 (21.6%)	16 (7.5%)	26 (12.1%)	44 (20.5%)	33 (13.8%)	57 (23.9%)	56 (23.5%)
DIARRHOEA	12 (5.7%)	28 (13.5%)	38 (18.6%)	7 (3.3%)	25 (11.7%)	28 (13.0%)	12 (5.0%)	31 (13.0%)	30 (12.6%)
DIZZINESS	6 (2.9%)	17 (8.2%)	14 (6.9%)	4 (1.9%)	8 (3.7%)	4 (1.9%)	4 (1.7%)	12 (5.0%)	10 (4.2%)
VOMITING	4 (1.9%)	14 (6.8%)	10 (4.9%)	5 (2.4%)	9 (4.2%)	10 (4.7%)	11 (4.6%)	11 (4.6%)	16 (6.7%)
FATIGUE	4 (1.9%)	4 (1.9%)	5 (2.5%)	0 (0.0%)	5 (2.3%)	4 (1.9%)	6 (2.5%)	12 (5.0%)	14 (5.9%)

Note: For Study USA-11, the preferred terms abdominal pain, abdominal pain upper, abdominal tenderness, abdominal discomfort, abdominal pain lower, stomach discomfort, epigastric discomfort, and gastrointestinal pain were combined. For Study USA-13, abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and stomach discomfort were combined. For Study INT-6, abdominal pain, abdominal pain upper, abdominal tenderness, stomach discomfort, abdominal discomfort, abdominal pain lower, and epigastric discomfort were combined.
Source: Reviewer's Table created in J-Review

The 2 mg dose was considered for the purposes of this comparative analysis given that it is the proposed indicated dose. In most cases, no clear pattern emerged when comparing the percentages of severe common TEAEs between the placebo and prucalopride 2 mg group across studies; however, headache was more likely to be severe compared to placebo for all three studies.

For abdominal pain, in study USA-11, 8 (17.0%) of the events in the placebo group versus 13 (26.5%) in the prucalopride 2 mg group were considered to be severe. For study USA-13, of the cases of abdominal pain, 10 (40.0%) in the placebo group versus 7 (17.5%) in the prucalopride 2 mg group were reported as severe. Finally, for study INT-6, of the cases of abdominal pain, 15 (32.0%) in the placebo group versus 11 (17.7%) in the prucalopride 2 mg group were considered to be severe.

For headache, in study USA-11, 2 (8.3.%) of the events in the placebo group versus 11 (20.4%) in the prucalopride 2 mg group were considered to be severe. For study USA-13, of the cases of headache, 4 (12.5%) in the placebo group versus 14 (26.0%) in the prucalopride 2 mg group were reported to be severe. Finally, for study INT-6, of the cases of headache, 5 (12.5%) in the placebo group versus 13 (21.3%) in the prucalopride 2 mg group were considered to be severe.

For nausea, in study USA-11, 1 (5.9%) event in the placebo group versus 8 (17.4%) in the prucalopride 2 mg group were considered to be severe. For study USA-13, of the cases of nausea, 2 (12.5%) in the placebo group versus 2 (7.7%) in the prucalopride 2 mg group were reported to be severe. Finally, for study INT-6, of the cases of nausea, 4 (12.1%) in the placebo group versus 11 (19.3%) in the prucalopride 2 mg group were considered to be severe.

For diarrhea, in study USA-11, 3 (25.0%) of the events in the placebo group versus 7 (25.0%) in the prucalopride 2 mg group were considered to be severe. For study USA-13, of the cases of diarrhea, 2 (28.6%) in the placebo group versus 1 (4.0%) in the prucalopride 2 mg group were reported to be severe. Finally, for study INT-6, of the cases of diarrhea, 4 (33.3%) in the placebo group versus 2 (6.5%) in the prucalopride 2 mg group were considered to be severe.

For dizziness, in study USA-11, none of the events in the placebo group versus 2 (11.8%) in the prucalopride 2 mg group were considered to be severe. For study USA-13, there were no cases of severe dizziness reported. Finally, for study INT-6, none of the events in the placebo group versus 2 (16.7%) in the prucalopride 2 mg group were considered to be severe.

Study 401:

For study 401, the most common TEAEs were the same as the other 5 studies: abdominal pain, headache, nausea, diarrhea and dizziness. Despite longer exposures (24 weeks), the percentages of these events were comparable or lower the those seen in the pivotal studies and were lower compared to studies USA-11, USA-13, and INT-6. The percentages of common TEAEs for study 401 is summarized in Table 67.

Table 67. Common Treatment Emergent Adverse Events for Study 401

PREFERRED TERM	PLACEBO (n=180)	PRUCALOPRIDE (n=181)
HEADACHE	10 (5.6%)	21 (11.6%)
ABDOMINAL PAIN	11 (6.1%%)	23 (12.7%)
NAUSEA	7 (3.9%)	13 (7.2%)
DIARRHOEA	4 (2.2%)	7 (3.9%)
DIZZINESS	4 (2.2%)	3 (1.7%)
VOMITING	4 (2.2%)	3 (1.7%)
FATIGUE	0 (0.0%)	1 (0.6%)

Note: The preferred terms abdominal pain, abdominal pain upper, and gastrointestinal discomfort were combined.
Source: Reviewer's Table created in J-Review

None cases of abdominal pain, headache, nausea, diarrhea and dizziness were considered severe for this study.

9.8.5. Laboratory Findings

The review of laboratory findings in these six studies did not raise clinical safety concerns including absence of evidence of drug-induced liver injury. There are no clinically significant differences in the data reported for chemistry and hematology.

9.8.6. Safety Analyses by Subgroup (Age, Sex, Race)

The following are findings of our review of the six studies submitted by the Applicant to support the efficacy of prucalopride. With respect to sex, study 302 was conducted entirely in males. The other studies were conducted primarily in females (≥85% females in these studies). Both sexes were adequately represented in all six studies. With respect to age, study 302 had the largest percentage of patients ≥65 years of age (40.8%). Study 3001 had the lowest geriatric population with only two patients (0.4%). The other studies, USA-11, USA-13, INT-6, and 401, had 14.0%, 14.2%, 10.9%, and 18.3% of patients ≥65 years of age respectively. Overall, the number of geriatric patients is reasonably representative of the United States geriatric population.

Finally, analysis of patients by race revealed that, except for study 3001 which were predominantly Asian, the majority of the patients were white; blacks were under-represented in the studies. Study 302 was roughly 97% white patients with 2.2% black patients, 0.3% Asian patients, 0.8% representing "other". In study 3001, 92% of the patients were Asian with 6.2% of patients being white. Given that the two pivotal studies were conducted outside of the United States and had fairly homogeneous subject populations, studies USA-11, USA-13 (both conducted in the United States), and INT-6 (conducted in Europe) were submitted to support generalizability of the efficacy and safety results of studies 302 and 3001 to the United States population. In studies USA-11 and USA-13, roughly 90% of the patients were white with higher percentages of black (6.5% and 8.4% respectively) and Hispanic patients (2.7% and 2.3% respectively) compared to the other studies. In study 401, 93% of the patients were white compared to 2.8% Hispanic patients. The race and ethnicity of 18 patients in study 401 were unknown. The demographics for all six studies are summarized in Table 68.

Table 68. Demographics of Safety Populations for Studies 302, USA-11, USA-13, INT-6, and 401; ITT Population for Study 3001

Characteristics	Statistics	Study 302	Study 401	Study 3001	Study INT-6	Study USA-11	Study USA-13
1. Sex	F	0 (0.0%)	308 (85.3%)	450 (89.8%)	650 (90.8%)	545 (87.9%)	555 (86.6%)
	M	370 (100.0%)	53 (14.7%)	51 (10.2%)	66 (9.2%)	75 (12.1%)	86 (13.4%)
2. Age	<65 years of age	219 (59.2%)	295 (81.7%)	499 (99.6%)	638 (89.1%)	533 (86.0%)	550 (85.8%)
	>=65 years of age	151 (40.8%)	66 (18.3%)	2 (0.4%)	78 (10.9%)	87 (14.0%)	91 (14.2%)
	>=75 years of age	69 (18.6%)	20 (5.5%)	0 (0.0%)	22 (3.1%)	26 (4.2%)	26 (4.1%)
3. Race	ASIAN	1 (0.3%)	1 (0.3%)	463 (92.4%)	8 (1.1%)	4 (0.6%)	3 (0.5%)
	BLACK	8 (2.2%)	1 (0.3%)	0 (0.0%)	9 (1.3%)	40 (6.5%)	54 (8.4%)
	NOT ALLOWED TO ASK PER LOCAL REGULATIONS	0 (0.0%)	18 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	OTHER	3 (0.8%)	4 (1.1%)	7 (1.4%)	26 (3.6%)	3 (0.5%)	5 (0.8%)
	WHITE	358 (96.8%)	337 (93.4%)	31 (6.2%)	669 (93.4%)	556 (89.7%)	564 (88.0%)
	HISPANIC OR LATINO	4 (1.1%)	10 (2.8%)	0 (0.0%)	4 (0.6%)	17 (2.7%)	15 (2.3%)
4. Ethnicity [n (%)]	NOT REPORTED	0 (0.0%)	0 (0.0%)	5 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	UNKNOWN	0 (0.0%)	0 (0.0%)	8 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Reviewer's Table created in J-Review

9.8.6.1. Age

Treatment Emergent Adverse Events by Age:

For Study 302, 47 (25.5%) of patients <65 and 31 (16.8%) of patients ≥65 in the prucalopride group had a treatment emergent adverse event. It is interesting to note that when totals are considered, there were higher percentages of treatment emergent adverse events in the <65-year-

old group for this study. This trend was also seen for all of the common treatment emergent adverse events. For Study 3001, there were no adverse events in patients ≥65; however, there were only two patients in this age category. The common treatment emergent adverse events analyzed by age groups is summarized in Table 95.

For studies USA-11, USA-13, and INT-6, comparisons based upon age using the proposed indicated dose, 2 mg. For Study USA-11, 143 (69.1%) of patients in the <65 years group versus 23 (11.1%) of patients in the ≥65 years group had a treatment emergent adverse event at the 2 mg dose. For study USA-13, 147 (68.7%) of patients in the <65 years group versus 26 (12.1%) of patients in the ≥65 years group had a treatment emergent adverse event at the 2 mg dose. For study INT-6, 160 (67.2%) of patients in the <65 years group versus 10 (4.2%) of patients in the ≥65 years group had a treatment emergent adverse event at the 2 mg dose. Interestingly, there were higher percentages of patients having one of the common treatment emergent adverse events in the <65 years group compared to the ≥65 years group for all three of these studies. The common treatment emergent adverse events analyzed by age group (less than or greater than/equal to 65) are summarized in Table 96.

For Study 401, 61 (33.7%) of patients in the <65 years group versus 15 (8.3%) of patients in the ≥65 years group had a treatment emergent adverse event in the prucalopride group. Here again, the common treatment emergent adverse events occurred in higher percentages in the ≥65 years group who received prucalopride. This trend is consistent with the other studies. The common treatment emergent adverse events analyzed by age group (less than or greater than/equal to 65) are summarized in Table 97.

9.8.6.2. Sex

As study 302 was conducted in males, it is not relevant to this discussion. For Study 3001, roughly 90% of the patients were female. With this in mind, 8 (3.2%) of the males versus 134 (53.8%) of the females had a treatment emergent adverse event in the prucalopride group. The common treatment emergent adverse events also occurred in higher percentages in females receiving prucalopride. Of interest, the rate of diarrhea in this study among females is larger than in any of the other studies (20%). The common treatment emergent adverse events analyzed by sex are summarized in Table 98.

Again, for studies USA-11, USA-13, and INT-6, the comparisons made are based upon sex using the proposed indicated dose, 2 mg treatment group. For study USA-11, 11 (5.3%) males versus 155 (74.9%) females had a treatment emergent adverse event at the 2-mg dose. For study USA-13, 27 (12.6%) males versus 146 (68.2%) females had a treatment emergent adverse event at the 2 mg dose. For study INT-6, 13 (5.5%) males versus 157 (66.0%) females had a treatment emergent adverse event at the 2-mg dose. In general, the common treatment emergent adverse events occurred in higher percentages in females, and this is summarized in Table 99.

For Study 401, 9 (5.0%) males versus 67 (37.0%) females had a treatment emergent adverse event in the prucalopride group. Here again, the common treatment emergent adverse events occurred in higher percentages in females who received prucalopride. This trend is consistent with the other studies as summarized in Table 102.

9.8.6.3. Race and Ethnicity

Meaningful comparisons by races or ethnic groups are limited because the number of non-white patients included in the studies were small. Each of the studies were considered individually and discussed further as appropriate. Study 302 contained roughly 97% white patients from Europe. The other race/ ethnic groups in this study were under 1% except for 8 black patients (2.2%). The subgroup analysis of study 302 showed that most treatment emergent adverse events, including the common TEAEs, occurred in white patients; however, this would be expected given the demographics of this trial. As such, no meaningful comparisons can be made within this study. This is summarized further in Table 101.

Study 3001 contained 92% Asian patients and 6% white patients. Other races and ethnic groups are not represented in this study. The subgroup analysis of this study also showed higher numbers of treatment emergent adverse events, including the common TEAEs, in Asian patients. This is further summarized in Table 101.

Studies USA-11 and USA-13 were conducted in the United States. Both had roughly 90% white patients. USA-11 had 6.5% black patients, and USA-13 had 8.4% black patients. Both trials had minimal numbers of Hispanic patients, roughly 2% for USA-11 and 3% for USA-13. The subgroup analysis of these studies shows higher percentages of treatment emergent adverse events, including the common TEAEs in white patients. Given the large imbalances in the percentages of the other demographics compared to white patients, meaningful comparisons are difficult. However, these trials have the highest numbers of black patients compared to any of the others in this submission offering the best opportunity to evaluate the safety of prucalopride in this population. A review of all treatment adverse events occurring in black patients at the 2-mg dose did not show any evidence of any new or unique safety signals in this population (Table 104).

Study INT-6 was had predominantly white patients with minimal representations of the other races/ ethnicities. Meaningful comparisons in this study could not be made. The common treatment emergent adverse events analyzed by race/ethnicity for studies USA-11, USA-13, and INT-6 are summarized in Table 102.

Study 401 had 93% white patients with minimal representations of the other races/ethnicities. Furthermore, there sites that were not allowed to ask race due to local regulations. No meaningful comparisons can be made for this study. The common treatment emergent adverse events analyzed by race/ethnicity for studies 401 is summarized in Table 103 for completeness.

9.8.7. Safety Summary From Six Clinical Efficacy Trials

The overall safety of prucalopride (common adverse events, serious adverse events and withdrawals due to adverse events) among these six clinical trials is acceptable for approval.

There were few SAEs. Withdrawals due to AEs were generally similar between the U.S. and non-U.S. studies. Study 3001 was conducted in Asian females who had a higher rate of diarrhea compared to the other studies. The reason for this is unknown. These patients had a shorter duration of CIC prior to study entry compared to the other trials; however, the BMI was not substantially different, and the drug is primarily excreted by the kidneys. Too few, black or Hispanic patients were enrolled to draw any meaningful conclusions across racial subgroups. Within the limitations of the data submitted, the safety analysis by demographic subgroups did not reveal any safety issues that preclude the approval of prucalopride.

10. Integrated Summary of Safety: Adverse Events of Special Interest

Overview of Safety Database

Safety data from Pool D, Pool E, and the patient population included in the adjudicated CV analysis were evaluated in our review of AEs of special interest. Below we describe the results for the CV and psychiatric events of special interest. For an overview of the integrated summary of safety for SAEs and TEAEs, refer to the Appendix.

10.1. Methodology for MACE Analysis

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 (BMI) >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 CV mortality (including sudden cardiac death, death due

to acute myocardial infarction, heart failure, stroke, and other CV causes), nonfatal MI, and 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 two cardiologists and one 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 prespecified process was utilized to identify cases for adjudication.

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

The Applicant used a prespecified standard medical query with the Standardized MedDRA, version 15, to create a listing of all CV 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 CV 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.

10.2. Summary of Results of MACE Analysis

Nineteen double-blind (n = 5354 patients: 3366 prucalopride and 2019 placebo) and nine open-label (n = 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 BMI 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 69.

Table 69. Baseline Risk Characteristics in CIC Patients (MACE Analysis)

		DB PRU			
Parameter	DB PLA N=2019	DB PRU All Doses[a] N=3366	DB PRU 2 mg N=1545	DB PRU 4 mg N=1369	All PRU[b] (DB and OL) N=4476
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 two other CV 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 one 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 70.

Table 70. 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)

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 patients who have taken at least 1 dose of prucalopride in DB or OL studies included in the MACE analysis dataset

Source: Reviewer's table, adapted from Applicant submission, MACE report, Table 4, page 15

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 71) shows a summary of adjudication information (standard MACE and extended MACE). Non-MACE events are also included.

Table 71. 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: Section 5, Tables, Figures, and Listings, MACE Statistical Analysis Chronic Idiopathic Constipation, Table 5A and Table 5B

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 are numerically higher compared to the data obtained from the double-blind trials (see blue box in above Table). 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 106) for individual narratives patients treated with prucalopride with standard MACE.

As shown in the table above, non-MACE events were also evaluated. The nonischemic 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 nonischemic 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 (nonischemic arrhythmias, other CV events, and insufficient information to adjudicate) are shown in Table 72 below.

Table 72. 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

Abbreviations: CV, cardiovascular; PRU, prucalopride
Source: Applicant's submission, response to FDA information request, received 05/14/2018

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; CV and Cerebrovascular Ischemic Events; and ECG Abnormalities. Some events that were not listed in Table 72 under "Insufficient info to adjudicate" included paralysis, myocardial ischemia, myocardial infarction, deep vein thrombosis, and hemiparesis. These events occurred in one patient each and represent the five 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 CV risk factors among the patients determined to have MACE are listed below. Table 73 shows the baseline risk factor groups for patients with MACE.

Table 73. Baseline Ischemic Risk: High-Risk Analysis Group for Patients 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 CV 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 CV 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). AEs 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, ECG abnormalities, unadjudicated CV 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 CV 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.

10.3. 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 AEs.

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 patient 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 patients in the prucalopride ≤2 mg group had a history of predisposing CV or pulmonary disease. Two of these patients also took concomitant medication with known associated palpitations, tachycardia or arrhythmic events. An additional three patients used concomitant medication with known associated to CV side effects and had no history of predisposing CV or pulmonary disease.

Additional, extensive information is obtained from a frail elderly CV 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 patients) of

elderly patients with constipation living in a nursing facility. Extensive Holter evaluations, ECG monitoring and assessment for arrhythmia, ischemia and other cardiac parameters were performed. The patients had a mean age of 83 years and more than 80% had a history of CV disease. No episodes of palpitations were reported, and no increase in arrhythmogenicity was observed on ECGs and continuous Holter monitoring.

10.4. 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 74) shows the specific types of events.

Table 74. 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 of this document. The thorough QT study was found to be acceptable; at a dose 5 times the maximum recommended dose, prucalopride did not prolong the QT interval to any clinically relevant extent. See consult review by the Division of Cardiorenal Products QT Interdisciplinary Review Team, dated 4/17/18. 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 (b) (6) days of prucalopride, a 59-year-old female patient 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 (b) (6) 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 CV 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 (nonsustained) on day 1 of treatment. His medical history includes an extensive CV 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 of 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 AEs or ventricular arrhythmias were reported, except for two cases of ventricular tachycardia in patients with an extensive history of CV disease and use of concomitant medications with known associations to arrhythmias.

As shown in Table 74 above, syncope was more frequent in the placebo group than in the prucalopride 2 mg group.

10.5. 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 two 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 75).

Table 75. 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.

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

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

The patients that had clinically meaningful cardiac conditions have already been discussed except for those with atrial fibrillation. There were several patients in the total prucalopride group that had a history of atrial fibrillation; however, according the patient 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 CV 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 postmarketing retrospective cohort (observational) study to measure the incidence of MACE in European patients with exposure to prucalopride compared to that of PEG 3350 were submitted and are reviewed below.

10.6. Clinical Safety: Psychiatric Events

Given the concern for potential psychiatric risks with the 5-HT_4 receptor agonist class, including suicidal ideation and behavior (SIB), an analysis of such events was conducted. Following the

receipt of three postmarketing 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 postmarketing safety evaluations by the Applicant. The table below summarizes the Applicant's triggers and findings.

Table 76. 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 patients 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 reported in the safety database: 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 CIC 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.

For the completed suicides, the 70-year-old male is of particular interest because it appears prucalopride was discontinued around the time he was started on antidepressants. Therefore, the possibility of recurrence or development of psychiatric symptoms, which may have contributed to his suicide, while he was still on prucalopride cannot be ruled out. In the case of the 40-year-old female, although the 52-day interval between her last dose of prucalopride and her completed suicide diminishes the causal contribution of prucalopride, her mental state while she was on prucalopride is unknown. In general, reports that the patients were off prucalopride when they committed suicide does not exclude the causal contribution of prucalopride because patients were not actively queried about suicidal thoughts and behavior while they were on prucalopride, so prucalopride-induced psychiatric prodromes to suicide could have been missed. Furthermore, the lack of completed suicides among patients randomized to placebo during the development program is cause for concern for a potential relationship between prucalopride and suicide.

Three cases of the suicide attempts and once case of suicidal ideation were reported in the safety database. There was one patient with a reported suicide attempt from the double-blind studies. The patient 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. (b) (6) 7 days after the end of treatment, the patient attempted suicide by ingesting cocaine and rivotril (clonazepam intoxication). The patient's medical history of depression and illicit drug use confound the ability to conclude that the event was related to prucalopride. That said, the elimination half-life of repeated dosing of prucalopride being about 30.5±4.6 hours, makes the 7 days that had elapsed since the last dose of prucalopride inadequate to exclude a causal contribution of prucalopride, since prucalopride may not have been completely eliminated. The two cases of suicide attempts and one case of suicidal ideation that occurred in the open label studies are described below. In each case, the patient 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 patient prematurely discontinued the trial on December 5, 1996. The only other documented medication taken by this patient prior to the event was Bisacodyl. At follow-up (b) (6), this patient 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 female 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 AEs for this patient 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 patient 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), suicide ideation, and homicidal thoughts after 452 days of treatment (total treatment duration was 548 days including 11 days off treatment). Other relevant reported AEs for this patient included insomnia, hallucination, and depression. Relevant concomitant medications included nefazodone hydrochloride, risperidone, and venlafaxine hydrochloride. The patient did recover, and these events were considered severe and doubtfully related to the study medication by the Investigator.

All patients in the clinical trial safety database had comorbid psychiatric conditions except for the 38-year old patient with no documented psychiatric history who reported “personal problems” (described above). The WHO Global Individual Case Safety Report (ICSR) database, VigiBase® as of December 2014 (WHO Pharmaceuticals Newsletter No. 3, 2015), reported three cases reports from healthcare professionals in Germany, Italy, and United Kingdom in which the patients developed suicidal ideation within hours to days after taking the first dose of prucalopride. The patients did not appear to have a documented psychiatric history and symptoms were reported to have resolved after discontinuation of prucalopride (Gasparotto and Chandler 2015; Lindholm 2015). One of the patients described in the WHO database was also reported in another publication; a 61 year old patient with no documented psychiatric history who reported suicidal ideation a few hours after administration of prucalopride 2 mg for CIC; the symptoms resolved within 24 hours of drug discontinuation (Carnovale et al. 2013). The onset of suicidal ideation and resolution after drug discontinuation supports the concern for potential new or worsening neuropsychiatric events.

An 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.

10.7. Review of Observational Study SPD555-802

SPD555 802, *A Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort*, followed a common protocol to measure the incidence of MACE in European patients with exposure to PRU or PEG 3350. Designed to exclude 3-fold risk from prucalopride, a primary analysis pooled results from studies separately conducted in four European data sources. With MACE defined as a composite of nonfatal myocardial infarction, nonfatal stroke, and in-hospital death, this primary analysis estimated MACE incidence in PRU versus PEG with standardized incidence rate ratio 0.64, 95% CI 0.36-1.14. Subgroup analysis in ≥55-year-old men estimated risk from prucalopride at SIRR 2.57, 95% CI 0.71-9.26. Declaring results otherwise consistent across prespecified primary, secondary, subgroup, and sensitivity analyses, SPD555 802 concluded by finding "no evidence of an increased risk of MACE in patients with chronic constipation using prucalopride as compared with PEG."

Primarily because of a concern about serious risk of bias due to confounding, we 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 our assessment of serious risk of bias due to confounding included,

- Generalized potential for channeling profoundly different patients to treatment with prucalopride or PEG.
- 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, we accepted the findings from SPD555-802 as evidence that reasonably excludes a greater than three-fold MACE risk from prucalopride use. FDA could not use SPD555-802 to reliably bound MACE risk at levels lower than three-fold. For details, see a separate review of SPD555 802 completed by the Department of Epidemiology I in the Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, dated 10/25/18.

11. Summary of Safety

The safety review of prucalopride revealed few safety concerns, based upon the 6 clinical efficacy studies as well as a larger safety database of pooled analyses of double-blind, randomized controlled and opened label trials. The routine safety review was based on an analysis of the six clinical efficacy studies. Few serious adverse reactions were seen among these studies. In the 6 clinical trials described above, 5% of patients treated with 2 mg of prucalopride

discontinued due to adverse reactions, compared to 3% of patients in the placebo group. The most common adverse reactions leading to discontinuation were nausea (2% prucalopride, 1% placebo), headache (1% prucalopride, 1% placebo), diarrhea (1% prucalopride, <1% placebo), or abdominal pain (1% prucalopride, 1% placebo). The pooled review of the six studies revealed the following common adverse reactions more frequently associated with the use of prucalopride compared to placebo; headache, abdominal pain, nausea, diarrhea, abdominal distension, dizziness, vomiting, flatulence, and fatigue. When the 4 mg treatment groups were reviewed for diarrhea, there appeared to be a slight dose-related increase in events.

This review also considered each study separately because of the demographics. In general, the common TEAEs leading to discontinuation were seen across all six studies. The percentages of total events leading to discontinuation were low, and comparable between U.S. and non-U.S. studies. Study 3001 was conducted in Asian females who had a higher rate of diarrhea compared to the other studies. The reason for this is unknown. These patients had a shorter duration of CIC prior to study entry compared to the other trials; however, the BMI was not substantially different, and the drug is primarily excreted by the kidneys. Too few black or Hispanic patients were enrolled to draw any meaningful conclusions across racial subgroups. However, no new or unique safety signals were seen in these patients compared to the overall safety evaluation.

In order to review adverse reactions of special interest in the clinical trial database pooled analyses and blinded adjudication of MACE events was performed. Safety data from Pool D, Pool E, and the patient population included in the adjudicated CV analysis were evaluated. Review of potential CV risk did not reveal an increased risk of MACE in the randomized clinical trials between placebo and the 2 mg prucalopride group.

FDA obtained additional information from the Applicant regarding the specific types of nonischemic arrhythmias, other CV events, and the events with insufficient information to adjudicate to help determine whether further evaluation was warranted. The safety data from the controlled trials (12 weeks duration) did not reveal clear imbalances in CV events, including MACE. Because the controlled trial data was shorter than 12 months duration, and that prucalopride may be used chronically, additional comparison was sought. A post-marketing retrospective cohort (observational) study to measure the incidence of MACE in European patients with exposure to prucalopride compared to that of PEG 3350 was reviewed. The findings from SPD555-802 provide evidence that reasonably excludes a greater than three-fold MACE risk from prucalopride use. FDA could not use SPD555-802 to reliably bound MACE risk at levels lower than three-fold.

Further review of CV safety was discussed under clinical pharmacology section and nonclinical sections. No signals of CV risk were detected. A thorough QT study was conducted, which was negative for QT prolongation.

Given the concern for potential psychiatric risks with the 5-HT_4 receptor agonist class, including suicidal ideation and behavior, an analysis of such events was conducted. Overall, the numbers of patients in the total safety database (4476 patients 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. 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). Two cases completed suicide were reported among patients previously treated with prucalopride 2 mg or 4 mg; both discontinued prucalopride for at least one month prior to the event. Three cases of the suicide attempts and one case of suicidal ideation were reported. One patient reported a suicide attempt 7 days after the end of treatment with prucalopride 2 mg in a double-blind trial; none were reported among patients in the placebo group. Two patients reported suicide attempts and one patient reported suicidal ideation in the open-label trials. In addition, the WHO Pharmaceuticals Newsletter (No. 3, 2015) includes a discussion of case reports of three patients who developed suicidal ideation within hours to days after taking the first dose of prucalopride. These patients did not appear to have a documented psychiatric history and symptoms were reported to have resolved after discontinuation of prucalopride (positive dechallenge). In summary, with suicidal ideation occurring subsequent to initiation of prucalopride, suicidal attempts and completed suicides reported in patients who had been exposed to prucalopride, and absence of SIB reports among patients who were randomized to placebo in the double-blind trials, a possible association between prucalopride and suicidal ideation and behavior cannot be excluded.

The applicant provided adequate numbers of patients across several controlled and uncontrolled studies in patients with CIC. While there were no randomized studies of one year in duration, prucalopride has been approved in many countries including the EU since 2009. In addition, study SPD555-802 provided additional safety information from healthcare databases. The frequency and severity of the safety findings do not preclude the approval of prucalopride. The findings from this application reasonably exclude a greater than three-fold MACE risk from prucalopride use. The identified safety issues (including suicidal ideation and behavior) can be mitigated with labeling alone, without need for a Risk Evaluation and Mitigation Strategies. In addition to routine pharmacovigilance, postmarketing activities will include pediatric studies under PREA, two pregnancy registries, and a milk-only lactation study.

11.1. Advisory Committee Meeting and Other External Consultations

The Gastrointestinal Drugs Advisory Committee (GIDAC) of the Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), met on October 18, 2018 at the Bethesda Marriott, the Grand Ballroom, 5151 Pooks Hill Road, Bethesda, Maryland. Prior to the meeting, the members and temporary voting members were provided briefing materials from the FDA and Shire Development, LLC. The meeting was called to order by Jean-Pierre Raufman, MD (Chairperson). The conflict of interest statement was read into the record by Jay R. Fajiculay, PharmD (Designated Federal Officer). There were approximately 50 people in attendance. There were eight Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

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

Attendance:

Gastrointestinal Drugs Advisory Committee Members Present (Voting): Joy McVey Hugick, BA (Consumer Representative); Sandeep Khurana, MBBS; Jennifer C. Lai, MD, MBA; Benjamin Lebwohl, MD, MS; Jean-Pierre Raufman, MD

Gastrointestinal Drugs Advisory Committee Members Not Present (Voting): David N. Assis, MD; Lin Chang, MD; Christopher S. Coffey, PhD, MS; Darrell S. Pardi, MD, MSc; Rachel L. Rosen, MD, MPH; Lisa L. Strate, MD, MPH

Gastrointestinal Drugs Advisory Committee Member Present (Non-Voting): Douglas Levine, MD (Industry Representative)

Temporary Members (Voting): Sally Hunsberger, PhD; Sabrina Numann (Patient Representative); Steven F. Solga, MD; John Teerlink, MD; Udho Thadani, MD

FDA Participants (**Non-Voting):** Victor Crentsil, MD, MHS; Joyce Korvick, MD, MPH; Juli Tomaino, MD; Charles Line, MD; Ling Lan, PhD; Joel Weissfeld, MD, MPH

Designated Federal Officer (Non-Voting): Jay R. Fajiculay, PharmD

Open Public Hearing Speakers: Varuna Srinivasan, MD (National Center for Health Research); Ellen Stein, MD (Johns Hopkins Bayview Gastroenterology and Hepatology); Baha Moshiree, MD, MSc (statement read by Ellen Stein, MD); William Hasler, MD (American Neurogastroenterology and Motility Society); Brad Conway (American College of Gastroenterology); Trent Nichols Jr, MD (Quietmind Foundation); Jeffrey Roberts, MSEd, BSc (IBS Patient Group); Jessica Roth (American Gastroenterological Association)

Questions to the Committee:

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

   Vote Result: **Yes: 10** **No: 0** **Abstain: 0**

   Committee Discussion: *The committee unanimously agreed that the clinical trial data provides substantial evidence of effectiveness of prucalopride for the treatment of adults with chronic idiopathic constipation (CIC). Please see the transcript for details of the committee discussion.*

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

   Vote Result: **Yes: 10** **No: 0** **Abstain: 0**

Committee Discussion: *The committee unanimously agreed that the potential risk of cardiovascular adverse events with the use of prucalopride in adults with CIC has been adequately addressed by the Applicant. Members of the committee cited that the nonclinical data, selectivity of the drug for 5-HT_4 receptor, adjudicated, pooled cardiovascular safety analysis from 19 randomized, placebo-controlled clinical trials and lack of cardiovascular safety signal with extensive use of prucalopride in other countries as reasons for their approval. Please see the transcript for details of the committee discussion.*

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

Committee Discussion: *This sub-question is not applicable.*

3. **VOTE:** Does the risk-benefit profile of prucalopride support the approval of this application? Discuss your answer.

Vote Result: **Yes: 10** **No: 0** **Abstain: 0**

Committee Discussion: *The committee unanimously agreed that the risk-benefit profile of prucalopride supports the approval of this application. Several members of the committee expressed concern regarding the neuropsychiatric events that occurred in patients treated with prucalopride. Given the increased predisposition of CIC patients to neuropsychiatric issues such as depression, members of the panel recommended the addition of a warning in the label detailing relevant neuropsychiatric issues. Some committee members also suggested a long-term epidemiological study for further evaluation of a potential suicidality signal. One member of the committee was concerned about the potential long-term carcinogenic effects related to prucalopride. Please see the transcript for details of the committee discussion.*

12. Pediatrics

The Applicant conducted a pediatric trial outside of the United States in pediatric patients 6 months to 18 years of age with functional constipation; however, this product is not labeled for pediatric patients in Europe. The trial was an 8-week double-blind, placebo-controlled trial (N=213), followed by a 16-week open-label, active controlled (PEG 4000) study of up to 24 weeks (N=197). The starting dose administered was 0.04 mg/kg/day titrated between 0.02 and 0.06 mg/kg/day (to a maximum of 2 mg daily) for children weighing ≤50 kg given as an oral solution of prucalopride or matching placebo. Children weighing >50 kg received 2 mg/day prucalopride tablets or matching placebo. Response to the treatment was defined as having an average of ≥3 SBMs per week and an average number of fecal incontinence episodes of ≤1 per 2 weeks. (b) (4)

[redacted] Of note, the sponsor has also completed two pediatric PK studies in patients 4 to 12 years of age in the United States.

A PPSR is currently under review; collaboration with the Applicant on the PPSR submission was ongoing at the time of this document.

13. Labeling Recommendations

13.1. Prescription Drug Labeling

Prescribing Information

Refer to the approved label for the final language. The substantial changes to the label are summarized below.

Section 2: Dosage and Administration

- [redacted]

Section 4: Contraindications

- Clarified the contraindication in patients with hypersensitivity reactions and obtained data from the Applicant to support that there have been demonstrated cases of hypersensitivity with the product or such reactions may be anticipated based on data from similar drugs (e.g., those in the same pharmacological class or with similar chemical structures, or when cross-sensitivity within a class is a recognized phenomenon). The Applicant provided MedWatch forms describing the reports of hypersensitivity. In addition, Motegrity will be contraindicated in patients with intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract such as Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum
- [redacted]

Section 5: Warnings and Precautions

- [redacted] (b) (4)
- [redacted] (b) (4)
- Added the following warning for suicidal ideation and behavior based on our findings and the concerns raised during the AC meeting:
    - In clinical trials, suicides, suicide attempts, and suicidal ideation have been reported *[see Adverse Reactions (6.1)]*. A causal association between treatment with MOTEGRITY and an increased risk of suicidal ideation and behavior has not been established.

      Monitor all patients treated with MOTEGRITY for persistent worsening of depression or the emergence of suicidal thoughts and behaviors. Counsel patients, their caregivers, and family members of patients to be aware of any unusual changes in mood or behavior and alert the healthcare provider. Instruct patients to discontinue MOTEGRITY immediately and contact their healthcare provider if they experience any of these symptoms.

Section 6: Adverse Events

- Revised to include demographics and adverse reactions based on data obtained from the six clinical trials submitted to support product approval for efficacy. Patients who received only the 1mg dose (i.e., no dose escalation to 2 mg) or the 4 mg dose are not described in section 6 of the label since the 2mg dose is the indicated dose.
- Added a description of severe diarrhea, onset and duration for headache, and adverse reactions leading to discontinuation.
- Added a subsection on AEs of special interest to describe the CV safety analysis conducted using data from the adjudication of events from the 28 clinical trials (19 double-blind and 9 open-label).
- Added a subsection on suicide ideation and behavior because of the suicide ideation, attempts, and completed suicides that were reported in the safety database, the class concern, our inability to exclude the contribution of prucalopride, and to address the concerns expressed during the Advisory Committee (AC) meeting:
    - *Suicide Ideation/Behavior:* In the double-blind trials, one patient reported a suicide attempt 7 days after the end of treatment with MOTEGRITY 2 mg; none were reported in patients on placebo. In the open-label trials, two patients reported a suicide attempt and another patient reported suicidal ideation. Completed suicide was reported in two patients, previously treated with MOTEGRITY 2 mg or 4 mg; both discontinued MOTEGRITY for at least one month prior to the event.
- Added Section 6.2 Postmarketing Experience to describe hypersensitivity events. The sponsor provided MedWatch forms describing the reports of hypersensitivity.

Section 8.1: Pregnancy and Section 8.2 Lactation

- Revised to note that available data from case reports with prucalopride use in pregnant women are insufficient to identify any drug associated risks of miscarriage, major birth defects, or adverse maternal or fetal outcomes.
- Revised Subsection 8.2 Lactation to note that prucalopride is present in breast milk and that there are no data on the effects of prucalopride on the breastfed infant or the effects on milk production.
- (b) (4)

Section 8.4: Pediatric Use

- (b) (4)
- Added the following sentence: The safety and effectiveness of MOTEGRITY have not been established in pediatric patients.

Section 8.5: Geriatric Use

- (b) (4)
- Added language describing that there were no overall differences in safety and effectiveness between elderly and younger patients.

Section 8.6: Renal Impairment

- Revised to state: MOTEGRITY is known to be substantially excreted by the kidney, and the risk of ARs may be greater in patients with impaired renal function. A decreased dosage is recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min) *[see Dosage and Administration (2)]*.
- Avoid MOTEGRITY in patients with end stage renal disease requiring dialysis *[see Clinical Pharmacology (12.3)]*

Section 12.1 Mechanism of Action and 12.2 Pharmacodynamics

- (b) (4)
- Simplified language in the cardiac electrophysiology subsection based on the recommendation from the TQT Consult: At a dose 5 times the maximum approved recommended dose, MOTEGRITY does not prolong the QT interval to any clinically relevant extent.

Section 12.3 Pharmacokinetics

- [redacted] (b) (4)

Section 14: Clinical Studies

- [redacted] (b) (4)
- [redacted] (b) (4)

Section 17: Patient Counseling

- Added language communicating the risk of suicidal ideation/behavior. DMPP reviewed the Patient Information and provided recommendations.

    - Advise the patient to read the FDA-approved patient labeling (Patient Information)

      Suicidal Ideation and Behavior: Inform patients, their caregivers, and family members that suicidal ideation and behavior have been reported in patients treated with MOTEGRITY. Advise them to be aware of any unusual changes in mood or behavior, persistent worsening of symptoms of depression, or the emergence of suicidal thoughts or behavior. Instruct patients, caregivers, and family members that if any of these symptoms occur, they should discontinue MOTEGRITY immediately and contact their healthcare provider *[see Warnings and Precautions (5.1)]*.

Refer to DPMH (pediatric) review, dated 9/5/18, for pediatric-related labeling recommendations and DPMH (maternal health) review, dated 9/10/18, and amended on 12/4/2018, for maternal-health related labeling recommendations. In addition to the review team and consultants, the labeling was also reviewed by the Division of Medication Error Prevention and Analysis (review dated August 16, 2018), the Office of Prescription Drug Promotion (OPDP), and the Division of Medical Policy Products (DMPP) patient labeling team. Their comments and recommendations have been incorporated into final labeling. For final labeling agreements, the reader is referred to the approved product label for Motegrity.

14. Risk Evaluation and Mitigation Strategies

No REMS beyond the standard labeling and postmarketing safety monitoring are recommended. No safety concerns or signals were identified that would require a REMS at this time.

15. Postmarketing Requirements and Commitment

The following language is proposed for the Pediatric Research Equity Act PMRs. See Approval Letter for final language.

We are issuing a partial waiver for the pediatric study requirement in patients with chronic idiopathic constipation birth to less than 6 months of age because the necessary studies are impossible or highly impractical. The following studies are deferred because the product is ready for approval in adults and the pediatric studies have not been completed.

3529-1 Evaluate the pharmacokinetics, efficacy, and safety of Motegrity (prucalopride) in pediatric patients with chronic idiopathic constipation (CIC) who are 6 months to less than 18 years of age by performing a randomized, double-blind, placebo-controlled, parallel group, 12-week treatment study.

Draft Protocol Submission: 03 /2019
Final Protocol Submission: 07 / 2019
Study/Trial Completion: 03 / 2022
Final Report Submission: 09 / 2022

3529-2 Assess the long-term safety of Motegrity (prucalopride) in pediatric patients with chronic idiopathic constipation (CIC) who are 6 months to less than 18 years of age and have completed a confirmatory efficacy and safety study with Motegrity (prucalopride) by performing an active comparator-controlled safety and tolerability study.

Draft Protocol Submission: 03 / 2019
Final Protocol Submission: 09 / 2019
Study/Trial Completion: 06 / 2023
Final Report Submission: 09 / 2023

The following language is proposed for PMRs under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA). See Approval Letter for final language.

3529-3 A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Motegrity (prucalopride) during pregnancy to an unexposed control

population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Draft Protocol Submission:	06/2019
Final Protocol Submission:	10/2019
Study/Trial Completion:	12/2025
Interim /Other:	09/2021, 09/2022, 09/2023, 09/2024, 09/2025
Final Report Submission:	06/2026

3529-4 An additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to Motegrity (prucalopride) during pregnancy compared to an unexposed control population.

Draft Protocol Submission:	06/2019
Final Protocol Submission:	10/2019
Study/Trial Completion:	12/2025
Interim /Other:	09/2021, 09/2022, 09/2023, 09/2024, 09/2025
Final Report Submission:	06/2026

3529-5 Perform a milk only lactation trial in lactating women who have received therapeutic doses of Motegrity (prucalopride) using a validated assay to assess concentrations of prucalopride in breast milk and the effects on the breastfed infant.

Draft Protocol Submission:	09/2019
Final Protocol Submission:	12/2019
Study/Trial Completion:	04/2024
Interim/Other:	09/2021, 09/2022, 09/2023
Final Report Submission:	08/2024

16. Division Director (DGIEP) (or Designated Signatory Authority) Comments

I concur with the recommendation of the reviewers that prucalopride (Motegrity), a serotonin-4 (5-HT4) receptor agonist, be approved. The product will provide an additional class of drugs for the treatment of CIC compared to the currently available therapies approved in the U.S. and will address an unmet medical need. Not all available therapies are effective in all patients, and some may have unacceptable side effects in some patients.

The Pediatric Research Equity Act (PREA) applies to this application. A partial waiver is granted for pediatric patients under 6 months of age because the necessary studies are impossible or highly impracticable, and a deferral in pediatric patients at least 6 months because the product is ready for approval in adults. PREA PMRs will be required.

The data used to support the approval of this product include:

Efficacy: Two studies were relied upon primarily for the demonstration of efficacy; Studies 302 and 3001. Four additional studies in adults with CIC supported the approval of prucalopride: Studies USA-11, USA-12, INT-6, 401. Study 401, a phase 4 trial, conducted in Europe evaluated prucalopride for 24 weeks. The primary efficacy endpoint failed to achieve statistical significance at both weeks 12 and 24 in Study 401; however, statistical significance was achieved at 12 weeks in the other five trials. For the primary efficacy endpoint, a responder was defined as a patient with an average of 3 or more CSBMs per week over the 12 week treatment period. An additional alternative efficacy endpoint was analyzed. In this analysis, a responder was defined as a patient who had at least 3 CSBMs and an increase of at least 1 CSBM from baseline in a given week for at least 9 weeks out of the 12-week treatment period and for at least 3 of the last 4 weeks of the treatment period. The results support the efficacy findings of the original study endpoints.

Safety: the safety review of prucalopride, based upon the 6 clinical efficacy studies as well as a larger safety database of pooled analyses of double-blind, randomized controlled and opened label trials, revealed few safety concerns. An analysis of safety was undertaken by age, race and sex across the six efficacy studies. Study 3001 was conducted in Asian females who had a higher rate of diarrhea compared to the other studies. The reason for this is unknown. These patients had a shorter duration of CIC prior to study entry compared to the other trials; however, their BMI was not substantially different, and the drug is primarily excreted by the kidneys. Too few, black or Hispanic patients were enrolled to draw any meaningful conclusions across racial subgroups. However, no new safety signals were seen in these patients compared to the overall safety evaluation.

A review of adverse reactions of special interest in the clinical trial database pooled analyses and blinded adjudication of MACE events was performed. This review did not reveal an imbalance in CV safety risk between the prucalopride 2 mg and placebo treatment groups. Overall, there were few events, and they occurred equally in the placebo and prucalopride arms in the

controlled clinical trials: two (0.1%) for the placebo group (N=2019) and two (0.1%) for the double-blind all doses of prucalopride group (N=3366).

Because this drug was marketed in Europe since 2009, the sponsor undertook to do an analysis of safety databases rather than conduct an additional randomized trial to assess CV safety. The findings from SPD555-802 provide evidence that reasonably excludes a greater than three-fold MACE risk from prucalopride use. FDA could not use SPD555-802 to reliably bound MACE risk at levels lower than three-fold.

Finally, selectivity in the mechanism of action, preclinical data, a through QT study, and pharmacokinetic/ pharmacodynamic studies were negative for signals relating to a potential CV risk. In vitro prucalopride did not significantly potential the platelet aggregation induced by platelet agonists.

The application was discussed at the GIDAC meeting October 18, 2018. The committee recommended approval. The committee unanimously agreed that the clinical trial data provides substantial evidence of effectiveness of prucalopride for the treatment of adults with chronic idiopathic constipation (CIC). The committee unanimously agreed that the potential risk of cardiovascular adverse events with the use of prucalopride in adults with CIC has been adequately addressed by the Applicant. Members of the committee cited that the nonclinical data, selectivity of the drug for 5-HT4 receptor, adjudicated, pooled cardiovascular safety analysis from 19 double-blind, randomized, placebo-controlled clinical trials and lack of cardiovascular safety signal with extensive use of prucalopride in other countries as reasons for their approval. Several members of the committee expressed concern regarding the neuropsychiatric events that occurred in patients treated with prucalopride and suggest that appropriate wording be added to the labeling.

Product labeling will contraindication the use of prucalopride in patients with:

- A history of hypersensitivity to MOTEGRITY. Reactions including dyspnea, rash, pruritus, urticaria, and facial edema have been observed.
- Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract such as Crohn’s disease, ulcerative colitis, and toxic megacolon/megarectum.

Product labeling with describe the potential for the following serious risks with use of prucalopride: In clinical trials, suicides, suicide attempts, and suicidal ideation have been reported *[see Adverse Reactions (6.1)]*. A causal association between treatment with MOTEGRITY and an increased risk of suicidal ideation and behavior has not been established.

Monitor all patients treated with MOTEGRITY for persistent worsening of depression or the emergence of suicidal thoughts and behaviors. Counsel patients, their caregivers, and family members of patients to be aware of any unusual changes in mood or behavior and alert the

healthcare provider. Instruct patients to discontinue MOTEGRITY immediately and contact their healthcare provider if they experience any of these symptoms.

A REMS will not be required. Labeling will be sufficient to address risk management with the use of prucalopride.

As noted above PREA PMRs will be required to study prucalopride in pediatric patients with CIC who are at least 6 months to 18 years of age. In addition, a pregnancy cohort study, pregnancy registry and lactation trial will be required.

Based upon the review of the NDA submission, taken together, these data support a finding of substantial evidence of effectiveness and safety for the following indication: the treatment of chronic idiopathic constipation (CIC) in adults.

I recommend approval of prucalopride (Motegrity).

17. Office Director (or Designated Signatory Authority) Comments

I concur with the recommendation of the Division of Gastroenterology and Inborn Errors Products (DGIEP) to approve NDA 210166 for Motegrity (prucalopride). Motegrity (prucalopride) is a selective 5-hydroxytryptamine type 4 (5-HT_4) receptor agonist proposed for the treatment of chronic idiopathic constipation in adults.

As discussed in detail in this review, the benefits of Motegrity (prucalopride) outweigh the risks for the sought indication. Five of the six clinical trials submitted to support product approval achieved statistical significance for the primary efficacy endpoint. The identified safety issues can be mitigated with labeling without need for Risk Evaluation and Mitigation Strategies.

Prucalopride belongs to a class of drugs for which risks for cardiovascular (CV) events and suicidal ideation and behavior (SIB) are of special interest. For CV risk, no significant QTc prolonging effect of prucalopride was detected in a thorough QT study and the safety data from the controlled trials did not reveal notable differences in CV events between prucalopride and placebo. The CV safety was further characterized by assessing the risk for major adverse cardiovascular events (MACE) through a retrospective cohort study (study SPD555-802), which was conducted to estimate the adjusted incidence rate ratio for MACE in prucalopride users compared to polyethylene glycol users. The findings from study SPD555-802 reasonably excluded a greater than three-fold MACE risk associated with prucalopride use. For SIB events, two completed suicides were reported among patients previously treated with prucalopride. Three cases of suicide attempt were reported in the safety database; of the three cases of suicide attempt, one occurred 7 days after the end of treatment with prucalopride in a double-blind trial, and two were during the open-label trials. One case of suicidal ideation occurred in the open label trials. The patients who reported a suicide attempt or suicidal ideation had completed a double-blind trial prior to entering the open label trial. No SIB events were reported among patients in the placebo group. Furthermore, a 2015 WHO Pharmaceuticals Newsletter (No. 3) included postmarketing reports of three patients who developed suicidal ideation within hours to days after initiation of prucalopride. Prucalopride is approved and marketed in many countries including the European Union where it has been approved since 2009; therefore, instead of a long-term epidemiologic study to assess SIB risk, it will be more prudent to protect public health through appropriate and timely product labeling. Given the seriousness of SIB, our findings will be described in the Warnings and Precautions section of product labeling.

The application was discussed during a public Gastrointestinal Advisory Committee (GIDAC) meeting on October 18, 2018. The GIDAC voted 10 to 0 to support approval. Postapproval activities will include routine pharmacovigilance (of which SIB will continue to be of special interest), pediatric trials under PREA, two studies to assess infant outcomes when prucalopride is given to pregnant women, and a milk only lactation trial to assess concentrations of prucalopride in breast milk and the effects of prucalopride on the breastfed infant.

18. Appendix

18.1. References

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18.2. Financial Disclosure

Covered Clinical Study: SPD555-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 243		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator: N/A Sponsor of covered study: Shire		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

The Sponsor originally submitted documentation that (b) (6) had disclosable financial interests, both in an investigator list and in FDA Form 3455 where the box was checked documenting "any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such

as a grant to fund ongoing research, compensation in the form of equipment, retainer of ongoing consultation, or honoraria". Shire also submitted a due diligence statement in an IR received on 11/19/2018 describing a very reasonable process in an attempt to obtain the required financial documentation. There was documentation that (b) (6) received significant payments "of other sorts" exceeding 25,000 USD. Review of the study data did not suggest that these payments biased the efficacy or safety results.

Covered Clinical Study: PRU-CRC-3001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 194		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator: N/A Sponsor of covered study: Johnson and Johnson Pharmaceutical Research & Development, LLC.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Please note, one of the Subinvestigators, (b) (6) incorrectly filled out Janssen Pharmaceutical Limited's Financial Disclosure form. (b) (6) had no financial interests in this study, and this was confirmed by the applicant by telephone on October 26,2018. This information was communicated in an information request submitted to the FDA on 10/30/2018. Amended investigator list was received from Shire on 11/19/2018. In addition, Shire submitted FDA Form 3454 and checked box 2, documenting that Shire was not the Sponsor during this trial and that these investigators had no proprietary interest in this product or significant equity of interest in the sponsor of this study as defined in 21 CFR 54.2 (b and f).

Covered Clinical Study: PRU-USA-11

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 358		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator: N/A Sponsor of covered study: Janssen Research Foundation		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

There was 1 investigator who Shire had originally provided documentation for potential financial conflicts (b) (6) (b) (6) Shire submitted FDA Form 3454 and checked box 2, documenting that Shire was not the Sponsor during this trial and that these investigators had no proprietary interest in this product or significant equity of interest in the sponsor of this study as defined in 21 CFR 54.2 (b and f). Shire also submitted a due diligence statement in an IR received on 11/19/2018 describing a very reasonable process in an attempt to obtain the required financial documentation. There was documentation that (b) (6) received significant payments from "Honoraria from a variety of sources" exceeding 25,000 USD. Review of the study data did not suggest that these payments to (b) (6) (b) (6) biased the efficacy or safety results.

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Motegrity (prucalopride)

Covered Clinical Study: PRU-USA-13

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 351		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator: 1 Sponsor of covered study: Janssen Research Foundation		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

There were 5 investigators who Shire had originally provided documentation for potential financial conflicts: (b) (6) (b) (6) According to an Information Request received from Shire on 11/19/2018, did not have a financial conflict. For the other 4 investigators, Shire submitted FDA Form 3454 and checked box 2, documenting that Shire was not the Sponsor during this trial and that these investigators had no proprietary interest in this product or significant equity of interest in the sponsor of this study as defined in 21 CFR 54.2 (b and f). Shire also submitted a due diligence statement describing a very reasonable process in an attempt to obtain the required financial documentation. There was documentation that (b) (6) received significant payments from "research funds and funds to run laparoscopy courses" exceeding 25,000 USD. (b) (6) received significant payments from "honoraria for presentations and advisory/ consultation capacities" exceeding 25,000 USD (may have been 30,000). (b) (6) received significant payments (b) (6) exceeding 25,000 USD. (b) (6) was employed by Janssen and purchased J&J stock within her stock plan which was documented as "significant equity of interest." Review of the study data did not suggest that compensation to these investigators biased the efficacy or safety results.

NDA 210166

Motegrity (prucalopride)

Covered Clinical Study: PRU-INT-6

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 190		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4, with 1 investigator refusing to disclose financial information, 58 investigators for which Shire was unable to obtain financial information		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 2 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator: N/A Sponsor of covered study: Janssen Research Foundation		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

There was 3 investigators who Shire provided documentation for potential financial conflicts [redacted (b) (6)]. In an IR received on 11/20/2018, Shire submitted FDA Form 3454 and checked box 2, documenting that they were not the Sponsor during this trial and that these investigators had no proprietary interest in this product or significant equity of interest in the sponsor of this study as defined in 21 CFR 54.2 (b and f). There were 2 investigators that were listed as having unknown financial conflicts according to Shire's Site Financial Disclosure Form: [redacted (b) (6)] In addition, there were 58 investigators for which Shire was unable to obtain financial information. To address this, Shire also submitted a due diligence statement describing a very reasonable process in an attempt to obtain the required financial documentation. A FDA Form 3454 was also submitted for the 58 subjects where box 3 was checked attesting to due diligence. There was documentation that [redacted (b) (6)] received significant payments from "lab equipment and salary" exceeding 25,000 USD. [redacted (b) (6)] received significant payments from GI motility fellowships for 3 and 4 years, receiving 46,000 USD. [redacted (b) (6)] received significant payments from a research fellowship sponsored by Janssen Research Foundation resulting in payments exceeding 25,000 USD. Review of the study data did not suggest that compensation to these investigators biased the efficacy or safety results. With respect to the 2 investigators with "unknown" financial conflicts, [redacted (b) (6)] declined to provide any financial information, and [redacted (b) (6)] reported salary for "motility studies nurse" exceeding 25,000 USD. The investigators listed as N/A due to Shire being unable to obtain financial information were listed in the Site Financial Disclosure Form. Review of the study data did not suggest that compensation to these investigators biased the efficacy or safety results.

Covered Clinical Study: SPD555-401

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 170		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator: N/A Sponsor of covered study: Shire		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant)

Because there were no disclosable financial interests, no further documentation is required.

18.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

18.3.1. Bioanalytical Method Report

Prucalopride in human plasma and urine

The Applicant used two assays for the measurement of plasma prucalopride concentrations. Throughout their early clinical development that occurred roughly between 1994 and 2000, plasma concentrations of prucalopride were determined by radioimmunoassay (RIA) method when routine use of LC-MS/MS was not yet established. LC-MS/MS method was used in later stage of the applicant's clinical development (around 2008 and afterwards).

Briefly, for the RIA method, 0.1 mL aliquots of the test plasma were incubated with 0.1 mL of 2% bovine serum albumin solution containing about 0.06 ng ^{3}H-prucalopride and 0.1 mL of the diluted antiserum for 2 hours under continuous rotation at room temperature in the dark. Bound and free prucalopride were separated by selective absorption of the free ligand using 0.2 mL of a

2% dextran-coated charcoal suspension. The charcoal was precipitated by centrifugation, and the supernatants, containing the antibody-bound prucalopride fractions, were aspirated and transferred to scintillation vials. The radioactivity was counted for 2 min in a liquid scintillation analyzer. Stability studies showed that prucalopride is stable in human plasma during 2 freeze-thaw cycles, for at least 72 hours at room temperature, and for at least 27 months at temperatures ≤-18°C.

For the LC-MS/MS method, prucalopride calibration standards were prepared in human plasma and urine at 10 nominal concentrations with liquid/liquid extraction. Prucalopride QC samples were prepared at low, mid, and high nominal concentrations. The mass spectrometer was operated in positive ESI mode with multiple reaction monitoring detection. The calibration range for plasma assay was 0.200 to 100 ng/mL and for urine assay was 2.00 to 2000 ng/mL.

In addition, prucalopride concentrations in human urine samples were measured by a HPLC method, with a calibration curve of urine concentrations ranging from 2.00 to 10000 ng/mL.

Table 77. Summary of Bioanalytical Assays for Prucalopride

Analyte	Validation Report/ Method	Study (Report)	Precision (%CV)	Accuracy (% Bias)
Prucalopride in plasma	FK1641: RIA method validation, Calibration range 0.10 to 10.0 ng/mL, Freeze/thaw 2 x F/T cycles	PRU-BEL-1, PRU-BEL-3, PRU-BEL-4, PRU-BEL-5, PRU-BEL-6, PRU-BEL-8, PRUBEL-9, PRU-BEL-10, , PRU-BEL-12, PRU-BEL-14, PRU-BEL-15, PRU-BEL-16, PRUBEL-20, PRU-BEL-25, PRU-BEL-29, PRU-BEL-30, PRU-BEL-31, PRU-BEL-32, PRUBEL-33, PRU-GBR-4, PRU-GBR-9, PRU-GBR-10, PRU-NED-1, PRU-NED-2, PRUNED-4, PRU-NED-6, PRU-NED-7 PRU-NED-8, PRU-NED-11, PRU-NED-12, PRUNED-13, PRU-NED-14, PRU-NED-15, PRU-USA-2, PRU-USA-3, PRU-USA-6, PRUUSA-12, PRU-USA-22, PRU-USA-24, PRU-USA-25, PRU-USA-26, PRU-USA-29, PRUUSA-31, PRU-USA-32, PRU-INT-2, PRU-INT-3, PRU-INT-4, PRU-INT-6, PRU-INT-10, PRU-INT-12, PRU-RSA-1	3.1% to 11.6%	-6.5% to 3.4%
Prucalopride in plasma	A6425M-SPD555: LC-MS/MS method validation, Calibration range 0.2 to 100ng/mL, Freeze/thaw 3 x F/T cycles	M0001-C101, M0001-C102, M0001-C103, SPD555-104, M0001-C301, M0001-C303, SPD555-403	1.8% to 7.7%	-3.0% to 2.0%

Analyte	Validation Report/ Method	Study (Report)	Precision (%CV)	Accuracy (% Bias)
Prucalopride in plasma	A6426M-SPD555: LC-MS/MS (partial revalidation), Calibration range 0.2 to 100ng/mL	M0001-C101, M0001-C102, M0001-C103, SPD555-104, M0001-C301, M0001-C303, SPD555-403	2.4% - 8.7%	-5.6% to 2.8%
Prucalopride in plasma	A5971M-SPD555: LC-MS/MS (additional validation), Calibration range 0.2 to 100ng/mL	SPD555-104, SPD555-403	2.1% to 5.5%	2.0% to 5.2%
Prucalopride in urine	ABL10134: LC-MS/MS validation, Calibration range 2.00 to 2000ng/mL	M0001-C103, SPD555-104	2.3% to 11.2%	0.1% to 2.8%
Prucalopride in urine	A5972M-SPD555: LC-MS/MS additional validation, Calibration range 2.00 to 2000ng/mL	SPD555-104	3.6% to 6.5%	-6.9% to -0.7%
Prucalopride in urine	A4442M-SPD555 HPLC, Calibration range 2 to 10000 ng/mL, Freeze/thaw 3 x F/T cycles	PRU-BEL-1	4.4% to 5.0%	0.1% to 6.1%

Summary of bioanalytical in-study analysis reports for prucalopride in human plasma/urine in presented as following.

Table 78. Bioanalytical In-Study Analysis Reports for Prucalopride in Human Plasma/Urine

Report Number	Studies Supported	Laboratory	Matrix	Instrumen-tation	Calibration Range	Interday Precision	Interday Accuracy	FT	Long Term Frozen Stability
R093877/001	PRU-BEL-2	JRF	Human plasma	RIA	0.20-40.0 ng/mL	≤ 16.2%	-2.5%-5.9%	NA	NA
R093877/001	PRU-BEL-2	JRF	Human urine	HPLC-fluorescence	10-10000 ng/mL	≤ 7.3%	-7.6%-20.5%	NA	NA
R093877/013	PRU-BEL-4	JRF	Human plasma	RIA	0.200 to 10.0ng/mL	≤ 17.2%	-0.9%-4.2%	3 x F/T cycles (A6425M-SPD555)	At least 23 months at ≤-18°C (A5678M-SPD555)
R093877/014	PRU-BEL-3	JRF	Human plasma	RIA	0.05 to 0.50 ng/mL	≤ 16.7%	-7.5%-1.9%		
R093877/015	PRU-BEL-3	JRF	Human urine	HPLC-UV	10 to 4000 ng/mL	≤ 8.9%	-9.0%-4.7%		
R093877/019	PRU-BEL-5	JRF	Human plasma	RIA	0.10 to 10.0 ng/mL	≤ 10.1%	4.1-10.7%		
R093877/021	PRU-BEL-9	JRF	Human plasma	RIA	0.10-40.0 ng/mL	≤ 9.6%	-6.8 to -2.2%		
R093877/023	PRU-USA-2	JRF	Human plasma	RIA	0.50-50.0 ng/mL	≤ 9.6%	-6.6 to -0.5%		
R093877/026	PRU-BEL-10	JRF	Human plasma	RIA	1.00-50.0 ng/mL	≤ 14.2%	5.8 to 10.8%		
R093877/030	PRU-BEL-6	JRF	Human plasma	RIA	0.10-40.0 ng/mL	≤ 6.9%	-19.3 to -5.6%		
R093877/032	PRU-BEL-12	JRF	Human plasma	RIA	0.100 to 10.0 ng/mL	≤ 6.6%	0.9% to 12.5%		
R093877/033	PRU-BEL-16	JRF	Human plasma and urine	RIA	0.10-10.0 ng/mL (plasma) 2.0-2000 ng/mL (urine)	≤ 5.1% (plasma); ≤ 21.9% (urine)	2.8% to 4.3% (plasma); -4.9% to 13.8% (urine)		
R093877/033	PRU-INT-2	JRF	Human plasma and urine	RIA	0.20-20.0 ng/mL	≤ 14.8	9.8% to -2.3%		
R093877/037	PRU-BEL-14	JRF	Human plasma	RIA	0.100 to 10.0ng/mL	≤ 4.7%	4.5%-6.9%		
R093877/040	PRU-USA-3	JRF	Human plasma	RIA	0.20-20.0 ng/mL	≤ 9.2%	-6.6 to -2.3%		
R093877/041	PRU-BEL-29	JRF	Human plasma	RIA	0.100 to 10.0 ng/mL	≤ 8.0%	-4.9% to -0.6%		
R093877/043	PRU-BEL-16	JRF	Human plasma	LC-MS/MS	0.035-7.06 ng/mL	≤ 7.7%	-3.9% to 2.1%	NA	NA
R093877/044	PRU-BEL-15	JRF	Human plasma	RIA	0.10-100 ng/mL	≤ 6.9%	-11.5% to 0.6%	3 x F/T cycles (A6425M-SPD555)	At least 23 months at ≤-18°C (A5678M-SPD555)
R093877/045	PRU-NED-7	JRF	Human plasma and urine	RIA	0.20-20.0 ng/mL (plasma); 20-2000 ng/mL (urine)	≤ 6.6% (plasma); ≤ 8.7% (urine)	-5.8% to -4.9% (plasma); 0.5% to 8.7% (urine)		
R093877/046	PRU-NED-6	JRF	Human plasma	RIA	0.10-20.0 ng/mL	≤ 6.3%	2.0% to 2.8%		
R093877/047	PRU-BEL-20	JRF	Human plasma	RIA	0.10-10.0 ng/mL	≤ 8.5%	-14.2% to -7.3%		
R093877/050	PRU-NED-2	JRF	Human plasma	RIA	0.20-20.0 ng/mL	≤ 45.1%	-2.8% to 18.6%		
R093877/051	PRU-BEL-8	JRF	Human plasma	RIA	0.10 or 020-100 ng/mL depending on sample volume	≤ 16.6%	-10.2% to 6.6%		
R093877/052	PRU-NED-11	JRF	Human plasma	RIA	0.20-100 ng/mL	6.3%	-5.3%		

Report Number	Studies Supported	Laboratory	Matrix	Instrumen-tation	Calibration Range	Interday Precision	Interday Accuracy	FT	Long Term Frozen Stability
R093877/053	PRU-BEL-25	JRF	Human plasma	RIA	0.10-5.00 or 1.1-55.0 ng/mL depending on assay volume	≤ 10.3%	-3.1% to 4.8%		
R093877/054	PRU-BEL-30	JRF	Human plasma	RIA	0.100 to 5.00 ng/mL	≤ 8.4%	0.4% to 10.2%		
R093877/055	PRU-BEL-31	JRF	Human plasma	RIA	0.100 to 5.00 ng/mL	≤ 8.3%	-10.3% to 8.3%		
R093877/056	PRU-BEL-1	JRF	Human plasma	RIA	0.10 to 10.0 ng/mL (0.40-40.0 ng/mL for the 4-mg dose)	≤ 5.4%	-4.8% to 2.8%		
R093877/057	PRU-BEL-1	JRF	Human urine	HPLC-fluorescence	10-4000 ng/mL	Not reported	Not reported	3 x F/T cycles (A4442M-SPD555)	Up to 12 months at ≤-20°C (A4442M-SPD555)
R093877/058	PRU-GBR-4	JRF	Human plasma	RIA	0.10-5.00 ng/mL	≤ 15.7%	5.1% to 7.1%	3 x F/T cycles (A6425M-SPD555)	At least 23 months at ≤-18°C (A5678M-SPD555)
R093877/059	PRU-BEL-32	JRF	Human plasma	RIA	0.100 to 50.0 ng/mL	≤ 6.3%	-0.6%-18.1%		
R093877/061	PRU-USA-29	JRF	Human plasma and urine	RIA	0.10-5.0 ng/mL	≤ 14.8%	-1.5% to 10.3%		
R093877/065	PRU-USA-26	JRF	Human plasma and urine	RIA	1.0-10.0 ng/mL	≤ 10.0%	-4.3% to 4.0%		
R093877/066	PRU-USA-24	JRF	Human plasma and urine	RIA	0.10-55.0, 0.10-5.00, or 1.1-55.0 ng/mL depending on the sample volume	≤ 8.9%	-1.8% to 4.5%	3 x F/T cycles (A6425M-SPD555)	At least 23 months at ≤-18°C (A5678M-SPD555)
R093877/067	PRU-USA-12	JRF	Human plasma and urine	RIA	0.10-55.0, 0.10-5.00, or 1.1-55.0 ng/mL depending on sample volume (plasma); 20-11110, 20-1010or 220-1110 ng/mL depending on sample volume (urine)	≤ 10.6% (plasma) and ≤ 6.0% (urine)	-9.2% to -2.3%; -14.5% to -13.1% (urine)		
R093877/069	PRU-NED-12	JRF	Human plasma	RIA	0.10-55.0 ng/mL	≤ 5.5%	-4.1% to 5.3%		
R093877/070	PRU-INT-4	JRF	Human plasma and urine	RIA	0.10 to 5.00, 0.10 to 10.0, 1.0-100, 1.1-55.0, or 2.2-110 ng/mL depending on sample volume	≤ 21.0%	-7.4% to 8.6%		
R093877/072	PRU-USA-31	JRF	Human plasma	RIA	0.200 to 10.0 ng/mL	≤ 7.2%	-6.1% to 7.3%		
R093877/073	PRU-USA-32	JRF	Human plasma	RIA	0.100 to 5.00 ng/mL	≤ 4.8%	-0.3% to 5.3%		
R093877/074	PRU-BEL-33	JRF	Human plasma	RIA	0.100-5.00 ng/mL	≤ 4.8%	-8.3% to 4.4%		

Report Number	Studies Supported	Laboratory	Matrix	Instrumen-tation	Calibration Range	Interday Precision	Interday Accuracy	FT	Long Term Frozen Stability
R093877/075	PRU-USA-25	JRF	Human plasma	RIA	0.2-20.0 ng/mL (1.1-110 ng/mL for reanalysis of out of range samples)	≤ 9.7%	3.8% to 7.4%		
R093877/076	PRU-INT-3	JRF	Human plasma	RIA	0.10-10.0 ng/mL, 1.0-100 ng/mL, 0.10-5.00 ng/mL, 1.1-55.0 ng/mL, 2.1-105 ng/mL, 2.2-110 ng/mL, or 24-1210 ng/mL depending on the sample volume	≤ 21.0%	-7.4% to 10.6%		
R093877/078	PRU-GBR-9	JRF	Human plasma	RIA	0.2-10.0 ng/mL (2.2-110 ng/mL for reanalysis of out of range samples)	≤ 11.8%	-3.2% to 9.4%		
R093877/079	PRU-INT-6	JRF	Human plasma	RIA	0.2-10.0 ng/mL (2.1-105 ,g/mL and 2.2-110 ng/mL for reanalysis of out of range samples)	≤ 13.7%	-7.6% to -3.4%		
R093877/085	PRU-NED-8	JRF	Human plasma	RIA	0.2-10.0 ng/mL (2.2-110 ng/mL for reanalysis of out of range samples)	≤ 20.2%	-13.6% to 0.7%	3 x F/T cycles (A6425M-SPD555)	At least 23 months at ≤-18°C (A5678M-SPD555)
R093877/086	PRU-USA-22	JRF	Human plasma	RIA	0.10-5.00 ng/mL, 1.10-55.0 ng/mL, 0.20-10.0, or 2.20-110 ng/mL depending on the assay volume	≤ 12.5%	-10.0% to 4.3%		
R093877/089	PRU-RSA-1	JRF	Human plasma	RIA (plasma); LC-MS/MS (breast milk)	0.10-5.00 ng/mL or 1.1-55.0 ng/mL (plasma); 0.10-50.00 ng/mL (breast milk)	≤ 9.8% (plasma) Breast milk values not available	0.9% to 1.7% (plasma) Breast milk values not available		
R093877/091	PRU-INT-10	JRF	Human plasma	RIA	0.10-5.00 ng/mL or 1.10-55.0 ng/mL depending on sample volume	≤ 9.3%	-9.0% to 10.2%		
R093877/092	PRU-USA-26	JRF	Human plasma	RIA	0.20-10.0 ng/mL, 0.10-5.00 ng/mL, or 1.10-55.0 ng/mL depending on sample volume	≤ 9.9%	-8.6% to 0.9%		
R093877/095	PRU-NED-13	JRF	Human plasma	RIA	0.10-5.00 ng/mL (undiluted); 1.10-55.0 ng/mL (1/11 dilution)	≤ 7.4%	-14.8 to -3.9%		
R093877/096	PRU-NED-14	JRF	Human plasma	RIA	1.10-55.0 and 0.10-5.0 ng/mL (depending on plasma sample volume)	≤ 15.9% for both plasma and urine	-14.1% to 5.1% for both plasma and urine		
R093877/097	PRU-NED-15	JRF	Human plasma	RIA	010-5.00 or 1.10-55.0 ng/mL depending on sample volume	≤ 9.5%	6.3% to 15.8%		

Report Number	Studies Supported	Laboratory	Matrix	Instrumen-tation	Calibration Range	Interday Precision	Interday Accuracy	FT	Long Term Frozen Stability
R093877/098	PRU-INT-12	JRF	Human plasma	RIA	0.20-20.0 or 2.20-110 ng/mL depending on sample volume	≤ 22.3%	-11.9% to 3.9%		
R093877/100	PRU-NED-4	JRF	Human plasma	RIA	0.10-50.0 or 1.10-55.0 ng/mL depending on sample volume	≤ 6.9%	0.6% to 7.1%		
R093877/101	PRU-NED-1	JRF	Human plasma	RIA	0.10-10.0 ng/mL	≤ 5.0%	-3.1% to -0.9%		
R093877/102	PRU-GBR-10	JRF	Human plasma	RIA	1.10-55.0 ng/mL (0.10-5.00 ng/mL for reanalysis for samples < 1.1 ng/mL; 2.10-105 ng/mL for samples > 55 ng/mL; 12.1-605 ng/mL for samples > 105 ng/mL)	≤ 8.4%	-7.6% to 13.4%		
ABL9137 A5671M	M0001-C101, SPD555-104, M0001-C303, SPD555-403	(b) (4)	Human heparin plasma	LC-MS/MS	0.200 to 100 ng/mL	≤ 4.2%	-0.4% to 3.4%	3 x F/T cycles (A6425M-SPD555)	At least 23 months at ≤-18°C (A5678M-SPD555)
ABL9138 A5674M	M0001-C101		Human heparin plasma	LC-MS/MS	3.00 to 600 pg/mL	≤ 4.8%	Not reported		
ABL9139/ A5677M	M0001-C101		Human heparin plasma	LC-MS/MS	0.0500 to 20 ng/mL	≤ 5.8%	0.0% to 1.2%		
ABL9222	M0001-C102		Human heparin plasma	LC-MS/MS	0.200 to 100 ng/mL	≤ 4.3%	-2.1% to 0.3%		
ABL10137 A5678M	M0001-C103 SPD555-104, M0001 C303, SPD555-403		Human heparin plasma	LC-MS/MS	0.200-100.0 ng/mL	≤ 3.4%	-1.7% to -1.2%		
ABL10138/ A6260M	M0001-C103, SPD555-104		Human urine	LC-MS/MS	2.0 to 2000 ng/mL	≤ 8.0%	-0.9% to 3.8%		
ABL10139/ A5679M	M0001-C103		Human heparin plasma	LC-MS/MS	0.0500 to 25.0 ng/mL	≤ 2.9%	4.1% to 5.8%		
ABL10140/ A4927M	M0001-C301		Human plasma	LC-MS/MS	0.200 to 100 ng/mL	≤ 6.0%	-2.7% to -0.3%		

Report Number	Studies Supported	Laboratory	Matrix	Instrumen-tation	Calibration Range	Interday Precision	Interday Accuracy	FT	Long Term Frozen Stability
ABL10297/ A45557M	M0001-C303	(b) (4)	Human lithium heparin plasma	LC-MS/MS	0.2 to 100 ng/mL	≤ 4.2%	-0.8% to 3.2%		
ABL12301/ A5664M	SPD555-403		Human plasma	LC-MS/MS	0.200 to 100 ng/mL	≤ 5.3%	-0.7% to 4.6%		
ABL13153/ A6036M	SPD555-104		Human urine	LC-MS/MS	2.00-2000 ng/mL	≤2.6%	-0.5% to 1.0%		
ABL13168/ A6035M	SPD555-104		Human plasma	LC-MS/MS	0.200 to 100 ng/mL	≤ 3.0%	-4.2% to -1.2%		
ABL13168/ A6035M	SPD555-104		Human plasma	LC-MS/MS	0.200 to 100 ng/mL	≤ 3.0%	-4.2% to – 1.2%		

(b) (4) FT = freeze/thaw; JRF = Janssen Research Foundation; HPLC = high performance liquid chromatography; LC-MS/MS = liquid chromatography mass spectrometry; NA = not available; RIA = radioimmunological determination; UV = ultraviolet

18.3.2. Pharmacometrics Assessment

Population PK Analysis

The Applicant's population PK (popPK) analysis included data from four phase 1, six phase 2 and three phase 3 studies. Only four phase 1 studies were selected for the analysis in order to keep a balance between the data from intensive PK sampling and those from sparse sampling. The final dataset consisted of 1343 subjects (intensive sampling from 130 subjects and sparse sampling from 1213 subjects), with 4702 measurements of prucalopride plasma concentration. See Table 79, Table 80 and Table 81 for the summary of studies included in the analyses.

Table 79. Summary of Phase 1 Studies Included in the Analysis

Item	Study 001	Study 002	Study 003	Study 004
Aim and Design	Multiple dose escalation study	Multiple dose escalation study	Young versus Elderly subjects study	Single dose renal impairment study
Movetis Code	GBR-09	GBR-10	NED-05	USA-06
No. and type of subjects	33 healthy subjects	32 healthy subjects	24 healthy subjects	34 subjects
Data used	Prucalopride	Prucalopride	Prucalopride	Prucalopride
No of available subjects for PK analysis	33	32	24	34
Dose	2 up to 10 mg o.d. for 8 days. Dose was daily increased by 2 mg, with 4 days at 10 mg o.d.	2 up to 20 mg o.d. for 13 days. Dose was daily increased by 2 mg, with 4 days at 20 mg o.d.	Single dose of 1 mg (Day 1) followed by a 7-day treatment of 1 mg o.d. from Day 5 to Day 11	Single dose of 2 mg
Periods	2 (first from D1 to D7 and last at D8)	2 (first from D1 to D12 and last at D13)	2 (single and multiple)	1 (single dose)
Single/Multiple	Multiple	Multiple	Single and Multiple	Single
Formulation	Tablet	Tablet	Tablet	Capsule
No samples/ period	D1 to D7 2 samples D8 13 samples	D1, D4, D7, D10, D12 2 samples D13 13 samples	Single dose 14 samples D8, D9, D10 1 sample D11 14 samples	Single dose 20 samples
Assay (LLOQ)	RIA (0.2 ng/ml)	RIA (0.1 ng/ml)	RIA (0.1 ng/ml)	RIA (0.1 ng/ml)
Time range	D1 to D7 0,3h D8 0-120h	D1,D4,D7,D10,D12 0,3h D13 0-120h	D1, D11 0-96h D8, D9, D10 0h	D1 0-120h

Source: Applicant's Clinical PopPK Modeling Analysis Report (07-mov-045-1011a), Table 1

Table 80. Summary of Phase 2 Studies Included in the Analysis

Item	Study 005	Study 006	Study 007	Study 008	Study 009	Study 010
Aim and Design	double-blind placebo-controlled randomized	double-blind placebo-controlled randomized	double-blind placebo-controlled randomized dose-finding	double-blind placebo-controlled randomized cross-over	double-blind placebo-controlled randomized cross-over	double-blind placebo-controlled randomized dose-finding
Movetis Code	BEL-06	GBR-04	INT-02	NED-02	NED-13	USA-03
No. and type of subjects	53 patients with severe chronic constipation	74 patients with chronic constipation	253 patients with chronic constipation	28 patients with chronic constipation	8 Patients with chronic constipation	185 patients with chronic constipation
Data used	Prucalopride	Prucalopride	Prucalopride	Prucalopride	Prucalopride	Prucalopride
No of available subjects for PK analysis	27	35	167	24	7	162
Dose	4 mg o.d. for 4 weeks	1 mg o.d. for 4 weeks	0.5,1,2 mg b.i.d. for 12 weeks	1 & 2 mg o.d. for 2 weeks	4 mg o.d. for 10 days	0.5,1,2,4 mg o.d. for 4 weeks
Periods	2 (one per visit))	1	2 (one per visit)	2 (one per visit)	1	1
Single/Multiple	Multiple	Multiple	Multiple	Multiple	Multiple	Multiple
Formulation	Capsule	Capsule	Capsule	Capsule	Capsule/Tablet	Capsule
No samples/ period	1 sample / visit 2 visits	1 sample	1 sample / visit 2 visits	1 sample / visit 2 visits	6 samples for one visit	1 sample / visit
Assay (LLOQ)	RIA (0.1 ng/ml)	RIA (0.1 ng/ml)	RIA (0.2 ng/ml)	RIA (0.2 ng/ml)	RIA (0.1 ng/ml)	RIA (0.2 ng/ml)
Time range	Split over a dosing interval	Trough concentration	Split over a dosing interval	Trough concentration and t+3h	Dosing interval (0-24h)	Split over a dosing interval

Source: Applicant's Clinical PopPK Modeling Analysis Report (07-mov-045-1011a), Table 2

Table 81. Summary of Phase 3 Studies Included in the Analysis

Item	Study 011	Study 012	Study 013
Aim and Design	double-blind placebo-controlled randomized	double-blind placebo-controlled randomized in elderly patients	double-blind placebo-controlled randomized to evaluate the effect of dose-titration
Movetis Code	INT-06	INT-12	USA-25
No. and type of subjects	720 patients with chronic constipation	303 elderly patients with chronic constipation	347 patients with chronic constipation
Data used	Prucalopride	Prucalopride	Prucalopride
No of available subjects for PK analysis	428	208	205
Dose	2 & 4 mg o.d. for 12 weeks	1,2 & 4 mg o.d. for 4 weeks	4 mg o.d. or titration up to 4 mg o.d. for 4 weeks
Periods	2 (one per visit)	2 (one per visit)	2 (one per visit)
Single/Multiple	Multiple	Multiple	Multiple
Formulation	Tablet	Tablet	Tablet
No samples/ period	1 sample / visit 2 visits	1 sample / visit 2 visits	1 sample / visit 2 visits
Assay (LLOQ)	RIA (0.2 ng/ml)	RIA (0.2 ng/ml)	RIA (0.2 ng/ml)
Time range	Split over a dosing interval	Split over a dosing interval	Split over a dosing interval

Source: Applicant's Clinical PopPK Modeling Analysis Report (07-mov-045-1011a), Table 3

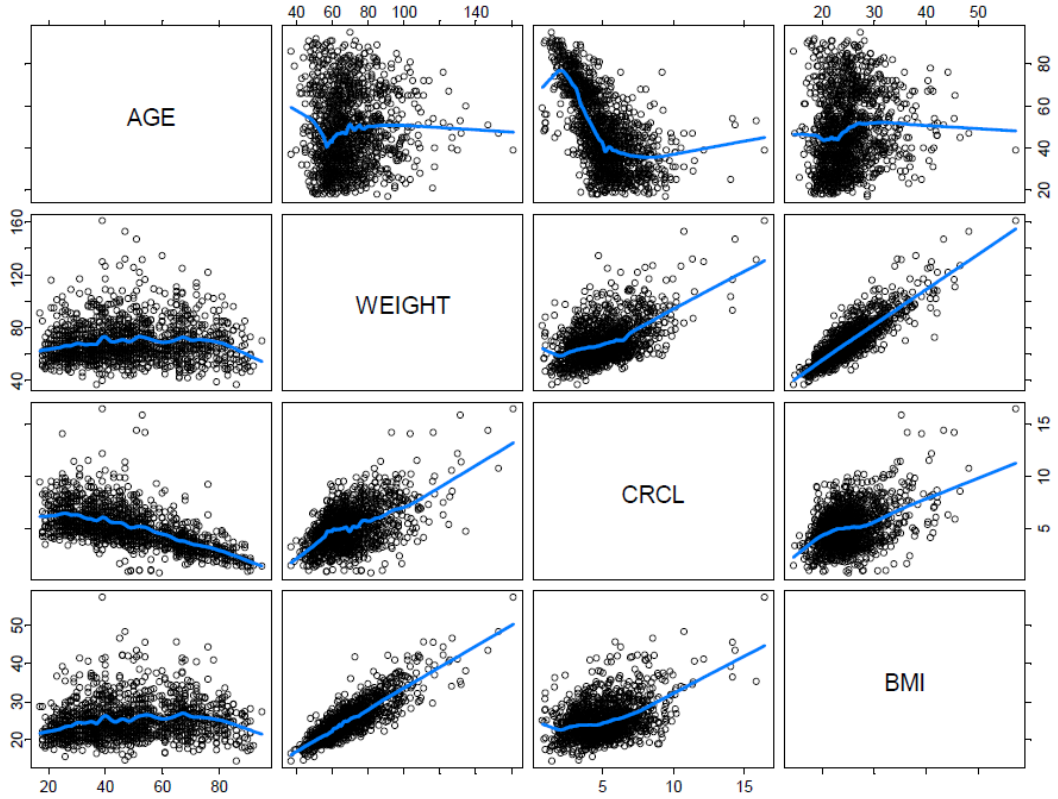
First, the model was built using phase 1 data and then further developed using all data including those from phase 2 and phase 3. The prucalopride PK was described with two-compartment

model with first order absorption. Based on the phase 1 data, a lag time was included in the based model.

For covariate analyses, age, BMI, body weight, creatinine clearance (CRCL), daily dose, patient population, race, sex and dosing regimen (single versus multiple) were tested for their potential influence on the apparent clearance of prucalopride. Among them, creatinine clearance had correlations with age, body weight or BMI (Figure 11). This was expected based on the method of calculating creatinine clearance with Cockcroft-Gault's formula (see Equation 1). Once CRCL was added to the model, no other covariates showed impact on the CL/F of prucalopride. The correlations between covariates and random effects for CL/F are shown in Figure 12 and Figure 13, and the PK parameter estimates from the final model are summarized in Table 82.

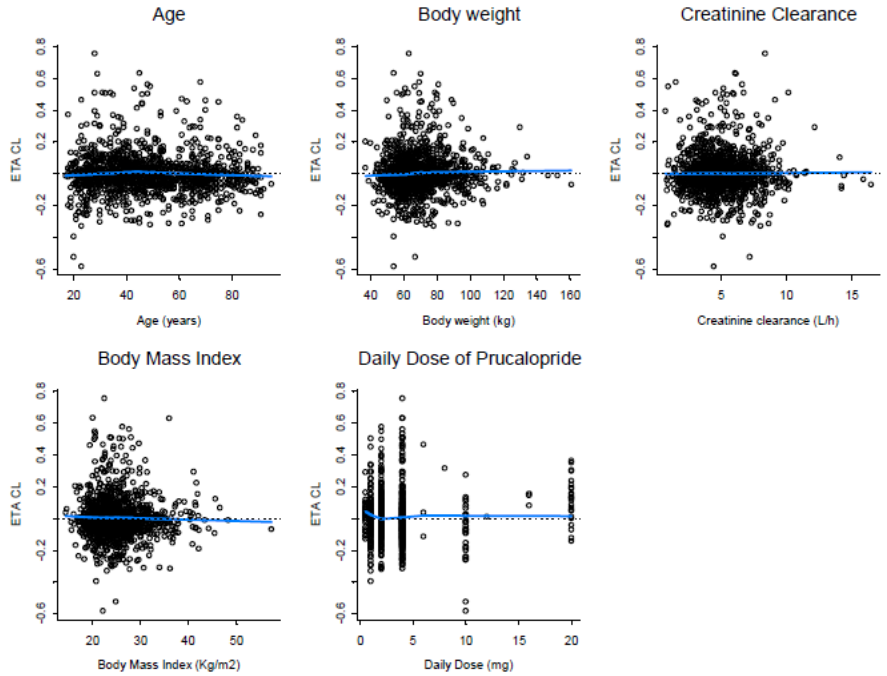
$$\mathrm{CRCL\,[L/h]} = 0.85(females) \cdot 0.073746 \frac{(140 - Age[years]) \cdot \mathrm{Body\ Weight\,[kg]}}{SerumCreatinine[\mu M / L]} \qquad \textbf{Equation 1}$$

Figure 11. Correlations Between AGE, WT, CRCL and BMI



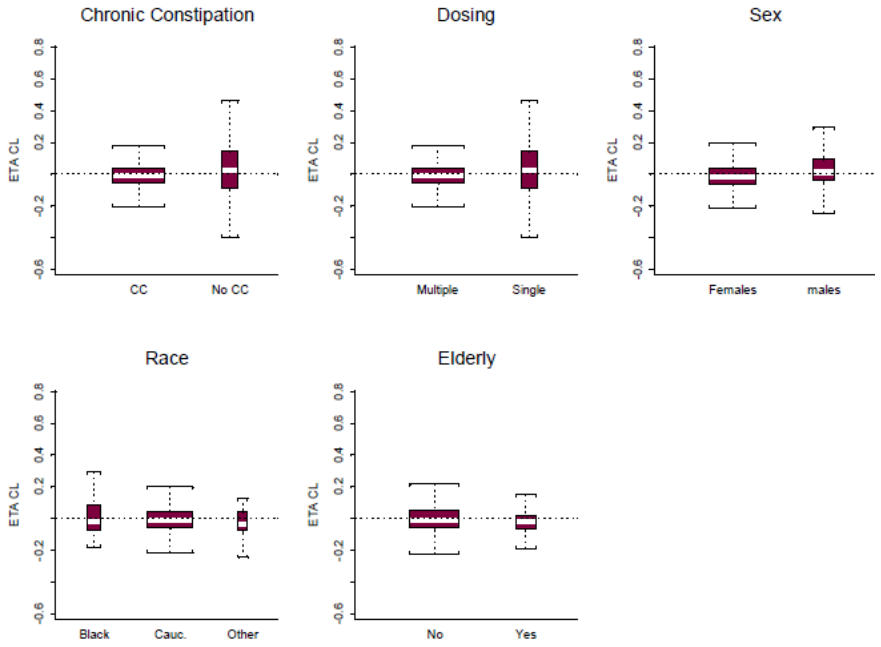
Source: Applicant's Clinical PopPK Modeling Analysis Report (07-mov-045-1011a), Figure 5

Figure 12. Continuous Covariate Relationships for the Random Effect on Prucalopride CL/R



Source: Applicant's Clinical PopPK Modeling Analysis Report (07-mov-045-1011a), Figure23

Figure 13. Categorical Covariate Relationships for the Random Effect on Prucalopride CL/F



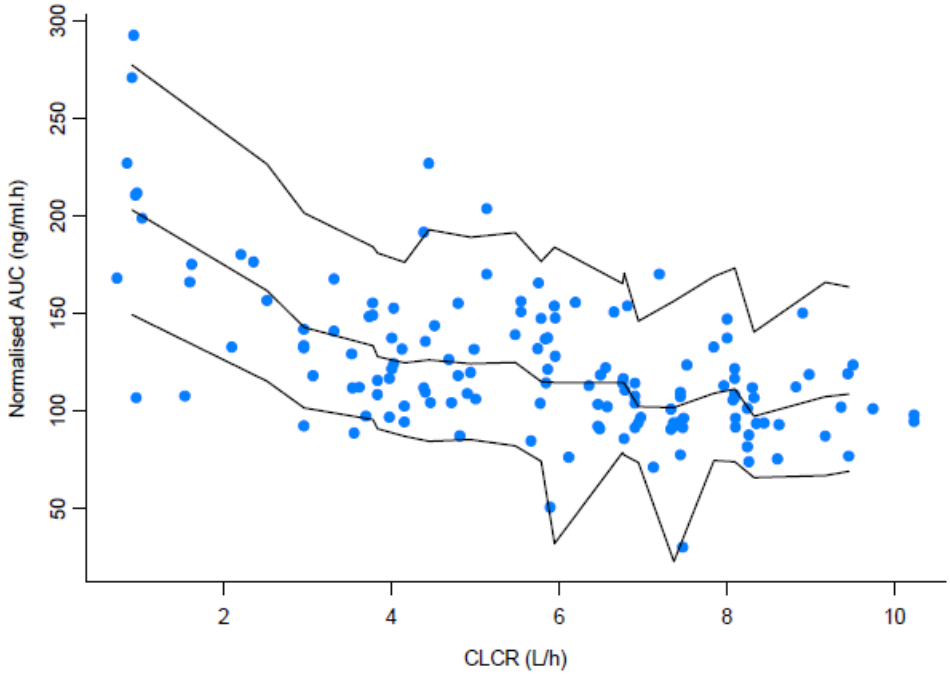
Source: Applicant's Clinical PopPK Modeling Analysis Report (07-mov-045-1011a), Figure 24

Table 82. Prucalopride Parameter Estimates for the Final Model

Parameter	Estimate	SE (CV %) [2]
Structural model RUN0399		
CL/F (L/h) [1]	16.3	~0
V2/F (L)	426	-
K23 (1/h)	0.0127	-
K32 (1/h)	0.0396	-
Ka (1/h)	2.67	-
Lag (h)	0.420	-
Influence of CRCL on CL/F	+0.426	~0
F1 Study 2 dose > 4mg [3]	+0.273	-
F1 CC patients	0.891	1.4
Statistical model		
	IIV (CV %)	SE (CV %)
CL/F	23.3	18
V2/F	28.3	-
K23	94.1	-
K32	75.5	-
Ka	76.5	-
Lag	45.3	-
F1 CC patients	27.2	34
Correlation (V2/F)/Ka	-0.518	
Correlation K23/K32	+0.948	
Proportional error Phase-I data	13.6%	4.6
Proportional error Phase-II-III data	38.9.%	7.0

Source: Applicant's Clinical PopPK Modeling Analysis Report (07-mov-045-1011a), Figure 14

Figure 14. Visual Predictive Check: Comparison of Simulated and Observed Dose-Normalized AUC vs. CRCL

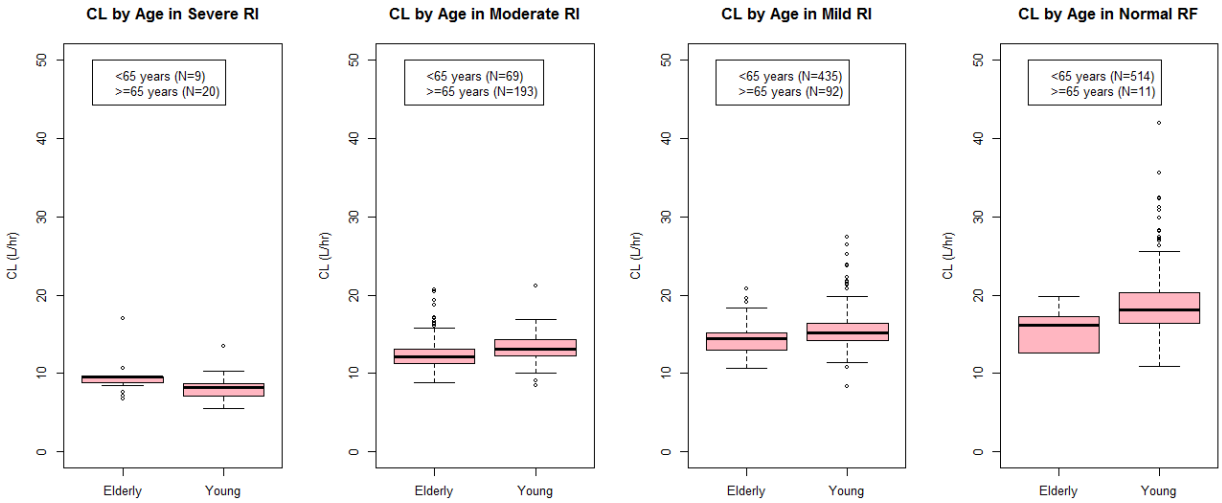


Note: Lines represents the 5, 50 and 95 percentiles of the simulated AUC and dots represent the observed AUC
Source: Applicant's Clinical PopPK Modeling Analysis Report (07-mov-045-1011a), Figure 30

Comments: The effect of creatinine clearance on the apparent clearance of prucalopride appear to be reasonably characterized. Interindividual variability for the apparent clearance and volume of distribution were 23% and 28%, respectively, indicating the final model adequately describe the observed PK data of prucalopride. The visual predictive check confirms the adequacy of the final model. Median creatinine clearance values were 7.4 L/hr and 4.7 L/hr in healthy young subjects and patients with chronic constipation, respectively. Estimates of the apparent oral clearance of prucalopride for these populations were 18.6 L/hr and 15.4 L/hr, respectively. The elimination half-life was estimated to be 29 hrs in healthy young subjects and 33 hours in patients with chronic constipation.

The Applicant proposed a lower dose (1 mg) for severe renal impairment based on results from a dedicated renal impairment study. In addition, the applicant also proposed a starting dose of 1 mg for geriatric patients based on the effect of age (≥65 years) on CL/F of prucalopride. Given the high correlation between age and CRCL (Figure 11), the review team evaluated if there is an additional effect of age on CL/F of prucalopride after accounting for the effect of renal function.

Figure 15. Apparent Clearance of Prucalopride by Age and Renal Function



Source: Reviewer's analysis

As shown in Figure 15, the apparent clearance of prucalopride differ by renal function in both patients <65 years of age and ≥65 years of age. However, the effect of age is not present in patients within each renal function category. These results imply that the effect of age is attributed to effect of renal impairment, and thus there is no need for an additional dose adjustment for elderly patients.

18.3.3. In Vitro Drug Interaction Studies

Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. The potential in vivo drug-drug interaction that was predicted by in-vitro studies were followed up by in-vivo drug interaction studies. See details given in the following sub-sections.

Is the drug a substrate of CYP enzymes and transporters?

CYP enzymes

Yes. Prucalopride is a substrate of CYP3A4. In in vitro studies, [^{14}C]Prucalopride (10µM) was incubated with each human recombinant CYP enzymes (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP3A5). Only CYP3A4 recombinant enzyme at high concentration (150 pmol/mL) metabolized prucalopride to form metabolites which accounted for 2.1% (O-desmethyl prucalopride acid) and 4.7% (N-desalkyl prucalopride) of total chromatogram radioactivity (study report of V5993M-SPD555).

In a mass balance study in healthy subjects, 3.2% and 3.1% of the dose was excreted as O-desmethyl prucalopride acid in urine and feces, respectively.

Transporters

Prucalopride is a substrate of MDR1 (P-gp) and BCRP in vitro. The calculated Km was 116 and 15μM and Vmax was 156 and 25 pmol/min for MDR1 (P-gp) and BCRP in MDCKII-MDR1 and MDCKII-BCRP monolayer cells, respectively. In the presence of verapamil (MDR1 inhibitor) and Ko134 (BCRP inhibitor), the background corrected efflux ratio of prucalopride was reduced from 6.91 to 0 for MDR1 and from 3.37 to -0.04 for BCRP, in addition, the positive control experiments confirmed the function of the transporters.

In vitro prucalopride is not a substrate for OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2K, BSEP and MRP2 (Study report V5981M-SPD555).

Effect of other drugs on prucalopride?

Ketoconazole and other azoles (itraconazole and hydroxy-itraconazole, 10μM) did not inhibit metabolism of prucalopride in human liver microsomes, although prucalopride is the substrate of CYP3A4. The positive control confirmed the function of the enzymes in human liver microsomes.

In addition, ketoconazole dose-dependently reduced the efflux of prucalopride in MDCKII-MDR1 and MDCKII-BCRP cells with an IC_{50} value of 1.85μM and 7.66μM, respectively. In the same assay, ketoconazole inhibited MDR1-mediated digoxin transport and BCRP-mediated prazosin transport with an IC_{50} value of 6.12μM and 11.94μM, respectively (study V6587M-SPD555).

In vivo, multiple doses of ketoconazole increased the prucalopride C_{max} and AUC by approximately 40% (study PRU-NED-6). In in vivo DDI study with ketoconazole, O-desmethyl prucalopride acid, a metabolite formed by CYP3A4 was not measured. The Applicant claimed that the effects of ketoconazole on prucalopride PK is mainly due to p-gp inhibition. However, as the metabolite was not measured to rule out the contribution of CYP3A4 inhibition, a definitive conclusion cannot be drawn.

Effect of prucalopride on other drugs?

In vitro CYP and transporter assays suggested that the potential for prucalopride to affect other drugs is low.

CYP inhibition:

Prucalopride inhibited CYP2D6, with an IC_{50} value of 38μM in vitro (Study report V5994M-SPD555). However, in vivo DDI potential via inhibition of CYP2D6 appears low at the proposed dose based on $C_{max}/IC_{50}=0.02/38=0.0005<0.1$ per FDA DDI guidance. The plasma prucalopride C_{max} of 7.45 ng/mL is equivalent to 0.02μM.

Prucalopride did not directly or time-dependently inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1 and 3A4 at concentrations up to 100μM.

Table 83. Direct and Time-Dependent Inhibition of Cytochrome P450 Enzymes by Prucalopride Succinate

Direct and Time-Dependent Inhibition of Cytochrome P450 Enzymes by Prucalopride Succinate				
		DIRECT INHIBITION		TIME-DEPENDENT INHIBITION
		Prucalopride succinate		Prucalopride succinate
CYP	Substrate	IC_{50} (µM)	% Control activity at 100 µM	Fold Change in IC_{50}
1A2	Phenacetin	>100	101%, 106%	NA
2A6	Coumarin	>100	110%, 135%	NA
2B6	Bupropion	>100	133%, 131%	NA
2C8	Amodiaquine	>100	113%, 103%	NA
2C9	Diclofenac	>100	74%, 79%	NA
2C19	(S)-mephenytoin	>100	88%, 80%	NA
2D6	Dextromethorphan	38	22%, 23%	NA
2E1	Chlorzoxazone	>100	95%, 105%	NA
3A4	Testosterone	>100	83%, 79%	NA
3A4	Midazolam	>100	85%, 87%	NA

For assessment of direct inhibition the following positive control inhibitors were used: 7,8-Benzoflavone (1A2), Tranylcypromine (2A6), Ketoconazole (2B6), Montelukast (2C8), Sulfaphenazole (2C9), S-Benzylnirvanol (2C19), Quinidine (2D6), Chlormethiazole (2E1), and Ketoconazole (3A4).

For assessment of time-dependent inhibition the following positive control inhibitors were used: Furafylline (1A2), 8-Methoxypsoralen (2A6), Ticlopidine (2B6), Gemfibrozil-glucuronide (2C8), Tienilic Acid (2C9), S-fluoxetine (2C19), Paroxetine (2D6), DDTC (2E1) and Azamulin (3A4).

The fold change in IC_{50} was not applicable (NA) for time-dependent inhibition evaluation. This is because there was insufficient inhibition for IC_{50} values to be calculated.

Source: Study report V5994M-SPD555

In vitro CYP induction:

Prucalopride did not induce CYP1A2 and CYP3A4 mRNA expression nor enzyme activity up to 100 µM.

Prucalopride at 10µM caused a maximal 2.5-fold induction in CYP2B6 mRNA which was less than 20% of a prototype inducer (phenobarbital) in primary hepatocytes from three donors (Study report V5995M-SPD555). However, an in vivo drug interaction via induction of CYP2B6 appears unlikely at the proposed dose with mean prucalopride C_{max} of 7.45 ng/mL (equivalent to 0.02 µM).

Transporter inhibition:

In vitro prucalopride did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, BSEP and MRP2 at concentrations up to 300 µM in the transport inhibition assays. Therefore is not likely to translate to an in vivo drug interaction at the prucalopride therapeutic concentration with C_{max} 7.45 ng/mL (equivalent to 0.02 µM) (Study report V5981M-SPD555).

Prucalopride at 50 µM did not inhibit digoxin and prazosin transport in the MDCKII-MDR1 and MDCKII-BCRP monolayer cells. In the vesicular transport assays, the maximum inhibition by prucalopride obtained was 26% and 53% at 300µM (IC_{50} ≥300µM) on MDR1 (P-gp) and BCRP, respectively (Study report V5981M-SPD555).

In vitro, prucalopride inhibited transporters, MATE1 (IC_{50} =4.0μM), OCT2 (IC_{50} =7.8μM) and OCT1 (IC_{50} =9.4μM), and MATE2-K (IC_{50} =69μM). Nevertheless, in vivo drug-drug interaction via inhibition of OCT1, OCT2, MATE1, and MATE2-K is unlikely based on the calculation using the prucalopride C_{max} of 7.45 ng/mL (0.02μM) following 2 mg QD dosage (study report V5981M-SPD555).

Table 84. Transporter Inhibition Data

Transporter	OCT1	OCT2	MATE1	MATE2-K
Calculated IC_{50} (μM)	9.4	7.8	4.0	69
Estimated Ki (μM)	4.7	3.9	2.0	35
Total Plasma C_{max} (μM)	0.020	0.020	0.020	0.020
Unbound Plasma C_{max} (μM)	0.014	0.014	0.014	0.014
Total plasma C_{max}/IC_{50}	0.0021	N/A	0.0050	N/A
Unbound plasma C_{max}/IC_{50}	0.0015	0.0018	0.0035	0.00020
Cut-off for in vivo DDI studies not needed (unbound C_{max}/IC_{50})	<0.1	<0.1	<0.02	<0.02
In vivo DDI study needed (FDA)	No	No	No	No

Abbreviations: C_{max}, maximum plasma concentration; DDI, drug-drug interaction; IC_{50}, concentration to inhibit at 50%; PP, per protocol

18.3.4. PBPK Modeling and Simulation

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK analyses to (1) evaluate the effects of inhibitors and inducers of CYP3A4, P-gp, and BCRP on the PK of prucalopride, and (2) investigate the inhibition effect of prucalopride on metformin (an OCT and MATE substrate), and digoxin (a P-gp substrate).

In vitro, prucalopride is a substrate of P-gp, BCRP, and CYP3A. The Applicant conducted in vivo drug-drug interaction (DDI) studies to evaluate the effect of ketoconazole (a CYP3A, P-gp and BCRP inhibitor) on prucalopride PK, and the effect of prucalopride on digoxin (a P-gp substrate) among many other DDI studies (See the clinical pharmacology review).

Among all the in vivo DDI studies that evaluated the effect of other drugs (cimetidine, probenecid, erythromycin, ketoconazole, and paroxetine) on prucalopride, ketoconazole showed the most profound effect where C_{max} and AUC of prucalopride was increased by 38% and 37%, respectively when it was co-administered with ketoconazole.

In vivo DDI studies that evaluated the effects of prucalopride on other drugs were conducted for warfarin, digoxin, alcohol, erythromycin, paroxetine, and ethinyl estradiol/norethisterone. Prucalopride showed the largest effects on erythromycin among all the drugs evaluated where 40% and 28% increase in erythromycin C_{max} and AUC were observed, respectively.

The Applicant conducted PBPK modeling to evaluate

- the effects of other drugs (ketoconazole, verapamil, cyclosporine, quinidine, and rifampin) on prucalopride PK, and
- the effects of prucalopride on PK of other drugs (metformin, and digoxin).

We conducted additional simulation using the Applicant submitted PBPK models to explore

- the effect of erythromycin (a moderate CYP3A inhibitor) on prucalopride PK,
- the effect of ketoconazole on digoxin PK, and
- the contribution of each pathway (i.e., P-gp/BCRP or CYP3A) to the observed effect of ketoconazole.

Conclusions from the PBPK review are the followings.

- The basic prucalopride PBPK model could describe its PK profiles.
- It is inconclusive regarding which pathway (P-gp/BCRP or CYP3A) was the major contributor to the observed ketoconazole effect on prucalopride PK as in vitro studies and PBPK modeling suggested differently.
- As the effect of rifampin on P-gp and/or BCRP is not clear and the effects of rifampin on P-gp and/or BCRP substrates were not verified, the simulations of rifampin effect on prucalopride PK should be interpreted with caution.

Background

Prucalopride has high aqueous solubility. Following a single oral dose of 2 mg in healthy subjects, prucalopride is rapidly absorbed, reaching peak plasma concentrations within 2 to 3 hours after administration. The absolute oral bioavailability of prucalopride is 93.2%. The plasma protein binding of prucalopride is approximately 30%. These data suggested that prucalopride has high intestinal permeability and the role of P-gp in absorption is expected to be minimal.

In vitro microsomal study showed slow metabolism, and only minor amounts of metabolites are found. Prucalopride is a substrate of the breast cancer resistance protein (BCRP) transporters, P-gp transporters and cytochrome P450 3A4 (CYP3A4). Renal excretion is the main route of elimination of prucalopride. Renal clearance (CL_R) of prucalopride (12.76 (12.02 to 13.54) L/h (GeoMean (95% CI)) involves both passive filtration and active secretion via P-gp and BCRP transporters.

It should be noted that one of the pharmacodynamic effects of prucalopride is reducing colon transit time, which may or may not affect some drug products' absorption. The potential impact of reduced total colon transit time (TCTT) after multiple dose (MD) administration of prucalopride on PK of prucalopride and other co-medications was evaluated in the PBPK analyses.

The Applicant conducted multiple drug-drug interaction studies to evaluate the effects of cimetidine, probenecid, erythromycin, ketoconazole, and paroxetine on prucalopride PK, and the effects of prucalopride on PK of warfarin, digoxin, alcohol, erythromycin, paroxetine, and ethinyl estradiol/norethisterone. The Applicant further conducted PBPK analyses to predict the change in exposure due to co-administration of verapamil (P-gp, BCRP and CYP3A4 inhibitor), cyclosporine (P-gp, BCRP and CYP3A4 inhibitor), quinidine (P-gp and CYP3A4 inhibitor), and

rifampicin (P-gp, BCRP and CYP3A4 inhibitor, P-gp and CYP3A4 inducer). The developed PBPK model for prucalopride was applied to evaluate the effect of prucalopride on PK of metformin (an OCT2 and MATE substrate) and digoxin (a P-gp substrate). Both young (18 to less than 65 years of age) and elderly (65 to 95 years of age) healthy volunteers (HVs) were simulated. The decreased liver and kidney size with age was accounted in the elderly population model.

Methods

Prucalopride model structure and input parameters

- Absorption: Advanced dissolution absorption metabolism (ADAM) model was used so that the intestinal apical efflux transporters, P-gp and BCRP could be incorporated. Prucalopride is known to reduce the TCTT after MD. This effect was considered by reducing the TCTT in MD administration of prucalopride.
- Distribution: Full body PBPK model with 'permeability-limited' liver model (PerL) and permeability limited mechanistic kidney model (Mech KiM)
- Metabolism: 'permeability-limited' liver model
- Excretion: Mech KiM, median clearance from each pathway: 75% renal clearance, 19% CYP3A4, and 6% biliary clearance. A basolateral uptake transporter was manually fitted to recover observed renal clearance as well as amount of prucalopride excreted in the urine unchanged. The elderly population had reduced renal function (lower glomerular filtration rate) compared to the young population.

The input data used for the prucalopride PBPK model are listed in Table 85. The values in bold were used in the final model. The actual TCTTs used in simulation after single dose (SD) and MD are summaries in Table 86. The inhibition and induction values for perpetrators were summarized in Table 87.

Table 85. Input Parameters for the Prucalopride PBPK Model

Parameter	Value/ Model	Comment	Reference / Source
Physicochemical and Blood binding			
MW [g/mol]	**367.87**	Free Base	
Log Po:w [unit less]	**2.25**		(IB-Ed-8); page 21
Compound type	**Diprotic Base**		
pka 1 [unit less]	**8.5**	Piperidine moiety	(IB-Ed-8)
pka 2 [unit less]	**3**	Amino moiety	(IB-Ed-8)
B/P [unit less]	**1.4857**	B/P was fitted as no measured value was available – see section 4.8.2	
B/P – predicted	2.36	Was not used in the final model and is just supplied as information	Simulator V14R1
fu [unit less]	**0.7**		(Product summary); page 7
Main plasma binding protein	**Human serum albumin**	Assumed	
Absorption	**ADAM model**	Required to include intestinal transporter kinetics and to account for Colon transit time changes	(Jamei et al., 2009)
$P_{eff,man}$ estimation model	**MDCK-II passive, apical pH: basolateral pH: 7.4:7.4**		
$P_{app,\ Prucalopride}\ 10^{-6}$ [cm/s]	**20**	see section 4.8.3	
$P_{app,\ Propranolol}\ 10^{-6}$ [cm/s]	**22**	Used as calibrator	
$P_{eff,man\ predicted}\ 10^{-4}$ [cm/s]	2.54	On screen prediction	
Predicted fa [unit less]	0.94	On screen prediction	
Predicted ka [1/h]	1.04	On screen prediction	
***Intestinal transporter*: Apical efflux for ABCB1 (P-gp) and ABCG2 (BCRP)**			
$J_{max,\ P\text{-}gp}$ [pmoL/min/cm^2]	**156**		Shire Ref. No. (V5993M-SPD555) - page 28
$Km_{\ P\text{-}gp}$ [µM]	**116**	$Km_{\ P\text{-}gp}$ is the same in all organs	Shire Ref. No. (V5993M-SPD555) -

			page 28
REF $_{P\text{-}gp}$ [unit less]	**1.5**	Default in Simcyp for MDCK II cells	(Troutman and Thakker, 2003b)
$J_{max, BCRP}$ [pmoL/min/cm^2]	**25**		Shire Ref. No. (V5993M-SPD555) - page 28
Km $_{BCRP}$ [µM]	**15**	Km $_{BCRP}$ is the same in all organs	Shire Ref. No. (V5993M-SPD555) - page 28
REF $_{BCRP}$ [unit less]	**1.14**	Relative to P-gp based upon mRNA	(Gutmann et al., 2005)
Distribution	**Full PBPK – Method 2**	Required to include the permeability-limited model for liver and kidney	(Neuhoff et al., 2013c; Jamei et al., 2014)
Observed V_{ss} [L/kg]	7.99	Not used as input in the final model	(PRU-NED-5; PRU-BEL-32)
Kp scalar	**1**	Default	
Predicted V_{ss} [L/kg]	7.99	On screen prediction; the B/P was adjusted to match the predicted V_{ss} to the observed V_{ss}. See section 4.8.2.	
Hepatic elimination	Enzyme kinetics; PerL	Required to simulate CYP3A4 DDIs and to include a Permeability-limited liver model	(Neuhoff et al., 2013c; Jamei et al., 2014)
CL_{iv} [L/h]	19.02	Not used as input in the final model	(Frampton, 2009)
CL_{po} [L/h]	18.84	Not used as input in the final model	(PRU-NED-5)
$CL_{int, CYP3A4, HLM}$ [µL/min/mg protein]	**1.627** (15%)	See section 4.8.1.	(PRU-BEL-16; SPD555-104)
$fu_{mic, CYP3A4}$ [unit less]	**1**	The Simcyp prediction was 0.85 (@1 mg protein/mL and pH 7.4), however as the CL_{int} value was set to recover the clinical data, the default value of 1 was used.	
$CL_{int, bile}$ [µL/min/10^6 HHEP]	**0.18342** (5.1%)	See section 4.8.1. Value was fitted to match observed CL $_{bile}$ contribution; i.e. 5.1% (range in the BEL-16 study: 3.7-8.1%) was recovered as parent compound in faeces.	(PRU-BEL-16; SPD555-104)
CL_{PD} [µL/min/10^6 HHEP]	**0.1**	Default, i.e. the hepatic uptake is not limited by permeability but by the hepatic blood flow. This value is required for PerL, which than allows more mechanistic description of the biliary clearance process (via	

		transporter kinetics option).	
Renal elimination	**Mech KiM [Apical efflux for ABCB1 (P-gp) and ABCG2 (BCRP); basolateral uptake for SLC22A2 (OCT2)]**	Required to include renal transporter kinetics	(Neuhoff et al., 2013a; Hsu et al., 2014)
CL_R [L/h]	**13.27**	Not used as input in the final model	(PRU-NED-5; SPD555-104, 2014)
$CL_{PD, PTC}$ [µL/min/10^6 PTC]	**0.0016824**	Scaled via surface area, see section 4.8.4.	
fu_{Kidney}	**1**	Default	
fu_{Urine}	**1**	Default	
$CL_{int, OCT2}$ [µL/min/10^6 PTC]	**73**	See section 4.8.4.	
REF $_{OCT2}$ [unit less]	**1**	Default	
$J_{max, P-gp}$ [pmoL/min/10^6 PTC]	**156**	Assuming that 1cm^2 of MDCK-II on Transwell filters are comparable in P-gp activity to 10^6 PTC. The corresponding fitted REF is accounting for the difference in activity between the *in vivo* system and the *in vitro* system (PTC).	Shire Ref. No. (V5993M-SPD555)-page 28
Km $_{P-gp}$ [µM]	**116**	Km $_{P-gp}$ is assumed to be the same in all organs	Shire Ref. No. (V5993M-SPD555) - page 28
REF $_{P-gp}$ [unit less]	**27.95**	See section 4.8.4.	
$J_{max, BCRP}$ [pmoL/min/10^6 PTC]	**25**	Assuming that 1cm^2 of MDCK-II on Transwell filters are comparable in BCRP activity to 10^6 PTC. The corresponding fitted REF is accounting for the difference in activity between the *in vivo* system and the *in vitro* system (PTC).	Shire Ref. No. (V5993M-SPD555) - page 28
Km $_{BCRP}$ [µM]	**15**	Km $_{BCRP}$ is assumed to be the same in all organs	Shire Ref. No. (V5993M-SPD555) - page 28
REF $_{BCRP}$ [unit less]	**21.24**	See section 4.8.4.	
Interaction			
Ki_{OCT1} [µM] (hepatic)	**4.7**	fu_{inc} set to **1**	Shire Ref. No (V5981M-SPD555) – page 30
Ki_{OCT2} [µM] (renal)	**3.9**	fu_{inc} set to **1**	Shire Ref. No (V5981M-SPD555) - page 30
Ki_{MATE1} [µM] (hepatic)	**2**	fu_{inc} set to **1**	Shire Ref. No

			(V5981M-SPD555) - page 30
$Ki_{MATE2-K}$ [µM] (renal)	**35**	fu_{inc} set to **1**	Shire Ref. No (V5981M-SPD555) - page 30
Ki_{P-gp} [µM] (intestinal and hepatic)	**300**	fu_{inc} set to **0.85**, predicted using the Simcyp Simulator V14R1 prediction toolbox for fu_{mic} and assuming comparable binding. This fu_{inc} in combination with a value of 300 µM represents a worst case scenario as at 300 µM prucalopride P-gp activity was still NOT completely inhibited in the *in vitro* assay.	Shire Ref. No (V5981M-SPD555) - page 30

Source: Table 3 of PBPK analyses report V6934M-SHP555

Table 86. The TCTT Used for Simulation of Single Dose and Multiple Dose of Prucalopride

	Healthy volunteer (18-55 years)		Northern European Caucasian (18-95 years)	
SD	Mean TCTT [h]	CV [%]	Mean TCTT [h]	CV [%]
Male & Female	34.5	38	41	72
Male	28.0	48	34.7	65
Female	42.4	33	51.9	74
MD	Mean TCTT [h]	CV [%]	Mean TCTT [h]	CV [%]
Male & Female	25	30	35	30

Source: Table 5 of PBPK analyses report V6934M-SHP555)

Table 87. Inhibition and Induction Parameters for P-gp, BCRP and CYP3A4 Used for the Perpetrator Models

Inhibitor	P-gp			BCRP			CYP 3A4							
	Competitive inhibition		Induction	Competitive inhibition		Induction	Competitive inhibition		MBI			induction		
	K_i [µM]	fu_{inc}	Fold increase in abundance	K_i [µM]	fu_{inc}	Fold increase in abundance	K_i [µM]	fuinc	K_{app}	K_{inac}	fu_{inc}	Ind_{max}	$IndC_{50}$	fu_{inc}
Ketoconazole	0.925*	1	-	3.83	1	-	0.015	0.97	-	-	-	no	-	-
Cyclosporine	0.02	1	-	0.5	1	-	0.89	1; 0.02^	-	-	-	No	-	-
M17	-	-	-	-	-	-	-	-	-	-	-	No	-	-
Quinidine	1	1	-	no	-	-	40	0.58	-	-	-	No	-	-
3-OH-quinidine	-	-	-	-	-	-	-	-	-	-	-	No	-	-
Verapamil	0.1	1	-	25	1	-	-	-	2.21	2	1	No	-	-
Norverapamil	0.3	1	-	no	1	-	-	-	-	-	-	No	-	-
Rifampicin	23.8	1	3.5	2	1	1	15	1	-	-	-	16	0.32	1

Ketoconazole: (Keogh and Kunta, 2006; V6587M-SPD555, 2015) *See Appendix 9 for sensitivity evaluation on this parameter.
Cyclosporine/M17: (Rao and Scarborough, 1994; Ozvegy et al., 2001; Amundsen et al., 2012; Englund et al., 2014) ^See section 5.5 for evaluation of this parameter
Quinidine/ 3-OH-quinidine: (Matsson et al., 2009; Sugimoto et al., 2011)
Verapamil/Norverapamil: (Pauli-Magnus et al., 2000; Matsson et al., 2009; Rowland Yeo et al., 2011b; Ellens et al., 2013)
Rifampicin: (Acocella et al., 1971a; Greiner et al., 1999; Tran et al., 1999; Kajosaari et al., 2005; Gunawan et al., 2013; Prueksaritanont et al., 2014)

Source: Table 4 of PBPK analyses report V6934M-SHP555)

Comments: *Although the B:P was not available at the time of simulation, the fitted value of 1.5 was close to the measured value (1.6, source: page 20 of summary of clinical pharmacology).*

Model development, training, and verification

The population PK model was developed based on prucalopride plasma concentration data for both IV (2 mg) and oral (1 mg and 2 mg) administration in young healthy adults (PRU-BEL-32) and elderly subjects (PRU-NED-5), as well as the ketoconazole drug-drug interaction study (PRU-NED-6). The SD predictive performance of the model was tested and verified using six phase 1 PK studies. The clinical studies used for model development, training and verification are summarized in Table 88.

Table 88. Summary of Clinical Studies Used for Model Development, Training, and Testing

Study	Design	Test set / Training s set	PV
(SPD555-104, 2014).	2 mg SD; fasted; young	Trainings set (mass balance)	00
(PRU-NED-5)	1 mg SD; fasted; young	Trainings set (CLR; Vss)	01, 02
(PRU-NED-5)	1 mg SD; fasted; elderly	Test set	03, 04
(PRU-BEL-16)	0.5 mg SD; fasted; young [^{14}C]	Trainings set (% metabolised)	05
(PRU-BEL-32)	2 mg SD; fasted; young	Test set	06
(PRU-BEL-32)	2 mg SD; 10 min infusion; fasted; young	Trainings set (CL; Vss)	07
(PRU-BEL-32)	2 mg SD; fed; young	Test set	08
(PRU-NED-5)	1 mg MD; young	Trainings set (Ae)	09, 10
(PRU-NED-5)	1 mg MD; elderly	Test set	11, 12
(PRU-NED-11)	4 mg MD; young	Test set	13
(PRU-NED-6)	2mg SD; fasted; young	Test set	14

Abbreviations: PV, Performance Verification
Source: Table 6 of PBPK analyses report V6934M-SHP555

Model application

The verified PBPK models were applied to simulate the scenarios summarized in Table 89.

Table 89. Summary of Simulated Scenarios

Simulations (S)	Design	DDI mechanisms involved
S1	2 mg QD +/- 200 mg BID ketoconazole; elderly with reduced TCTT	inhibitor of CYP3A, P-gp and BCRP
S2, S3	2 mg SD +/- 120 mg TID verapamil	inhibitor of P-gp, BCRP and CYP3A4
S4, S5	2 mg QD +/- 120 mg TID verapamil; with reduced TCTT	
S6 – S7	2 mg QD +/- 200 mg QD cyclosporine; young and elderly with reduced TCTT	inhibitor of P-gp, BCRP and CYP3A4
S8 – S9	2 mg QD +/- 200 mg QD cyclosporine using a fu_{mic} of 0.02 for Ki_{CYP3A4}; young and elderly with reduced TCTT	
S10, S11	SD 2 mg on day 2 +/- 200 mg QD quinidine; young and elderly	inhibitor of P-gp and CYP3A4

Simulations (S)	Design	DDI mechanisms involved
S12	SD 2 mg +/- SD 600 mg rifampicin IV; young	inhibitor of P-gp, BCRP and CYP3A4; inducer of P-gp and CYP3A4
S13	SD 2 mg +/- SD 600 mg rifampicin oral; young	
S14	QD 2 mg +/- 600 mg QD rifampicin oral; young with reduced TCTT	
S15	QD 2 mg +/- 600 mg QD rifampicin oral; elderly with reduced TCTT	
S16, S17	metformin 2 mg QD +/- prucalopride 2 mg QD; young and elderly with reduced TCTT	substrate of OCTs and MATEs
PV13, S18	digoxin (day 1 as 0.25 mg TID, on day 2 as 0.25 mg BID and from day 3 until day 8 as 0.25 mg QD) +/- prucalopride 4 mg QD; young with reduced TCTT	substrate of P-gp

Abbreviations: BID, twice daily; CYP, cytochrome P; MATE, multi-antimicrobial extrusion protein; OCT, organic cation transporter; P-gp, P-glycoprotein; QD, once daily; SD, single dose; TCTT, total colon transit time; TID, three times daily

Comments: The Applicant's overall modeling approach is acceptable.

Results

- **Does prucalopride PBPK models adequately describe the PK profiles of prucalopride in various exposure scenarios?**

Yes. The SD predictive performance of the model was verified using six phase 1 PK studies. All clearance, AUC, C_{max} and tmax predictions were within 20% to 50% of the observed data (Figure 16).

Figure 16. Comparison of Simulated and Observed Prucalopride PK Parameters Following Single Dose Administration

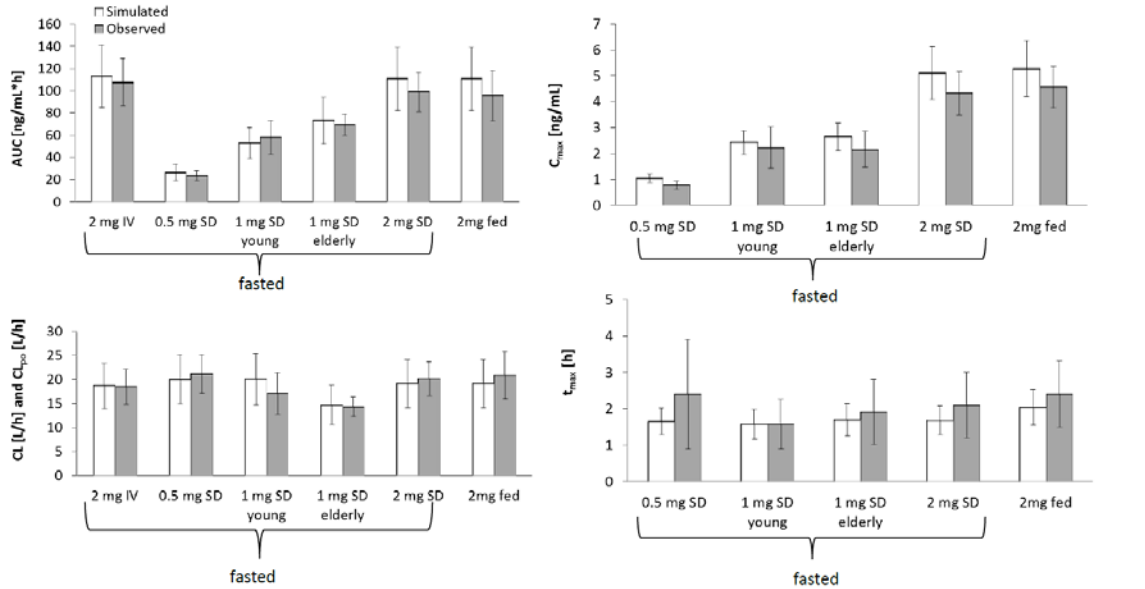
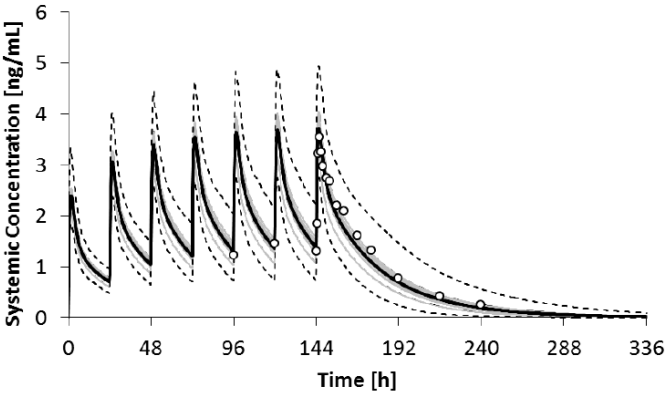


Figure 24 – Comparison of the simulated (white bars) *versus* observed (PRU-NED-5; PRU-BEL-16; PRU-BEL-32) (grey bars) AUC, clearance, c_{max} and t_{max} for prucalopride. Data are reported as mean ± SD; t_{max} data as median values. The urine pH was kept at 7.4 for all simulations unless otherwise indicated; for the 1mg dosing in young and in elderly the urine pH was set to 6.66 and 6.05, respectively. The TCTT was set to 44.3 (CV = 57%) for the 1 mg PO study in the elderly population and to 28 h (CV= 48%) for the 0.5 mg PO study simulated in a young male HV population. All other simulations were using the TCTT of a young Caucasian population of 34.5 h (CV = 38%). Note that the 2 mg IV, 0.5 mg and 1 mg oral SD studies in young individuals were part of the trainings set for the model. The urine pH was set to 7.4 for all simulations.

Source: Figure 24 of PBPK analyses report

Simulated plasma drug concentrations after oral administration of 1 mg prucalopride QD for 7 days were compared with observed data from healthy young (20 to 32 years) and elderly (65 to 81 years) volunteers to verify the MD performance of the model. The AUC, and C_{max} predictions were within 40% of the observed data (Figure 17, and Table 90). The model was also verified against the observed urine excretion (Figures 31 and 32 in the PBPK analyses report).

Figure 17. Simulated Plasma Concentration vs. Time Profiles of Prucalopride (Following Multiple 1 mg QD Oral Doses for 7 Days) in HVs



Abbreviations: HV, healthy volunteer; QD, once daily
Note: The grey thin lines represent simulated individual trials (10) of 12 subjects (20 to 32 years) with a proportion of females of 0.33, the black thin dotted lines represent the upper (95%) and lower (5%) confidence intervals and the solid black line represents the simulated mean of the HV population (n=120). Urine pH was set to 7.4. The white filled circles denote mean values from the clinical study NED-5 (PRU-NED-5)
Source: Figure 26 (A) of PBPK analyses report

Age effect on PK: The model captured the PK differences in young and elderly populations. The model accounts for the reduced renal function in elderly population by lowering the glomerular filtration rate. There was no age-dependent change in transporter expression that has been included in the model. Exposures were about 40% higher (simulated) or 20% higher (observed) in elderly patient due to the reduced kidney function and consequently clearance (Table 7 of PBPK analyses report).

Total colon transit times effect on PK: The changes in prucalopride PK due to reduced TCTT were negligible (Figure 25 of PBPK analyses report). However, PK of other co-medication may be affected by this pharmacodynamic effect of prucalopride, depending on the physicochemical properties, formulation characteristics, and ADME properties of the co-medications.

Tubule pH effect on PK: The model is sensitive to the changes in pH of the filtrate along the nephron as prucalopride is a diprotic base with pKa values of 8.5 and 3. The unionized fraction is reduced when the tubule pH is low and therefore, the passive reabsorption is reduced. When the pH along the nephron was set to 7.4, simulations captured the elimination phase of the observed prucalopride PK profiles and amount of prucalopride excreted in the urine (Figures 11, 12, 26, 28, 31, and 32 in the PBPK analyses report). When the pH along the nephron was set to 6.67 or 6.05, simulations under-predicted the elimination phase of the observed prucalopride PK profiles and over-predicted the amount of prucalopride excreted in the urine (Figures 13, 14, 27, 29, 31, and 32 in the PBPK analyses report). The simulated mean renal clearance was reduced from 29.63 to 13.48 L/h, when the pH was changed from 6.66 to 7.4. In the clinical study (NED-5), the measured urine pH was 6.66 and 6.05 in young and elderly subjects, respectively. The

Applicant stated that the pH in the urine may not be the same as the pH in the filtrate along the nephron. The Applicant kept the pH at the default value of 7.4 for all nephron segments in all DDI simulations as this value provided prediction close to the observed PK.

Table 90. Summary of Simulated (Different Urine pH) and Observed Prucalopride PK Parameters at Steady State Following 1 mg QD in a Young and an Elderly Population

Mean	Young HV population				Geriatric population			
Parameter	Observed[a]	Urine pH7.4	Urine pH6.7	Sim.pH7.4/ Sim.pH6.7	Observed[a]	Urine pH7.4	Urine pH6.7	Sim.pH7.4/ Sim.pH6.7
t_{max} (h)	1.83	1.62	1.48	1.1	2.33	1.72	1.51	1.1
C_{max} (ng/mL)	3.63	3.75	2.74	1.4	4.57	4.64	2.89	1.6
C_{min} (ng/mL)	1.55	1.31	0.55	2.4	2.18	1.89	0.60	3.2
AUC(0,τ) (ng.h/mL)	56.2	52.72	29.21	1.8	72.2	72.03	31.11	2.3
CL/F = Dose/AUC(0,τ) (L/h)	18.84	20.21	37.26	0.5	14.28	14.87	36.11	0.4
$t_{1/2}$ (h)	27.1	33.2	21.4	1.6	31.2	38.7	21.69	1.8
CL_R (L/h)	17.1	12.68	27.91	0.5	13.98	9.53	28.44	0.3

[a] (PRU-NED-5); τ = 24 h

Abbreviations: AUC, area under the curve; CL, clearance; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; PK, pharmacokinetic; QD, once daily; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration
Source: modified from Table 11 of PBPK analyses report

- **Does the PBPK model support the statement that the effect of ketoconazole was "likely due to the inhibition of the P-gp and BCRP renal transporters"?**

No. The effect of ketoconazole on prucalopride PK was likely due to the inhibition of CYP3A based on the reviewer's analysis using the Applicant submitted models. However, based on in vitro studies, ketoconazole did not alter prucalopride metabolism. Therefore, it is inconclusive regarding which pathway (P-gp/BCRP or CYP3A) was the major contributor to the observed ketoconazole effect on prucalopride PK as in vitro studies and PBPK modeling suggested differently.

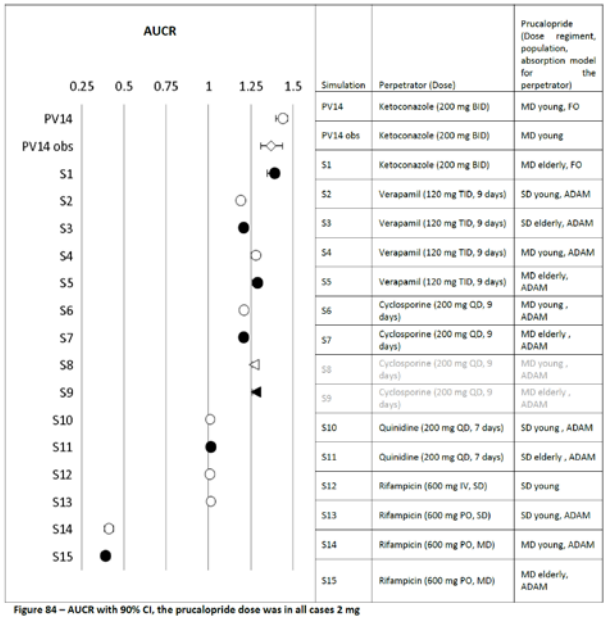
The overall effect of ketoconazole (a P-gp, BCRP, and CYP3A inhibitor) on prucalopride PK was verified against a clinical DDI study. The simulated C_{max}R and AUCR were close to the observed values (Figure 18). The Applicant further simulated the effects of verapamil, cyclosporine, quinidine, and rifampin on prucalopride PK (Figure 18). Simulation suggested that the level of DDI in the young and elderly populations were similar. Therefore, our DDI analysis was only conducted in young healthy subjects to evaluate the contribution from each pathway (i.e., P-gp/BCRP, and CYP3A) to the overall observed DDI effects.

To further confirm the CYP3A contribution to prucalopride clearance, we conducted a DDI simulation to evaluate the effect of erythromycin on prucalopride PK. The erythromycin model was the default model in Simcyp Version 17 which only incorporated its inhibition effect on CYP3A. The simulation suggested that erythromycin (500 mg BID for 7 days) increased prucalopride (2 mg QD for 7 days) C_{max} and AUC by 15% and 24%, respectively. In Study PRU-NED-14, erythromycin (500 mg BID for 7 days) did not show effect on prucalopride with C_{max}

ratio of 1.05, and AUC ratio of 1.02. Simulation slightly overpredicted observed erythromycin effect on prucalopride PK but was within 25% prediction error.

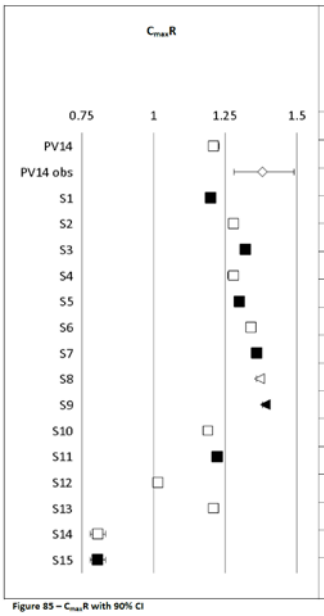
Ideally, the inhibition effect of ketoconazole for each pathway (P-gp/BCRP, and CYP3A) should be verified against a sensitive substrate of that specific pathway. The modulation effect of ketoconazole on CYP3A has been established by DDI studies between ketoconazole and other CYP3A substrates. In the current submission, only the overall effect of ketoconazole was verified against a clinical DDI study. A search in the University of Washington (UW) Drug Interaction Database for the effect of ketoconazole on digoxin suggested ketoconazole (200 mg per day for 4 days) increased digoxin (0.5 mg) AUC by 9% (Larsen UL, et al. 2007). We conducted a DDI simulation to evaluate the effect of ketoconazole on digoxin (a P-gp substrate) PK using the Applicant submitted ketoconazole and digoxin models. The simulation suggested that ketoconazole (200 mg QD for 4 days) would increase digoxin C_{max} and AUC by 19% and 7%, respectively.

Figure 18. Simulated AUCR and C_{max}R of prucalopride When Co-Administered With Ketoconazole (Observed Data Available), Verapamil, Cyclosporine, Quinidine, and Rifampin



Simulation	Perpetrator (Dose)	Prucalopride (Dose regiment, population, absorption model for the perpetrator)
PV14	Ketoconazole (200 mg BID)	MD young, FO
PV14 obs	Ketoconazole (200 mg BID)	MD young
S1	Ketoconazole (200 mg BID)	MD elderly, FO
S2	Verapamil (120 mg TID, 9 days)	SD young, ADAM
S3	Verapamil (120 mg TID, 9 days)	SD elderly, ADAM
S4	Verapamil (120 mg TID, 9 days)	MD young, ADAM
S5	Verapamil (120 mg TID, 9 days)	MD elderly, ADAM
S6	Cyclosporine (200 mg QD, 9 days)	MD young , ADAM
S7	Cyclosporine (200 mg QD, 9 days)	MD elderly , ADAM
S8	Cyclosporine (200 mg QD, 9 days)	MD young , ADAM
S9	Cyclosporine (200 mg QD, 9 days)	MD elderly , ADAM
S10	Quinidine (200 mg QD, 7 days)	SD young , ADAM
S11	Quinidine (200 mg QD, 7 days)	SD elderly , ADAM
S12	Rifampicin (600 mg IV, SD)	SD young
S13	Rifampicin (600 mg PO, SD)	SD young, ADAM
S14	Rifampicin (600 mg PO, MD)	MD young, ADAM
S15	Rifampicin (600 mg PO, MD)	MD elderly, ADAM

Figure 84 – AUCR with 90% CI, the prucalopride dose was in all cases 2 mg



Simulation	Perpetrator (Dose)	Prucalopride (Dose regiment, population, absorption model for the perpetrator)
PV14	Ketoconazole (200 mg BID)	MD young, FO
PV14 obs	Ketoconazole (200 mg BID)	MD young
S1	Ketoconazole (200 mg BID)	MD elderly, FO
S2	Verapamil (120 mg TID, 9 days)	SD young, ADAM
S3	Verapamil (120 mg TID, 9 days)	SD elderly, ADAM
S4	Verapamil (120 mg TID, 9 days)	MD young, ADAM
S5	Verapamil (120 mg TID, 9 days)	MD elderly, ADAM
S6	Cyclosporine (200 mg QD, 9 days)	MD young , ADAM
S7	Cyclosporine (200 mg QD, 9 days)	MD elderly , ADAM
S8	Cyclosporine (200 mg QD, 9 days)	MD young , ADAM
S9	Cyclosporine (200 mg QD, 9 days)	MD elderly , ADAM
S10	Quinidine (200 mg QD, 7 days)	SD young , ADAM
S11	Quinidine (200 mg QD, 7 days)	SD elderly , ADAM
S12	Rifampicin (600 mg IV, SD)	SD young
S13	Rifampicin (600 mg PO, SD)	SD young, ADAM
S14	Rifampicin (600 mg PO, MD)	MD young, ADAM
S15	Rifampicin (600 mg PO, MD)	MD elderly, ADAM

Figure 85 – C_{max}R with 90% CI

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; PO, oral; QD, once daily; TID, three times daily
Source: Figure 84 and 85 of PBPK simulation report

The proposed labeling stated that ketoconazole's effect on prucalopride PK was likely due to the inhibition of the P-gp and BCRP renal transporters, and similar magnitude may be expected with other potent P-gp or BCRP inhibitors, such as verapamil, cyclosporine A, and quinidine. Based on in vitro studies, those drugs (ketoconazole, verapamil, cyclosporine A, and quinidine) all have effects on P-gp, BCPR, and CYP3A (see Table 91) more or less. To evaluate whether the statement is appropriate, the reviewer conducted further analyses.

First, the inhibition potential was estimated by $C_{max,u,ss}$/Ki for each perpetrator against each transporter / enzyme (Table 91). The $C_{max,ss}$ values for each perpetrator were obtained from a

trial simulation, and were considered close to the observed values as the perpetrator PK models were verified. As shown in Table 91, ketoconazole has the most potent inhibition potential for CYP3A while cyclosporine has the most potent inhibition potential for P-gp based on the $C_{max,u,ss}$ / Ki values.

Table 91. Comparison of Inhibition Potentials for Various Perpetrators

						P-gp	BCRP	CYP3A	P-gp	BCRP	CYP3A	Cmax,ss source
	MW (g/mol)	Dose (mg)	Cmax, ss (ug/mL)	fup	Cmax,u, ss (uM)	Ki (uM)	Ki (uM)	Ki (uM)	inhibition potential	inhibition potential	inhibition potential	
ketoconazole	531.4	200 BID	4.53	0.029	0.25	0.925	3.83	0.015	0.27	0.06	16.48	sn-05d-prucalopride-v14r1-md-2mg-young-keto200bid-ned-6-001.xlsx
cyclosporine	1202	200 QD	1.17	0.036	0.04	0.02	0.5	0.89	1.75	0.07	0.04	sn07d2-1-prucalopride-v14r1-md-2mg-young-cycloa200qdm17-wks.xlsx
M17	1218		0.99	0.031	0.03	-	-	-	-	-	-	
quinidine	324.4	200 QD	1.1	0.203	0.69	1	-	40	0.69	-	0.02	sn-31d2-1-prucalopride-v14r1-sd-2mg-young-quinidine-metabol.xlsx
3-OH-quinidine	340.4		0.28	0.281	0.23	-	-	-	-	-	-	
verapamil	454.6	120 TID	0.29	0.091	0.06	0.1	25	-	0.58	0.00	-	sn18d1-prucalopride-v14r1-sd-2mg-young-vera-norvera-12-tid-.xlsx
norverapamil	440.6		0.09	0.080	0.02	0.3	-	-	0.05	-	-	
rifampin	823	600 QD	8.5	0.116	1.20	23.8	2	15	0.05	0.60	0.08	sn-23d2-1-prucalopride-v14r1-sd-2mg-young-rifampicin-md-cor.xlsx

Abbreviations: BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; CYP, cytochrome P; Ki, inh bitory constant; P-gp, P-glycoprotein; QD, once daily; TID, three times daily

Second, the ketoconazole (the most potent CYP3A inhibitor among the perpetrators simulated) and cyclosporine (the most potent P-gp/BCRP inhibitor among the perpetrators simulated) inhibition effects on prucalopride were evaluated separately by shutting down one pathway at a time. As illustrated by Table 92, shutting down the P-gp/BCRP inhibition effect of ketoconazole and cyclosporine did not change the $C_{max}R$ and AUCR much compared to the default models which incorporated both the P-gp/BCRP and CYP3A pathways. On the other hand, shutting down the CYP3A inhibition effect of ketoconazole brought the $C_{max}R$ and AUCR closer to 1, and shutting down the CYP3A inhibition effect of cyclosporine brought the AUCR close to 1.

Table 92. Summary of Simulated Prucalopride Geometric Mean C_{max} and AUC Ratios When It Was Co-Administered With Ketoconazole or Cyclosporine

Perpetrator	Model features	$C_{max}R$	AUCR	Workspace*
Ketoconazole (200 mg BID)	Default model	1.22	1.43	sn-05d-prucalopride-v14r1-md-2mg-young-keto200bid-ned-6-bcr.wksz
	No P-gp/BCRP interaction	1.22	1.43	
	No CYP3A interaction	1.04	1.00	
Cyclosporine (200 mg QD)	Default model	1.37	1.34	sn07d1-1-prucalopride-v14r1-md-2mg-young-cycloa200qdm17.wksz
	No P-gp/BCRP interaction	1.14	1.32	
	No CYP3A interaction	1.22	1.00	

Abbreviations: AUC, area under the curve; BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; CYP, cytochrome P; P-gp, P-glycoprotein; QD, once daily
*The workspace files used for simulations were provided by the Applicant with modifications by the reviewer

Finally, the PK of prucalopride was simulated by shutting off the P-gp transporter and BCRP transporter pathways. The simulation was conducted for multiple dosing of 1 mg prucalopride. Generally, the level of efflux transporters involvement in drug PK decreases with the increasing dose levels as transporters may get saturated at higher dose levels. In vivo study results indicated that the PK of prucalopride are dose-proportional in the studied dose range from 1 to 6 mg, after single dosing and at steady-state. Simulations (Table 93) also suggested that the P-gp/BCRP pathways did not have much impact on prucalopride PK.

Table 93. Summary of Simulated Prucalopride C_{max} and AUC Following Multiple Dosing of 1 mg Prucalopride When P-gp/BCRP Are Not Involved

Model features	C_{max} (ng/mL)	AUC (ng*hr/mL)	Workspace*
Default model	3.28	84.16	sn-03d-prucalopride-v14r1-7md-1mg-young-ned-5.wksx
No intestinal P-gp/BCRP	3.94	84.31	
No kidney intestinal P-gp/BCRP	3.29	84.47	
No intestinal and kidney P-gp/BCRP	3.94	84.62	

Abbreviations: AUC, area under the curve; BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; P-gp, P-glycoprotein
*The workspace file used for simulations was provided by the Applicant with modifications by the reviewer. One trial consisted of 12 subjects was simulated

Overall, our analyses suggested that the ketoconazole effect on prucalopride PK was likely due to the inhibition of CYP3A. As such, a P-gp/BCRP inhibitor is not expected to have much impact on the prucalopride PK. This was further confirmed by our sensitivity analyses on the inhibition potential (Ki). As shown in Table 94, when the Ki values for P-gp/BCRP were lowered by 10-fold, or when cyclosporine dose was increased by 2-fold, the simulated prucalopride C_{max} and AUC ratios were still less than 2 suggesting that prucalopride PK is less likely to be affected by a P-gp/BCRP inhibitor. However, ketoconazole did not show effects on prucalopride metabolism in in vitro studies. It is inconclusive regarding which pathway (P-gp/BCRP or CYP3A) was the major contributor to the observed ketoconazole effect on prucalopride PK as in vitro studies and PBPK modeling suggested differently.

Table 94. Summary of Simulated Prucalopride C_{max} and AUC Ratios When It Was Co-Administered With Cyclosporine Using Different Ki Values for P-gp/BCRP, and Dose Levels of Cyclosporine

Model Features	C_{max}R	AUCR	Workspace
Default model	1.37	1.34	sn07d1-1-prucalopride-v14r1-md-2mg-young-cycloa200qdm17.wksz
10-fold lower Ki (P-gp/BCRP) values	1.40	1.38	
2-fold higher dose (400 mg QD)	1.43	1.48	
10-fold lower Ki (P-gp/BCRP) values and 2-fold higher dose (400 mg QD)	1.47	1.58	

Abbreviations: AUC, area under the curve; BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; P-gp, P-glycoprotein; QD, once daily

- **Can the PBPK model be used to predict the effect of rifampicin (P-gp, BCRP and CYP3A4 inhibitor, P-gp and CYP3A4 inducer) on prucalopride PK?**

No. Although rifampin is a commonly used CYP3A inducer, its effects on P-gp and BCRP have not been well studied. The Applicant did not provide verification of rifampin effects on P-gp and BCRP. Ideally, the verification should be conducted with a P-gp substrate with minimal CYP3 metabolism, such as digoxin.

We conducted a query in the UW Drug Interaction Database. There were 7 reports suggested that rifampin may decrease digoxin AUC by 15 to 30%, and 2 reports suggested that rifampin may increase digoxin AUC by 30 to 46%. Overall, the effect of rifampin on P-gp and/or BCRP is not clear and the rifampin model on P-gp and/or BCRP substrates has not been verified. The simulations of rifampin effect on prucalopride PK should be interpreted with caution.

- **Does the PBPK model support that the effect of prucalopride on metformin is minimal?**

No. Metformin is a substrate of OCTs and MATEs. There was a concern that the metformin model may under-estimate the MATE-mediated clearance (Center For Drug Evaluation And Research 2018). Therefore, the PBPK model could not be used to simulate the effect of prucalopride on metformin.

- **Does the PBPK model support that the in vivo inhibition effect of prucalopride on a P-gp substrate is minimal?**

No. Prucalopride showed P-gp inhibition potential in vitro. DDI simulation suggested that digoxin C_{max} and AUC ratios were 1.0, and 1.0, respectively, when it was co-administered with prucalopride. The in vivo DDI study showed that the C_{max} and AUC_{tau} ratios were 96.6% (90% CI: 88.1-106%), and 89.8% (90% CI: 84.4-95.7%), respectively, when digoxin was co-administered with prucalopride compared to being administered alone. It was speculated that the slight decrease in AUC_{tau} could be due to the pharmacological change in TCTT after multiple dosing of prucalopride. Simulations indicated that a decrease in TCTT caused a very small decrease in the absorption of digoxin. As the PBPK model did not capture the small decrease in AUC_{tau} when digoxin was co-administered with prucalopride, the Applicant hypothesized that other mechanisms, such as interference with the bacteria in the GI tract (*Eubacterium lentum*), which is known to affect digoxin luminal metabolism and in turn absorption might be involved and to be included in the model.

Conclusions

The basic prucalopride PBPK model is adequate to describe prucalopride PK profiles. It is inconclusive regarding which pathway (P-gp/BCRP or CYP3A) was the major contributor to the observed ketoconazole effect on prucalopride PK as in vitro studies and PBPK modeling suggested differently. As the effect of rifampin on P-gp and/or BCRP is not clear and the rifampin model on P-gp and/or BCRP substrates was not verified, the simulations of rifampin's effect on prucalopride PK should be interpreted with caution.

18.3.5. Individual Study Review

Individual study review for PK and in vitro studies are presented in a separate document.[1]

[1] Refer to the OCP Review Memo for NDA 210166 in DARRTS.

18.4. Age, Race, Sex Analyses for Six Studies

18.4.1. Age

Table 95. Subgroup Analysis by Age for Common Treatment Emergent Adverse Events in Studies 302 (Safety Population) and 3001 (ITT Population)

	STUDY 302				Study 3001			
	PLACEBO		PRU		PLACEBO		PRU	
PREFERRED TERM	<65	>=65	< 65	>=65	< 65	>=65	< 65	>=65
HEADACHE	4 (2.2%)	3 (1.6%)	14 (7.6%)	3 (1.6%)	5 (2.0%)	0 (0.0%)	31 (12.4%)	0 (0.0%)
ABDOMINAL PAIN	8 (4.3%)	6 (3.2%)	10 (5.4%)	2 (1.1%)	14 (5.6%)	0 (0.0%)	29 (11.6%)	0 (0.0%)
DIARRHOEA	3 (1.6%)	0 (0.0%)	7 (3.8%)	5 (2.7%)	20 (7.9%)	0 (0.0%)	55 (22.1%)	0 (0.0%)
NAUSEA	3 (1.6%)	1 (0.5%)	8 (4.3%)	3 (1.6%)	8 (3.2%)	0 (0.0%)	29 (11.6%)	0 (0.0%)
DIZZINESS	0 (0.0%)	3 (1.6%)	3 (1.6%)	1 (0.5%)	4 (1.6%)	0 (0.0%)	5 (2.0%)	0 (0.0%)
VOMITING	2 (1.1%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	2 (0.8%)	0 (0.0%)	4 (1.6%)	0 (0.0%)
FATIGUE	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	2 (0.8%)	0 (0.0%)	2 (0.8%)	0 (0.0%)

Abbreviations: PRU, prucalopride
Source: Reviewer's Table created in J-Review

Table 96. Subgroup Analysis by Age for Common Treatment Emergent Adverse Events in Studies USA-11, USA-13, and INT-6 (Safety Population)

	Study USA-11						Study USA-13						Study INT-6					
	PLACEBO		PRU 2mg		PRU mg		PLACEBO		PRU 2mg		PRU mg		PLACEBO		PRU 2mg		PRU mg	
PREFERRED TERM	< 65	>=65	< 65	>=65	< 65	>=65	< 65	>=65	< 65	>=65	< 65	>=65	< 65	>=65	< 65	>=65	< 65	>=65
HEADACHE	22 (10.5%)	2 (1.0%)	8 (23.2%)	6 (2.9%)	54 (26.5%)	7 (3.4%)	32 (15.1%)	0 (0.0%)	48 (22.4%)	6 (2.8%)	51 (23.7%)	3 (1.4%)	38 (15.8%)	2 (0.8%)	60 (25.0%)	2 (0.8%)	65 (27.3%)	6 (2.5%)
ABDOMINAL PAIN	43 (20.6%)	4 (1.9%)	8 (23.2%)	1 (0.5%)	47 (23.0%)	8 (4.0%)	24 (11.3%)	1 (0.5%)	36 (16.8%)	4 (1.9%)	35 (16.3%)	2 (0.9%)	44 (18.3%)	3 (1.3%)	59 (24.8%)	2 (0.8%)	46 (19.3%)	6 (2.5%)
DIARRHOEA	11 (5.3%)	1 (0.5%)	25 (12.1%)	3 (1.4%)	35 (17.2%)	3 (1.5%)	7 (3.3%)	0 (0.0%)	22 (10.3%)	3 (1.4%)	27 (12.6%)	1 (0.5%)	10 (4.2%)	2 (0.8%)	31 (13.0%)	0 (0.0%)	27 (11.3%)	3 (1.3%)
NAUSEA	15 (7.2%)	2 (1.0%)	39 (18.8%)	7 (3.4%)	37 (18.1%)	7 (3.4%)	13 (6.1%)	3 (1.4%)	23 (10.7%)	3 (1.4%)	40 (18.6%)	4 (1.9%)	30 (12.5%)	3 (1.3%)	53 (22.3%)	4 (1.7%)	51 (21.4%)	5 (2.1%)
DIZZINESS	6 (2.9%)	0 (0.0%)	15 (7.2%)	2 (1.0%)	12 (5.9%)	2 (1.0%)	4 (1.9%)	0 (0.0%)	7 (3.3%)	1 (0.5%)	1 (0.5%)	3 (1.4%)	4 (1.7%)	0 (0.0%)	12 (5.0%)	0 (0.0%)	7 (2.9%)	3 (1.3%)
VOMITING	2 (1.0%)	2 (1.0%)	14 (6.8%)	0 (0.0%)	10 (4.9%)	0 (0.0%)	4 (1.9%)	1 (0.5%)	9 (4.2%)	0 (0.0%)	9 (4.2%)	1 (0.5%)	10 (4.2%)	1 (0.4%)	10 (4.2%)	1 (0.4%)	16 (6.7%)	0 (0.0%)
FATIGUE	4 (1.9%)	0 (0.0%)	4 (1.9%)	0 (0.0%)	4 (2.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	5 (2.3%)	0 (0.0%)	4 (1.9%)	0 (0.0%)	6 (2.5%)	0 (0.0%)	11 (4.6%)	1 (0.4%)	11 (4.6%)	3 (1.3%)

Abbreviations: PRU, prucalopride
Note: For Study USA-11, the preferred terms abdominal pain, abdominal pain upper, abdominal tenderness, abdominal discomfort, abdominal pain lower, stomach discomfort, epigastric discomfort, and gastrointestinal pain were combined. For Study USA-13, abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and stomach discomfort were combined. For Study INT-6, abdominal pain, abdominal pain upper, abdominal tenderness, stomach discomfort, abdominal discomfort, abdominal pain lower, and epigastric discomfort were combined
Source: Reviewer's Table created in J-Review

Table 97. Subgroup Analysis by Age for Common Treatment Emergent Adverse Events in Study 401 (Safety Population)

	Study 401			
	PLACEBO		PRU	
PREFERRED TERM	< 65	>=65	< 65	>=65
HEADACHE	8 (4.4%)	2 (1.1%)	17 (9.4%)	4 (2.2%)
ABDOMINAL PAIN	10 (5.6%)	1 (0.6%)	20 (11.0%)	3 (1.7%)
DIARRHOEA	2 (1.1%)	2 (1.1%)	7 (3.9%)	0 (0.0%)
NAUSEA	5 (2.8%)	2 (1.1%)	11 (6.1%)	2 (1.1%)
DIZZINESS	3 (1.7%)	1 (0.6%)	2 (1.1%)	1 (0.6%)
VOMITING	4 (2.2%)	0 (0.0%)	3 (1.7%)	0 (0.0%)
FATIGUE	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)

Abbreviations: PRU, prucalopride
Note: The preferred terms abdominal pain, abdominal pain upper, and gastrointestinal discomfort were combined.
Source: Reviewer's Table created in J-Review

18.4.2. Sex

Table 98. Subgroup Analysis by Sex for Common Treatment Emergent Adverse Events in Studies 302 (Safety Population) and 3001 (ITT Population)

	STUDY 302				Study 3001			
	PLACEBO		PRU		PLACEBO		PRU	
PREFERRED TERM	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
HEADACHE	7 (3.8%)	0 (0.0%)	17 (9.2%)	0 (0.0%)	1 (0.4%)	4 (1.6%)	1 (0.4%)	30 (12.0%)
ABDOMINAL PAIN	14 (7.5%)	0 (0.0%)	12 (6.5%)	0 (0.0%)	1 (0.4%)	13 (5.2%)	2 (0.8%)	27 (10.8%)
DIARRHOEA	3 (1.6%)	0 (0.0%)	12 (6.5%)	0 (0.0%)	3 (1.2%)	17 (6.7%)	5 (2.0%)	50 (20.1%)
NAUSEA	4 (2.2%)	0 (0.0%)	11 (6.0%)	0 (0.0%)	1 (0.4%)	7 (2.8%)	1 (0.4%)	28 (11.2%)
DIZZINESS	3 (1.6%)	0 (0.0%)	4 (2.2%)	0 (0.0%)	0 (0.0%)	4 (1.6%)	1 (0.4%)	4 (1.6%)
VOMITING	3 (1.6%)	0 (0.0%)	3 (1.6%)	0 (0.0%)	0 (0.0%)	2 (0.8%)	0 (0.0%)	4 (1.6%)
FATIGUE	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	2 (0.8%)	0 (0.0%)	2 (0.8%)

Abbreviations: ITT, intention to treat; PRU, prucalopride
Note: For Study 302, the preferred terms abdominal pain, abdominal pain upper, abdominal discomfort, and gastrointestinal pain were combined. For Study 3001, the preferred terms abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, and epigastric discomfort were combined.
Source: Reviewer's Table created in J-Review

Table 99. Subgroup Analysis by Sex for Common Treatment Emergent Adverse Events in Studies USA-11, USA-13, and INT-6 (Safety Population)

	Study USA-11						Study USA-13						Study INT-6					
	PLACEBO		PRU 2mg		PRU 4mg		PLACEBO		PRU 2mg		PRU 4mg		PLACEBO		PRU 2mg		PRU mg	
PREFERRED TERM	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
HEADACHE	2 (1.0%)	22 (10.5%)	3 (1.4%)	51 (24.6%)	3 (1.5%)	58 (28.4%)	1 (0.5%)	31 (14.6%)	5 (2.3%)	49 (22.9%)	6 (2.8%)	48 (22.3%)	1 (0.4%)	39 (16.3%)	2 (0.8%)	59 (24.8%)	4 (1.7%)	67 (28.2%)
ABDOMINAL PAIN	0 (0.0%)	47 (22.5%)	1 (0.5%)	48 (23.2%)	6 (2.9%)	49 (24.0%)	1 (0.5%)	24 (11.3%)	7 (3.3%)	33 (15.4%)	3 (1.4%)	34 (15.8%)	4 (1.7%)	43 (17.9%)	6 (2.5%)	56 (23.5%)	3 (1.3%)	49 (20.6%)
DIARRHOEA	1 (0.5%)	11 (5.3%)	2 (1.0%)	26 (12.6%)	4 (2.0%)	34 (16.7%)	1 (0.5%)	6 (2.8%)	4 (1.9%)	21 (9.8%)	3 (1.4%)	25 (11.6%)	0 (0.0%)	12 (5.0%)	2 (0.8%)	29 (12.2%)	2 (0.8%)	28 (11.8%)
NAUSEA	1 (0.5%)	16 (7.7%)	1 (0.5%)	45 (21.7%)	3 (1.5%)	41 (20.1%)	2 (0.9%)	14 (6.6%)	3 (1.4%)	23 (10.7%)	1 (0.5%)	43 (20.0%)	2 (0.8%)	31 (12.9%)	2 (0.8%)	55 (23.1%)	2 (0.8%)	54 (22.7%)
DIZZINESS	0 (0.0%)	6 (2.9%)	1 (0.5%)	16 (7.7%)	4 (2.0%)	10 (4.9%)	0 (0.0%)	4 (1.9%)	3 (1.4%)	5 (2.3%)	1 (0.5%)	3 (1.4%)	0 (0.0%)	4 (1.7%)	1 (0.4%)	11 (4.6%)	3 (1.3%)	7 (2.9%)
VOMITNG	1 (0.5%)	3 (1.4%)	0 (0.0%)	14 (6.8%)	1 (0.5%)	9 (4.4%)	0 (0.0%)	5 (2.4%)	1 (0.5%)	8 (3.7%)	0 (0.0%)	10 (4.7%)	0 (0.0%)	11 (4.6%)	0 (0.0%)	11 (4.6%)	2 (0.8%)	14 (5.9%)
FATIGUE	0 (0.0%)	4 (1.9%)	0 (0.0%)	4 (1.9%)	0 (0.0%)	5 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.3%)	1 (0.5%)	3 (1.4%)	2 (0.8%)	4 (1.7%)	2 (0.8%)	10 (4.2%)	1 (0.4%)	13 (5.5%)

Abbreviation: PRU, prucalopride
Note: For Study USA-11, the preferred terms abdominal pain, abdominal pain upper, abdominal tenderness, abdominal discomfort, abdominal pain lower, stomach discomfort, epigastric discomfort, and gastrointestinal pain were combined. For Study USA-13, abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and stomach discomfort were combined. For Study INT-6, abdominal pain, abdominal pain upper, abdominal tenderness, stomach discomfort, abdominal discomfort, abdominal pain lower, and epigastric discomfort were combined.
Source: Reviewer's Table created in J-Review

Table 100. Subgroup Analysis by Age for Common Treatment Emergent Adverse Events in Study 401 (Safety Population)

	Study 401			
	PLACEBO		PRU	
PREFERRED TERM	MALE	FEMALE	MALE	FEMALE
HEADACHE	0 (0.0%)	10 (5.6%)	2 (1.1%)	19 (10.5%)
ABDOMINAL PAIN	0 (0.0%)	11 (6.1%)	0 (0.0%)	23 (12.7%)
DIARRHOEA	1 (0.6%)	3 (1.7%)	0 (0.0%)	7 (3.9%)
NAUSEA	0 (0.0%)	7 (3.9%)	1 (0.6%)	12 (6.6%)
DIZZINESS	0 (0.0%)	4 (2.2%)	1 (0.6%)	2 (1.1%)
VOMITING	0 (0.0%)	4 (2.2%)	0 (0.0%)	3 (1.7%)
FATIGUE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)

Abbreviation: PRU, prucalopride
Note: The preferred terms abdominal pain, abdominal pain upper, and gastrointestinal discomfort were combined.
Source: Reviewer's Table created in J-Review

18.4.3. Race

Table 101. Subgroup Analysis by Race/Ethnicity for Common Treatment Emergent Adverse Events in Studies 302 (Safety Population) and 3001 (ITT Population)

	STUDY 302									
	PLACEBO					PRU				
PREFERRED TERM	ASIAN	BLACK	OTHER	WHITE	HISPANIC	ASIAN	BLACK	OTHER	WHITE	HISPANIC
HEADACHE	0 (0 0%)	1 (0.5%)	0 (0.0%)	6 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (9.2%)	0 (0.0%)
ABDOM NAL PA N	1 (0 5%)	1 (0.5%)	0 (0.0%)	12 (6.5%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	11 (6.0%)	0 (0.0%)
DIARRHOEA	0 (0 0%)	0 (0.0%)	0 (0.0%)	3 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (6.5%)	0 (0.0%)
NAUSEA	0 (0 0%)	0 (0.0%)	0 (0.0%)	4 (2.2%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	10 (5.4%)	0 (0.0%)
DIZZ NESS	0 (0 0%)	0 (0.0%)	0 (0.0%)	3 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (2.2%)	0 (0.0%)
VOMITING	1 (0 5%)	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
FATIGUE	0 (0 0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)
	Study 3001									
	PLACEBO					PRU				
PREFERRED TERM	ASIAN	BLACK	OTHER	WHITE	HISPANIC	ASIAN	BLACK	OTHER	WHITE	HISPANIC
HEADACHE	5 (2 0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	24 (9.6%)	0 (0.0%)	0 (0.0%)	7 (2.8%)	0 (0.0%)
ABDOM NAL PA N	11 (4.4%)	0 (0.0%)	0 (0.0%)	3 (1.2%)	0 (0.0%)	26 (10.4%)	0 (0.0%)	0 (0.0%)	3 (1.2%)	0 (0.0%)
DIARRHOEA	20 (7.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	53 (21.3%)	0 (0.0%)	1 (0.4%)	1 (0.4%)	0 (0.0%)
NAUSEA	5 (2 0%)	0 (0.0%)	1 (0.4%)	2 (0.8%)	0 (0.0%)	27 (10.8%)	0 (0.0%)	0 (0.0%)	2 (0.8%)	0 (0.0%)
DIZZ NESS	4 (1 6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
VOMITING	0 (0 0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)	0 (0.0%)	3 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
FATIGUE	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	2 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: ITT, intention to treat; PRU, prucalopride
Note: For Study 302, the preferred terms abdominal pain, abdominal pain upper, abdominal discomfort, and gastrointestinal pain were combined. For Study 3001, the preferred terms abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, and epigastric discomfort were combined.
Source: Reviewer's Table created in J-Review

Table 102. Subgroup Analysis by Race/Ethnicity for Common Treatment Emergent Adverse Events in Studies USA-11, USA-13, and INT-6 (Safety Population)

	Study USA-11														
	PLACEBO					PRU 2mg					PRU 4mg				
PREFERRED TERM	ASIAN	BLACK	OTHER	WHITE	HISPANIC	ASIAN	BLACK	OTHER	WHITE	HISPANIC	ASIAN	BLACK	OTHER	WHITE	HISPANIC
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	24 (11.5%)	0 (0.0%)	0 (0.0%)	6 (2.9%)	0 (0.0%)	46 (22.2%)	2 (1.0%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	57 (27.9%)	2 (1.0%)
ABDOMINAL PAIN	1 (0.5%)	5 (2.4%)	2 (1.0%)	37 (17.7%)	1 (0.5%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	44 (21.3%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	50 (24.5%)	1 (0.5%)
DIARRHOEA	0 (0.0%)	0 (0.0%)	1 (0.5%)	11 (5.3%)	0 (0.0%)	0 (0.0%)	3 (1.4%)	0 (0.0%)	24 (11.6%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (17.6%)	2 (1.0%)
NAUSEA	0 (0.0%)	1 (0.5%)	1 (0.5%)	15 (7.2%)	0 (0.0%)	0 (0.0%)	5 (2.4%)	0 (0.0%)	40 (19.3%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	43 (21.1%)	0 (0.0%)
DIZZINESS	0 (0.0%)	1 (0.5%)	0 (0.0%)	5 (2.4%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	15 (7.2%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	12 (5.9%)	1 (0.5%)
VOMITING	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (6.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (4.4%)	1 (0.5%)
FATIGUE	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.9%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	4 (2.0%)	0 (0.0%)
	Study USA-13														
	PLACEBO					PRU 2mg					PRU 4mg				
PREFERRED TERM	ASIAN	BLACK	OTHER	WHITE	HISPANIC	ASIAN	BLACK	OTHER	WHITE	HISPANIC	ASIAN	BLACK	OTHER	WHITE	HISPANIC
HEADACHE	0 (0.0%)	2 (0.9%)	0 (0.0%)	28 (13.2%)	2 (0.9%)	0 (0.0%)	4 (1.9%)	0 (0.0%)	49 (22.9%)	1 (0.5%)	0 (0.0%)	6 (2.8%)	1 (0.5%)	46 (21.4%)	1 (0.5%)
ABDOMINAL PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	25 (11.8%)	0 (0.0%)	0 (0.0%)	3 (1.4%)	1 (0.5%)	36 (16.8%)	0 (0.0%)	0 (0.0%)	5 (2.3%)	1 (0.5%)	30 (14.0%)	1 (0.5%)
DIARRHOEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (3.3%)	0 (0.0%)	0 (0.0%)	2 (0.9%)	0 (0.0%)	22 (10.3%)	1 (0.5%)	0 (0.0%)	7 (3.3%)	1 (0.5%)	20 (9.3%)	1 (0.5%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (7.5%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	24 (11.2%)	1 (0.5%)	0 (0.0%)	5 (2.3%)	1 (0.5%)	36 (16.7%)	2 (0.9%)
DIZZINESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.4%)	1 (0.5%)
VOMITING	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.4%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	7 (3.3%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (4.2%)	1 (0.5%)
FATIGUE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.9%)	0 (0.0%)
	Study INT-6														
	PLACEBO					PRU 2mg					PRU 4mg				
PREFERRED TERM	ASIAN	BLACK	OTHER	WHITE	HISPANIC	ASIAN	BLACK	OTHER	WHITE	HISPANIC	ASIAN	BLACK	OTHER	WHITE	HISPANIC
HEADACHE	0 (0.0%)	0 (0.0%)	2 (0.8%)	38 (15.8%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)	59 (24.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	68 (28.6%)	2 (0.8%)
ABDOMINAL PAIN	0 (0.0%)	0 (0.0%)	2 (0.8%)	45 (18.8%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)	60 (25.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	50 (21.0%)	1 (0.4%)
DIARRHOEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	31 (13.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	28 (11.8%)	1 (0.4%)
NAUSEA	1 (0.4%)	1 (0.4%)	1 (0.4%)	30 (12.5%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	2 (0.8%)	54 (22.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	53 (22.3%)	2 (0.8%)
DIZZINESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	11 (4.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	9 (3.8%)	0 (0.0%)
VOMITING	0 (0.0%)	1 (0.4%)	0 (0.0%)	10 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (4.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (6.7%)	0 (0.0%)
FATIGUE	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (5.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	13 (5.5%)	0 (0.0%)

Abbreviation: PRU, prucalopride
Note: For Study USA-11, the preferred terms abdominal pain, abdominal pain upper, abdominal tenderness, abdominal discomfort, abdominal pain lower, stomach discomfort, epigastric discomfort, and gastrointestinal pain were combined. For Study USA-13, abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and stomach discomfort were combined. For Study INT-6, abdominal pain, abdominal pain upper, abdominal tenderness, stomach discomfort, abdominal discomfort, abdominal pain lower, and epigastric discomfort were combined.
Source: Reviewer's Table created in J-Review

Table 103. Subgroup Analysis by Age for Common Treatment Emergent Adverse Events in Study 401 (Safety Population)

PREFERRED TERM	Study 401									
	PLACEBO					PRU				
	ASIAN	BLACK	OTHER	WHITE	HISPANIC	ASIAN	BLACK	OTHER	WHITE	HISPANIC
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (5.6%)	0 (0 0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	20 (11.0%)	2 (1.1%)
ABDOMINAL PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (4.4%)	0 (0 0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	22 (12.2%)	2 (1.1%)
DIARRHOEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (2.2%)	0 (0 0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (3.9%)	0 (0.0%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.8%)	0 (0 0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	11 (6.1%)	0 (0.0%)
DIZZINESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (2.2%)	0 (0 0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.7%)	0 (0.0%)
VOMIT NG	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.7%)	0 (0 0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.7%)	0 (0.0%)
FATIGUE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0 0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)

Abbreviation: PRU, prucalopride
Note: The preferred terms abdominal pain, abdominal pain upper, and gastrointestinal discomfort were combined.
Source: Reviewer's Table created in J-Review

18.5. Integrated Summary of Safety Analyses

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, SAEs, treatment-emergent adverse events (TEAEs), and discontinuations due to 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 poststudy.

Deaths- ISS

There were eight total deaths among patients in Pool D and Pool E; seven deaths occurred in patients receiving prucalopride. In Pool D, there were two deaths in the prucalopride group, and 1 in placebo, and in Pool E, there were five deaths (in open-label trials). The causes of death included lobar pneumonia, respiratory failure, bronchitis, myocardial infarction (MI), and suicide. No deaths occurred double blind period of 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 two 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. [2]

- 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 SAE 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, noninsulin dependent diabetes, and CV accident died of an MI on day 48 of the open-label study while on prucalopride 4 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. The narrative for this patient in described above in Section 10.6.

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

- A 40-year-old female with a history of depression, drug-dependency, and drug abuse died by completed suicide by hanging 52 days posttreatment with prucalopride 4 mg. The narrative for this patient is described above in Section 10.6.

None of these cases were attributed to the study drug by the investigators. However, for the two completed suicides, the reasons for which prucalopride was discontinued are not stated and it cannot be ascertained if the patients developed psychiatric symptoms including suicidal ideation while on prucalopride because the studies did not include prospective assessment or active ascertainment of suicidal ideation and behavior. The concern for development of psychiatric symptoms as the reason for discontinuation of prucalopride is particularly relevant for the 70-year-old male because antidepressants were started around the time prucalopride was discontinued (30 days or 1 month prior to the completed suicide), so it is possible he developed recurrent or new psychiatric symptoms on prucalopride. Initiation of antidepressants does not guarantee the avoidance of suicidal behavior. Therefore, the causal contribution of prucalopride to the suicides cannot be excluded.

Serious Treatment-Emergent Adverse Events- ISS

The serious treatment-emergent events that occurred in Pool D are summarized in the table below.

Table 104. Serious TEAEs in at Least Two 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.

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

Treatment-Emergent Adverse Events- ISS

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 GI 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.

18.6. Study Overview and Patient Narratives

Table 105. 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

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

Table 106. Narratives of CIC Patients Treated With Prucalopride With Standard MACE

#	Event	Narrative
1	Nonfatal Stroke	77-year-old male patient with a medical history of hypertension started treatment with prucalopride 2 mg daily in a study investigating the efficacy of prucalopride in patients 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 patient 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 patient 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 patient 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 patient'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 patient 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 patient rolled over from a 4-week double-blind study, where he was randomized to prucalopride 4 mg. Total duration of treatment 272 days. On (b) (6), the patient discontinued intake of the study medication. On (b) (6), the patient died due to myocardial infarction (MI) (67 days after discontinuing prucalopride). The patient was not hospitalized prior to his death. No other TEAEs were reported for this patient 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 patient'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 patient rolled over from a 12-week double-blind study, where she was randomized to prucalopride. Total duration of treatment 190 days in the open-label study. During the study, the patient 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 to 220) and 212 (50 to 190), respectively, and her blood pressure was 140/90 mm Hg. The patient 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 patient rolled over from a 12-week double-blind study, where she was randomized to placebo. In December 1998, the patient was diagnosed with a torn rotator cuff. On (b) (6) (112 days of treatment), the patient was hospitalized and had the cuff repaired. The intake of study medication was temporarily interrupted (prucalopride 4 mg). While in the hospital, the patient started experiencing chest pain. She also experienced shortness of breath, palpitations, and diaphoresis. An ECG was performed and revealed anterior T-wave inversions. The patient was diagnosed with a MI. Troponin and myoglobin levels were elevated. The patient was started on intravenous heparin and topical nitrates. This event was reported as a serious TEAE, considered severe in intensity. On (b) (6), the patient underwent a diagnostic cardiac catheterization that showed the circumflex coronary artery was 85% stenosed. The patient was treated with heparin sodium and on (b) (6) (b) (6) a stent was inserted. The patient 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 patients with chronic idiopathic constipation and started treatment on (b) (6). On (b) (6), after 12 weeks of treatment, the patient 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 patient 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 in the open-label study, the patient 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 patient rolled over from a 12-week double-blind study, where she was randomized to prucalopride. The patient 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 patient experienced a right-sided stroke and was hospitalized. Cerebrovascular accident was reported as a serious TEAE, considered moderate in intensity. After the event, the patient 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 patient 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 patient 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 patient 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 patient rolled over from a 4-week double-blind study, where he was randomized to prucalopride. On (b) (6), the patient was hospitalized with a MI. The patient 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.

Abbreviations: AE, adverse event; BMI, body mass index; ECG, electrocardiogram; MI, myocardial infarction; QD, daily; TEAE, treatment-emergent adverse event
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

18.7. Analyses of Efficacy Appendix

Table 107. Patients Disposition in Studies 3001 and 302 (ITT/mITT Population)

	Study PRU-CRC-3001			Study SPD555-302		
	PLA N = 252	PRU 2 mg N = 249	Total N = 501	PLA N = 181	PRU ≤2 mg N = 177	Total N = 358
	n (%)					
Completed	231 (91.7)	231 (92.8)	462 (92.2)	160 (85.6)	158 (84.5)	318 (85.0)
Withdrawn	21 (8.3)	18 (7.2)	39 (7.8)	27 (14.4)	29 (15.5)	56 (15.0)
Withdrawal of consent	8 (3.2)	3 (1.2)	11 (2.2)	9 (4.8)	10 (5.3)	19 (5.1)
AE	3 (1.2)	8 (3.2)	11 (2.2)	7 (3.7)	6 (3.2)	13 (3.5)
Noncompliance	0	0	0	5 (2.7)	4 (2.1)	9 (2.4)
Lost to follow-up	2 (0.8)	3 (1.2)	5 (1.0)	0	2 (1.1)	2 (0.5)
Lack of efficacy	6 (2.4)	0	6 (1.2)	0	0	0
Protocol violation	2 (0.8)	2 (0.8)	4 (0.8)	0	0	0
Selection criteria not met	0	0	0	3 (1.6)	1 (0.5)	4 (1.1)
Noncompliance of study drug	0	1 (0.4)	1 (0.2)	0	0	0
Other	0	1 (0.4)	1 (0.2)	3 (1.6)	5 (2.7)	8 (2.1)
Sponsor decision	0	0	0	0	1 (0.5)	1 (0.3)

Abbreviations: PLA, placebo; PRU, prucalopride
Source: Applicant's Table 8 of integrated-summary-of-efficacy.pdf, verified by the reviewer

Table 108. Patients Disposition in Studies INT-6, USA-11, and USA-13 (ITT Population)

	PRU-INT-6				PRU-USA-11				PRU-USA-13			
	PLA N = 240	PRU 2 mg N = 238	PRU 4 mg N = 238	Total N = 716	PLA N = 209	PRU 2 mg N = 207	PRU 4 mg N = 204	Total N = 620	PLA N = 212	PRU 2 mg N = 214	PRU 4 mg N = 215	Total N = 641
	n (%)											
Completed	207 (86.3)	207 (87.0)	183 (76.9)	597 (83.4)	182 (87.1)	172 (83.1)	173 (84.8)	527 (85.0)	188 (88.7)	194 (90.7)	185 (86.0)	567 (88.5)
Withdrawn	33 (13.8)	31 (13.0)	55 (23.1)	119 (16.6)	27 (12.9)	35 (16.9)	31 (15.2)	93 (15.0)	24 (11.3)	20 (9.3)	30 (14.0)	74 (11.5)
Withdrawal of consent	5 (2.1)	5 (2.1)	8 (3.4)	18 (2.5)	7 (3.3)	3 (1.4)	5 (2.5)	15 (2.4)	5 (2.4)	4 (1.9)	7 (3.3)	16 (2.5)
AE	16 (6.7)	15 (6.3)	35 (14.7) [a]	66 (9.2)	4 (1.9)	18 (8.7)	16 (7.8)	38 (6.1)	5 (2.4)	8 (3.7)	13 (6.0)	26 (4.1)
Noncompliance	1 (0.4)	0	2 (0.8)	3 (0.4)	4 (1.9)	4 (1.9)	4 (2.0)	12 (1.9)	1 (0.5)	4 (1.9)	3 (1.4)	8 (1.2)
Lost to follow-up	1 (0.4)	3 (1.3)	2 (0.8)	6 (0.8)	3 (1.4)	3 (1.4)	2 (1.0)	8 (1.3)	2 (0.9)	3 (1.4)	2 (0.9)	7 (1.1)
Lack of efficacy [b]	7 (2.9)	3 (1.3)	5 (2.1)	15 (2.1)	5 (2.4)	2 (1.0)	1 (0.5)	8 (1.3)	3 (1.4)	1 (0.5)	0	4 (0.6)
Other	2 (0.8)	4 (1.7)	2 (0.8)	8 (1.1)	4 (1.9)	2 (1.0)	3 (1.5)	9 (1.5)	5 (2.4)	0	5 (2.3)	10 (1.6)
Ineligible to continue	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)	0	3 (1.4)	0	3 (0.5)	3 (1.4)	0	0	3 (0.5)

Abbreviations: AE, adverse event; ITT, intention to treat; PLA, placebo; PRU, prucalopride
Source: Applicant's Table 9 of integrated-summary-of-efficacy.pdf, verified by the reviewer

Table 109. Patients Disposition in Study 401 (All Randomized Population)

	Study SPD555-401		
	PLA N = 182	PRU 2 mg N = 182	Total N = 364
	n (%)		
Completed	126 (69.2)	135 (74.2)	261 (71.7)
Withdrawn	56 (30.8)	47 (25.8)	103 (28.3)
Withdrew consent	27 (14.8)	11 (6.0)	38 (10.4)
AE	10 (5.5)	14 (7.7)	24 (6.6)
Sponsor's decision	9 (4.9)	12 (6.6)	21 (5.8)
Other	6 (3.3)	8 (4.4)	14 (3.8)
Did not fulfill inclusion/exclusion criteria	2 (1.1)	2 (1.1)	4 (1.1)
Non-compliance	2 (1.1)	0	2 (0.5)

Abbreviations: AE, adverse event; PLA, placebo; PRU, prucalopride
Source: Applicant's Table 10 of integrated-summary-of-efficacy.pdf, verified by the reviewer

Table 110. Summary of Demographics for Study 302 in mITT Population

Characteristic	PLA N=181	PRU ≤2 mg N=177	Total N=358
Age, years			
Mean (StdDev)	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 (StdDev)	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)

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

Table 111. Summary of Demographics for Study 3001 in ITT Population

Characteristic	PLA N=252	PRU 2 mg N=249	Total N=501
Age, years			
Mean (StdDev)	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 (StdDev)	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)

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

Table 112. Summary of Demographics for Studies INT-6, USA 11 and 13 in ITT Population

	PRU-INT-6		PRU-USA-11		PRU-USA-13	
Characteristic	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)

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

Table 113. Summary of Demographics for Study 401 in ITT Population

Characteristic	Placebo N=169	PRU ≤2 mg N=171	Total N=340
Age (years)			
Mean (StdDev)	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 (StdDev)	24.8 (4.34)	25.4 (4.80)	25.1 (4.58)

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

Table 114. Summary of Baseline Disease Characteristics for Study 302 in mITT Population

Characteristic	PLA N=181	PRU ≤2 mg N=177	Total N=358
History of constipation, years			
Mean (StdDev)	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)

Characteristic	PLA N=181	PRU ≤2 mg N=177	Total N=358
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 (%)			
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)

Abbreviations: BM, bowel movement; max, maximum; min, minimum; mITT, modified intent-to-treat; N, number of patients in treatment group; n, number of patients 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
Source: Applicant's Table 14 on Pages 74-75 of integrated-summary-of-efficacy.pdf, verified by the reviewer

Table 115. Summary of Baseline Disease Characteristics for Study 3001 in ITT Population

Characteristic	PLA N=252	PRU 2 mg N=249	Total N=501
History of constipation, years			
Mean (StdDev)	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)

Characteristic	PLA N=252	PRU 2 mg N=249	Total N=501
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			
<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)

Abbreviations: BM, bowel movement; ITT, intent-to-treat; max, maximum; min, minimum; NA, not applicable; N, number of patients in treatment group; n, number of patients with characteristic; PLA, placebo; PRU, prucalopride; SBM, spontaneous bowel movement; StdDev, standard deviation
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

Table 116. 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	
Characteristic	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 (StdDev)	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)

Characteristic	PRU-INT-6 PLA N=240	PRU-INT-6 PRU 2 mg N=238	PRU-USA-11 PLA N=209	PRU-USA-11 PRU 2 mg N=207	PRU-USA-13 PLA N=212	PRU-USA-13 PRU2 mg N=214
Percentage of BMs that are hard/very hard, n (%)						
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)

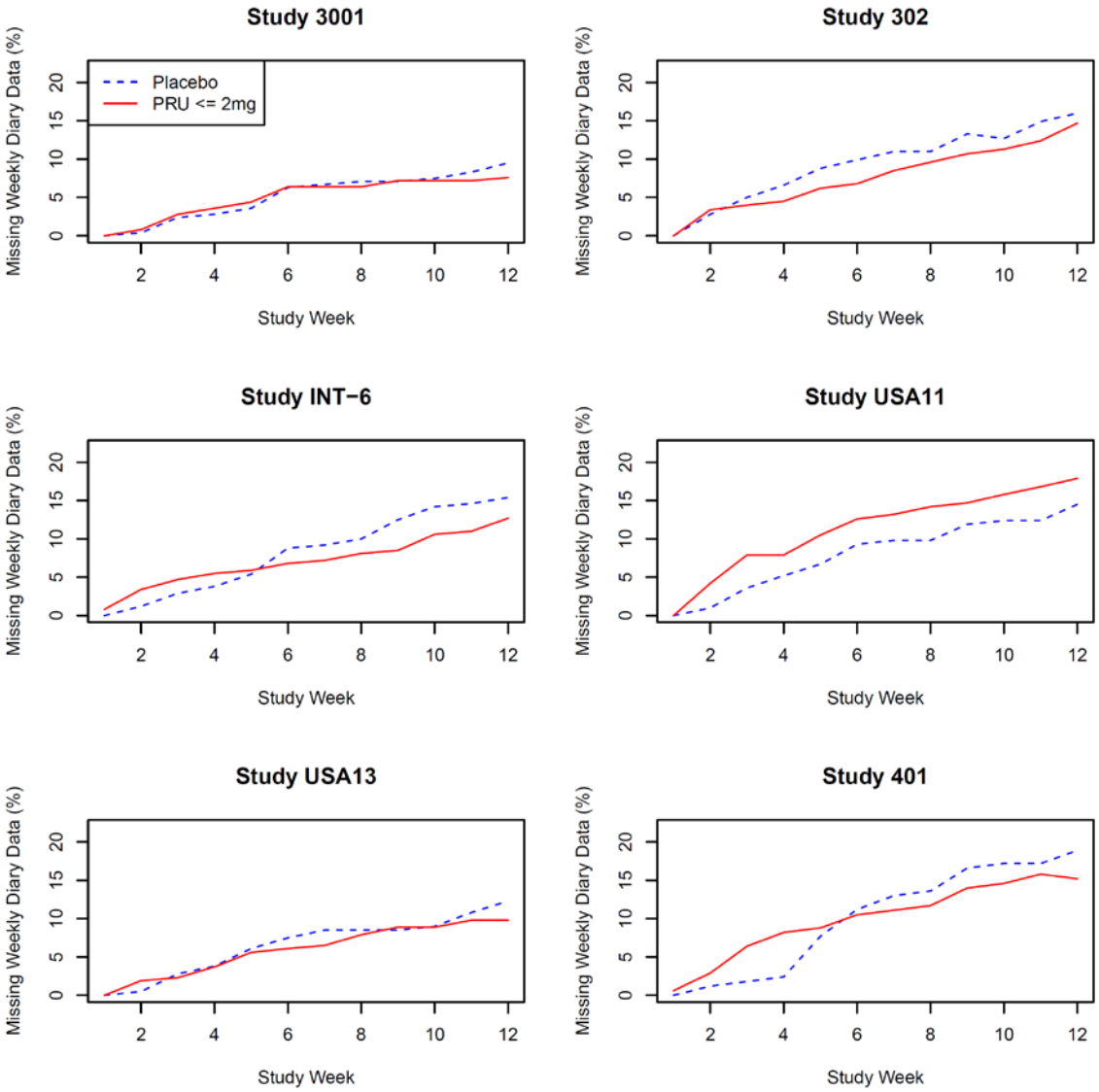
Abbreviations: BM, bowel movement; ITT, intent-to-treat; max, maximum; min, minimum; N, number of patients in treatment group; n, number of patients with characteristic; PLA, placebo; PRU, prucalopride; SBM, spontaneous bowel movement; StdDev, standard deviation
Source: Applicant's Table 15 on Pages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

Table 117. Summary of Baseline Disease Characteristics for Study 401 in ITT Population

Characteristic	Placebo N=169	PRU ≤2 mg N=171	Total N=340
Duration of constipation (years)			
Patients with available data	135	135	270
Mean (StdDev)	14.1 (13.33)	16.3 (16.00)	15.2 (14.74)
Number of baseline SCBMs per week			
Patients 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)
Patient'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)

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

Figure 19. Distribution of Missing Weekly Diary Records by Week During Weeks 1 to 12 in Each Study



Abbreviation: PRU, prucalopride

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Babatunde. E Akinshola, Ph.D.	ODE 3/DGIEP	Sections: Section 5	**Select one:** _X_ Authored ___ Approved
	Signature: Babatunde Akinshola -S Digitally signed by Babatunde Akinshola -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000342685, cn=Babatunde Akinshola -S Date: 2018.12.07 16:01:41 -05'00'			
Nonclinical Supervisor	Sushanta Chakder, Ph.D.	ODE 3/DGIEP	Sections: Section 5	**Select one:** ___ Authored _X_ Approved
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Nonclinical Associate Director	Ronald Wange, Ph.D.	OND IO	Sections: Section 5	**Select one:** ___ Authored _X_ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Shen Li, Ph.D.	OTS/OCP/DCPIII	Sections: 6 & Appendix 18.3	**Select one:** _X_ Authored ___ Approved
	Signature: Shen Li -S Digitally signed by Shen Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shen Li -S, 0.9.2342.19200300.100.1.1=2001772066 Date: 2018.12.11 10:47:25 -05'00'			
Clinical Pharmacology Team Leader	Insook Kim, Ph.D.	OTS/OCP/DCPIII	Section: 6 & Appendix 18.3	**Select one:** _X_ Authored _X_ Approved
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Clinical Pharmacology Director	Shirley Seo, Ph.D.	OTS/OCP/DCPIII	Section: 6 & Appendix 18.3	**Select one:** ___ Authored _X_ Approved
	Signature: Shirley K. Seo -S Digitally signed by Shirley K. Seo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shirley K. Seo -S, 0.9.2342.19200300.100.1.1=1300365375 Date: 2018.12.12 08:39:20 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer (in vitro and BE)	Jie Cheng, Ph.D.	OTS/OCP/DCPIII	Sections: Appendix 18.3.3	**Select one:** _X_ Authored ___ Approved
	Signature: Jie Cheng -S (Affiliate) Digitally signed by Jie Cheng -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=00135 73366, cn=Jie Cheng -S (Affiliate) Date: 2018.12.11 11:04:14 -05'00'			
Pharmacometrics Reviewer	Jee Eun Lee, Ph.D.	OTS/OCP/DPM	Sections: Appendix 18.3.2	**Select one:** _X_ Authored ___ Approved
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Pharmacometrics Team Leader	Lian Ma, Ph.D.	OTS/OCP/DPM	Sections: Appendix 18.3.2	**Select one:** ___ Authored _X_ Approved
	Signature: Lian Ma -S Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2018.12.10 20:23:20 -05'00'			
PBPK Reviewer	Xinyuan Zhang, Ph.D.	OTS/OCP/DPM	Sections: Appendix 18.3.4	**Select one:** _X_ Authored ___ Approved
	Signature: Xinyuan Zhang -S Digitally signed by Xinyuan Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xinyuan Zhang -S, 0.9.2342.19200300.100.1.1=2000431943 Date: 2018.12.11 10:11:32 -05'00'			
PBPK Team Leader	Yuching Yang, Ph.D.	OTS/OCP/DPM	Sections: Appendix 18.3.4	**Select one:** ___ Authored _X_ Approved
	Signature: Yuching Yang -S Digitally signed by Yuching Yang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuching Yang -S, 0.9.2342.19200300.100.1.1=2000846164 Date: 2018.12.11 10:16:24 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Charles Line, M.D.	ODEIII/DGIEP	Sections: 2, 3, 8, 9, 10, 18.2, 18.6	**Select one:** _X_ Authored ___ Approved
	Signature: Charles G. Line -S Digitally signed by Charles G. Line -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002224834, cn=Charles G. Line -S Date: 2018.12.12 10:33:06 -05'00'			
Clinical Team Leader	Juli Tomaino, M.D.	ODEIII/DGIEP	Sections: (authored) 1, 2, 3, 4, 7, 8.4, 8.5, 8.6, 8.8, 8.10, 9, 10, 11.1, 12, 13, 14, 15, 18.5, 18.6	**Select one:** _X_ Authored _X_ Approved (all sections)
	Signature: Juli A. Tomaino -S Digitally signed by Juli A. Tomaino -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001149989, cn=Juli A. Tomaino -S Date: 2018.12.12 11:00:38 -05'00'			
Division Director DGIEP	Joyce Korvick, M.D., M.P.H.	ODEIII/DGIEP	Sections: All sections approved (Authored Sections 11 and 16)	**Select one:** ___ Authored _X_ Approved
	Signature: Joyce A. Korvick -S Digitally signed by Joyce A. Korvick -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300087128, cn=Joyce A. Korvick -S Date: 2018.12.12 14:18:59 -05'00'			
ODEIII Director	Victor Crentsil, M.D., M.H.S.	ODEIII	Sections: All sections	**Select one:** ___ Authored _X_ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Ling Lan, Ph.D.	OB/DB 3	Sections: 7, 8 (except for 8.4, 8.5, 8.6, 8.10) and 18.7	**Select one:** _X_ Authored ___ Approved
	Signature: Ling Lan -S Digitally signed by Ling Lan -S Date: 2018.12.10 10:48:13 -05'00'			
Statistical Team Leader	George Kordzakhia, Ph.D.	OB/DB 3	Sections: (authored) 7, 8 (except for 8.4, 8.5, 8.6, 8.10) Sections: (approved) 7, 8 (except for 8.4, 8.5, 8.6, 8.10), and 18.7	**Select one:** _X_ Authored _X_ Approved
	Signature: George Kordzakhia -S Digitally signed by George Kordzakhia -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300390764, cn=George Kordzakhia -S Date: 2018.12.10 11:25:26 -05'00'			
Division Director (OB)	Laura Lee Johnson, Ph.D.		Sections: 7, 8 (except for 8.4, 8.5, 8.6, 8.10), and 18.7	**Select one:** ___ Authored _X_ Approved
	Signature: Laura L. Johnson -S Digitally signed by Laura L. Johnson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011413414, cn=Laura L. Johnson -S Date: 2018.12.10 14:50:40 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
DEPI Reviewer	Joel Weissfeld, M.D. M.P.H.	OPE/DEPI-I	Sections: 10.7 Review of Observational Study SPD555-802	**Select one:** _X_ Authored ___ Approved
	Signature: Joel L. Weissfeld -S Digitally signed by Joel L. Weissfeld -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001545844, cn=Joel L. Weissfeld -S Date: 2018.12.10 09:13:29 -05'00'			
DEPI Team Leader	Patricia Bright, M.S.P.H. Ph.D.	OPE/DEPI-I	Sections: 10.7 Review of Observational Study SPD555-802	**Select one:** ___ Authored _X_ Approved
	Signature: Patricia L. Bright -S Digitally signed by Patricia L. Bright -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000563850, cn=Patricia L. Bright -S Date: 2018.12.10 09:46:34 -05'00'			
Deputy Division Director (DEPI)	Sukhminder Sandhu, Ph.D. M.P.H. M.S.	OPE/DEPI-I	Sections: 10.7 Review of Observational Study SPD555-802	**Select one:** ___ Authored _X_ Approved
	Signature: Sukhminder K. Sandhu -S Digitally signed by Sukhminder K. Sandhu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300396896, cn=Sukhminder K. Sandhu -S Date: 2018.12.10 09:50:20 -05'00'			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANDREW R KELLEHER
12/14/2018

VICTOR CRENTSIL
12/14/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 8/1/2018

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to Insepect Memo**

RE: NDA 210166

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) declines to conduct the inspection of the sites below. The rationale for this decision is noted below:

(b) (4)

THIS SITE IS PERMANENTLY CLOSED. In addition, the availability and location of the study records is uncertain, given that this study was conducted 19 years ago. The permanently closed site, age of the study, and uncertainty of the availability of the study records present impediments to OSIS for conducting an inspection.

(b) (4)

The availability and location of the study records is uncertain, given that this study was conducted 19 years ago. The age of the study and uncertainty of the availability of the study records present impediments to OSIS for conducting an inspection.

(b) (4)

THIS SITE IS NO LONGER IN BUSINESS. In addition, the availability and location of the study records is uncertain, given that this study was conducted 19 years ago. The permanently closed site, age of the study, and uncertainty of the availability of the study records present impediments to OSIS for conducting an inspection.

Inspection Sites

Facility Type	Facility Name	Facility Address
Analytical	Janssen Pharmaceutica N.V.	Department of Pharmacokinetics, Turnhoutseweg 30, B-2340 Beerse, Belgium
Clinical	(b) (4)	
Clinical		
Clinical		

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHILA S NKAH
08/02/2018