CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210166Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)

Epidemiology: ARIA Sufficiency Memo
Version: 2018-01-24

Date:	December 14, 2018
Reviewer/Team Leader:	Patricia L. Bright, MSPH PhD Division of Epidemiology I
Deputy Division Director:	Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Subject:	Active Risk Identification and Assessment (ARIA) Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Prucalopride (Motegrity®)
Application Type/#:	NDA 210166
Applicant/Sponsor:	Shire Pharmaceuticals
OSE RCM #:	2018-622

1. BACKGROUND INFORMATION

1.1. Medical Product

NDA 210166 seeks U.S. approval for prucalopride (Motegrity®), a serotonin 4 (5-HT4) agonist indicated for treatment of chronic idiopathic constipation (CIC) in adults. Prucalopride stimulates colonic peristalsis. Pharmacokinetic studies estimate a 1-day terminal half-life for prucalopride. Published studies place adult constipation prevalence at 16%, with women seeking health care more often than men.[1]

The recommended prucalopride dosage by patient population is (1) 2 mg tablet by mouth once daily in adults and (2) 1 mg tablet by mouth once daily in patients with severe renal impairment[2]. It is anticipated that patients will take this medication chronically, rather than on an as-needed basis.

1.2. Describe the Safety Concern – Pregnancy Risk

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.[3]

A September 2018 pregnancy and lactation labeling review (PLLR) of NDA 210166 by the Division of Pediatric and Material Health (DPMH) recommended that two required postmarket studies be issued by FDA to provide additional evidence for the safety of this medication in pregnant women. The DPMH memo included the following details.[4]

- Prucalopride (Tradenames: Resolor, Restorans, and Resotran) has been approved and marketed since 2009 for the treatment of chronic idiopathic constipation in several regions including the European Union (EU), Switzerland, Canada, China, and Japan.
- Adverse embryofetal developmental effects not observed in studies completed in rats and rabbits.
- Pregnant women excluded by design from clinical trials, with serum pregnancy tests performed before enrollment and women of reproductive potential advised to use effective birth control.[4]
- Clinical trials with 31 outcomes, from 30 prucalopride-exposed pregnancies, including 8 live births, 1 stillbirth, 7 spontaneous abortions, 1 pregnancy termination, 1 unspecified abortion, 1 ectopic pregnancy, and 12 pregnancies with unknown outcome.
    - Of the 7 subjects experiencing spontaneous abortions, 5 had stopped prucalopride treatment prior to the occurrence of the spontaneous abortion (2-81 days previously). In all but 1 case of spontaneous abortion following exposure to prucalopride, other risks or confounding factors could be identified (e.g., age [4 out of 7 spontaneous abortions reported on prucalopride occurred in women ≥35 years of age]; relevant medical history, relevant concomitant medication), possibly explaining the number of spontaneous abortions.

- One infant, with 1st trimester prenatal exposure to prucalopride, liveborn with congenital malposition of the intestines[a].
- 22 prucalopride-exposed pregnancies identified through post-market surveillance.

DPMH concluded, "the available pregnancy data for prucalopride from published literature, clinical trials, and postmarketing experience have not identified any drug associated risks of miscarriage, congenital malformations, or other adverse maternal or fetal outcomes."

Section 8.1 of the FDA label for prucalopride summarizes FDA's current understanding of the pregnancy risk2, as follows.

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. In animal reproduction studies, no adverse developmental effects were observed with prucalopride administration during the period of organogenesis to pregnant rats and rabbits at doses up to approximately 390 times and 780 times, respectively, the recommended human dose of 2 mg/day.

As shown below, in Section 2.5, DPMH requests two pregnancy-related post-market requirements under FDAAA because "data are needed on the safe use of prucalopride during pregnancy as there is currently limited available human data to inform the safety of prucalopride during pregnancy."

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

[a] We believe that intestinal malrotation might have a genetic basis and occur as a consequence of perturbed first-trimester intercellular signaling, in the endoderm of the primitive digestive tract, involving the Sonic Hedgehog and the Indian Hedgehog family of genes.[5]

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☒ Electronic database study with chart review
☐ Electronic database study without chart review
☐ Other, please specify: A non-registry study using a "different design"

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☐ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

Because broad-based signal detection in not currently available, other parameters were not assessed.

2.5. Please include the proposed PMR language in the approval letter.

The following language (in draft form, as of November 16, 2018) has been proposed for PMRs related to pregnancy outcomes:

PMR 3529-3: A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to 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.

PMR 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 prucalopride during pregnancy compared to an unexposed control population.

The finalized PMR language will be issued upon approval.

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[1] Bharucha AE, Pemberton JH, Locke GR, January 2013, American Gastroenterological Association Technical Review on Constipation, Gastroenterology, 144(1):218-238.
[2] Draft labeling for Prucalopride (Motegrity), NDA 210166, Dec 13, 2018, to be finalized upon approval.
[3] Dinatale M. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR). https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf. Accessed October 11, 2018.
[4] Baisden K, Johnson T, Yao L. September 6, 2018, Division of Pediatric and Maternal Health Memorandum: Motegrity (prucalopride succinate). Filed in DARRTS under NDA 210166 on September 10, 2018.
[5] Penco JMM, Murillo JC, Hernández, A, De La Calle Pato U, Masjoan DF, Aceituno FR, May 2007, Anomalies of intestinal rotation and fixation: consequences of late diagnosis beyond two years of age, Pediatr Surg In, 23:723-730.

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/s/

PATRICIA L BRIGHT
12/14/2018

SUKHMINDER K SANDHU
12/14/2018

JUDITH W ZANDER
12/14/2018

MICHAEL D NGUYEN
12/14/2018

ROBERT BALL
12/14/2018

Division of Gastroenterology and Inborn Errors Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 210166

Name of Drug: MOTEGRITY (prucalopride) oral tablets

Applicant: Shire Development LLC

Labeling Reviewed

Submission Date: December 21, 2017

Receipt Date: December 21, 2017

Background and Summary Description: This new drug application provides for the use of prucalopride oral tablets to treat chronic idiopathic constipation. This standard application is considered a new molecular entity. Prucalopride is currently marketed in Europe. The Sponsor is seeking approval for marketing in the United States.

Review

Preliminary labeling comments were provided to the Sponsor on March 3, 2018 in a Day 74 letter. A revised label was received on March 26, 2018 for review. Labeling discussion comments were conveyed to the Sponsor on November 8, 2018. The Agency asked for additional revisions to the label on December 4, 6 and 10, 2018. Final labeling revisions to the prescribing information and patient package insert are planned for December 12, 2018.

Recommendations

The labeling materials (prescribing information and patient package insert) are recommended for approval pending further evaluation by the review team.

Andrew R. Kelleher -S
Digitally signed by Andrew R. Kelleher -S
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Date: 2018.12.12 10:41:39 -05'00'

12/12/2018

Regulatory Project Manager — Date

Brian K. Strongin -S
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Chief, Project Management Staff — Date

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/s/

ANDREW R KELLEHER
12/13/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Addendum to Division of Pediatric and Maternal Health Review

Date: November 28, 2018 **Date consulted:** December 22, 2017

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

To: Andrew Kelleher, Regulatory Project Manager (RPM)
Division of Gastroenterology and Inborn Error Products (DGIEP)

Drug: Motegrity (prucalopride)

NDA: 210166

Indication: Treatment of Chronic Idiopathic Constipation in adults

Applicant: Shire Development LLC

Subject: Pregnancy and Lactation Postmarketing Requirements
(PMR 3529-3, 3529-4, and 3529-5)

Materials Reviewed:

- NDA 210166 submitted on December 21, 2017
- 120-day Safety Update including SHP555-804 Clinical Study Report "A Drug Utilization Study to Examine Characteristics of Patients Prescribed Prucalopride and a Pharmacoepidemiological Study of the Occurrence of Major Cardiovascular Events, Pregnancy, and Pregnancy Outcomes in the UK CPRD Database" submitted on April 16, 2018.
- Previous DPMH Review of Motegrity (NDA 210166) by Kristie Baisden, DO, dated September 6, 2018.

INTRODUCTION AND BACKGROUND

On December 21, 2017, the applicant, Shire Development LLC, submitted a new NDA (210166) for a new molecular entity (NME), Motegrity (prucalopride). On December 22, 2017, DGIEP consulted DPMH to provide input on the proper format and content of the *Pregnancy* and *Lactation* subsections of Motegrity labeling to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

Prucalopride is a selective 5-HT_4 serotonin receptor agonist with a proposed indication to treat chronic idiopathic constipation in adults. Prucalopride has been approved and marketed since 2009 (Tradenames: Resolor, Restorans, and Resotran) for the treatment of chronic idiopathic constipation in several regions outside of the U.S. including the European Union (EU), Switzerland, Canada, China, and Japan. At the time of initial approval in 2009, limited information was available regarding the use of prucalopride during pregnancy, so a postmarketing pregnancy surveillance study was performed from April 1, 2010 to April 30, 2017.

On April 16, 2018, at the time of the 120-safety update, the applicant submitted the final clinical study report for SHP555-804 "A Drug Utilization Study to Examine Characteristics of Patients Prescribed Prucalopride and a Pharmacoepidemiological Study of the Occurrence of Major Cardiovascular Events, Pregnancy, and Pregnancy Outcomes in the UK CPRD Database." The results indicated a total of 14 pregnancies in 12 women were classified as exposed to prucalopride, with all exposures occurring during the first trimester. Pregnancy outcomes included: 5 live births, 4 spontaneous abortions, 3 elective terminations, and 2 unknown outcomes. The investigators noted there were no malformations and the rate of spontaneous abortions (28.5%) was within the range of previous studies.[1,2]

Reviewer's Comment
Limitations of the above postmarketing study include small sample size, lack of randomization, and the inability to control for confounders such as underlying maternal disease or maternal use of concomitant medications. One explanation for the small sample size may be the restrictive language in the UK labeling recommending against prucalopride use during pregnancy.

DPMH previously reviewed[3] the available pregnancy data for prucalopride from clinical trials with Motegrity, published literature, and the applicant's pharmacovigilance database related to exposures outside the U.S. from the time of initial approval. Pregnant women were excluded from clinical trials with prucalopride. A total of 36 pregnancies occurred during clinical trials with outcomes as follows: 8 live births (1 congenital malformation), 1 stillbirth, 7 spontaneous abortions, 1 pregnancy termination, 1 unspecified abortion, 1 ectopic pregnancy, and 12 unknown outcomes. There are no published reports of prucalopride use during pregnancy in the published literature. The applicant identified 22 pregnancy cases from the pharmacovigilance database of which 18 pregnancy outcomes were unknown.

[1] Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. N Engl J Med. 1999 Jun 10;340(23):1796-9.
[2] Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. N Engl J Med. 1988 Jul 28;319(4):189-94.
[3] Previous DPMH Review of Motegrity (prucalopride) NDA 210166 by Kristie Baisden, DO, dated September 6, 2018.

DPMH previously reviewed[3] the available lactation data for prucalopride from the open-label lactation study in 8 healthy women who were in the weaning stages of lactation. The relative infant dose was calculated as 6%. Prucalopride effects on milk production and the breastfed infant were not evaluated. No other reports of prucalopride exposure during lactation were identified in the published literature. One case of prucalopride exposure during lactation without associated adverse events was reported to the applicant's pharmacovigilance database.

Reviewer's Comment
An important limitation of the above lactation study is only healthy women were studied rather than patients with chronic idiopathic constipation on therapeutic doses of prucalopride. In addition, the women studied were in the weaning phase of lactation rather than the stage of full milk production which prevents an accurate determination of the concentration of prucalopride in mature milk.

DISCUSSION AND CONCLUSIONS

Pregnancy

DPMH concludes there is insufficient human data available to inform the safety of prucalopride use during pregnancy. Overall, the limited available human pregnancy data from the postmarketing pregnancy surveillance study, published literature, clinical trial experience, and applicant's pharmacovigilance database have not identified any drug-associated risks for birth defects, miscarriage, or adverse maternal or fetal outcomes. However, these data are insufficient to exclude pregnancy risk. Considering prucalopride is a systemically absorbed new molecular entity with a potential for wide use amongst females of reproductive potential, gathering additional pregnancy exposure data is important to assess the safety of prucalopride use during pregnancy.

Lactation

DPMH concludes there is also insufficient human data available to inform the safety of prucalopride use during lactation. The only available lactation data are from a small study performed in healthy women during the weaning stages. Considering that women who take prucalopride during pregnancy would likely continue to use this drug while breastfeeding, wide use is anticipated for the lactating population. Data are needed regarding the presence of prucalopride in breast milk of lactating women, who are taking the drug therapeutically, during full (mature) milk production. In addition, data are needed regarding any reported adverse effects of prucalopride on the breastfed infant.

RECOMMENDATIONS
DPMH recommends the following:

1) The applicant perform a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to 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.

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

3) The applicant perform a lactation study (milk only) in lactating women who have received therapeutic doses of prucalopride using a validated assay to assess concentrations of prucalopride in breast milk and the effects on the breastfed infant.

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/s/

KRISTIE W BAISDEN
11/28/2018

TAMARA N JOHNSON
12/04/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 29, 2018
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Error Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel Position Title **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	MOTEGRITY (prucalopride)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	210166
Applicant:	Shire Development LLC (Shire)

1 INTRODUCTION

On December 21, 2017, Shire Development LLC (Shire) submitted for the Agency's review a Original New Drug Application for Motegrity (prucalopride) 1 mg and 2 mg tablets. The proposed indiciation is for the treatement of chronic idiopathic constipation (CIC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) on January 30, 2017 and February 5, 2018, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for MOTEGRITY (prucalopride) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft MOTEGRITY (prucalopride) PPI received on December 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 23, 2018.
- Draft MOTEGRITY (prucalopride) Prescribing Information (PI) received on December 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 23, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

AMANPREET K SARAI
11/29/2018

MARCIA B WILLIAMS
11/29/2018

MEETA N PATEL
11/29/2018

LASHAWN M GRIFFITHS
11/29/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 28, 2018

To: Andrew Kelleher, Regulatory Project Manager, (DGIEP)

Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for Motegrity (prucalopride) tablets, for oral use

NDA: 210166

In response to DGIEP's consult request dated February 5, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert, PPI, and carton and container labeling for the original NDA submission for Motegrity.

PI and PPI: OPDP has no comments on the proposed labeling are based on the draft PI received by electronic mail from DGIEP on November 21, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 21, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
11/28/2018

Amended Clinical Inspection Summary

Date	November 8, 2018
From	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Charles Line, M.D., Medical Officer, DGIEP
NDA #	210166
Applicant	Shire Development LLC.
Drug	Prucalopride Succinate
NME	Yes
Division Classification	Constipation
Proposed Indication	Chronic Idiopathic Constipation
Consultation Request Date	March 2, 2018
Summary Goal Date	September 4, 2018
Action Goal Date	December 7, 2018
PDUFA Date	December 21, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This amendment to the original clinical inspection summary (CIS) that was finalized in DARRTS on August 27, 2018 contains the following revisions and corrections:

- Explanation of discrepancy between FDA Advisory Committee briefing document and CIS concerning percent of missing source documents for the clinical trials
- Update with final classifications for two clinical investigator inspections

The above items do not change the overall conclusions for the clinical inspection summary.

II. Explanation of Discrepancy

Two of the clinical trials submitted in support of the application, Studies PRU-USA-11 and PRU-USA-13, were conducted from 1998 to 1999 by Janssen Research Foundation (JRF). 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.

The original CIS provided the percentage of missing records for each study that was obtained from Shire during preNDA discussions with FDA. The FDA briefing document for the

advisory committee contained the Table 7 below with the Summary of Missing Source that was derived from the reviewer's analysis. This differed only slightly from Shire's estimate of the extent of missing records stated during the preNDA. The difference had no impact on how sites were chosen for inspection and is being corrected in this CIS for the record.

Table excerpted from AC Briefing document page 17 accessed at:https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM623493.pdf

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

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

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

III. Updated RESULTS with final classifications for Dr. Kim and Dr. Cheon:

Name and Type of Inspected Entity/Address	Protocol #/ Site #/ # of Subjects randomized	Inspection Dates	Classification*
CI: Hyo Jong Kim, M.D. Kyung Hee University Medical Center 23, Kyung Hee Dae-ro Dongdaemun-gu, Seoul, 02447, Korea	SPD555-C3001 Site 10375 Subjects: 20	August 6 to 10, 2018	NAI
CI: Jae Hee Cheon, M.D. Yonsei University Hospital (Severance Hospital) 50-1, Yonsei-ro, Seodaemun-gu Seoul, 03722, Korea	SPD555-C3001 Site 10382 Subjects: 10	June 13 and 14 and June 16 and 17, 2018	NAI

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data may be unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Hyo Jong Kim, M.D.**
   Kyung Hee University Medical Center, Seoul, 02447, Korea

At this site, for Protocol SPD555-C3001, a total of 29 subjects was screened, 20 subjects enrolled in the study, and 18 subjects completed the study. A total of 15 subject records were reviewed. The data in the line listings was compared with the source documents. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events. There were minor deviations to the protocol such as out of window visits and missing laboratory values. The deviations were documented and submitted to the IRB.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

2. **Jae Hee Cheon, M.D.**
   Yonsei University Hospital (Severance Hospital), Seoul, 03722, Korea

At this site, for Protocol SPD555-C3001, a total of 15 subjects was screened, 10 subjects enrolled in the study, and 7 subjects completed the study. Fifteen subject records were reviewed. The data in the line listings was compared with the source documents. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events. There were minor deviations from the protocol such as out of window visits and missing laboratory values. The deviations were documented and submitted to the IRB.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm.
Review Division /Acting Division Director/Dragos Roman
Review Division /Medical Team Leader/Juli Tomaino
Review Division /Project Manager/Andrew Kelleher
Review Division/Medical Officer/Charles Line
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Susan D. Thompson
OSI/DCCE/GCP Reviewer/ Susan Leibenhaut
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/

SUSAN LEIBENHAUT
11/08/2018

SUSAN D THOMPSON
11/09/2018

KASSA AYALEW
11/09/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of a Final Study Report

Date:	October 24, 2018
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Team Leader:	Patricia L. Bright, MSPH PhD Division of Epidemiology I
Deputy Director:	Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Drug Name:	prucalopride (Motegrity®)
Subject:	A Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort (SPD555-802)
Application Type/Number:	NDA 210166
Applicant/sponsor:	Shire Pharmaceuticals
OSE RCM #:	2017-2646, 2018-622

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EXECUTIVE SUMMARY

To help the Division of Gastroenterology and Inborn Error Products (DGIEP) assess the cardiovascular safety of prucalopride, the Division of Epidemiology I (DEPI) reviewed SPD555-802, A Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort.

NDA 210166 seeks FDA approval for prucalopride (Motegrity®), a 5-hydroxytryptamine receptor 4 (5-HT_4) agonist marketed in Europe as a laxative for chronic constipation. Prucalopride belongs to the same 5-HT_4 class as tegaserod (Zelnorm®), a product voluntarily withdrawn from the U.S. market because of a cardiovascular signal seen in clinical trials.

Designed to exclude 3-fold risk from prucalopride, SPD555-802 followed a protocol for a retrospective cohort (observational) study, which measured the incidence of Major Adverse Cardiovascular Events (MACE; non-fatal acute myocardial infarction, non-fatal stroke, or in-hospital cardiovascular death) in five European data sources. Pooling results from four data sources, SPD555-802 found a 36% lower incidence of MACE in patients prescribed prucalopride than matched patients prescribed a comparator, polyethylene glycol 3350.

DEPI found important problems in SPD555-802. Despite these problems, DEPI concluded that SPD555-802 provided evidence that reasonably excluded a 3-fold MACE risk from prucalopride.

1. INTRODUCTION

1.1 Background

To help the Division of Gastroenterology and Inborn Error Products (DGIEP) assess the cardiovascular safety of prucalopride, the Division of Epidemiology I (DEPI) reviews SPD555-802, A Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort.

NDA 210166 seeks FDA approval for prucalopride (Motegrity®), a 5-hydroxytryptamine receptor 4 (5-HT_4) agonist marketed in Europe for treatment of chronic constipation. Prucalopride belongs to the same 5-HT_4 class as tegaserod (Zelnorm®), a product voluntarily withdrawn from the U.S. market because of a cardiovascular signal seen in clinical trials.[1]

NDA 210166 submits results from SPD555-802 to support the cardiovascular safety of

[1] Food and Drug Administration, March 30, 2007, Public Health Advisory: Tegaserod maleate (marketed as Zelnorm), Accessed at https://wayback.archive-it.org/7993/20170723100330/https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051284 htm on July 27, 2018.

prucalopride. SPD555-802 used a retrospective cohort (observational) study design to measure the incidence of Major Adverse Cardiovascular Events (MACE) in European patients prescribed prucalopride. The Sponsor conducted and reported SPD555-802 with input previously provided by DEPI.[2]

At a pre-NDA meeting with the Sponsor, DGIEP accepted, as a reasonable requirement for NDA 210166, results from SPD555-802 that exclude a 3-fold MACE risk from prucalopride with 95% statistical confidence.[3] DGIEP continued; "Depending on the results of SPD555-802, a post-marketing study to rule out an IRR [incidence rate ratio] of 2 might be required."

1.2. Regulatory History

Date	Event
October 15, 2009	The European Commission granted prucalopride (Resolor) marketing authorization valid throughout the European Union
December 21, 2017	NDA 210166 submitted to FDA

2. REVIEW METHODS AND MATERIALS

2.1 Documents Reviewed

Date	Documents
May 30, 2014	(b) (4) Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort (SPD555-802), Study Protocol, Version 2.0, submitted to NDA 210166, eCTD 0001, Module 5.3.6, on December 21, 2017
May 30, 2014	(b) (4) Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort (SPD555-802), Statistical Analysis Plan, Version 2.0, submitted to NDA 210166, eCTD 0001, Module 5.3.6, on December 21, 2017

[2] Taylor, LG, November 20, 2013, Review of Sponsor's Study Protocol and Submitted Questions, filed under IND 055078 on November 21, 2013.

Taylor, LG, July 21, 2014, Review of Sponsor's Revisions to Teduglutide PMR Protocol, SPD555-802: Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort, filed under IND 055078 on July 21, 2014.

Weissfeld, JL, March 7, 2017, Table Formats for Presenting Results from SPD555-802, filed under IND 055078 on March 7, 2017.

[3] FDA, Meeting Minutes from August 8, 2017, filed under IND 055078 on September 1, 2017, page 5.

Date	Documents
July 20, 2016	[redacted] (b) (4) Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort (SPD555-802): A Swedish Sub-study, Study Protocol, Version 1.0, submitted to NDA 210166, eCTD 0001, Module 5.3.6, on December 21, 2017
February 20, 2017	[redacted] (b) (4) Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort (SPD555-802): A Swedish Sub-study, Statistical Analysis Plan, Version 1.0, submitted to NDA 210166, eCTD 0001, Module 5.3.6, on December 21, 2017
October 2, 2017	[redacted] (b) (4) Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort (SPD555-802), Full Study Data Development Plan, Version 7.0, submitted to NDA 210166, eCTD 0001, Module 5.3.6, on December 21, 2017
April 2017	[redacted] (b) (4) Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort (SPD555-802), Validation Plan, Version 4.0, submitted to NDA 210166, eCTD 0001, Module 5.3.6, on December 21, 2017
May 14, 2018	Shire Pharmaceuticals, Clinical Information Amendment Responding to FDA Information Request 02-May-2018, submitted to NDA 210166, eCTD 0027, on May 14, 2018
May 25, 2018	[redacted] (b) (4) Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort (SPD555-802), Final Study Report, Version 1.0, Addendum 1.0, with Supplemental Full Results File (spd555-802-tables.xlsx), submitted to NDA 210166, eCTD 0031, Module 5.3.6, on June 11, 2018
July 16, 2018	Shire Pharmaceuticals, Clinical Information Amendment Responding to FDA Information Request 02-JUL-2018, submitted to NDA 210166, eCTD 0037, on July 16, 2018

Date	Documents
August 13, 2018	Shire Pharmaceuticals, Clinical Information Amendment Responding to FDA Information Request 06-AUG-2018, submitted to NDA 210166, eCTD 0042, on August 13, 2018
August 24, 2018	Shire Pharmaceuticals, Clinical Information Amendment Responding to FDA Information Request 14-AUG-2018, submitted to NDA 210166, eCTD 0044, on August 24, 2018
August 31, 2018	Shire Pharmaceuticals, Clinical Information Amendment Responding to FDA Information Request 02-JUL-2018, submitted to NDA 210166, eCTD 0049, on August 31, 2018
September 19, 2018	Shire Pharmaceuticals, Clinical Information Amendment Responding to FDA Information Request 14-SEP-2018, submitted to NDA 210166, eCTD 0053, on September 19, 2018
October 8, 2018	Shire Pharmaceuticals, Supplemental Tables for Study SPD555-802 for Follow-Up to Information Request 14-SEP-2018 (Programming Error SPD555-802), submitted to NDA 210166, eCTD 0054, on October 9, 2018
October 11, 2018	(b) (4) Root Cause Analysis for the Programming Error in Sweden Relating to SPD555-802, submitted to NDA 210166, eCTD 0056, on October 11, 2018

2.2 Criteria Applied to Review

DEPI used the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool to assess SPD555-802 [1] for internal validity.

ROBINS-I uses signaling questions to guide risk-of-bias assessments in seven domains, including, (1) confounding, (2) patient selection, (3) exposure classification, (4) co-intervention and other deviations from intended intervention, (5) missing data, (6) outcome classification, and (7) selective reporting. ROBINS-I uses a four-level ordinal scale to express judgments about **risk of material bias**, described as the level of concern about issues "likely to affect the ability to draw valid conclusions from the study." Response options for ROBINS-I risk of bias judgments include,

- Low risk of bias, to describe a non-randomized study considered comparable to a well-performed randomized trial.
- Moderate risk of bias, to describe a sound non-randomized study not considered comparable to a well-performed randomized trial.

- Serious risk of bias, to describe a non-randomized study with important problems.
- Critical risk of bias, to describe a non-randomized study too problematic to provide any useful evidence.

A study can receive an overall judgment of serious risk of bias, if judged at serious risk of bias for at least one domain.

3. REVIEW RESULTS

3.1 Study Overview

SPD555-802 used a common protocol and a retrospective cohort design to measure the incidence of Major Adverse Cardiovascular Events (MACE) in five data sources,

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

3.2 Study Objective

SPD555-802 aimed to estimate a Standardized Incidence Rate Ratio (SIRR), with 95% Confidence Interval (CI), for MACE, comparing patients starting treatment with prucalopride (PRU) *vs.* polyethylene glycol 3350 (PEG).

3.3 Swedish National Registers (SNR)

3.3.1 Study Methods

3.3.1.1 Study Setting

SNR combined five population-based databases to cover the Swedish resident population for study exposures (PRU and PEG) and outcomes (MACE) occurring between 2012 and 2015. See **APPENDIX 1** for a tabular summary of SNR.

Beginning in 2001, one database (National Patient Register, NPR) captured diagnosis and procedure codes attached to inpatient and outpatient encounters. Beginning in 2006, a second database (Swedish Prescribed Drug Register, PDR) captured information about prescription

drugs dispensed to patients. SNR used diagnosis, procedure, and prescription drug codes in these two databases to define the other variables (covariates) used in analysis.[4]

3.3.1.2 Eligibility Criteria

SNR defined two study populations, PRU and PEG, separately identified by the first (index) prescription filled during the 2012-2015 study period. SNR excluded from these populations,

- Patients with <12 months data available before an index date defined by the dispensing date for the index prescription
- Patients <18 years of age on the index date
- PEG patients with an index prescription supplying ≤4 days of treatment
- PRU patients, filling before 2012, a prucalopride prescription
- PEG patients filling, before 2012, a PEG prescription supplying >4 days of treatment
- PRU or PEG patients filling, within 12 months + 10 days before the index date, a PEG prescription supplying ≤4 days of treatment
- Patients filling, on a PRU index date, a prescription for PEG
- Patients filling, on a PEG index date, a prescription for prucalopride
- PRU patients with prucalopride-exposed time completely covered by treatment with PEG
- PEG patients with PEG-exposed time completely covered by treatment with prucalopride

A person starting PRU and PEG on different dates could qualify for both populations.

3.3.1.3 Exposure

For primary analysis, SNR defined prucalopride exposure by treatment time (in days) covered uniquely by prucalopride prescriptions (ATC A06AX05, with "the days of supply equal to the number of tablets dispensed"),[5] with 7-day gaps allowed between a sequence of prescriptions, 7-

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[4] A Clinical Information Amendment, submitted by the Sponsor to BLA 210166 (eCTD 0037) on July 16, 2018, in response to a Request for Information, asserted that SNR used data from the Swedish Cancer Register to specify one variable, *i.e.*, history of cancer. See FDA Request for Information, July 2, 2018, filed under BLA 210166 on July 3, 2018 (Reference ID: 4286396).

[5] ATC refers to WHO Anatomical Therapeutic Chemical classification code. See https://www.whocc.no/.

day extension added to the last prescription in a sequence, and follow-up terminated on first switch to PEG, as indicated by first post-PRU-index PEG prescription supplying >4 days of treatment.

Likewise, SNR defined PEG exposure by treatment time (in days) covered uniquely by PEG prescriptions supplying >4 days of treatment (ATC A06AD65, "excluding packages normally used prior to diagnostic examination or surgical procedures," with days of supply equal to the number of defined daily doses dispensed), with 7-day gaps allowed between a sequence of prescriptions, 7-day extension added to the last prescription in a sequence, and follow-up terminated on first switch to prucalopride, as indicated by first post-PEG-index prucalopride prescription.

These exposure definitions,

- Implemented a stockpiling algorithm, which added days of supply remaining from previous prescriptions to the days supplied by a current prescription.

- Excluded overlapping exposure, *i.e.*, time covered by prescriptions for both PRU and PEG.

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

3.3.1.4 Outcomes

SNR defined one primary outcome, MACE, a composite of non-fatal acute myocardial infarction (AMI), non-fatal stroke, and in-hospital cardiovascular death. As shown in **APPENDIX 2**, SNR defined MACE solely by diagnosis codes in the primary or secondary positions of NPR hospital records and underlying cause of death in the Causes of Death Register (CDR).

3.3.1.5 Other Variables

Variables used for cohort matching included,

- Sex

- Calendar year of index date

- Year of birth

- Recent hospitalization (**APPENDIX 3**)

- Prescriber specialty, in four categories, (1) oncology, (2) surgery or orthopedics, (3)

gastroenterology or general practice, and (4) internal medicine or other

SNR developed a propensity score model from 35 variables in eight domains (**APPENDIX 3**), including,

- Demographic factors (3 variables)
- Prescription opioid history (2 variables)
- History of gastrointestinal (GI) problem (4 variables)
- History of cardiovascular hospitalization (5 variables)
- History of cardiovascular procedure (2 variables)
- Prescription drug history (9 variables)
- Medical history (8 variables)
- Health care utilization (2 variables)

3.3.1.6 Statistical Analysis

Data analysis entailed five steps.

Step 1. Use sex, calendar year of index date, closest year of birth (±10 years allowed), recent hospitalization, and provider specialty to find five PEG matches for every PRU patient, with any PEG match used only once and a PEG patient never matched to himself/herself as a patient also in PRU.

Step 2. Use logistic regression and the other variables (**APPENDIX 3**) to calculate, for every patient from Step 1, a propensity score (*i.e.*, predicted probability of PRU, given the values for the other variables).

Step 3. Trim Step 1 cohorts by excluding patients with extreme propensity scores. Start by excluding patients in PRU or PEG with propensity scores below the 1st percentile for patients in PRU or above the 99th percentile for patients in PEG. In necessary, continue trimming until propensity score distributions for PRU and PEG overlap completely.

Step 4. Calculate MACE incidence (Incidence Rate, IR) as the number of events per 1000 patient-years, with 95% CI estimated per Dobson, *et al.*, 1991 [2].

Step 5. For controlled comparison,

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

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

- Calculate Standardized Incidence Rate Ratio (SIRR) as the ratio between the SIRs for PRU and PEG, with 95% CI estimated per equation 15-11 in Rothman, *et al.*, 2008 [3].

SPD555-802 used the standardized difference (SD), as defined in Austin, 2011 [4], to express dissimilarity between patients in PRU and PEG.

3.3.2 Study Results

3.3.2.1 Eligible cohort

During the 2012-2015 study period, SNR identified 4,423 patients with a dispensing for PRU. SNR excluded 767 (17.3%) as ineligible (Section 3.3.1.2 Eligibility Criteria). A recent PEG prescription with ≤4 days of supply accounted for more than half of patients excluded (55.4%, 425 of 767).

SNR identified 676,031 patients with a dispensing for PEG, including 433,286 dispensed >4 days of supply. SNR excluded 118,226 (27.3%) from the latter group.[6]

Patients remaining, 3,656 PRU and 315,060 PEG, formed the eligible patient population.

3.3.2.2 Baseline characteristics of the matched population

SNR successfully found five PEG matches for every PRU patient. As shown in Table 1, the matched patient cohorts included 91.0% female sex and 46.3% aged 18-54 years. Other variables with notable differences (SD ≥ 0.10) between patients in PRU *vs.* PEG included, (1) low socioeconomic level (25.0% *vs.* 30.0%), (2) recent opioid (25.4% *vs.* 35.8%), and (3) history of gastrointestinal problems (*e.g.*, constipation outpatient diagnosis, 36.6% *vs.* 7.2%).

On a per patient basis,

- PRU women accumulated more time on treatment than men, mean 5.2 *vs.* 3.0 months.

- Younger (18-54 year-old) PRU patients accumulated more time on treatment than older (≥55 year-old) patients, 5.5 *vs.* 4.6 months.

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[6] PEG prescription before 2012 supplying >4 days of treatment and age <18 years explained most exclusions.

- Younger PEG patients accumulated less time on treatment than older patients, 2.2 *vs.* 2.9 months.

Because of these sex- and age-specific differences in mean exposure, women and younger patients accounted for larger fractions of total patient-year exposure in PRU than PEG (Table 1), as reproduced below,

- Female sex, 94.6% *vs.* 91.8%, SD 0.11

- 18-54 years of age, 50.5% *vs.* 39.7%, SD 0.22

Other variables with notable differences (SD ≥ 0.10) between PRU and PEG patient-years included,

- Outpatient prescription drug history for aspirin or platelet inhibitor, 16.6% *vs.* 23.3%

- Medical history for cancer, 6.5% *vs.* 10.4%, hyperlipidemia, 5.6% *vs.* 8.0%, and hypertension, 18.0% *vs.* 25.4%

Table 1: Swedish National Registers (SNR), baseline characteristics of the prucalopride (PRU) cohort (3,656 patients with 1,531 patient-years) and the matched polyethylene glycol 3350 (PEG) cohort (18,280 patients with 3,951 patient-years).

	PATIENTS			PATIENT-YEARS [2]		
Baseline variable [1]	PRU %	PEG %	SD	PRU %	PEG %	SD
Matching variable						
Female sex	91.0	91.0	0.00	94.6	91.8	0.11
Age 18-54 years	46.3	46.3	0.00	50.5	39.7	0.22
Year 2012	5.5	5.5	0.00	9.9	7.5	0.09
Recent hospitalization	2.8	2.8	0.00	1.8	2.1	0.02
Low socioeconomic level [3]	25.0	30.0	0.11	23.3	34.6	0.25
Outpatient prescription opioid history						
Recent opioid	25.4	35.8	0.23	25.2	33.9	0.19
Chronic opioid	22.2	23.0	0.02	22.9	25.7	0.06
History of GI problem						
IBS outpatient diagnosis	19.8	3.0	0.55	21.7	2.7	0.61
Constipation outpatient diagnosis [4]	36.6	7.2	0.76	38.3	7.2	0.80
Other outpatient GI diagnosis	51.3	31.3	0.42	51.0	31.8	0.40
Constipation inpatient diagnosis	11.6	2.0	0.39	10.9	2.6	0.33
Other inpatient GI diagnosis	28.7	14.4	0.35	27.9	16.0	0.29
Any cardiovascular hospitalization	6.6	6.7	0.00	5.8	7.9	0.09
Outpatient prescription drug history						
Anticoagulant	16.9	15.6	0.04	14.4	16.7	0.06
Antidiabetic	9.4	9.9	0.02	10.3	11.3	0.03

Baseline variable [1]	PATIENTS PRU %	PATIENTS PEG %	PATIENTS SD	PATIENT-YEARS [2] PRU %	PATIENT-YEARS [2] PEG %	PATIENT-YEARS [2] SD
Antihypertensive	49.9	46.6	0.07	48.2	51.3	0.06
Aspirin or platelet inhibitor	19.7	20.1	0.01	16.6	23.3	0.17
HMG CoA reductase inhibitor	23.9	22.7	0.03	21.7	25.2	0.08
Medical history						
Asthma	8.8	6.4	0.09	8.7	7.1	0.06
Bronchitis, emphysema, and COPD	3.8	5.1	0.06	3.6	5.1	0.08
Cancer	8.8	11.3	0.08	6.5	10.4	0.14
Chronic kidney disease	1.1	1.4	0.03	1.0	1.7	0.06
Diabetes	8.3	8.9	0.02	9.5	10.4	0.03
Hyperlipidemia	7.3	6.9	0.01	5.6	8.0	0.10
Hypertension	21.3	22.6	0.03	18.0	25.4	0.18

REFERENCE: Table assembled by DEPI from Table 2 and Table 3 in Supplemental Full Results File.
ABBREVIATIONS: COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; IBS, irritable bowel syndrome; SD, standardized difference
FOOTNOTES:
1. See APPENDIX 3 for variable definitions.
2. Patient-years of exposure before first MACE. See Section 3.3.1.3 Exposure.
3. Variable definition uncertain, possibly low quartile income, as defined in PRU cohort.
4. At least one outpatient encounter, between 2001 and index date (inclusive), with ICD-10 K59.0 (Other functional intestinal disorders).

3.3.2.3 Exposure

The 3,656 PRU and 18,280 matched PEG patients in SNR accumulated 1,531 and 3,951 patient-years on treatment, respectively, with mean patient exposures higher in PRU than PEG (5.0 *vs.* 2.6 months, Figure 1). As shown in Figure 2, 40.0% in PRU and 23.1% in PEG accumulated >90 days exposure. First episodes of treatment accounted for approximately 61% and 54% of total exposure in PRU and PEG, respectively.

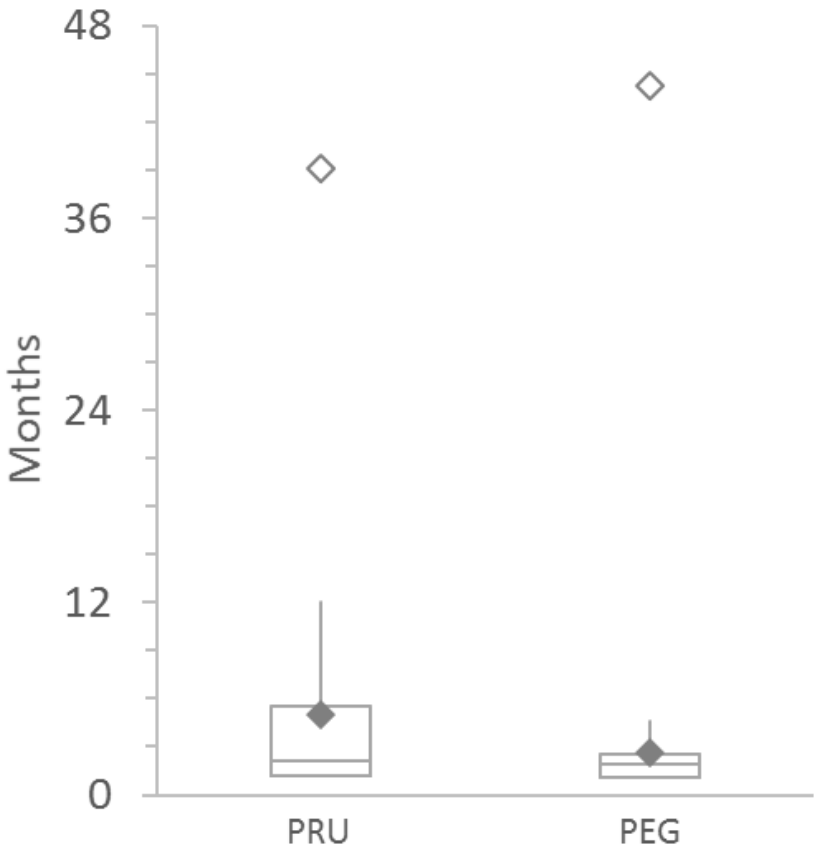


Figure 1: Swedish National Registers (SNR), box plots summarizing patient exposures for 3,656 and 18,280 patients in prucalopride (PRU) and polyethylene glycol 3350 (PEG) cohorts, respectively, with means shown as solid diamonds, maximum values as open diamonds, and 25th, 50th, and 75th percentiles as horizontal lines. Each whisker connects a 75th percentile to a value equal to 1.5 times the interquartile range added to the 75th percentile. Plot prepared by DEPI from Table 4 in Supplemental Full Results File.

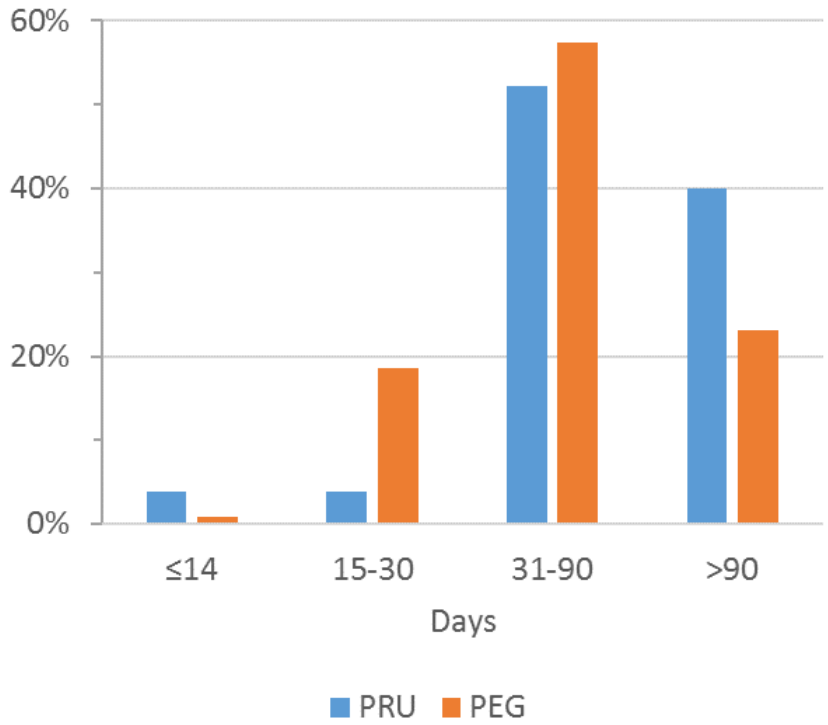


Figure 2: Swedish National Registers (SNR), 3,656 and 18,280 patients from prucalopride (PRU) and polyethylene glycol 3350 (PEG) cohorts, respectively, distributed by cumulative exposure to study drug. Plot prepared by DEPI from Table 4 in Supplemental Full Results File.

3.3.2.4 Sex- and age-adjusted results in matched cohorts

The primary outcome of MACE occurred during current treatment in 16 of 3,656 (0.44%) and in 72 of 18,280 (0.39%) patients from PRU and PEG, respectively (Table 2). The secondary outcomes of non-fatal AMI, non-fatal stroke, and cardiovascular death occurred in 5, 8, and 3 PRU patients, respectively.

Table 2: Swedish National Registers (SNR), Major Adverse Cardiovascular Events (MACE).

	PRU	PEG
Patients	3,656	18,280
Patient-years	1,531	3,951
MACE	16	72
non-fatal AMI	5	21
non-fatal stroke	8	37
cardiovascular death	3	17

REFERENCE: Table assembled by DEPI from Tables 9a1, 9a2, 9a3, and 9a4 in Supplemental Full Results File.

ABBREVIATIONS: AMI, Acute Myocardial Infarction; PRU, prucalopride; PEG polyethylene glycol 3350
FOOTNOTES:
1. The count for cardiovascular deaths in PEG (N=17) deviates from the count (N=16) previously reported in Clinical Information Amendment, eCTD 0049, page 5.

MACE occurred at crude incidence of 10.5 and 18.2 per 1000 patient-years (Incidence Rate Ratio, IRR, 0.57, 95% CI 0.31-1.00). As shown in Table 3, MACE incidence increased with age. No MACE occurred in PRU women below age 50 years or men below age 70 years. Among 60-69 year-old women, MACE occurred less often in PRU than PEG (6.4 *vs.* 16.0 per 1000 patient-years, IRR 0.40, 95% CI 0.04-1.78).

Table 3: Swedish National Registers (SNR), sex- and age-specific MACE incidence in prucalopride (PRU) cohort (3,656 patients with 1,531 patient-years) and the matched polyethylene glycol 3350 (PEG) cohort (18,280 patients with 3,951 patient-years).

Sex, Age on index date (years)	PRU				PEG			
	N	P-YRs	MACE	IR	N	P-YRs	MACE	IR
Women								
<50	1,273	578.7	0	0.0	6,365	1,144.9	5	4.4
50-59	617	328.1	3	9.1	3,085	697.5	6	8.6
60-69	680	311.2	2	6.4	3,400	814.7	13	16.0
70-79	517	166.9	5	30.0	2,585	627.8	21	33.4
≥80	241	62.9	3	47.7	1,205	342.9	15	43.8
Men								
<50	95	28.5	0	0.0	475	75.9	0	0.0
50-59	58	17.0	0	0.0	290	53.8	2	37.2
60-69	67	15.6	0	0.0	335	71.6	4	55.8
70-79	77	14.5	2	137.5	385	79.8	3	37.6
≥80	31	7.2	1	138.5	155	42.7	3	70.2

REFERENCE: Table assembled by DEPI from Table 9a1 in Supplemental Full Results File.
ABBREVIATIONS: N, number of patients; P-YRs, patient-years; MACE, Major Adverse Cardiovascular Events; IR, incidence per 1000 patient-years

3.3.2.5 Cohort trimming and propensity score stratification

SPD555-802 evaluated 30 covariates in SNR for patient-year balance achieved by cohort trimming and propensity score stratification.[7] Figure 3 shows results for three illustrative covariates, (1) age at index, (2) other inpatient GI diagnosis, and (3) hypertension.

In nine propensity score deciles, with differences regarded as non-negligible in four deciles (SD > 0.10), younger patients (18-54 years at baseline) supplied relatively more patient-years in PRU

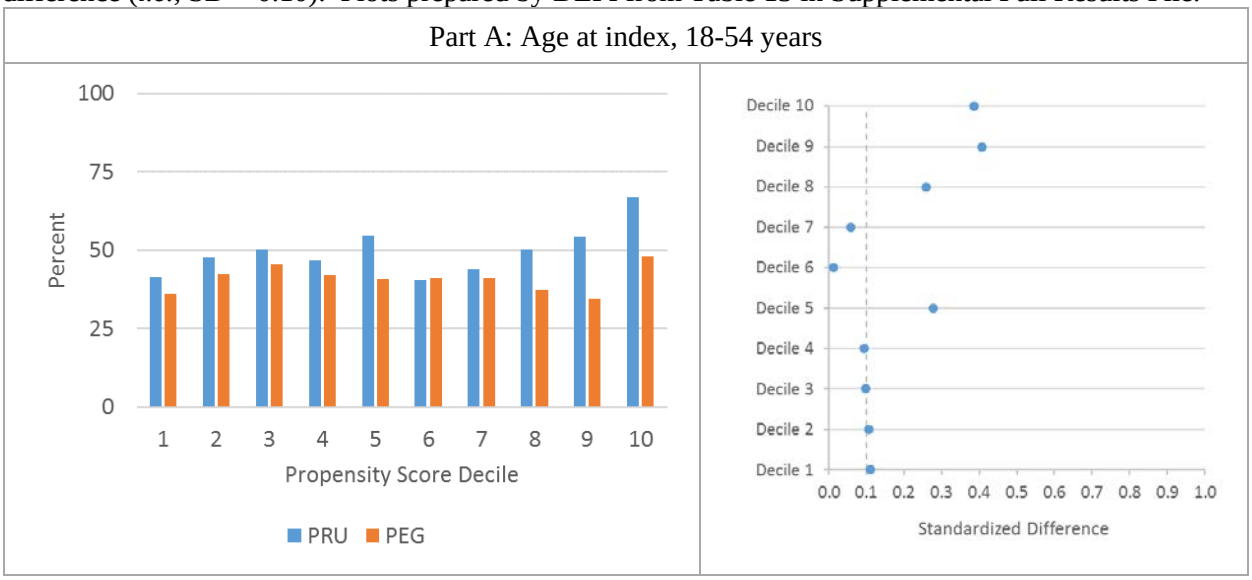
[7] See Table 13 in Supplemental Full Results File.

than PEG (Figure 3, Part A).

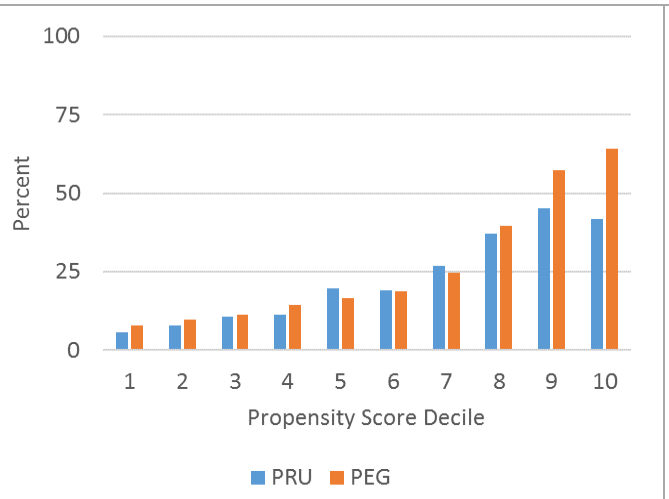
In two deciles (Deciles 9 and 10), patients with a baseline history of other inpatient GI diagnosis supplied relatively fewer patient-years in PRU than PEG (Figure 3, Part B). Overall, before trimming, patients with a baseline history of other inpatient GI diagnosis supplied relatively more patient-years in PRU than PEG (27.9% *vs.* 16.0%, SD 0.29; Table 1).

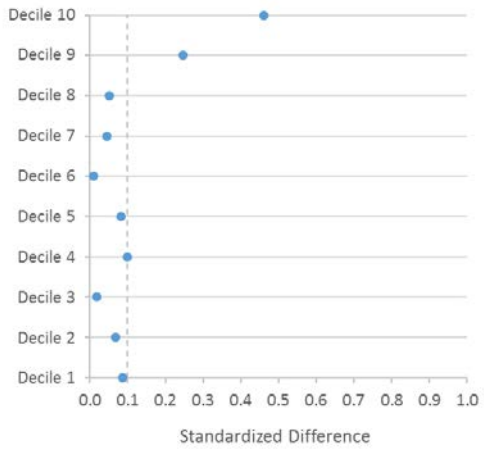
In nine deciles, patients with a baseline history of hypertension supplied relatively fewer patient-years in PRU than PEG (Figure 3, Part C). SDs for three deciles (Deciles 4, 7, and 8) exceeded 0.18, the SD observed overall, before trimming (18.0% *vs.* 25.4%, Table 1).

Figure 3: Swedish National Registers (SNR), patient-year balance achieved between prucalopride (PRU) and polyethylene glycol 3350 (PEG). Results shown (in trimmed cohorts, by propensity-score stratum) for three variables (risk factors), age at index (Part A), other inpatient GI diagnosis (Part B), and hypertension (Part C). The left-hand plots compare, by propensity score decile, percent of person-years in PRU and PEG with the indicated risk factor. The right-hand plots express covariate balance in each propensity score decile as a standardized difference (SD), with a vertical dashed line defining the upper boundary for negligible difference (*i.e.*, SD = 0.10). Plots prepared by DEPI from Table 13 in Supplemental Full Results File.

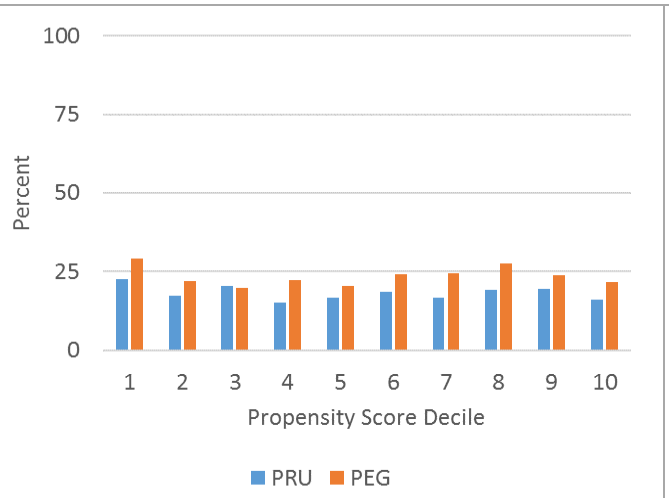


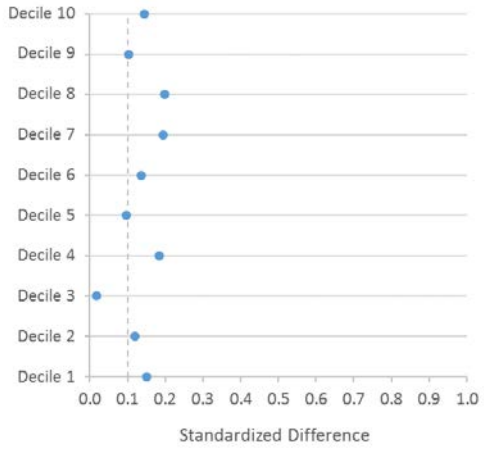
Part B: Other inpatient GI diagnosis (**APPENDIX 3**)





Part C: Hypertension (**APPENDIX 3**)





REFERENCE: Plot prepared by DEPI from Table 13 in Supplemental Full Results File.

3.3.2.6 Primary results

Trimming eliminated 462 of 3,656 (12.6%) patients from PRU and 1,511 of 18,280 (8.3%) patients from PEG. After trimming, the two study cohorts contained,

- PRU: N=3,194 patients with 14 MACEs over 1,327 patient-years, IR 10.5 per 1000 patient-years.
- PEG: N=16,769 patients with 64 MACEs over 3,682 patient-years, IR 17.4 per 1000 patient-years.

Accordingly, after trimming, SNR estimated crude MACE incidence in PRU relative to PEG at IRR 0.61, 95% CI 0.31-1.09. Stratifying by propensity score decile (Table 4), SNR estimated

standardized MACE incidence in PRU relative to PEG at SIRR 0.63, 95% CI 0.33-1.20.[8]

Table 4: Swedish National Registers (SNR), MACE incidence in trimmed prucalopride (PRU) and polyethylene glycol 3350 (PEG) cohorts, stratified by propensity score decile.

Propensity score decile	PRU 3,194 patients with 1,327 P-YRs				PEG 16,769 patients with 3,682 P-YRs			
	N	P-YRs	MACE	IR	N	P-YRs	MACE	IR
Decile 1	320	118.1	2	16.9	4,349	948.2	22	23.2
Decile 2	319	120.7	2	16.6	3,071	671.3	12	17.9
Decile 3	320	138.1	1	7.2	2,033	415.4	5	12.0
Decile 4	319	132.2	0	0.0	1,932	419.0	8	19.1
Decile 5	319	143.5	2	13.9	1,448	318.0	6	18.9
Decile 6	320	142.2	0	0.0	1,462	325.5	4	12.3
Decile 7	319	134.7	0	0.0	1,051	240.4	0	0.0
Decile 8	320	126.7	2	15.8	770	185.8	4	21.5
Decile 9	319	126.7	2	15.8	410	95.1	1	10.5
Decile 10	319	144.3	3	20.8	243	63.3	2	31.6

REFERENCE: Table assembled by DEPI from Table 14a in Supplemental Full Results File.
ABBREVIATIONS: N, number of patients; P-YRs, patient-years; MACE, Major Adverse Cardiovascular Events; IR, incidence per 1000 patient-years

3.3.2.7 Results for secondary outcomes

For completeness, Table 5 summarizes results from SNR for the secondary outcomes of non-fatal AMI, non-fatal stroke, and in-hospital cardiovascular death.

Table 5: Swedish National Registers (SNR), results for primary and secondary outcomes, before and after trimming.

Outcome	Untrimmed				Trimmed					
	PRU	PEG	IRR	95% CI	PRU	PEG	IRR	95% CI	SIRR	95% CI
MACE	16	72	0.57	0.31-1.00	14	64	0.61	0.31-1.09	0.63	0.33-1.20
non-fatal AMI	5	21	0.62	0.18-1.68	4	17	0.65	0.16-2.01	0.89	0.29-2.71
non-fatal stroke	8	37	0.56	0.22-1.22	7	34	0.57	0.21-1.31	0.49	0.20-1.31
CV death	3	17	0.46	0.09-1.58	3	15	0.56	0.10-1.97	0.75	0.21-2.74

REFERENCE: Table assembled by DEPI from Tables 9a1, 9a2, 9a3, 9a4, 14a, 14b, 14c, and 14d in Supplemental Full Results File.
ABBREVIATIONS: AMI, acute myocardial infarction; CV death, in-hospital cardiovascular death; PRU, prucalopride; PEG, polyethylene glycol 3350; IRR, incidence rate ratio; CI, confidence interval; SIRR, standardized incidence rate ratio
FOOTNOTES:
1. The count for CV deaths in PEG (N=17) deviates from the count (N=16) previously reported in Clinical Information Amendment, eCTD 0049, page 5.

[8] Using data aggregated by propensity score decile (Table 14a, Supplemental Full Results File), DEPI reproduced this SIRR and 95% CI.

3.3.2.8 Results from subgroup analyses

For completeness, Table 6 summarizes crude results for MACE in subgroups defined by sex, age, and other baseline measures of cardiovascular disease risk. The documents available to DEPI omitted SNR-specific results from subgroup analyses controlled for propensity score.

Table 6: Swedish National Registers (SNR), crude results for MACE, before cohort trimming, in categories of sex, age, and other baseline measures of cardiovascular disease risk.

	PRU		PEG			
Group	MACE	IR	MACE	IR	IRR	95% CI
Overall	16	10.5	72	18.2	0.57	0.31-1.00
Sex and age, years						
Women, 18-54	1	1.4	6	4.1	0.33	0.01-2.74
Women, ≥55	12	16.8	54	25.0	0.67	0.33-1.27
Men, 18-54	0	0.0	1	9.8	0.00	0.00-103.
Men, ≥55	3	68.2	11	49.7	1.37	0.25-5.19
Age, years						
18-54	1	1.3	7	4.5	0.29	0.01-2.25
≥55	15	19.8	65	27.3	0.73	0.38-1.29
History of CV hospitalization						
No	12	8.3	50	13.7	0.61	0.29-1.15
Yes	4	45.4	22	70.2	0.65	0.16-1.91
≥1 CV risk factor [1]						
No	1	1.4	5	2.9	0.47	0.01-4.21
Yes	15	18.5	67	29.7	0.62	0.33-1.10

REFERENCE: Table assembled by DEPI from Table 9a1 in Supplemental Full Results File.
ABBREVIATIONS: MACE, Major Adverse Cardiovascular Event; CV, cardiovascular; PRU, prucalopride; PEG, polyethylene glycol 3350; IR, incidence rate (per 1000 patient-years); IRR, incidence rate ratio; CI, confidence interval

1. Age ≥55 years, history of CV hospitalization, hypertension, hyperlipidemia, diabetes, or obesity.

3.3.2.9 Results from sensitivity analyses

The documents available to DEPI omitted SNR-specific results from sensitivity analysis.

3.4 Information Services Division (ISD) of Scotland

3.4.1 Study Methods

3.4.1.1 Study Setting

ISD combined three population-based databases to cover the Scottish resident population for study exposures (PRU and PEG) and outcomes (MACE) occurring between January 2010 and

May 22, 2016.

One database (Scottish Morbidity Register, SMR) captured diagnosis and procedure codes attached to discharges from non-psychiatric hospitals.[9] A second database captured information about prescription drugs covered by national health insurance, written by general practice physicians, and dispensed by outpatient pharmacies [5].[10] A third database (National Records of Scotland) provided information about deaths and causes of death.[11] With data availability beginning in 2009, ISD used diagnosis, procedure, and prescription drug codes in the first two of these three databases to define the other variables (covariates) used in analysis.

3.4.1.2 Eligibility Criteria

ISD used the same eligibility criteria as SNR. See Section 3.3.1.2 Eligibility Criteria.

3.4.1.3 Exposure

Except for one difference, ISD and SNR defined exposure alike (Section 3.3.1.3 Exposure). Unlike SNR, ISD did not stockpile, *i.e.*, extend the exposure period when patients refilled prescriptions before exhausting the days supplied by earlier prescriptions. ISD replaced missing values for days of supply with the age- and sex-specific modal values for patients with non-missing values for days of supply.[12]

3.4.1.4 Outcomes

ISD used a two-stage procedure to identify the primary outcome, MACE, a composite of non-fatal AMI, non-fatal stroke, and in-hospital cardiovascular death.

To identify events for adjudication at the second stage, the first stage selected SMR records that satisfied any one of the following three conditions,

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[9] For information about SMR, see, Information Services Division, NHS National Services, General Acute Inpatient and Day Case - Scottish Morbidity Record (SMR01), accessed at http://www ndc.scot.nhs.uk/National-Datasets/data.asp?ID=1&SubID=5 on June 28, 2018.

[10] Sponsor-submitted documents do not name the ISD outpatient prescription database analyzed for SPD555-802. However, these documents describe a database with features matching the Prescribing Information System (PIS). For information about PIS, see, Information Services Division, NHS National Services, Prescribing and Medicines, accessed at http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Prescribing-Datamarts/ on June 28, 2018.

[11] For information about National Records of Scotland, see, Vital Events – Deaths, accessed at https://www nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths on June 28, 2018.

[12] All prescriptions missing values for days of supply in 16.3% and 4.8% of patients in PRU and PEG, respectively, per Clinical Information Amendment, eCTD 0027, page 2.

- AMI (ICD-10 I21) or stroke (ICD-10 H34.1, I60-I64) in a primary or secondary position.

- A non-AMI, non-stroke, cardiovascular diagnosis (as listed under **In-hospital Cardiovascular Death** in **APPENDIX 2**), in the primary position, with death occurring within 30 days of admission, as determined by linkage to the National Records of Scotland.

- A cardiac procedure, with death occurring within 30 days of admission, as determined by linkage to the National Records of Scotland.[13]

To adjudicate events identified at the first stage,

- Research nurses reviewed patients' medical charts, completed Medical Record Chart Abstraction Forms with brief (≈20 word) event summaries and causes of death from death certificates, if available, and attached supporting documents, such as, hospital discharge summaries, electrocardiograms, and reports from computerized tomography of brain.

- Two clinicians from the University of Dundee independently reviewed the packets prepared by the research nurses and adjudicated events according to levels of certainty,

    - AMI or stroke events, without death occurring within 30 days of hospitalization, adjudicated as definite, probable, possible, or non-case.

    - Cardiovascular deaths, adjudicated as definite, possible, unknown cause of death, or non-case.[14]

SPD555-802 prepared the following adjudication guidelines. Adjudicating non-fatal AMI or stroke as definite required two items of supporting clinical evidence recorded within 30 days before or after the index code. Events with only one supporting clinical item could receive the probable adjudication result. Items of evidence supporting AMI included, (1) chest pain, (2) abnormal cardiac enzymes, (3) abnormal electrocardiogram, (4) abnormal imaging test, (5) thrombolysis treatment, or (6) coronary revascularization. Items of evidence supporting stroke included, (1) referral to a neurologist, (2) acute treatment for stroke, (3) residual damage from stroke, (4) abnormal brain imaging, or (5) physical therapy for neurological deficit.

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[13] Cardiac procedure defined by codes in OPCS4 Chapter K – Heart. See, NHS Office of Population Censuses and Surveys (OPCS), Classification of Interventions and Procedures (4th revision), accessed at https://www.datadictionary.nhs.uk/web_site_content/supporting_information/clinical_coding/opcs_classification_of_interventions_and_procedures.asp on June 29, 2018.

[14] The ISD Medical Record Chart Abstraction Form included *definite*, *probable*, and *possible* as response options for adjudicating cardiovascular death. However, guidelines for adjudicating suspected cardiovascular death distinguished only two levels of certainty, *i.e.*, definite or possible. The Validation Plan (page 37) indicates that ISD adjudicated cardiovascular death as either *confirmed case* or *noncase*.

Adjudicating cardiovascular death as definite required a finding of "cardiovascular death specifically reported," with cause of death subclassified as (1) acute MI, (2) sudden cardiac death, (3) heart failure, (4) stroke, (5) cardiovascular procedure-related, (6) cardiovascular hemorrhage, or (7) other cardiovascular. Absent a report attributing death specifically to a cardiovascular cause, clinicians could adjudicate cardiovascular death as possible if the chart abstract contained evidence of a cardiovascular event occurring within the 30 days before death.

Procedures blinded clinician adjudicators to the study exposure, prucalopride or PEG. If the two clinicians classified events differently, "a third clinician reviewed the case, and the case was discussed by all three reviewers until consensus was reached."[15]

With details not disclosed to FDA because of "data protection policies in place," SPD555-802 asserted, "medical chart abstraction [in ISD] could be performed for almost all potential cases evaluated."[16,17]

3.4.1.5 Other Variables

Variables used for cohort matching included,

- Sex
- Calendar year of index date
- Year of birth

ISD developed a propensity score model from 26 variables in eight domains (**APPENDIX 4**), including,

- Demographic factors (4 variables)
- Prescription opioid history (2 variables)
- History of gastrointestinal (GI) problem (2 variables)

[15] Final Study Report, page 41.

[16] Final Study Report, page 82.

[17] A flow diagram (Final Study Report, Figure 6, page 83) summarized the MACE adjudication procedure. The diagram identified three ISD events excluded from analysis possibly because of missing patient charts. This detail possibly contradicts the Validation Plan (page 29), which reads, "Any cases identified by the electronic algorithm where no chart abstraction form is available will be reviewed and given a final status based on available information in the database."

- History of cardiovascular hospitalization (5 variables)
- History of cardiovascular procedure (2 variables)
- Prescription drug history (5 variables)
- Medical history (5 variables)
- Health care utilization (1 variable)

3.4.1.6 Statistical Analysis

See Section 3.3.1.6 Statistical Analysis.

3.4.2 Study Results

3.4.2.1 Eligible cohort

During the January 2010 - May 2016 study period, ISD identified 1,530 patients with a dispensing for PRU. ISD excluded 281 (18.4%) as ineligible (Section 3.3.1.2 Eligibility Criteria). With patients possibly excluded for more than one reason, the three most frequently occurring reasons for exclusion included, (1) <12 months pre-index data available (N=106), (2) PEG prescribed on PRU index date (N=70), and (3) all follow-up in overlap with PEG (N=51).

ISD identified 700,215 patients with a dispensing for PEG. ISD excluded 254,920 (36.4%). With patients possibly excluded for more than one reason, two factors accounting for nearly every patient excluded, (1) <12 months pre-index data available (N=189,514) and (2) age <18 years (N=96,314).

Patients remaining, 1,249 PRU and 445,295 PEG, formed the eligible patient population.

3.4.2.2 Baseline characteristics of the matched population

ISD successfully found five PEG matches for every PRU patient. As shown in Table 7, the matched patient cohorts included 95.9% female sex and 77.5% aged 18-54 years. Patients in PRU *vs.* PEG differed markedly with respect to history of gastrointestinal problems, as measured by (1) pre-index hospitalization with constipation (47.3% *vs.* 6.5%) and (2) pre-index hospitalization with other gastrointestinal diagnosis (40.4% *vs.* 16.0%). "To avoid disclosure of small cell counts,"[18] the documents available to DEPI omitted a presentation from ISD of patient-years exposed to PRU and PEG in categories defined by baseline characteristics.

[18] Final Study Report, page 72.

Table 7: Information Services Division (ISD) of Scotland, baseline characteristics of the prucalopride (PRU) cohort (N=1,249) and the matched polyethylene glycol 3350 (PEG) cohort (N=6,245).

	PATIENTS		
Baseline variable [1]	PRU %	PEG %	SD
Matching variable			
Female sex	95.9	95.9	0.00
Age 18-54 years	77.4	77.5	0.00
Year 2010-2012	35.5	35.5	0.00
Recent hospitalization	8.5	11.1	0.09
Low socioeconomic level [3]	24.6	24.9	0.01
Outpatient prescription opioid history			
Recent opioid	41.4	44.9	0.07
Chronic opioid	38.1	35.2	0.06
History of GI problem			
Constipation hospitalization	47.3	6.5	1.04
Other inpatient GI diagnosis	40.4	16.0	0.56
Any cardiovascular hospitalization	7.0	5.5	0.06
Outpatient prescription drug history			
Anticoagulant	2.6	3.0	0.02
Antidiabetic	7.2	5.5	0.07
Antihypertensive	35.5	30.8	0.10
Aspirin or platelet inhibitor	11.8	10.2	0.05
HMG CoA reductase inhibitor	16.2	14.1	0.06
Medical history			
Cancer	4.6	6.6	0.08
COPD	2.4	2.4	0.00
Diabetes	6.4	3.3	0.14
Hyperlipidemia	2.6	1.6	0.07
Hypertension	8.0	6.8	0.05

REFERENCE: Table assembled by DEPI from Table 2 and Table 3 in Supplemental Full Results File.
ABBREVIATIONS: COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; SD, standardized difference
FOOTNOTE:
1. See **APPENDIX 4** for variable definitions.

3.4.2.3 Exposure

The documents available to DEPI omitted detailed information about patient-year exposure accrued by ISD patients in the PRU and matched PEG cohorts. A summary in the Final Study

Report placed median exposures in PRU and PEG at 63-70 days and 37 days, respectively.[19]

3.4.2.4 Sex- and age-adjusted results in matched cohorts

As summarized in Table 8, the primary outcome of MACE occurred with incidence during current treatment at 2.9 and 3.0 per 1000 patient-years in PRU and PEG, respectively (IRR, 0.99, 95% CI 0.09-6.93). PRU and PEG, each, contained <5 MACEs.[20]

Table 8: Information Services Division (ISD) of Scotland, MACE incidence rates (per 1000 patient-years) in matched cohorts.

	PRU N=1,249		PEG N=6,245			
Outcome	Rate	95% CI	Rate	95% CI	IRR	95% CI
MACE	2.9	0.4-10.6	3.0	0.8-7.6	0.99	0.09-6.93
non-fatal AMI	1.5	0.0-8.2	0.7	0.0-4.1	1.99	0.03-156.
non-fatal stroke	1.5	0.0-8.2	0.7	0.0-4.1	1.99	0.03-156.
cardiovascular death	0.0	0.0-5.4	2.2	0.5-6.5	0.00	0.00-4.81

REFERENCE: Table assembled by DEPI from Tables 9a1, 9a2, 9a3, and 9a4 in Supplemental Full Results File.
ABBREVIATIONS: AMI, Acute Myocardial Infarction; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiovascular Event; PRU, prucalopride; PEG polyethylene glycol 3350

3.4.2.5 Cohort trimming and propensity score stratification

SPD555-802 evaluated 26 covariates in ISD for patient-year balance achieved by cohort trimming and propensity score stratification.[21] Figure 4 shows results for three illustrative covariates, (1) age at index, (2) other inpatient GI diagnosis, and (3) antihypertension prescription drug history.

In six propensity score deciles (Deciles 1, 3, 5, 7, 9, and 10), younger patients (18-54 years at baseline) supplied relatively more patient-years in PRU than PEG, with differences regarded in each instance as non-negligible (SD > 0.10; Figure 4, Part A).

Patients with a baseline history of other inpatient GI diagnosis distinctively supplied more than one quarter of all patient-years accumulated by PRU or PEG patients in the top four propensity score deciles (Figure 4, Part B). In one decile (Decile 8), patients with a baseline history of other inpatient GI diagnosis supplied relatively more patient-years in PRU than PEG (95.1% *vs.* 84.6%, SD 0.35). In two deciles (Deciles 7 and 9), patients with a baseline history of other inpatient GI diagnosis supplied relatively fewer patient-years in PRU than PEG (Decile 7: 69.4%

[19] Final Study Report, Section 10.2.1 Duration of Use of Prucalopride and PEG, page 72.

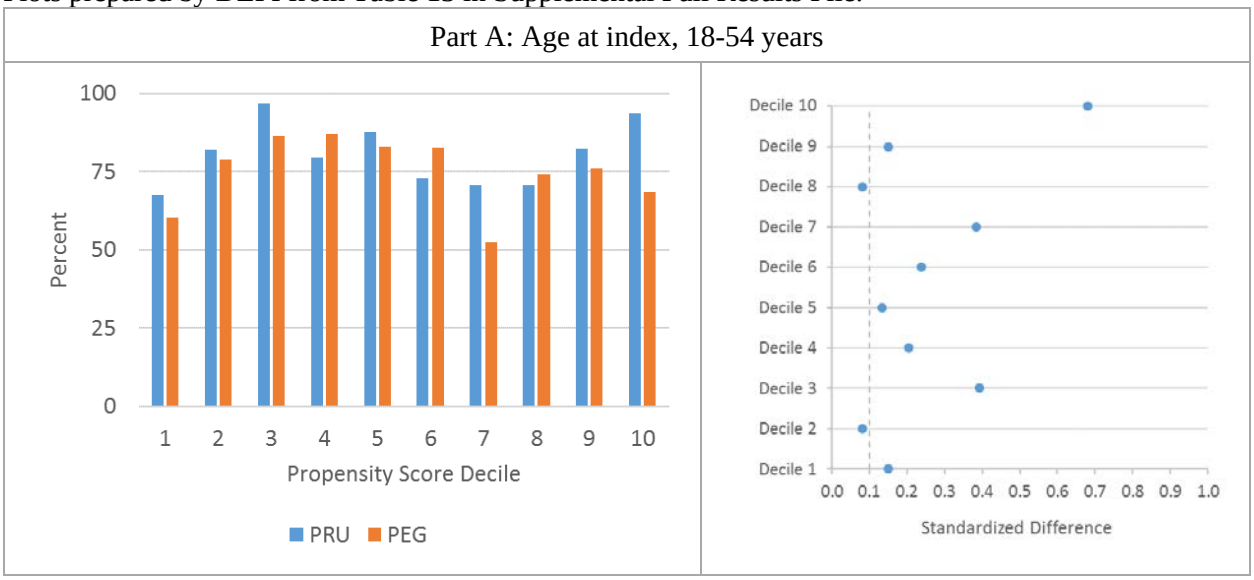
[20] Exact counts not reported as required by ISD patient privacy rules.

[21] See Table 13 in Supplemental Full Results File.

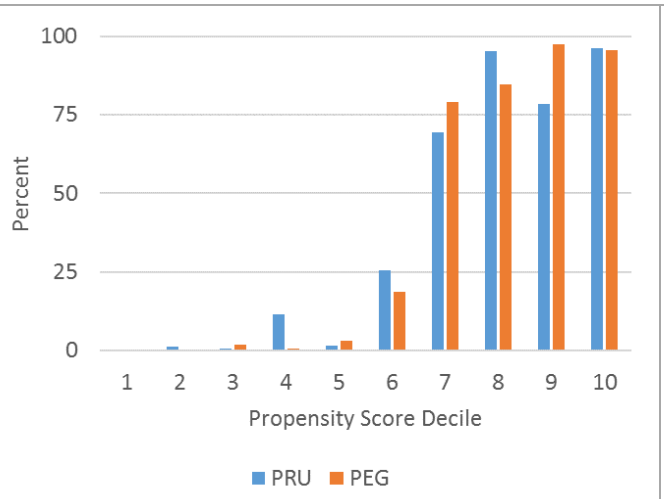
vs. 79.0%, SD 0.22; Decile 9: 78.4% *vs.* 97.4%, SD 0.61). Overall, before trimming, patients with a baseline history of other inpatient GI diagnosis supplied relatively more patient-years in PRU than PEG (40.4% *vs.* 16.0%, SD 0.56; Table 7).

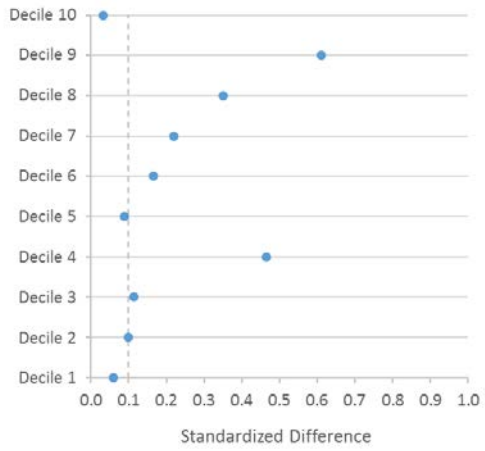
Overall, before trimming, patients with a baseline antihypertensive prescription history supplied relatively more patient-years in PRU than PEG (35.5% vs. 30.8%, SD 0.10; Table 7). After trimming, patients with a baseline antihypertensive prescription history supplied relatively more patient-years (SD > 0.10) in PRU than PEG in four deciles (Deciles 4, 6, 8, and 9) and relatively fewer patient-years in PRU than PEG in five deciles (Deciles 2, 3, 5, 7, and 10).

Figure 4: Information Services Division (ISD) of Scotland, patient-year balance achieved between prucalopride (PRU) and polyethylene glycol 3350 (PEG). Results shown (in trimmed cohorts, by propensity-score stratum) for three variables (risk factors), age at index (Part A), other inpatient GI diagnosis (Part B), and antihypertensive outpatient prescription drug history (Part C). The left-hand plots compare, by propensity score decile, percent of person-years in PRU and PEG with the indicated risk factor. The right-hand plots express covariate balance in each propensity score decile as a standardized difference (SD), with a vertical dashed line defining the upper boundary for negligible difference (*i.e.*, SD = 0.10). Plots prepared by DEPI from Table 13 in Supplemental Full Results File.

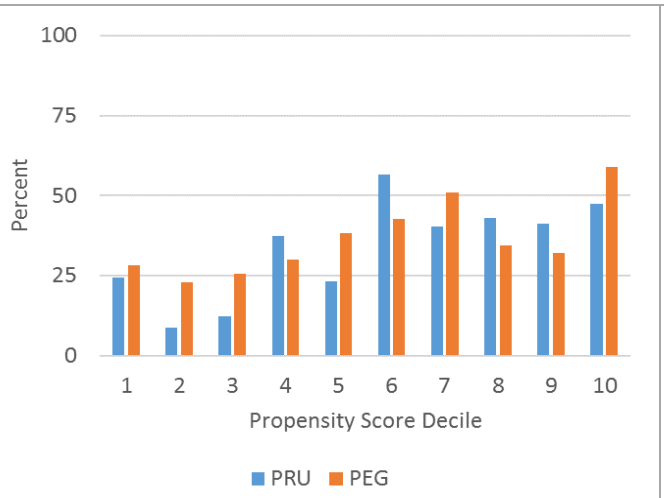


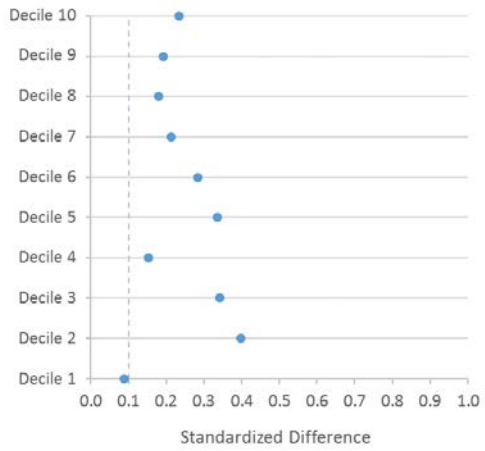
Part B: Other inpatient GI diagnosis (**APPENDIX 4**)





Part C: Antihypertensive prescription drug history (**APPENDIX 4**)





REFERENCE: Plot prepared by DEPI from Table 13 in Supplemental Full Results File.

3.4.2.6 Primary results

Trimming eliminated 95 of 1,249 (7.6%) patients from PRU and 439 of 6,245 (7.0%) patients from PEG. After trimming, with <5 MACEs confirmed in PRU and PEG each, the two study cohorts contained,

- PRU: N=1,154 patients with MACE incidence estimated at 1.6 per 1000 patient-years.
- PEG: N=5,806 patients with MACE incidence estimated at 2.4 per 1000 patient-years.

Accordingly, after trimming, ISD estimated crude MACE incidence in PRU relative to PEG at IRR 0.67, 95% CI 0.01-8.38. Stratifying by propensity score decile, ISD estimated standardized MACE incidence in PRU relative to PEG at SIRR 0.40, 95% CI 0.04-3.98.

3.4.2.7 Results for secondary outcomes

For completeness, Table 9 summarizes results from ISD for the secondary outcomes of non-fatal AMI, non-fatal stroke, and in-hospital cardiovascular death.

Table 9: Information Services Division (ISD) of Scotland, results for primary and secondary outcomes, before and after trimming.

	Untrimmed				Trimmed					
Outcome	PRU	PEG	IRR	95% CI	PRU	PEG	IRR	95% CI	SIRR	95% CI
MACE	<5	<5	0.99	0.09-6.93	<5	<5	0.67	0.01-8.38	0.40	0.04-3.98
non-fatal AMI	<5	<5	1.99	0.03-156.	<5	0				
non-fatal stroke	<5	<5	1.99	0.03-156.	0	<5	0.00	0.00-78.8		
CV death	0	<5	0.00	0.46-4.81	0	<5	0.00	0.00-10.8		

REFERENCE: Table assembled by DEPI from Tables 9a1, 9a2, 9a3, 9a4, 14a, 14b, 14c, and 14d in Supplemental Full Results File.
ABBREVIATIONS: AMI, acute myocardial infarction; CV death, in-hospital cardiovascular death; PRU, prucalopride; PEG, polyethylene glycol 3350; IRR, incidence rate ratio; CI, confidence interval; SIRR, standardized incidence rate ratio

3.4.2.8 Results from subgroup analyses

For completeness, Table 10 summarizes crude results for MACE in subgroups defined by sex, age, and other baseline measures of cardiovascular disease risk. The documents available to DEPI omitted ISD-specific results from subgroup analyses controlled for propensity score.

Table 10: Information Services Division (ISD) of Scotland, crude results for MACE, before cohort trimming, in categories of sex, age, and other baseline measures of cardiovascular disease risk.

	PRU		PEG			
Group	MACE	IR	MACE	IR	IRR	95% CI
Overall	<5	2.9	<5	3.0	0.99	0.09-6.93
Sex and age, years						
Women, 18-54	0	0.0	<5	2.1	0.00	0.00-9.45
Women, ≥55	<5	7.8	<5	5.7	1.37	0.02-26.2
Men, 18-54	0	0.0	0	0.0		
Men, ≥55	<5	270.	0	0.0		
Age, years						
18-54	0	0.0	<5	2.0	0.00	0.00-9.49
≥55	<5	15.2	<5	5.4	2.84	0.21-39.2
History of CV hospitalization						
No	<5	1.6	<5	2.4	0.68	0.01-8.43
Yes	<5	16.4	<5	10.6	1.55	0.02-122.
≥1 CV risk factor [1]						
No	0	0.0	0	0.0		
Yes	<5	6.0	<5	5.7	1.04	0.09-7.28

REFERENCE: Table assembled by DEPI from Table 9a1 in Supplemental Full Results File.
ABBREVIATIONS: MACE, Major Adverse Cardiovascular Event; CV, cardiovascular; PRU, prucalopride; PEG, polyethylene glycol 3350; IR, incidence rate (per 1000 patient-years); IRR, incidence rate ratio; CI, confidence interval
1. Age ≥55 years, history of CV hospitalization, hypertension, hyperlipidemia, diabetes, or obesity.

3.4.2.9 Results from sensitivity analyses

The documents available to DEPI omitted ISD-specific results from sensitivity analysis.

3.5 Clinical Practice Research Datalink (CPRD)

3.5.1 Study Methods

3.5.1.1 Study Setting

CPRD used the GOLD database, with partial linkage to Hospital Episode Statistics (HES)[22] and Office for National Statistics (ONS),[23] to capture study exposures (PRU and PEG) and outcomes (MACE) occurring between April 2010 through August 2016 in patients registered under select U.K. general practices outside Scotland.

GOLD provided access to clinical information recorded by U.K. general practitioners (GP) who used a popular electronic health record (EHR) software system[24] to manage patientcare [6]. CPRD used GOLD to produce spreadsheet-formatted longitudinal records (*i.e.*, patient profiles) of clinical events (diagnoses and symptoms), therapies, diagnostic tests, specialist referrals, hospital admissions, and death (including date of death and cause of death) in patients prescribed PRU or PEG by their GP.

A subset (≈65%) of CPRD practices in England permitted patient linkage to HES and ONS. CPRD used HES and ONS links to supplement GOLD longitudinal patient records with information about admissions to hospital (including date and reason for admission) and deaths (including date of death and cause of death).

For general information about CPRD capabilities, see, Herrett, *et al.*, 2015 [6].

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[22] For information about HES, a database containing information about admissions to National Health Service hospitals, see, Hospital Episode Statistics (HES), accessed at https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics on July 11, 2018.

[23] For information about ONS, a reference to a database of deaths registered in England or Wales, see, Office of National Statistics, Mortality Statistics: Use Guide to Mortality Statistics, July 2017, accessed at www.ons.gov.uk on July 11, 2018.

[24] VISION, https://www.visionhealth.co.uk/general-practice/

3.5.1.2 Eligibility Criteria

CPRD used the same eligibility criteria as SNR. See Section 3.3.1.2 Eligibility Criteria.

3.5.1.3 Exposure

Except for two differences, CPRD and SNR defined exposure alike (Section 3.3.1.3 Exposure). CPRD specified PRU or PEG exposure by prescriptions written for patients by physicians, whereas SNR specified exposures by prescriptions dispensed to patients by pharmacies. Unlike SNR, CPRD did not stockpile, *i.e.*, extend the exposure period when patients refilled prescriptions before exhausting the days supplied by earlier prescriptions. Like ISD, CPRD replaced missing values for days of supply with the age- and sex-specific modal values for patients with non-missing values for days of supply.[25]

3.5.1.4 Outcomes

CPRD used a two-stage procedure to identify the primary outcome, MACE, a composite of non-fatal AMI, non-fatal stroke, and in-hospital cardiovascular death.

To identify events for processing at the second stage, the first stage used an electronic search algorithm to screen GOLD and linked records in HES and ONS. The screening algorithm selected events satisfying any one of the following conditions,

- An HES code for AMI (ICD-10 I21) or stroke (ICD-10 H34.1, I60-I64)
- An ONS underlying-cause-of-death ICD-10 code for cardiovascular disease (as listed under **In-hospital Cardiovascular Death** in **APPENDIX 2**), with date of death coincident with a hospitalization record in HES
- A GOLD code for AMI or stroke, co-occurring (±30 days) with a code in GOLD for hospitalization
- A GOLD code for chest pain, co-occurring (±30 days) with a code in GOLD for hospitalization and at least one GOLD code for cardiac enzyme testing, cardiac enzyme abnormality, cardiac imaging abnormality, thrombolytic therapy, coronary revascularization, or stress testing
- Death in GOLD, coincident (±30 days) with a code in GOLD for hospitalization, provided

[25] All prescriptions missing values for days of supply in 18.5% and 74.0% of patients in PRU and PEG, respectively, per Clinical Information Amendment, eCTD 0027, page 2.

cause of death from ONS not available

Second-stage processing of events identified during the first stage entailed a sequence of four steps, as summarized below.

Step 1. Administrative processing,

- Accepted as definite non-fatal AMI or definite non-fatal stroke, without further adjudication, those events identified by AMI or stroke codes in the primary position of an HES record, provided death not recorded within 30 days of hospital admission.

- Accepted as definite cardiovascular death, without further adjudication, those events identified by ONS underlying-cause-of-death code.

- Excluded from further consideration those deaths identified in GOLD, if a preliminary assessment of the patient profile identified a non-cardiovascular cause of death.

Step 2. Events passing Step 1 triggered a request for information from general practitioners. Specifically, CPRD sent brief questionnaires to GPs, which requested GP-review of local medical records to confirm (1) diagnoses of AMI, stroke, or cardiovascular death, (2) event dates, (3) hospitalization, (4) hospitalization dates, and (5) elements central to diagnosis (*e.g.*, changes on electrocardiogram indicative of new myocardial ischemia).

Step 3. Up to two clinicians independently assessed patient profiles and GP questionnaires. CPRD referred events for formal outcome adjudication by committee, unless two clinicians both found no evidence for definite, probable, or possible MACE.

Step 4. Events passing Step 4 triggered committee adjudication of patient profiles and GP questionnaires, as described above for ISD under Section 3.4.1.4 Outcomes.

SPD555-802 asserted that procedures blinded Step 3 and Step 4 assessments to treatment group. SPD555-802 achieved this objective by redacting information about exposure (*i.e.*, treatment with PRU or PEG) from "patient database profiles, free-text entries, completed GP questionnaires, and electronic copies of other medical records."[26] Adjudication procedures did not use information in free-text EHR fields sometimes available to CPRD investigators. The SPD555-802 protocol had disclosed uncertainty about the availability of free-text information from CPRD.[27]

SPD555-802 reported (1) a GP rate of response to questionnaire "slightly less than initially

[26] Study Protocol, page 38.

[27] Study Protocol, page 33.

expected" and (2) linkage to HES and ONS possible for "approximately 50% of the patients."[28] CPRD requested GP questionnaires for 91 MACEs (including out-of-hospital cardiovascular death), with a completed response received for 52 (57%).

3.5.1.5 Other Variables

Variables used for cohort matching included,

- Sex
- Calendar year of index date
- Year of birth

CPRD developed a propensity score model from 38 variables in nine domains, including,

- Demographic factors (6 variables)
- Prescription opioid history (2 variables)
- History of gastrointestinal (GI) problem or procedure (4 variables)
- History of cardiovascular hospitalization (5 variables)
- History of cardiovascular procedure (3 variables)
- Prescription drug history (5 variables)
- Medical history (7 variables)
- Health care utilization (2 variable)
- Behavioral risk factor (4 variables)

Specifications for variables in the history of cardiovascular hospitalization, history of cardiovascular procedure, and medical history categories combined all pre-index data available in either GOLD or HES. Behavioral risk factor variables included,

- Smoking status, based on the most recent information available in GOLD during the 10 years before the index date, including the index date.

[28] Final Study Report, page 91.

- Alcohol use, based on the most recent information available in GOLD during the 10 years before the index date, including the index date.

- Body mass index (BMI) >30 kg/m^2, based on the most recent information available in GOLD during the three years before the index date, including the index date.

- Surgical or drug treatment for obesity, based on any information available in GOLD or HES during the three years before the index date, including the index date.

3.5.1.6 Statistical Analysis

To prevent overlap with ISD, SPD555-802 excluded CPRD practices in Scotland. To mitigate overlap between CPRD and THIN, SPD555-802 applied a complex method, analogous to one described by Cai, *et al.* [7], to identify anonymized practices in CPRD and THIN that appeared to be contributing the same patients to the study population. SPD555-802 excluded all patients from duplicated CPRD practices, unless linked to HES and ONS. Subsequent analysis followed procedures summarized above under Section 3.3.1.6 Statistical Analysis.

3.5.2 Study Results

3.5.2.1 Eligible cohort

During the April 2010 - August 2016 study period, CPRD identified 1,638 patients with a prescription written for PRU. CPRD excluded 686 (41.9%) as ineligible (Section 3.3.1.2 Eligibility Criteria), including 461 (28.1%) because of registration in Scotland or in a non-Scottish practice duplicated in THIN. With patients possibly excluded for more than one reason, the three other most frequently occurring reasons for exclusion included, (1) all follow-up in overlap with PEG (N=169), (2) <12 months pre-index data available (N=117), and (3) PEG prescribed on PRU index date (N=96).

CPRD identified 477,764 patients with a prescription written for PEG. CPRD excluded 279,421 (58.5%), including 138,445 patients (29.0%) because of registration in Scotland or in a non-Scottish practice duplicated in THIN. With patients possibly excluded for more than one reason, the three other most frequently occurring reasons for exclusion included, (1) prior use of PEG (N=88,874), (2) age <18 years (N=76,694), and (3) <12 months pre-index data available (N=52,753).

Patients remaining, 952 PRU and 198,343 PEG, formed the eligible patient population.

3.5.2.2 Baseline characteristics of the matched population

CPRD found five PEG matches for 950 PRU patients and four PEG matches for two PRU patients. Therefore, the matched cohorts contained 952 and 4,758 patients in PRU and PEG,

respectively, including 94.5% female and 64.6% aged 18-54 years.

On a per patient basis,

- PRU women accumulated more time on treatment than men, mean 6.7 *vs.* 3.6 months.
- Younger (18-54 year-old) PRU patients accumulated more time on treatment than older (≥55 year-old) patients, 6.8 *vs.* 6.0 months.
- Younger PEG patients accumulated less time on treatment than older patients, 2.4 *vs.* 3.4 months.

Because of these sex- and age-specific differences in mean exposure, women and younger patients accounted for larger fractions of total patient-year exposure in PRU than PEG (Table 11), as reproduced below,

- Female sex, 97.0% *vs.* 93.7%, SD 0.16
- 18-54 years of age, 67.5% *vs.* 56.4%, SD 0.23

Examples of other variables with notable differences (SD ≥ 0.10) between PRU and PEG patient-years included,

- History of other inpatient GI diagnosis, 40.9% *vs.* 26.7%
- History of any cardiovascular hospitalization, 4.8% *vs.* 7.7%
- Medical history for cancer, 7.4% *vs.* 10.3%, diabetes, 6.2% *vs.* 9.4%, and hypertension, 22.3% *vs.* 28.7%
- Body mass index >30 kg/m^2, 18.9% vs. 25.0%

Table 11: Clinical Practice Research Datalink (CPRD), baseline characteristics of the prucalopride (PRU) cohort (952 patients with 519 patient-years) and the matched polyethylene glycol 3350 (PEG) cohort (4,758 patients with 1,098 patient-years).

	PATIENTS			PATIENT-YEARS [1]		
Baseline variable	PRU %	PEG %	SD	PRU %	PEG %	SD
Matching variable						
Female sex	94.5	94.5	0.00	97.0	93.7	0.16
Age 18-54 years	64.6	64.6	0.00	67.5	56.4	0.23
Year 2010-2012	39.7	39.7	0.00	55.7	50.1	0.11
Recent hospitalization	5.1	7.4	0.09	4.2	6.3	0.10
Low socioeconomic level [2]	16.1	17.7	0.04	15.3	17.1	0.05
Outpatient prescription opioid history						
Recent opioid	33.1	33.1	0.00	35.8	38.2	0.05
Chronic opioid	32.8	25.9	0.15	34.9	33.1	0.04
History of GI problem						
IBS outpatient diagnosis	39.6	17.7	0.50	42.9	17.6	0.57
Constipation outpatient diagnosis	78.7	41.8	0.81	77.8	47.6	0.66
Other outpatient GI diagnosis	46.5	30.9	0.32	49.3	33.7	0.32
Constipation inpatient diagnosis	29.9	4.4	0.72	27.3	5.7	0.61
Other inpatient GI diagnosis	44.2	24.5	0.43	40.9	26.7	0.30
Any cardiovascular hospitalization	6.5	5.7	0.03	4.8	7.7	0.12
Outpatient prescription drug history						
Anticoagulant	2.7	3.7	0.05	2.1	5.0	0.16
Antidiabetic	8.3	7.3	0.04	6.8	8.0	0.05
Antihypertensive	49.6	42.3	0.15	52.4	49.6	0.06
Aspirin or platelet inhibitor	19.0	15.7	0.09	17.3	19.4	0.05
HMG CoA reductase inhibitor	21.8	19.3	0.06	21.0	23.9	0.07
Medical history						
Asthma	25.9	19.0	0.17	25.4	17.5	0.19
Bronchitis, emphysema, and COPD	5.4	5.4	0.00	3.9	7.8	0.17
Cancer	7.9	10.6	0.09	7.4	10.3	0.10
Chronic kidney disease	6.0	6.3	0.01	4.7	8.1	0.14
Diabetes	9.0	8.5	0.02	6.2	9.4	0.12
Hyperlipidemia	16.4	15.5	0.02	17.1	18.6	0.04
Hypertension	22.3	24.2	0.05	22.3	28.7	0.15
Behavioral risk factor						
Current smoker	18.3	22.0	0.09	18.0	18.3	0.01
Body mass index >30 kg/m^2	15.8	23.2	0.19	18.9	25.0	0.15

REFERENCE: Table assembled by DEPI from Table 2 and Table 3 in Supplemental Full Results File.
ABBREVIATIONS: COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; IBS, irritable bowel syndrome; SD, standardized difference
FOOTNOTES:
1. Patient-years of exposure before first MACE. See Section 3.3.1.3 Exposure.
2. Low-quintile Index of Multiple Deprivation, as defined in PRU cohort.

3.5.2.3 Exposure

The 952 PRU and 4,758 matched PEG patients in CPRD accumulated 519 and 1,098 patient-years on treatment, respectively, with mean patient exposures higher in PRU than PEG (6.5 *vs.* 2.8 months, Figure 5). As shown in Figure 6, 42.3% in PRU and 17.8% in PEG accumulated >90 days exposure. First episodes of treatment accounted for approximately 32% and 49% of total exposure in PRU and PEG, respectively.

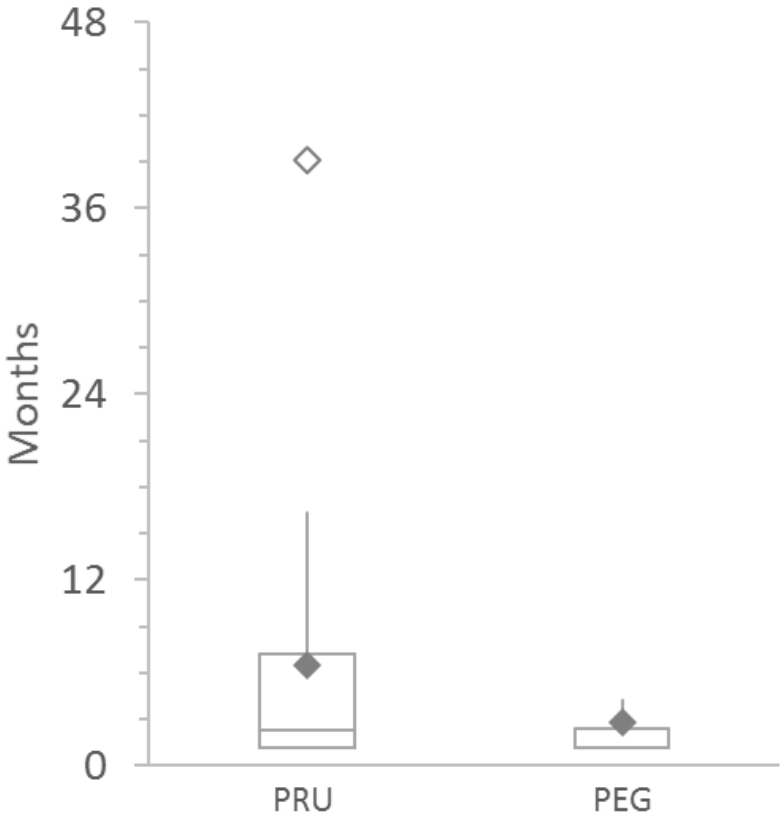


Figure 5: Clinical Practice Research Datalink (CPRD), box plots summarizing patient exposures for 952 and 4,758 patients in prucalopride (PRU) and polyethylene glycol 3350 (PEG) cohorts, respectively, with means shown as solid diamonds, maximum values as open diamonds, and 25th, 50th, and 75th percentiles as horizontal lines. Each whisker connects a 75th percentile to a value equal to 1.5 times the interquartile range added to the 75th percentile. Plot prepared by DEPI from Table 4 in Supplemental Full Results File.

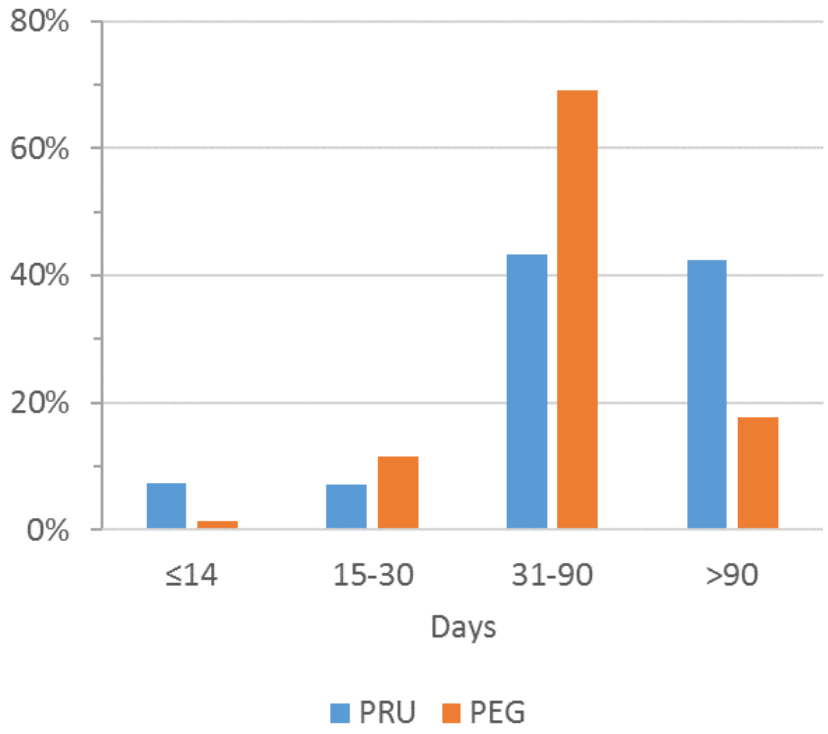


Figure 6: Clinical Practice Research Datalink (CPRD), 952 and 4,758 patients from prucalopride (PRU) and polyethylene glycol 3350 (PEG) cohorts, respectively, distributed by cumulative exposure to study drug. Plot prepared by DEPI from Table 4 in Supplemental Full Results File.

3.5.2.4 Sex- and age-adjusted results in matched cohorts

The primary outcome of MACE occurred during current treatment in 2 of 952 (0.21%) and in 4 of 4,758 (0.08%) patients from PRU and PEG, respectively (Table 12). The secondary outcomes of non-fatal AMI, non-fatal stroke, and in-hospital cardiovascular death occurred in 1, 1, and 0 PRU patients, respectively.

Table 12: Clinical Practice Research Datalink (CPRD), Major Adverse Cardiovascular Events (MACE).

	PRU	PEG
Patients	952	4,758
Patient-years	519	1,098
MACE	2	4
non-fatal AMI	1	2
non-fatal stroke	1	0
CV death	0	2

REFERENCE: Table assembled by DEPI from Tables 9a1, 9a2, 9a3, and 9a4 in Supplemental Full Results

File.
ABBREVIATIONS: AMI, Acute Myocardial Infarction; CV death, in-hospital cardiovascular death; PRU, prucalopride; PEG polyethylene glycol 3350

As summarized in Table 13, the primary outcome of MACE occurred with incidence during current treatment at 3.9 and 3.6 per 1000 patient-years in PRU and PEG, respectively (IRR, 1.06, 95% CI 0.10-7.38).

Table 13: Clinical Practice Research Datalink (CPRD), MACE incidence rates (per 1000 patient-years) in matched cohorts.

	PRU N=952		PEG N=4,758			
Outcome	Rate	95% CI	Rate	95% CI	IRR	95% CI
MACE	3.9	0.5-13.9	3.6	0.9-9.3	1.06	0.10-7.38
non-fatal AMI	1.9	0.1-10.7	1.8	0.2-6.6	1.06	0.02-20.3
non-fatal stroke	1.9	0.1-10.7	0.0	0.0-3.4		
cardiovascular death	0.0	0.0-7.1	1.8	0.2-6.6	0.00	0.00-11.2

REFERENCE: Table assembled by DEPI from Tables 9a1, 9a2, 9a3, and 9a4 in Supplemental Full Results File.
ABBREVIATIONS: AMI, Acute Myocardial Infarction; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiovascular Event; PRU, prucalopride; PEG polyethylene glycol 3350

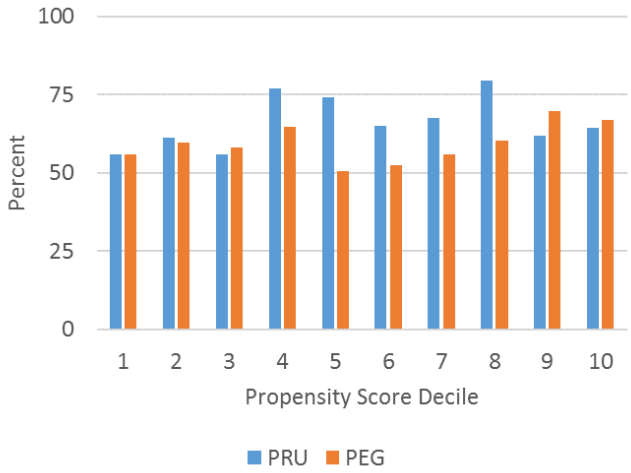
3.5.2.5 Cohort trimming and propensity score stratification

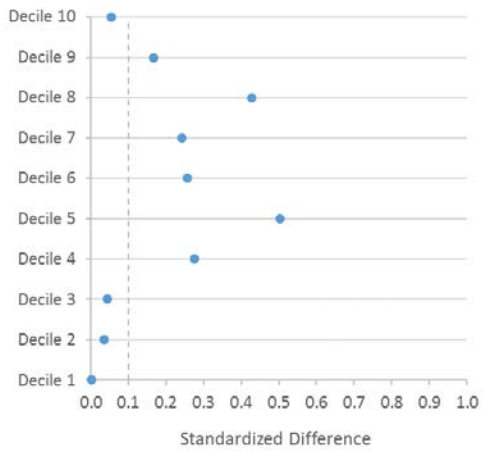
SPD555-802 evaluated 31 covariates in CPRD for patient-year balance achieved by cohort trimming and propensity score stratification.[29] Figure 7 shows results for three illustrative covariates, (1) age at index, (2) other inpatient GI diagnosis, and (3) antihypertension prescription drug history.

[29] See Table 13 in Supplemental Full Results File.

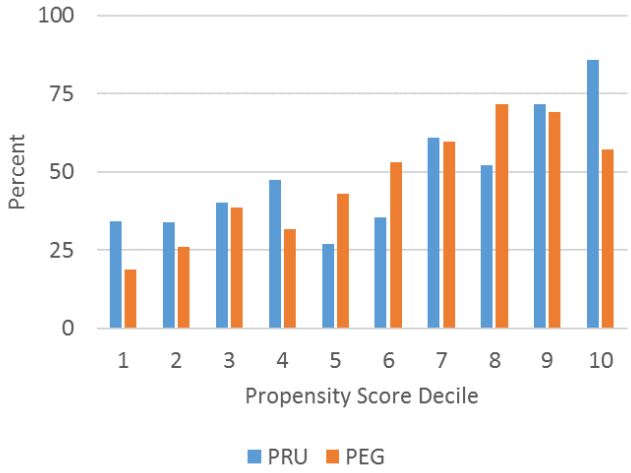
Figure 7: Clinical Practice Research Datalink (CPRD), patient-year balance achieved between prucalopride (PRU) and polyethylene glycol 3350 (PEG). Results shown (in trimmed cohorts, by propensity-score stratum) for three variables (risk factors), age at index (Part A), other inpatient GI diagnosis (Part B), and antihypertensive prescription drug history (Part C). The left-hand plots compare, by propensity score decile, percent of person-years in PRU and PEG with the indicated risk factor. The right-hand plots express covariate balance in each propensity score decile as a standardized difference (SD), with a vertical dashed line defining the upper boundary for negligible difference (*i.e.*, SD = 0.10). Plots prepared by DEPI from Table 13 in Supplemental Full Results File.

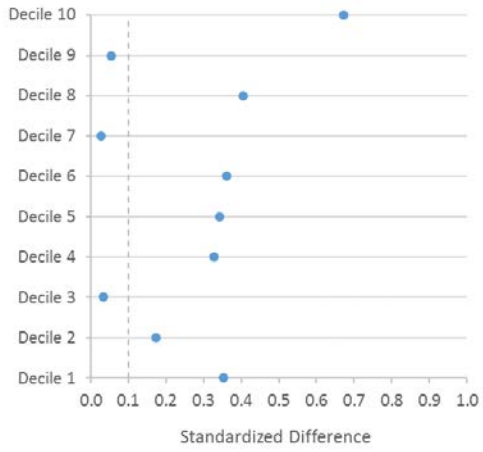
Part A: Age at index, 18-54 years

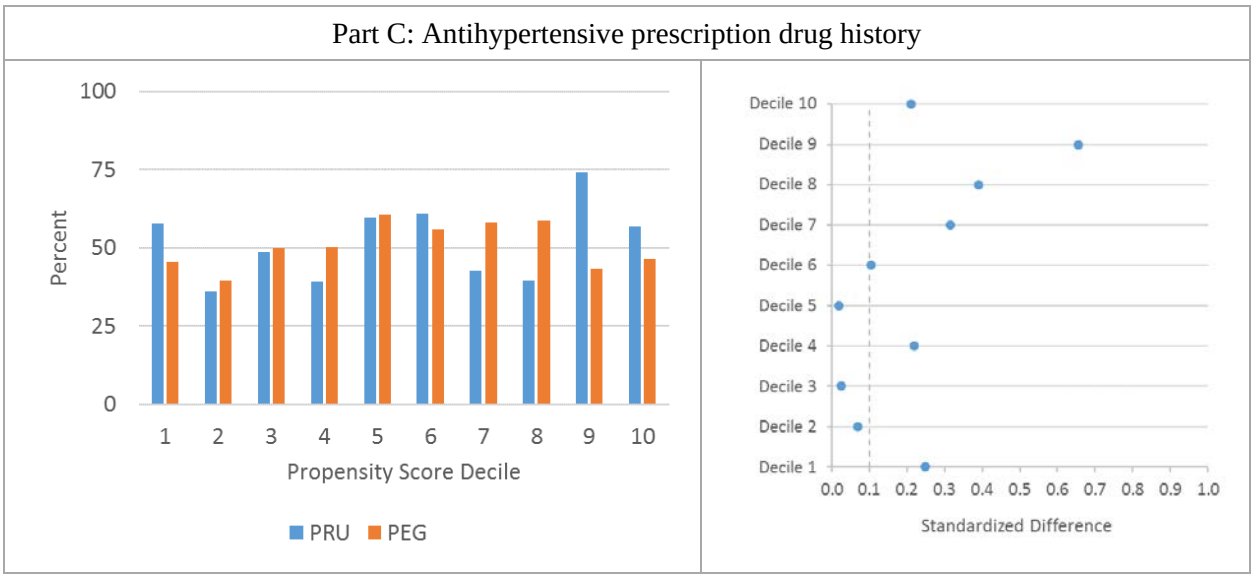




Part B: Other inpatient GI diagnosis







3.5.2.6 Primary results

Trimming eliminated 86 of 952 (9.0%) patients from PRU and 504 of 4,758 (10.6%) patients from PEG. After trimming, the two study cohorts contained,

- PRU: N=866 patients with 2 MACEs over 491 patient-years, IR 4.1 per 1000 patient-years.
- PEG: N=4,254 patients with 4 MACEs over 1,003 patient-years, IR 4.0 per 1000 patient-years.

Accordingly, after trimming, CPRD estimated crude MACE incidence in PRU relative to PEG at IRR 1.02, 95% CI 0.09-7.13. Stratifying by propensity score decile, CPRD estimated standardized MACE incidence in PRU relative to PEG at SIRR 1.40, 95% CI 0.25-7.77.

3.5.2.7 Results for secondary outcomes

For completeness, Table 14 summarizes results from CPRD for the secondary outcomes of non-fatal AMI, non-fatal stroke, and in-hospital cardiovascular death.

Table 14: Clinical Practice Research Datalink (CPRD), results for primary and secondary outcomes, before and after trimming.

	Untrimmed				Trimmed					
Outcome	PRU	PEG	IRR	95% CI	PRU	PEG	IRR	95% CI	SIRR	95% CI
MACE	2	4	1.06	0.10-7.38	2	4	1.02	0.09-7.13	1.40	0.25-7.97
non-fatal AMI	1	2	1.06	0.02-20.3	1	2	1.02	0.02-19.6	1.03	0.09-11.4
non-fatal stroke	1	0			1	0				
CV death	0	2	0.00	0.00-11.2	0	2	0.00	0.00-10.8		

REFERENCE: Table assembled by DEPI from Tables 9a1, 9a2, 9a3, 9a4, 14a, 14b, 14c, and 14d in Supplemental Full Results File.
ABBREVIATIONS: AMI, acute myocardial infarction; CV death, in-hospital cardiovascular death; PRU,

prucalopride; PEG, polyethylene glycol 3350; IRR, incidence rate ratio; CI, confidence interval; SIRR, standardized incidence rate ratio

3.5.2.8 Results from subgroup analyses

For completeness, Table 15 summarizes crude results for MACE in subgroups defined by sex, age, and other baseline measures of cardiovascular disease risk. The documents available to DEPI omitted CPRD-specific results from subgroup analyses controlled for propensity score.

Table 15: Clinical Practice Research Datalink (CPRD), crude results for MACE, before cohort trimming, in categories of sex, age, and other baseline measures of cardiovascular disease risk.

	PRU		PEG			
Group	MACE	IR	MACE	IR	IRR	95% CI
Overall	2	3.9	4	3.6	1.06	0.10-7.38
Sex and age, years						
Women, 18-54	0	0.0	0	0.0		
Women, ≥55	2	12.6	3	7.0	1.80	0.15-15.7
Men, 18-54	0	0.0	0	0.0		
Men, ≥55	0	0.0	1	20.3	0.00	0.00-207.
Age, years						
18-54	0	0.0	0	0.0		
≥55	2	11.9	4	8.4	1.42	0.13-9.92
History of CV hospitalization						
No	1	2.0	2	2.0	1.03	0.02-19.7
Yes	1	40.3	2	23.7	1.70	0.03-32.6
≥1 CV risk factor [1]						
No	0	0.0	0	0.0		
Yes	2	5.0	4	4.5	1.11	0.10-7.73

REFERENCE: Table assembled by DEPI from Table 9a1 in Supplemental Full Results File.
ABBREVIATIONS: MACE, Major Adverse Cardiovascular Event; CV, cardiovascular; PRU, prucalopride; PEG, polyethylene glycol 3350; IR, incidence rate (per 1000 patient-years); IRR, incidence rate ratio; CI, confidence interval

1. Age ≥55 years, history of CV hospitalization, hypertension, hyperlipidemia, diabetes, or obesity.

3.5.2.9 Results from sensitivity analyses

The documents available to DEPI omitted CPRD-specific results from sensitivity analysis.

3.6 The Health Improvement Network (THIN)

3.6.1 Study Methods

3.6.1.1 Study Setting

THIN captured study exposures (PRU and PEG) and outcomes (MACE) occurring between April 2010 through May 2016 in patients registered under select U.K. general practices outside Scotland.

THIN, currently managed by IQVIA™ Real World Insights product,[30] provided access to clinical information recorded by U.K. general practitioners (GP) who used a popular electronic health record (EHR) software system[31] to manage patientcare. THIN offered data content and analytic capabilities analogous to CPRD (Section 3.5.1.1 Study Setting, above).

SPD555-802 chose not to use the limited capabilities in THIN to link practices to HES and ONS.

3.6.1.2 Eligibility Criteria

THIN used the same eligibility criteria as SNR. See Section 3.3.1.2 Eligibility Criteria.

3.6.1.3 Exposure

Except for two differences, THIN and SNR defined exposure alike (Section 3.3.1.3 Exposure). THIN specified PRU or PEG exposure by prescriptions written for patients by physicians, whereas SNR specified exposures by prescriptions dispensed to patients by pharmacies. Unlike SNR, THIN did not stockpile, *i.e.*, extend the exposure period when patients refilled prescriptions before exhausting the days supplied by earlier prescriptions. Like ISD and CPRD, THIN replaced missing values for days of supply with the age- and sex-specific modal values for patients with non-missing values for days of supply.[32]

3.6.1.4 Outcomes

THIN used a two-stage procedure to identify the primary outcome, MACE, a composite of non-fatal AMI, non-fatal stroke, and in-hospital cardiovascular death.

To identify events for processing at the second stage, the first stage used an electronic search

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[30] IQVIA, The Health Improvement Network (THIN), accessed at https://www.iqvia.com/locations/uk-and-ireland/thin on July 16, 2018.

[31] VISION, https://www.visionhealth.co.uk/general-practice/

[32] All prescriptions missing values for days of supply in 8.8% and 27.7% of patients in PRU and PEG, respectively, per Clinical Information Amendment, eCTD 0027, page 2.

algorithm to screen codes in THIN. The screening algorithm selected events satisfying any one of the following conditions,

- A code for AMI or stroke, co-occurring (±30 days) with a code for hospitalization
- A code for chest pain, co-occurring (±30 days) with a code for hospitalization and at least one code for cardiac enzyme testing, cardiac enzyme abnormality, cardiac imaging abnormality, thrombolytic therapy, coronary revascularization, or stress testing
- Death coincident (±30 days) with a code for hospitalization

Second-stage processing of events identified during the first stage entailed a sequence of two steps, as summarized below.

Step 1. Up to two clinicians independently assessed THIN patient profiles, supplemented by GP notations entered as EHR free text during the 6 months before and after the index event. THIN referred events for formal outcome adjudication by committee, unless two clinicians both found no evidence for definite, probable, or possible MACE.

Step 2. Events passing Step 1 triggered committee adjudication of THIN patient profiles and GP free-text notations, as described above for ISD under Section 3.4.1.4 Outcomes.

SPD555-802 asserted that procedures blinded second stage assessments to treatment group. SPD555-802 achieved this objective by redacting information about exposure (*i.e.*, treatment with PRU or PEG) from "patient database profiles, free-text entries, completed GP questionnaires, and electronic copies of other medical records."[33]

3.6.1.5 Other Variables

Variables used for cohort matching included,

- Sex
- Calendar year of index date
- Year of birth

With variables specified "same as CPRD,"[34] THIN developed a propensity score model from 21

[33] Final Study Protocol, page 38.

[34] Full Study Data Development Plan, Appendix D, page D-9.

variables in nine domains, including,

- Demographic factors (4 variables)
- Prescription opioid history (2 variables)
- History of gastrointestinal (GI) problem or procedure (1 variable)
- History of cardiovascular hospitalization (1 variable)
- Prescription drug history (5 variables)
- Medical history (5 variables)
- Health care utilization (1 variable)
- Behavioral risk factor (2 variables)

3.6.1.6 Statistical Analysis

To prevent overlap with ISD, SPD555-802 excluded THIN practices in Scotland. To mitigate overlap between CPRD and THIN, SPD555-802 applied a complex method, analogous to one described by Cai, *et al.* [7], to identify anonymized practices in CPRD and THIN that appeared to be contributing the same patients to the study population. SPD555-802 excluded all patients from duplicated THIN practices, unless the matching CPRD practice prohibited data linkage to HES and ONS. Subsequent analysis followed procedures summarized above under Section 3.3.1.6 Statistical Analysis.

3.6.2 Study Results

3.6.2.1 Eligible cohort

During the April 2010 - May 2016 study period, THIN identified 1,191 patients with a prescription written for PRU.[35] THIN excluded 654 (54.9%) as ineligible (Section 3.3.1.2 Eligibility Criteria), including 587 (49.3%) because of registration in Scotland or in a non-Scottish practice duplicated in CPRD. With patients possibly excluded for more than one reason, the two other most frequently occurring reasons for exclusion included, (1) all follow-up in overlap with PEG (N=87) and (2) PEG prescribed on PRU index date (N=59).

[35] THIN limited data extraction to patients ≥18 years of age (Clinical Information Amendment, eCTD 0042, page 1). This decision explains the absence of patients <18 years of age in the Attrition Table for THIN (Supplemental Full Results File, Table 1).

THIN identified 314,203 patients with a prescription written for PEG. THIN excluded 209,060 (66.5%), including 177,408 (56.5%) because of registration in Scotland or in a non-Scottish practice duplicated in CPRD. The other most frequently occurring reason, prior use of PEG, excluded 69,203.

Patients remaining, 537 PRU and 105,143 PEG, formed the eligible patient population.

3.6.2.2 Baseline characteristics of the matched population

THIN successfully found five PEG matches for every PRU patient. As shown in Table 16, the matched patient cohorts included 95.0% female sex and 68.3% aged 18-54 years. Patients in PRU *vs.* PEG differed markedly with respect to history of gastrointestinal problems, as measured by pre-index outpatient code for irritable bowel syndrome (35.6% *vs.* 16.1%). The documents available to DEPI omitted a presentation from THIN of patient-years exposed to PRU and PEG in categories defined by baseline characteristics.

Table 16: The Health Improvement Network (THIN), baseline characteristics of the prucalopride (PRU) cohort (N=537) and the matched polyethylene glycol 3350 (PEG) cohort (N=2,685).

	PATIENTS		
Baseline variable	PRU %	PEG %	SD
Matching variable			
Female sex	95.0	95.0	0.00
Age 18-54 years	68.3	68.3	0.00
Year 2010-2012	40.4	40.4	0.00
Recent hospitalization	5.2	8.9	0.14
Low socioeconomic level	9.9	12.5	0.08
Outpatient prescription opioid history			
Recent opioid	38.4	34.2	0.09
Chronic opioid	35.0	25.8	0.20
History of GI problem			
Outpatient IBS diagnosis	35.6	16.1	0.46
Any cardiovascular hospitalization	1.9	1.9	0.00
Outpatient prescription drug history			
Anticoagulant	5.0	3.4	0.08
Antidiabetic	6.7	6.7	0.00
Antihypertensive	52.5	40.2	0.25
Aspirin or platelet inhibitor	18.1	13.3	0.13
HMG CoA reductase inhibitor	17.7	17.6	0.00
Medical history			
Cancer	5.6	7.8	0.09
COPD	3.2	3.2	0.00
Diabetes	6.3	6.7	0.01
Hyperlipidemia	12.5	10.8	0.05
Hypertension	13.8	19.0	0.14

REFERENCE: Table assembled by DEPI from Table 2 and Table 3 in Supplemental Full Results File.
ABBREVIATIONS: COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; IBS, irritable bowel syndrome; SD, standardized difference

3.6.2.3 Exposure

The 537 PRU and 2,685 matched PEG patients in THIN accumulated ≈316 and ≈661 patient-years on treatment, respectively, with mean patient exposures higher in PRU than PEG (7.1 *vs.* 3.0 months, Figure 8).[36] As shown in Figure 9, 44.3% in PRU and 19.4% in PEG accumulated >90 days exposure.

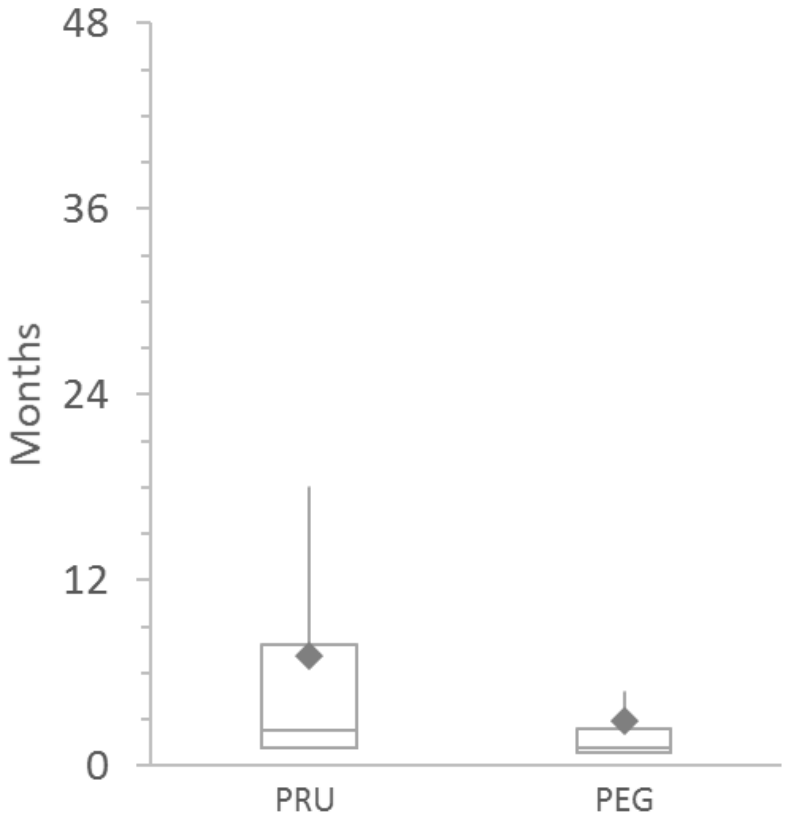


Figure 8: The Health Improvement Network (THIN), box plots summarizing patient exposures for 537 and 2,685 patients in prucalopride (PRU) and polyethylene glycol 3350 (PEG) cohorts, respectively, with means shown as solid diamonds, maximum values as open diamonds, and 25th, 50th, and 75th percentiles as horizontal lines. Each whisker connects a 75th percentile to a value equal to 1.5 times the interquartile range added to the 75th percentile. Plot prepared by DEPI from Table 4 in Supplemental Full Results File.

[36] The documents available to DEPI omitted information about patient-year exposure accrued by patients in THIN. DEPI estimated total patient-years in THIN from the number of patients and mean exposure durations reported by SPD555-802 for PRU and PEG. See Table 4 in Supplemental Full Results File.

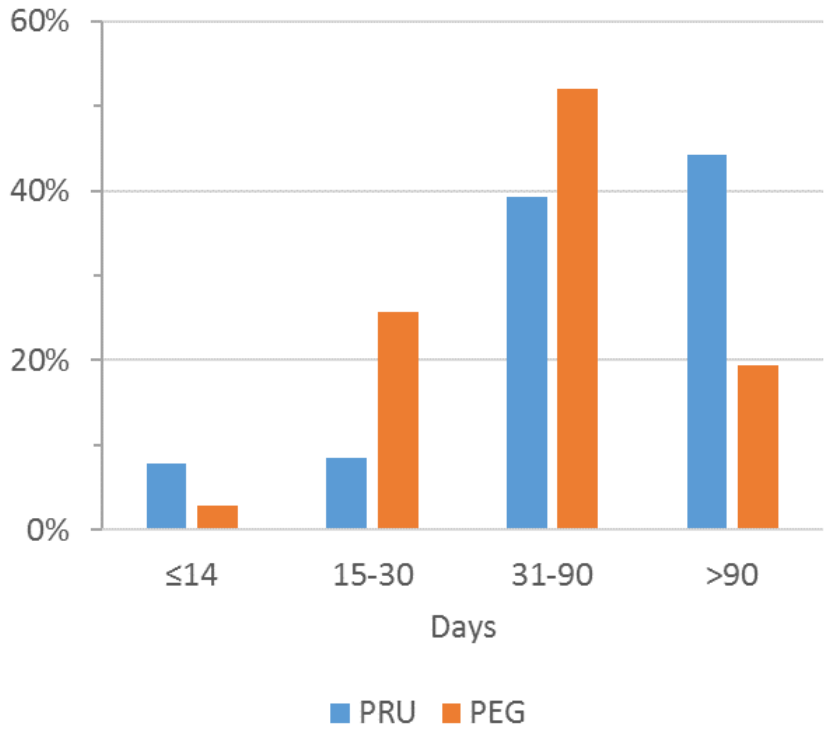


Figure 9: The Health Improvement Network (THIN), 537 and 2,685 patients from prucalopride (PRU) and polyethylene glycol 3350 (PEG) cohorts, respectively, distributed by cumulative exposure to study drug. Plot prepared by DEPI from Table 4 in Supplemental Full Results File.

3.6.2.4 Sex- and age-adjusted results in matched cohorts

As summarized in Table 17, the primary outcome of MACE occurred with incidence during current treatment at 3.2 and 3.0 per 1000 patient-years in PRU and PEG, respectively (IRR, 1.04, 95% CI 0.02-20.1). PRU and PEG, each, contained <5 MACEs.[37]

Table 17: The Health Improvement Network (THIN), MACE incidence rates (per 1000 patient-years) in matched cohorts.

	PRU N=1,249		PEG N=6,245			
Outcome	Rate	95% CI	Rate	95% CI	IRR	95% CI
MACE	3.2	0.1-17.6	3.0	0.4-10.9	1.04	0.02-20.1
non-fatal AMI	3.2	0.1-17.6	3.0	0.4-10.9	1.04	0.02-20.1
non-fatal stroke	0.0	0.0-11.7	0.0	0.0-5.6		
in-hospital CV death	0.0	0.0-11.7	0.0	0.0-5.6		

REFERENCE: Table assembled by DEPI from Tables 9a1, 9a2, 9a3, and 9a4 in Supplemental Full Results File.

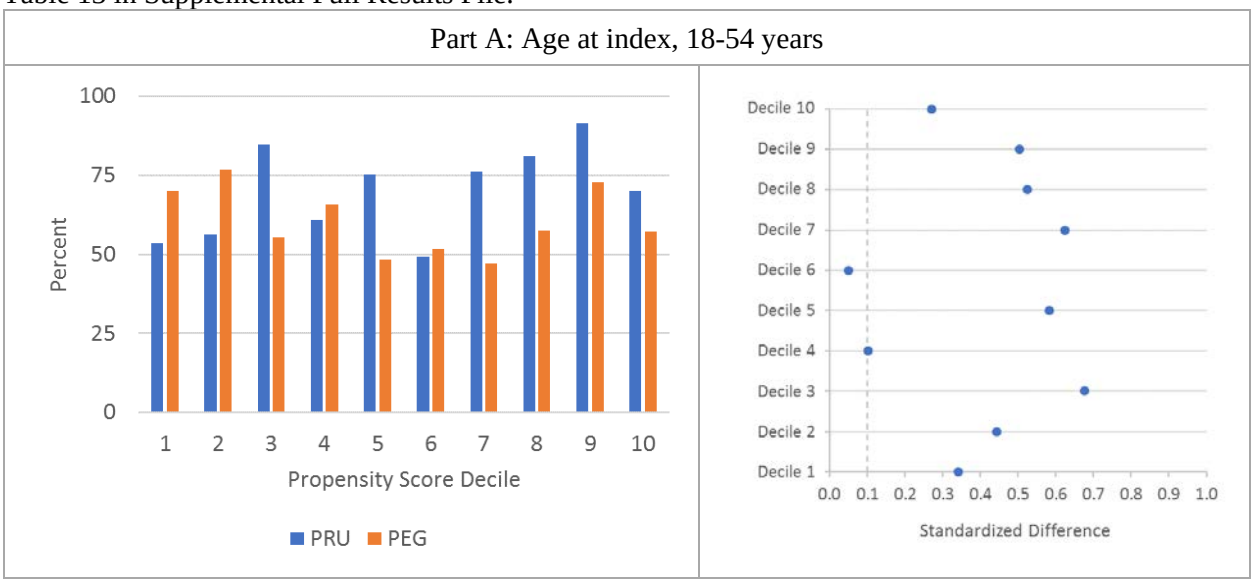
[37] Exact counts not reported as required by THIN privacy rules.

ABBREVIATIONS: AMI, Acute Myocardial Infarction; CV, cardiovascular; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiovascular Event; PRU, prucalopride; PEG polyethylene glycol 3350

3.6.2.5 Cohort trimming and propensity score stratification

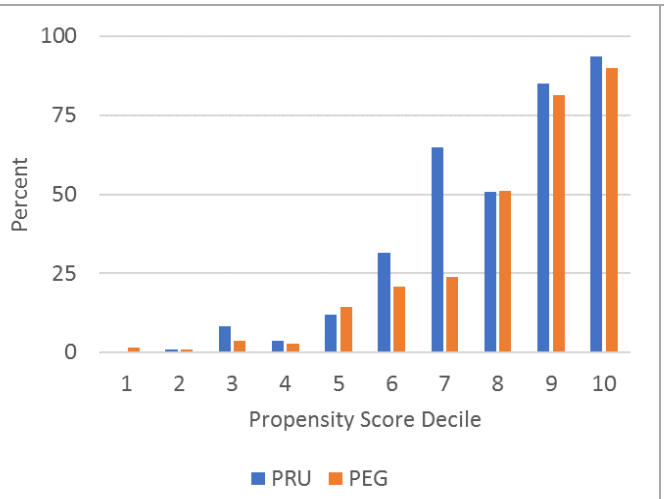
SPD555-802 evaluated 28 covariates in THIN for patient-year balance achieved by cohort trimming and propensity score stratification.[38] Figure 10 shows results for three illustrative covariates, (1) age at index, (2) outpatient IBS diagnosis, and (3) antihypertension prescription drug history.

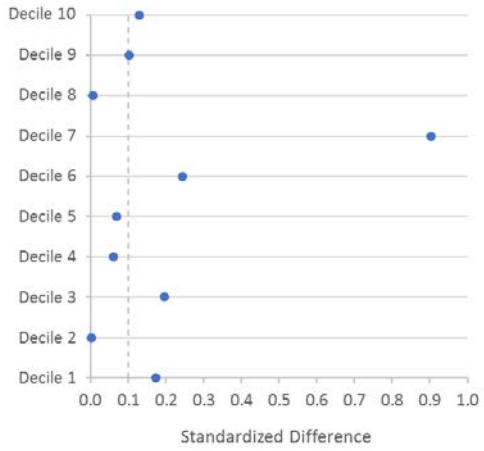
Figure 10: The Health Improvement Network (THIN), patient-year balance achieved between prucalopride (PRU) and polyethylene glycol 3350 (PEG). Results shown (in trimmed cohorts, by propensity-score stratum) for three variables (risk factors), age at index (Part A), outpatient IBS diagnosis (Part B), and antihypertensive prescription drug history (Part C). The left-hand plots compare, by propensity score decile, percent of person-years in PRU and PEG with the indicated risk factor. The right-hand plots express covariate balance in each propensity score decile as a standardized difference (SD), with a vertical dashed line defining the upper boundary for negligible difference (*i.e.*, SD = 0.10). Plots prepared by DEPI from Table 13 in Supplemental Full Results File.



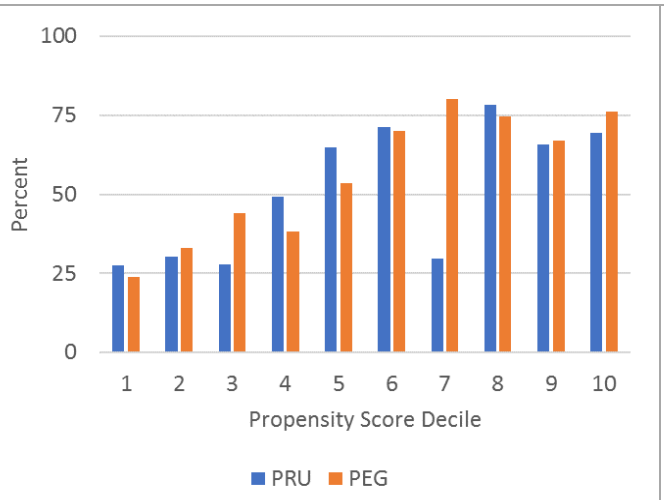
[38] See Table 13 in Supplemental Full Results File.

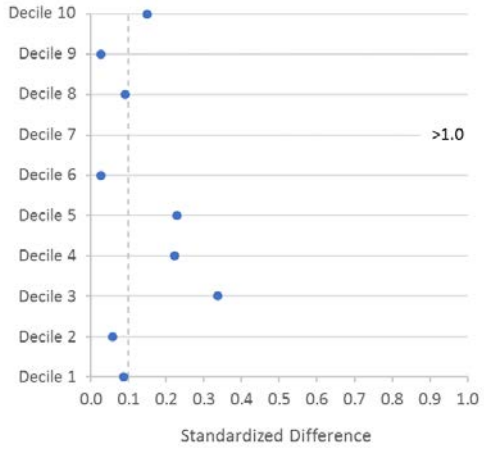
Part B: Outpatient IBS diagnosis





Part C: Antihypertensive prescription drug history





3.6.2.6 Primary results

Trimming eliminated 36 of 537 (6.7%) patients from PRU and 142 of 2,685 (5.3%) patients from PEG. After trimming, with <5 MACEs confirmed in PRU and PEG each, the two study cohorts contained,

- PRU: N=501 patients with MACE incidence estimated at 3.3 per 1000 patient-years.
- PEG: N=2,543 patients with MACE incidence estimated at 3.2 per 1000 patient-years.

Accordingly, after trimming, THIN estimated crude MACE incidence in PRU relative to PEG at IRR 1.04, 95% CI 0.02-20.0. Stratifying by propensity score decile, THIN estimated standardized MACE incidence in PRU relative to PEG at SIRR 0.52, 95% CI 0.04-6.44.

3.6.2.7 Results for secondary outcomes

For completeness, Table 18 summarizes results from THIN for the secondary outcomes of non-fatal AMI, non-fatal stroke, and in-hospital cardiovascular death.

Table 18: The Health Improvement Network (THIN), results for primary and secondary outcomes, before and after trimming.

	Untrimmed				Trimmed					
Outcome	PRU	PEG	IRR	95% CI	PRU	PEG	IRR	95% CI	SIRR	95% CI
MACE	<5	<5	1.04	0.02-20.1	<5	<5	1.04	0.02-20.0	0.52	0.04-6.44
non-fatal AMI	<5	<5	1.04	0.02-20.1	1	2	1.04	0.02-20.0	0.52	0.04-6.44
non-fatal stroke	0	0			0	0				
CV death	0	0			0	0				

REFERENCE: Table assembled by DEPI from Tables 9a1, 9a2, 9a3, 9a4, 14a, 14b, 14c, and 14d in Supplemental Full Results File.
ABBREVIATIONS: AMI, acute myocardial infarction; CV death, in-hospital cardiovascular death; PRU, prucalopride; PEG, polyethylene glycol 3350; IRR, incidence rate ratio; CI, confidence interval; SIRR, standardized incidence rate ratio

3.6.2.8 Results from subgroup analyses

For completeness, Table 19 summarizes crude results for MACE in subgroups defined by sex, age, and other baseline measures of cardiovascular disease risk. The documents available to DEPI omitted THIN-specific results from subgroup analyses controlled for propensity score.

Table 19: The Health Improvement Network (THIN), crude results for MACE, before cohort trimming, in categories of sex, age, and other baseline measures of cardiovascular disease risk.

	PRU		PEG			
Group	MACE	IR	MACE	IR	IRR	95% CI
Overall	<5	3.2	<5	3.0	1.04	0.02-20.1
Sex and age, years						
Women, 18-54	<5	4.5	0	0.0		
Women, ≥55	0	0.0	<5	8.8	0.00	0.00-13.4
Men, 18-54	0	0.0	0	0.0		
Men, ≥55	0	0.0	0	0.0		
Age, years						
18-54	<5	4.4	0	0.0		
≥55	0	0.0	<5	7.8	0.00	0.00-14.9
History of CV hospitalization						
No	<5	3.2	<5	1.6	2.07	0.03-162.
Yes	0	0.0	<5	61.0	0.00	0.00-143.
≥1 CV risk factor [1]						
No	0	0.0	0	0.0		
Yes	<5	5.4	<5	4.2	1.29	0.02-24.8

REFERENCE: Table assembled by DEPI from Table 9a1 in Supplemental Full Results File.
ABBREVIATIONS: MACE, Major Adverse Cardiovascular Event; CV, cardiovascular; PRU, prucalopride; PEG, polyethylene glycol 3350; IR, incidence rate (per 1000 patient-years); IRR, incidence rate ratio; CI, confidence interval
1. Age ≥55 years, history of CV hospitalization, hypertension, hyperlipidemia, diabetes, or obesity.

3.6.2.9 Results from sensitivity analyses

The documents available to DEPI omitted THIN-specific results from sensitivity analysis.

3.7 German Pharmacoepidemiological Research Database (GePaRD)

3.7.1 Study Methods

3.7.1.1 Study Setting

GePaRD captured study exposures (PRU and PEG) and outcomes (MACE) occurring between January 2010 through December 2014 among patients covered by Statutory Health Insurance (SHI) in Germany. The SHIs cover ≈90% of the German population. GePaRD, a data source developed for research purposes, integrates hospital discharge, outpatient encounter, and outpatient prescription data provided by willing SHI providers for "approximately 17% of the general population from all geographical regions of Germany."[39]

3.7.1.2 Eligibility Criteria

See Section 3.3.1.2 Eligibility Criteria.

3.7.1.3 Exposure

See Section 3.3.1.3 Exposure.

3.7.1.4 Outcomes

GePaRD used a two-stage procedure to identify the primary outcome, MACE, a composite of non-fatal acute myocardial infarction (AMI), non-fatal stroke, and in-hospital cardiovascular death.

To identify events for processing at the second stage, the first stage applied an electronic search algorithm to hospital records in GePaRD. The screening algorithm selected hospital records

[39] Leibniz Institute for Prevention Research and Epidemiology – BIPS, The German Pharmacoepidemiology Research Database, accessed at https://www.bips-institut.de/en/research/research-infrastructures/gepard.html on July 16, 2018.

satisfying any one of the following conditions,

- AMI (ICD-10 I21) or stroke (ICD-10 G45 or I60-I64) as the primary discharge diagnosis, provided death not recorded in GePaRD within 30 days of hospital admission.

- Death as the reason for discharge, with primary discharge diagnosis code corresponding to cardiovascular disease (as listed under **In-hospital Cardiovascular Death** in **APPENDIX 2**), provided date of death within 30 days of hospital admission.

The second stage entailed manual clinician review of GePaRD hospital claims. GePaRD accepted MACE as confirmed if this review identified a cardiovascular diagnosis or symptom as the reason for admission. GePaRD did not permit access to patient charts for more rigorous outcome validation.

3.7.1.5 Other Variables

Variables used for cohort matching included,

- Sex

- Calendar year of index date

- Year of birth

GePaRD developed a propensity score model from 32 variables (not including interaction terms) in seven domains, including,

- Demographic factors (3 variables)

- Prescription opioid history (2 variables)

- History of cardiovascular hospitalization (6 variables)

- History of cardiovascular procedure (3 variables)

- Prescription drug history (8 variables)

- Medical history (9 variables)

- Health care utilization (1 variable)

3.7.1.6 Statistical Analysis

See Section 3.3.1.6 Statistical Analysis.

3.7.2 Study Results

3.7.2.1 Eligible cohort

During the January 2010 – December 2014 study period, GePaRD identified 6,710 patients with a dispensing for PRU. GePaRD excluded 1,014 (15.1%) as ineligible (Section 3.3.1.2 Eligibility Criteria), including 544 (8.1%) for <12 months pre-index data available.

GePaRD identified 328,380 patients with a dispensing for PEG. GePaRD excluded 133,793 (40.7%), including 94,219 for age <18 years.

Patients remaining, 5,636 PRU and 194,587 PEG, formed the eligible patient population.

3.7.2.2 Baseline characteristics of the matched population

GePaRD found 5, 4, 3, 2, and 1 PEG match for 5,567, 17, 21, 20, and 11 PRU patients, respectively. Consequently, the matched PEG group contained 28,017 patients.

As shown in Table 20, the matched patient cohorts included 88.8% female sex and 33.3% aged 18-54 years. Other variables with notable differences (SD ≥ 0.10) between patients in PRU *vs.* PEG included, (1) recent hospitalization (within 14 days; 7.2% *vs.* 21.6%), (2) recent opioid (20.7% *vs.* 44.5%), (3) history of cancer (27.5% *vs.* 43.6%), and (4) history of gastrointestinal problems (*e.g.*, constipation outpatient diagnosis, 47.8% *vs.* 13.6%).

On a per patient basis,

- PRU women accumulated more time on treatment than men, mean 4.6 *vs.* 3.1 months.
- Younger (18-54 year-old) PRU patients accumulated more time on treatment than older (≥55 year-old) patients, 4.9 *vs.* 4.3 months.
- Younger PEG patients accumulated less time on treatment than older patients, 2.2 *vs.* 2.5 months.

Because of these sex- and age-specific differences in mean exposure, women and younger patients accounted for larger fractions of total patient-year exposure in PRU than PEG (Table 1), as reproduced below,

- Female sex, 92.2% *vs.* 89.3%, SD 0.10
- 18-54 years of age, 36.4% *vs.* 29.9%, SD 0.14

Examples of other variables with notable differences (SD ≥ 0.10) between PRU and PEG patient-years included,

- Recent opioid outpatient prescription, 19.0% *vs.* 51.9%

- Medical history for cancer, 23.6% *vs.* 36.3%, diabetes, 17.4% *vs.* 23.5%, and hypertension, 53.0% *vs.* 63.9%

Table 20: German Pharmacoepidemiological Research Database (GePaRD), baseline characteristics of the prucalopride (PRU) cohort (5,636 patients with 2,102 patient-years) and the matched polyethylene glycol 3350 (PEG) cohort (28,017 patients with 6,653 patient-years).

	PATIENTS			PATIENT-YEARS [1]		
Baseline variable	PRU %	PEG %	SD	PRU %	PEG %	SD
Matching variable						
Female sex	88.8	88.8	0.00	92.2	89.3	0.10
Age 18-54 years	33.6	33.2	0.01	36.4	29.9	0.14
Year 2012	53.0	52.9	0.00	67.7	67.0	0.02
Recent hospitalization	7.2	21.6	0.42	7.6	18.7	0.33
Outpatient prescription opioid history						
Recent opioid	20.7	44.5	0.52	19.0	51.9	0.73
Chronic opioid	17.7	36.0	0.42	16.2	44.8	0.65
History of GI problem						
IBS outpatient diagnosis	19.8	4.9	0.46	18.4	4.8	0.43
Constipation outpatient diagnosis	47.8	13.6	0.80	51.6	17.9	0.76
Other outpatient GI diagnosis	83.1	68.6	0.34	83.0	69.1	0.33
Constipation inpatient diagnosis	19.9	13.6	0.17	20.1	14.7	0.14
Other inpatient GI diagnosis	40.6	39.0	0.03	39.6	39.6	0.00
Any cardiovascular hospitalization	12.4	15.9	0.10	10.5	15.9	0.16
Outpatient prescription drug history						
Anticoagulant	20.2	29.8	0.22	17.4	29.3	0.28
Antidiabetic	10.0	13.2	0.10	9.9	13.5	0.11
Antihypertensive	56.7	62.4	0.12	55.5	66.1	0.22
Aspirin or platelet inhibitor	11.8	14.6	0.08	11.3	16.4	0.15
HMG CoA reductase inhibitor	22.9	22.9	0.00	22.4	24.4	0.05
Medical history						
Asthma	6.1	4.9	0.05	7.2	5.0	0.09
Bronchitis, emphysema, and COPD	35.6	36.4	0.02	33.0	36.7	0.08
Cancer	27.5	43.6	0.34	23.6	36.3	0.28
Chronic kidney disease	10.8	15.7	0.15	11.2	16.1	0.14
Diabetes	18.0	22.3	0.11	17.4	23.5	0.15
Hyperlipidemia	45.5	44.3	0.02	44.7	45.7	0.02
Hypertension	54.6	60.9	0.13	53.0	63.9	0.22

REFERENCE: Table assembled by DEPI from Table 2 and Table 3 in Supplemental Full Results File.
ABBREVIATIONS: COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; IBS, irritable bowel syndrome; SD, standardized difference
FOOTNOTE:
1. Patient-years of exposure before first MACE. See Section 3.3.1.3 Exposure.

3.7.2.3 Exposure

The 5,636 PRU and 28,017 matched PEG patients in GePaRD accumulated 2,102 and 6,653 patient-years on treatment, respectively, with mean patient exposures higher in PRU than PEG (4.5 *vs.* 2.8 months). The documents available to DEPI omitted detailed presentation of patient-year exposure, as provided for SNR (Section 3.3.2.3 Exposure).

3.7.2.4 Sex- and age-adjusted results in matched cohorts

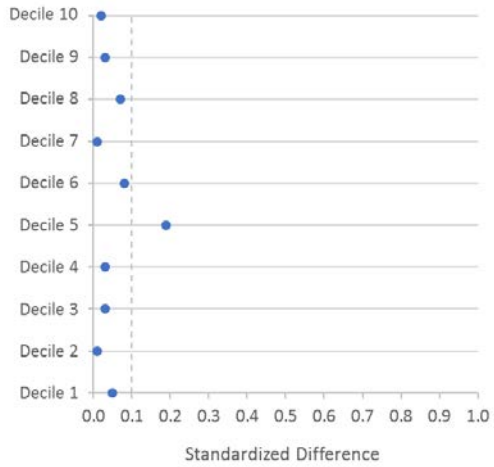
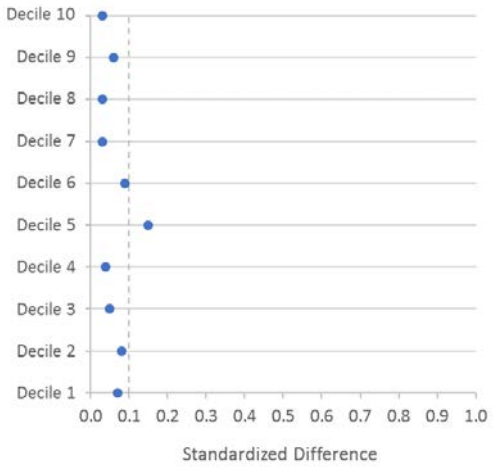
The documents available to DEPI omitted presentation of MACE incidence in matched cohorts from GePaRD.

3.7.2.5 Cohort trimming and propensity score stratification

The documents available to DEPI omitted presentation of patient-year balance achieved by trimming and propensity score stratification. Instead, SPD555-802 showed patient balance achieved for 32 covariates.[40] Figure 11 shows results for two representative covariates, (1) age at index and (2) antihypertensive prescription drug history.

[40] Presented by SPD555-802 as Table 7 in Data Development Plan Version 7.0, Appendix F. Documentation of Propensity Score Modeling for Germany, pages F17-F18.

Figure 11: German Pharmacoepidemiological Research Database (GePaRD), patient balance achieved between prucalopride (PRU) and polyethylene glycol 3350 (PEG) by cohort trimming and propensity score stratification. Results shown for two variables (risk factors), age at index (Part A) and antihypertensive prescription drug history (Part B). Plots express covariate balance in each propensity score decile as a standardized difference (SD), with a vertical dashed line defining the upper boundary for negligible difference (*i.e.*, SD = 0.10). Plots prepared by DEPI from Table 7 in Full Study Data Development Plan, Appendix F, pages F17-F18.

Part A: Age at index, 18-54 years	Part B: Antihypertensive prescription drug history
	

3.7.2.6 Primary results

Trimming eliminated 310 of 5,636 (5.5%) patients from PRU and 2,629 of 28,017 (9.4%) patients from PEG. After trimming, the two study cohorts contained,

- PRU: N=5,326 patients with MACE incidence estimated at 11.1 per 1000 patient-years.
- PEG: N=25,388 patients with MACE incidence estimated at 21.5 per 1000 patient-years.

Accordingly, after trimming, GePaRD estimated crude MACE incidence in PRU relative to PEG at IRR 0.51. Stratifying by propensity score decile, GePaRD estimated standardized MACE incidence in PRU relative to PEG at SIRR 0.51, 95% CI 0.37-0.71.

3.7.2.7 Results for secondary outcomes

Absent details, SPD555-802 reported, "estimates of IRR were also below 1.00 [in GePaRD] for each of the individual components of MACE."

3.7.2.8 Results from subgroup analyses

The documents available to DEPI omitted results from subgroup analyses in GePaRD.

3.7.2.9 Results from sensitivity analyses

The documents available to DEPI omitted GePaRD-specific results from sensitivity analysis.

3.8. Synthesis

3.8.1 Data Sources

SPD555-802 used five data sources with important differences that impact the interpretation of exposure, covariate, and outcome variables used for pooled analysis. As shown in Table 21,

- Two data sources qualified as population based (SNR and ISD).
- Two data sources (CPRD and THIN) captured medical information recorded by general practitioners in electronic health records. The other three data sources (SNR, ISD, and GePaRD) organized coded information used to administer healthcare systems.
- Three data sources (SNR, ISD, and GePaRD) used prescriptions dispensed to patients to define the study exposures. Whereas, two data sources (CPRD and THIN) defined exposure by prescriptions written by physicians.
- Capabilities for linking to death certificate registries for ascertaining and defining cardiovascular death ranged from none (GePaRD and THIN) to complete (SNR and ISD).
- Finally, the five data sources defined MACE with variable rigor. One data source (SNR) relied on coded information only. One data source (ISD) adjudicated information rigorously abstracted from medical charts. Three data sources (CPRD, THIN, and GePaRD) adjudicated lower quality clinical information.

Table 21: SPD555-802 data sources compared.

Data source feature	Data Source				
	SNR	ISD	CPRD	THIN	GePaRD
Study period	2012-2015	2010-2016	2010-2016	2010-2016	2010-2014
Region	Sweden	Scotland	U.K. except Scotland	U.K. except Scotland	Germany
Population-based	Yes	Yes	No	No	No
Data type [1]	Claims	Claims	GP EHR	GP EHR	Claims
Exposure	Prescriptions dispensed	Prescriptions dispensed	Prescriptions written	Prescriptions written	Prescriptions dispensed
Outpatient data used for baseline covariates	Yes	No	Yes	Yes	Yes
Lifestyle risk factors (i.e., smoking and BMI)	No	No	Yes	Yes	No
Data source linked to death certificates	Complete	Complete	Partial	None	None
MACE adjudication procedure	Not applicable	Medical chart review	Profile with questionnaire	Profile with EHR free text	Reason hosp-italized [2]

ABBREVIATIONS: SNR, Swedish National Registers; ISD, Information Services Division of Scotland; CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network; GePaRD, German Pharmacoepidemiological Research Database; BMI, body mass index; MACE, Major Adverse Cardiovascular Event; GP, general practitioner; EHR; electronic health record

FOOTNOTE:

1. Claims, a reference to databases used to manage healthcare systems.
2. Outcome determinations included examinations of diagnosis codes in administrative records for the reason hospitalized. GePaRD did not permit access to patient charts for more rigorous outcome validation.

3.8.2 Baseline Characteristics

The number of patients available in the five data sources varied over a 10-fold range (Table 22).

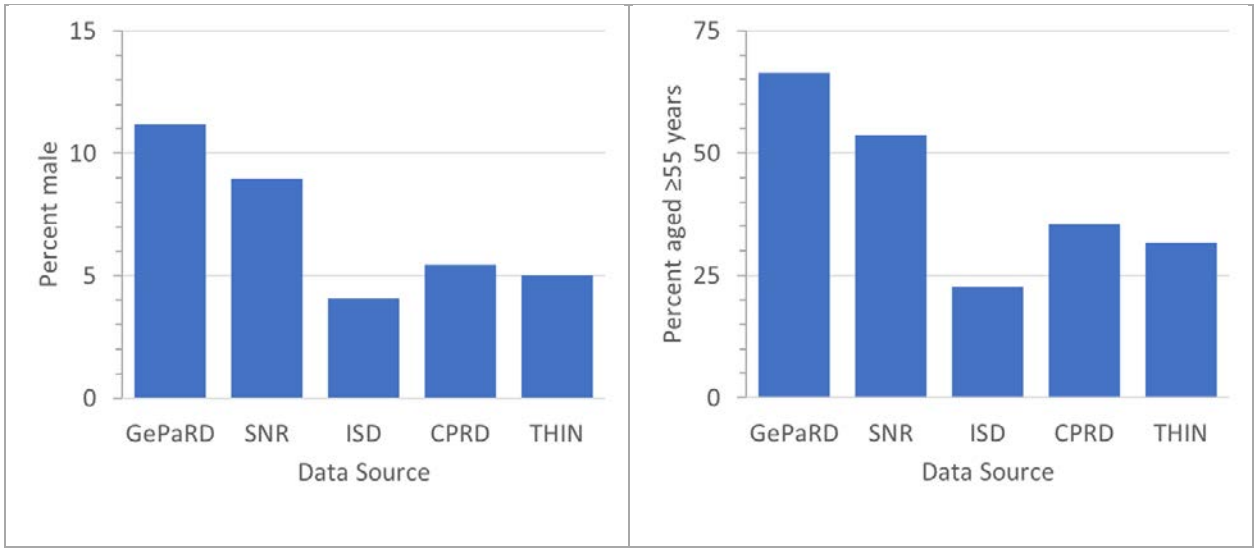
Table 22: Number of patients in matched prucalopride (PRU) and polyethylene glycol 3350 (PEG) cohorts, before and after trimming, by data source.

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

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

Results in Figure 12 show men and older patients (≥55 years) comprising a greater fraction of the prucalopride-exposed populations in Germany and Sweden (GePaRD and SNR) than the United Kingdom (ISD, CPRD, and THIN).

Figure 12: Percent male and percent aged ≥55 years in matched prucalopride cohorts, before trimming, by data source.



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

An analysis of baseline attributes, as summarized in Table 23, show,

- GePaRD distinguished by recent opioid, recent hospitalization, and history of cancer more frequent in PRU than PEG.

- History of cancer more frequent in GePaRD than Swedish or U.K. data sources.

These results, combined with evidence for structural channeling (Section 4. DISCUSSION), supported the decision by SPD555-802 to exclude GePaRD from pooled analyses.

Table 23: Frequency of three selected baseline attributes in matched prucalopride (PRU) and polyethylene glycol 3350 (PEG) cohorts, after trimming, by data source, showing differences (D) and standardized differences (SD) between PRU and PEG.

Baseline attribute	PRU (%)	PEG (%)	D (%)	SD
Recent opioid [1]				
GePaRD	20.8	44.0	-23.2	0.51
SNR	25.3	31.3	-5.9	0.13
ISD	39.9	41.9	-2.0	0.04
CPRD	31.6	30.2	1.4	0.03
THIN	37.1	33.3	3.9	0.08
Recent hospitalization [2]				
GePaRD	5.9	15.9	-10.1	0.33
SNR	2.7	2.5	0.2	0.01
ISD	8.1	8.5	-0.3	0.01
CPRD	5.2	6.3	-1.1	0.05
THIN	4.6	7.5	-2.9	0.12
History of cancer				
GePaRD	27.3	40.9	-13.6	0.29
SNR	9.1	10.5	-1.4	0.05
ISD	4.6	4.7	-0.1	0.00
CPRD	7.6	9.1	-1.5	0.05
THIN	5.8	7.0	-1.2	0.05

REFERENCE: Table assembled by DEPI from Table 13 in Supplemental Full Results File.
ABBREVIATIONS: GePaRD, German Pharmacoepidemiological Research Database; SNR, Swedish National Registers; ISD, Information Services Division of Scotland; CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network
FOOTNOTES:
1. Any opioid prescription within 6 months before index date.
2. Hospitalization within 14 days before index date.

3.8.3 MACE Adjudication in U.K. Data Sources

Electronic search of U.K. data sources (ISD, CPRD, and THIN) identified 260 MACE events in PRU or PEG, including 247 assessed for MACE. Adjudication procedures assessed 100 events (40.5% of 247) in 93 patients as confirmed or definite MACE (Table 24).

Sixteen events (in 15 patients) of confirmed or definite MACE occurred during current use of PRU (5 patients) or PEG (10 patients). Cohort trimming eliminated two patients, one from each cohort. Therefore, the primary analysis included 4 and 9 U.K. patients with MACE during the current use of PRU and PEG, respectively.

Table 24: Events (non-fatal AMI, non-fatal stroke, or in-hospital cardiovascular death) identified by electronic codes in U.K. data sources combined (ISD, CPRD, and THIN).

Adjudication result	N	%
MACE confirmed by HES or ONS	38	14.6
Assessed as definite MACE	62	23.8
Assessed as probable MACE	10	3.8
Assessed as possible MACE	13	5.0
Assessed as not MACE [1]	124	47.7
Not assessed [2]	13	5.0
Total	260	100.0

REFERENCE: Table assembled by DEPI from Figure 6 on page 83 in Final Study Report.
ABBREVIATIONS: AMI, acute myocardial infarction; ISD, Information Services Division; CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network; MACE, Major Adverse Cardiovascular Event; HES, Hospital Episode Statistics; ONS, Office for National Statistics
FOOTNOTES:
1. Assessed as not MACE in 91 and 33 by administrative procedure and adjudication committee, respectively.
2. Including 10 and 3 events with missing patient profile and patient chart in THIN and ISD, respectively.

3.8.4 MACE Incidence

Results summarized in Figure 13 suggest higher baseline MACE incidence in Swedish than U.K. data sources, even after adjustments for sex and age.[41]

[41] Standardized presumably using 10-year age groups. See Statistical Analysis Plan, page 26.

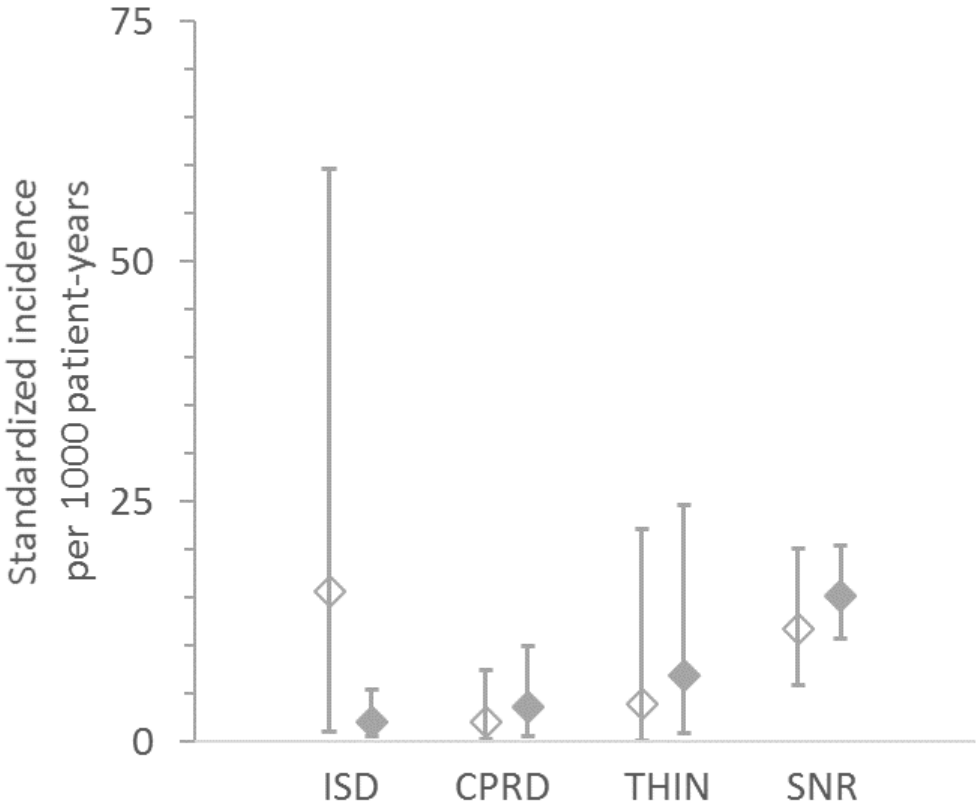


Figure 13: MACE incidence (per 1000 patient-years) in matched and trimmed cohorts, prucalopride (open diamond symbol) and polyethylene glycol 3350 (solid diamond symbol), sex-, age-, and calendar-time-standardized against patient-years summed across both cohorts and all four data sources. Plot prepared by DEPI from Table 10a in Supplemental Full Results File.

3.8.5 Integrated Results

Pooling results from SNR, ISD, CPRD, and THIN, Table 25 shows results from the primary analysis, three secondary analyses, and one selected subgroup analysis. SPD555-802 reported results from the primary analysis for MACE (non-fatal AMI, non-fatal stroke, or in-hospital cardiovascular death) in PRU *vs.* PEG as SIRR 0.64, 95% CI 0.36-1.14.

Table 25: Results integrating four data sources.

Result	Events, N PRU	PEG	SIRR	95% CI
MACE				
U.K. and SNR (Primary)	18	73	0.64	0.36-1.14
United Kingdom (U.K. [1])	4	9	0.68	0.19-2.38
Sweden (SNR)	14	64	0.63	0.33-1.20
Secondary Analyses				
non-fatal AMI	7	21	0.95	0.38-2.39
non-fatal stroke	8	35	0.54	0.23-1.29
in-hospital CV death [2]	3	19	0.47	0.13-1.67
Subgroup Analyses (MACE)				
18-54 year-old women	1	8	0.22	0.03-1.90
≥55 year-old women	13	53	0.71	0.37-1.37
18-54 year-old men	0	1		
≥55 year-old men	4	11	2.57	0.71-9.26

REFERENCE: Table assembled by DEPI from Tables 15a and 15b in Supplemental Full Results File.
ABBREVIATIONS: AMI, acute myocardial infarction; CV, cardiovascular; MACE, Major Adverse Cardiovascular Event as a composite of non-fatal AMI, non-fatal stroke, or in-hospital CV death; PRU, prucalopride; PEG, polyethylene glycol 3350; SIRR, standardized incidence rate ratio; CI, confidence interval; SNR, Swedish National Registers
FOOTNOTE:
1. Combining Information Services Division (ISD) of Scotland, Clinical Practice Research Datalink (CPRD), and The Health Improvement Network (THIN).
2. See Footnote 1, Table 2 and Table 5, above.

Pooling results from Swedish and U.K. data sources, one sensitivity analysis evaluated the effect of adding out-of-hospital cardiovascular death to the outcome definition. With 18 PRU and 119 PEG events, this sensitivity analysis estimated MACE risk (including out-of-hospital cardiovascular death) in PRU *vs.* PEG at SIRR 0.43, 95% CI 0.25-0.73.

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

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

- The second sensitivity analysis evaluated the effect of considering past use as time at risk. With 6 PRU and 75 PEG events, this sensitivity analysis estimated risk for MACE during

current or past use in PRU *vs.* PEG at SIRR 0.51, 95% CI 0.22-1.20.[42] (Adding results from SNR, this sensitivity analysis identified 39 PRU and 341 PEG events and estimated MACE risk during current or past use in PRU *vs*. PEG at SIRR 0.65, 95% CI 0.45-0.92.[43])

3.9 Study Conclusions

SPD555-802 concluded with a "finding of no evidence of an increased risk of MACE in patients with chronic constipation using prucalopride as compared with PEG."[44]

4. DISCUSSION

4.1 Overview

SPD555-802 used a common protocol and a retrospective cohort (observational) study design to measure MACE incidence (non-fatal AMI, non-fatal stroke, or in-hospital cardiovascular death) in five European data sources. Designed to exclude 3-fold risk from prucalopride, SPD555-802 initially planned to combine results from four data sources (GePaRD, ISD, CPRD, and THIN). For reasons discussed below, SPD555-802 replaced GePaRD with SNR. Pooling results from SNR, ISD, CPRD, and THIN, a primary analysis estimated MACE incidence in PRU *vs.* PEG at SIRR 0.64, 95% CI 0.36-1.14. A subgroup analysis, in ≥55 year-old men, estimated risk at SIRR 2.57, 95% CI 0.71-9.26. Declaring results otherwise consistent across primary, secondary, subgroup, and sensitivity analyses, the investigators for SPD555-802 concluded by finding no evidence of increased MACE risk from prucalopride.

4.2 Decision to Exclude GePaRD

Pre-NDA, the Sponsor proposed to exclude GePaRD from pooled analysis.[45] FDA agreed to this proposal "due to the age skewness of the German data."[46]

SPD555-802 attested to serious problems in GePaRD. Germany restricts prescription coverage for laxatives, such as prucalopride. Classifying PEG as a medical device, Germany regulates PEG even more strictly. Because of these policies, SPD555-802 concluded that a prescription in GePaRD selected a distinctly sicker and older study population, especially for PEG. This "disparate clinical profile … precluded combining the study population of GePaRD with those of

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[42] Clinical Information Amendment, eCTD 0037, page 3.

[43] Clinical Information Amendment, eCTD 0049, page 2.

[44] Final Study Report, page 16.

[45] Shire Pharmaceuticals, SPD555 (Prucalopride Succinate Tablets 1 mg and 2 mg) Type B Meeting Pre-NDA Briefing Book, submitted to IND 055078 (eCTD 0054) on June 29, 2017.

[46] Meeting Minutes, *op. cit.*, page 5.

UK and Sweden."[47]

Figure 12 confirms the older aged population captured by GePaRD, especially compared with U.K. data sources. Though a concern for pooled analysis, this baseline difference alone does not eliminate GePaRD as a possibly valid source of information about the cardiovascular safety of prucalopride.

More at issue, Table 23 documents the worrisome baseline differences in GePaRD between PEG and PRU. Despite matching on age, a prescription for PEG identified a study population distinctly characterized by history of cancer, recent opioid prescription, and recent hospitalization, confounding factors plausibly associated with MACE.

SPD555-802 used an analytic approach (*i.e.*, stratification by propensity score) to control comparisons between PRU and PEG for confounding. Despite these tools, DEPI assessed GePaRD at serious risk of bias due to confounding, an assessment supported by the demonstrated baseline differences between patients in PRU and PEG, combined with institutional policies, which evidently channeled patients with different characteristics to either PRU or PEG.

4.2 Interval Validity

DEPI used the ROBINS-I template to assess one result in SPD555-802 for internal validity (**APPENDIX 5**). Viewing SPD555-802 as a study designed to measure the effect of starting and adhering to intervention, DEPI used ROBINS-I to assess the association between intervention with prucalopride and the outcome of MACE. SPD555-802 measured this association at SIRR 0.64, 95% CI 0.36-1.14 (Table 25).

DEPI found (1) serious risk of bias due to confounding and (2) at least moderate risk of bias due to deviation from intended intervention. Judging across all domains, DEPI assessed overall risk of bias as serious. In accordance with ROBINS-I guidance, a serious overall risk-of-bias judgment means the study has "important problems" [8]. In many settings, DEPI views prescriptions as acceptable, though imperfect, proxies for actual patient use. For PRU or PEG, laxatives possibly prescribed for use as needed, DEPI judged SPD555-802 at moderate or possibly greater risk of bias due to deviation from the intended intervention (*i.e.*, starting and adhering to treatment with PRU or PEG). A discussion of DEPI's risk-of-bias assessment for confounding follows, below.

ROBINS-I starts by judging observational (non-randomized) studies at moderate risk of bias due to confounding. From this starting point, DEPI downgraded SPD555-802 to serious risk of bias

[47]Final Study Report, page 16.

because of,

- Age imbalance for patient-years in PRU *vs.* PEG after propensity score stratification (Figure 3, Figure 4, Figure 7, and Figure 10).

- Major imbalances in some propensity-score strata between PRU and PEG with respect to pre-index gastrointestinal (GI) diseases, for example, other inpatient GI diagnosis (Figure 3, Figure 4, and Figure 7) and outpatient irritable bowel disease diagnosis (Figure 10).

- Potential for channeling, as demonstrated in GePaRD (Section 4.2 Decision to Exclude GePaRD).

Despite tight patient matching on age, age imbalance for patient-years entered analysis because of age-related differences in the durations of current use in PRU relative to PEG, as explained in Section 3.3.2.2 Baseline characteristics of the matched population.

Comparative observational studies of drug safety typically include elements designed to mitigate confounding through treatment indication, also known as channeling bias. These design elements attempt to reproduce conditions seen in randomized clinical trials. To emulate a randomized clinical trial, an observational study might simultaneously,

- Apply strict inclusion and exclusion criteria to establish a study population with the medical condition (*e.g.*, chronic constipation) suited to the drug of interest (*e.g.*, prucalopride).

- Identify a comparator drug viewed in clinical practice as interchangeable with the drug of interest.[48]

These design elements aim to create conditions whereby treatment with drug or comparator practically occurs by chance, at least with respect to factors associated with the treatment outcome (*e.g.*, MACE).

These favorable conditions do not pertain for SPD555-802, which merely used a prescription for PRU or PEG to infer presence of the treatment indication, chronic constipation. PRU prescription plausibly identified predominantly patients with idiopathic constipation or irritable bowel disease. PEG prescription plausibly identified a more diverse patient population, including patients with secondary constipation possibly associated with other confounding medical conditions or drug treatments.

Prescribers might not view PRU and PEG as equally appropriate treatment choices. Clinical

[48] By interchangeable, DEPI means two drugs viewed by prescribers as equally appropriate treatment choices in most clinical settings.

notions about the most appropriate laxative in different clinical contexts create potential for patient channeling, whereby patient factors related to MACE might lead physicians to choose one treatment instead of the other. In this context, DEPI observed that official U.K. guidance, published in 2010 and updated in 2014, recommends prucalopride "as an option for the treatment of chronic constipation only in women for whom treatment with at least two laxatives from different classes … has failed to provide adequate relief [9]."[49] Prucalopride, if viewed as second-line treatment, plausibly identified a patient population with more severe or treatment-resistant constipation, a notion supported by the longer exposure durations in PRU than PEG (Figure 1, Figure 2, Figure 5, and Figure 6).

With bias possibly mitigated by propensity score stratification, shortcomings in the PEG comparator could introduce material bias if factors related to intrinsic cardiovascular disease risk strongly determined treatment with PRU or PEG. To assess this possibility, SPD555-802 presented results from sensitivity analyses, which modeled the effects of an unmeasured cardiovascular disease risk factor with prevalence higher in PRU than PEG.[50] Assessing results in SNR, ISD, CPRD, and THIN separately, SPD555-802 concluded that "adjustment for hypothetical additional confounding factors under various assumptions did not change the direction of the associations observed in the main analyses, *i.e.*, the results were robust and unlikely to be the consequence of residual confounding."[51]

To press this conclusion, DEPI used equations in Schneeweiss, 2006 [10], as implemented in a publicly available spreadsheet, to conduct the two sensitivity analyses shown in Figure 14.[52] Both analyses assessed the primary result in SPD555-802, which estimated relative MACE incidence in PRU *vs*. PEG at SIRR 0.64. Both analyses assumed an unmeasured cardiovascular disease risk factor present in 10% of patients treated with prucalopride.

The first analysis modeled a risk factor associated with 8-fold MACE risk (Figure 14, Part A). Correction for this risk factor, if present in 16% of patients treated with PEG, changed the observed SIRR of 0.64 to a fully adjusted SIRR of 0.80. Correction for this risk factor, if present in 24% of patients treated with PEG, changed the observed SIRR of 0.64 to a fully adjusted SIRR of 1.00 (*i.e.*, null condition indicating no difference in MACE incidence in PRU *vs.* PEG).

The second analysis modeled a risk factor present in 20% of patients treated with PEG (Figure

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[49] For PRU cohorts in SPD555-802 (before trimming), 30.4% in SNR, 53.2% in CPRD, and 45.9% THIN received during the 12-month pre-index period at least one PEG prescription with >4 days of supply. See Table 4 in Supplemental Full Results File.

[50] See Table 18 in Supplemental Full Results File, with analytic results shown confirmed by DEPI.

[51] Final Study Report, page 88.

[52] Division of Pharmacoepidemiology & Pharmacoeconomics, Department of Medicine, Harvard Medical School, Accessed at http://www.drugepi.org/dope-downloads/ on July 24, 2018.

14, Part B). Correction for this risk factor, if associated with 4.3-fold MACE risk, changed the observed SIRR of 0.64 to a fully adjusted SIRR of 0.80. Correction for this risk factor, if associated with 13.9-fold MACE risk, changed the observed SIRR of 0.64 to a fully adjusted SIRR of 1.00.

Circumstances in SPD555-802 arguably permitted an unmeasured cardiovascular disease risk factor with 10% prevalence in PRU and 20% prevalence in PEG. However, to explain even half of the PRU *vs.* PEG difference in MACE incidence, lower in PRU than PEG, as observed in SPD555-802, this unmeasured risk factor must increase MACE incidence by more than 4-fold. In younger women (e.g., 40-49 years of age), current smoking, a risk factor unmeasured in SNR and ISD, might increase cardiovascular disease risk by more than 4-fold [11, 12]. Nevertheless, confounding through unmeasured behavioral risk factors (*e.g.*, smoking) appears to DEPI as an incomplete explanation for the primary result in SPD555-802. Rather, DEPI offers the following alternative explanation as possibly more credible. In SPD555-802, as discussed in detail, above, PEG prescription might simply identify a patient population containing an unrecognized subset of severely ill patients strongly predisposed to cardiovascular disease.

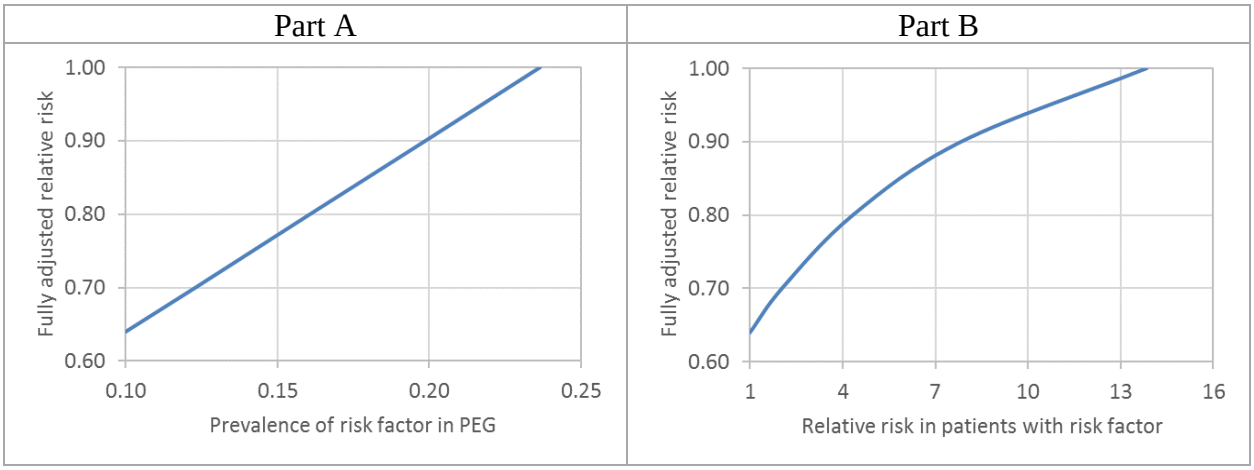

Figure 14: Sensitivity analyses for the primary result in SPD555-802 (*i.e.*, MACE SIRR 0.64, PRU *vs.* PEG). These sensitivity analyses define the fully adjusted relative risk as MACE incidence in PRU *vs.* PEG after adjusting the primary result in SPD555-802 for an unmeasured cardiovascular disease risk factor. Both plots set the prevalence of this risk factor in PRU at 0.10. Assuming 8-fold MACE risk in patients with the risk factor, the left-hand plot shows fully adjusted relative risk as a function of the prevalence of the risk factor in PEG. Assuming a 0.20 prevalence of the risk factor in PEG, the right-hand plot shows fully adjusted relative risk as a function of MACE relative risk in patients with the risk factor.

The five SPD555-802 data sources defined MACE with variable rigor (Section 3.8.1 Data Sources). Nevertheless, DEPI assessed the SPD555-802 MACE outcome as internally valid overall (*i.e.*, outcome classified with low risk of bias; **APPENDIX 5**). Two principles under ROBINS-I determined this low risk-of-bias judgment. First, SPD555-802 used information previously recorded to identify MACE. Second, SPD555-802 assessed MACE using procedures blind to treatment with PRU or PEG. Therefore, DEPI regarded the MACE outcome as internally valid, as defined by protocol.

Despite this favorable assessment, DEPI recognized that SNR, the dominating data source in pooled analysis, used a less rigorous method to identify MACE. SNR identified MACE using diagnosis codes in NPR hospital records and cause-of-death codes in CDR. As a matter of routine, DEPI regards the NPR and CDR databases as superior data sources [13] and the approach used by SNR to identify AMI and stroke in NPR as acceptable for many purposes [14, 15].

Still, SNR did not use gold-standard medical chart review to validate MACE. At a minimum, the gold standard would have recognized 10 or 20 percent of MACE in SNR as false. Falsely identified MACE in SNR might partially explain differences in age-standardized MACE incidence, generally higher in SNR than U.K. data sources, as shown in Figure 13.

Therefore, SNR plausibly overestimated MACE incidence in both PRU and PEG and the risk difference between PRU and PEG. However, these errors should not bias estimates of relative risk (*i.e.*, SIRR), unless codes identified MACE falsely more often in PRU or PEG. This circumstance might apply to SPD555-802, for example, if (1) diagnosis codes occasionally and improperly indicated a pre-existing condition (*e.g.*, history of stroke) instead of a new event (*i.e.*, acute stroke) and (2) methods inadequately controlled for baseline differences between PRU and PEG with respect to the prevalence of these pre-existing conditions.[53]

As noted in Section 3.4.1.4 Outcomes, above, ISD possibly excluded as MACE three events that could not be adjudicated because of missing patient charts. With <5 patients with MACE in both PRU and PEG (Table 9), any effort to reclassify these three unclassified MACE events to PRU or PEG could dramatically change the SIRR point estimate for ISD.[54] Because SNR dominated ISD, however, outcome misclassification errors related to missing patient charts in ISD should minimally impact the results expected from pooled analysis.

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[53] Typically, diagnosis codes in the primary position of hospital records more reliably identify acute events. Accordingly, FDA asked the Sponsor, on July 2, 2018, to provide the number of patients in SNR with AMI and stroke identified by codes in the primary position of NPR hospital records. On August 31, 2018, the Sponsor responded with Clinical Information Amendment, eCTD 0049, which reported codes in the primary position as having identified AMI or stroke during current use of PRU in 11 of 13 (85%) patients and during current use of PEG in 47 of 58 (81%) of patients (before trimming). While preparing its response to FDA's request, SNR discovered and corrected a programming error, which affected SPD555-802 study results previously reported to FDA. This programming error had improperly linked patients with MACE identified through both the National Patient Register (NPR) and the Causes of Death Register (CDR). The Sponsor explained the programming error and provided corrected study results in Clinical Information Amendment, eCTD 0053, Supplemental Tables for SPD555-802, eCTD 0054, and Root Cause Analysis for the Programming Error, eCTD 0056. DEPI used the corrected results, as provided in eCTD 0054, to prepare this review of SPD555-802.

[54] The three unadjudicated ISD events occurred in PEG patients, per Clinical Information Amendment, eCTD 0044, page 1.

4.3 External Validity and Interpretation

Pooled analyses used data sources regarded as valid representations of Sweden (SNR), Scotland (ISD), and patients registered with U.K. general practitioners (CPRD and THIN).

In U.K. data sources, eligibility criteria excluded ≈5% of prucalopride users because of a PEG prescription written or filled on the PRU index date.

Cohort trimming removed prucalopride-exposed patients with the highest predicted probabilities of treatment with prucalopride. The subset removed by trimming might contain patients regarded by clinicians as the most suited for treatment with prucalopride. Specifically, trimming patients, with propensity scores either too high or too low, removed 12.6%, 7.6%, 9.0%, and 6.7% from PRU in SNR, ISD, CPRD, and THIN, respectively.

GePaRD lacked a way to identify out-of-hospital death. To enforce uniformity across all data sources, the primary MACE composite excluded cardiovascular deaths not occurring in association with hospitalization. However, the four data sources included in pooled analyses could identify out-of-hospital death. In SNR, ISD, CPRD, and THIN combined, 0 and 46 out-of-hospital cardiovascular deaths occurred during current treatment with PRU and PEG, respectively. In a sensitivity analysis, adding these out-of-hospital cardiovascular deaths changed the risk estimated for PRU from SIRR 0.64 (95% CI 0.36-1.14) to SIRR 0.43 (95% CI 0.25-0.73). Unlike in-hospital cardiovascular death, ISD did not use patient charts to validate out-of-hospital cardiovascular death. Like SNR, ISD identified out-of-hospital cardiovascular deaths solely by cause-of-death codes in national death records. CPRD and THIN used similar methods to validate cardiovascular deaths occurring in and out of hospital. The previously expressed concern about PEG as a plausibly weak comparator for PRU might explain the peculiar dissimilarity between PRU and PEG with respect to out-of-hospital cardiovascular death.

To gauge relevance of SPD555-802 to the United States, DEPI aligned age-specific MACE rates in SNR (combining PRU and matched PEG cohorts, before trimming, Table 3) with hospital discharge and mortality rates in 2014 for the general U.S. population. After accounting for the different age groupings and female predominance in SNR,[55] MACE incidence in SNR appeared grossly comparable to a U.S. benchmark formed as the simple sum of the hospital discharge rates for AMI and stroke and the mortality rate for cardiovascular disease.

[55] With 92.6% of patient-years accrued by women.

Table 26: Major Adverse Cardiovascular Events (MACE) during current use of prucalopride (PRU) or polyethylene glycol 3350 (PEG) in Swedish National Registers (SNR) [1], 2014 U.S. hospital discharges with a diagnosis (any listed) for acute myocardial infarction (AMI) [2], 2014 U.S. hospital discharges with a diagnosis (any listed) for acute cerebrovascular disease (Stroke) [1], and 2014 U.S. mortality due to a disease of the circulatory system (Death) [3].

Swedish National Registers (SNR)					2014 U.S. Rates, by Age			
Age, years	P-YRs	MACE	IR	95% CI	Age, years	AMI	Stroke	Death
18-49	1,828	5	2.7	0.9-6.4	18-44 [4]	0.4	0.4	0.2
50-69	2,309	30	13.0	8.8-18.6	45-64	3.8	2.7	1.6
70-79	889	31	34.9	23.7-49.5	65-85	10.9	9.0	8.2
≥80	456	22	48.3	30.2-73.0	≥85	24.1	22.3	52.4

ABBREVIATIONS: P-YRs, patient-years; MACE, number of patients with a Major Adverse Cardio-vascular Event (non-fatal AMI, non-fatal stroke, or in-hospital cardiovascular death); IR, incidence per 1000 patient-years; CI, confidence interval

FOOTNOTES:

1. Age-specific MACE IRs in SNR calculated by DEPI from Table 9a1 in Supplemental Full Results File and 95% CIs estimated by DEPI using the Byar approximation to the Poisson distribution, as implemented in OpenEpi, Open Source Epidemiologic Statistics for Public Health, Version 3.01, accessed at http://www.openepi.com/Menu/OE_Menu.htm on August 20, 2018.
2. 2014 U.S. hospital discharge rates, per 1000 persons, obtained by DEPI from the HCUPnet on-line query system, accessed at https://hcupnet.ahrq.gov/ on July 25, 2018. AMI and stroke discharges defined by ICD-9 codes in Clinical Classification Software (CCS) categories for Acute Myocardial Infarction and Acute Cerebrovascular Disease, respectively. For ICD-9 codes in CCS categories, see https://www.hcup-us.ahrq.gov/toolssoftware/ccs/AppendixASingleDX.txt.
3. 2014 U.S. mortality due to diseases of the circulatory system (ICD-10 I00-I99), per 1000 persons, obtained by DEPI from the Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999-2016 on CDC WONDER Online Database, released December 2017, accessed at http://wonder.cdc.gov/ucd-icd10.html on July 25, 2018.
4. Showing hospital discharge rates for 18-44 year-old persons and the cardiovascular mortality rate for 15-44 year-old persons.

Statistical uncertainty possibly presented the most important limitation to the usefulness of SPD555-802. With SNR contributing 14 patients, pooled analyses included only 18 patients with MACE during current use of PRU.[56] With so few patients, data-source-specific, secondary, and subgroup analyses produced no new understanding (Table 25). Because of statistical uncertainty, DEPI attaches little weight to subgroup analyses that suggest elevated MACE risk in ≥55 year-old men.

4.4 Final Synthesis

To facilitate interpretation, SPD555-802 makes two arguably reasonable assumptions. First, PEG, as a poorly absorbed osmotic laxative, exerts no systemic effects that predispose to MACE. Second, the possible adverse effects from prucalopride derive solely from acute pharmacological properties (*e.g.*, platelet aggregation), which dissipate soon after discontinuation of use.

[56] SNR and U.K. data sources identified 21 additional patients with MACE occurring during time defined as past use of PRU, per Clinical Information Amendment, eCTD 0049, page 2.

Regardless, the statistically non-significant primary result from SPD555-802 suggests two possible, though unexpected and counter-intuitive, casual interpretations. Relative to placebo, (1) prucalopride protects users against MACE and (2) PEG acutely causes MACE. Both statements might be true. However, the serious threats to internal validity demand a more cautious interpretation.

For decision-making purposes, FDA might simply attribute any apparent protection from prucalopride to bias in the design or conduct of SPD555-802. Accordingly, FDA might amend the primary result from SPD555-802 (*i.e.*, SIRR = 0.64) to reflect no effect of prucalopride on MACE (*i.e.*, SIRR = 1.00, the null hypothesis). This path implies that FDA finds evidence in SPD555-802, however weak, that supports the null hypothesis. As a final step, FDA might use the variance estimated by SPD555-802 for the SIRR to place an upper bound on the 95% confidence interval for the amended SIRR.

Following this cautious path, DEPI places the upper bound for the amended SIRR at 1.78.[57] An even more cautious approach, which doubles the variance estimated by SPD555-802, moves the upper bound to 2.26.[58] Accordingly, despite the important problems identified by DEPI in SPD555-802, FDA might confidently conclude that SPD555-802 reasonably excludes a greater than 3-fold MACE risk from prucalopride, yet express uncertainty about possible risks of lower magnitude.

5. CONCLUSIONS

SPD555-802 provides evidence that reasonably excludes 3-fold MACE risk from prucalopride.

6. RECOMMENDATIONS FOR DGIEP

DEPI recommends that DGIEP align decisions about NDA 210166 with the following conclusions.

- SPD555-802 satisfies a pre-NDA expectation for a European post-marketing observational study that reasonably excludes, with 95% statistical confidence, 3-fold MACE risk from prucalopride.

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

Recognizing important problems in SPD555-802 (*e.g.*, serious risk of bias due to confounding),

[57] Calculated as $e^{\ln(1.14)-\ln(0.64)}$.

[58] Calculated as $e^{\sqrt{2}(\ln(1.14)-\ln(0.64))}$.

DEPI recommends that the FDA label for prucalopride not include results from SPD555-802.

7. REFERENCES

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CC: Pinheiro S / Sandhu S / Hua W / Bright P / Iannacone M / Billings M / Jackson S / Calloway P (OSE)

Korvick J / Tomaino J / Line C / Kelleher A (DGIEP)

Kim C / Tran T (DB VII)

APPENDIX 1: Tabular summary of Swedish National Registers

Domain	Description
1.1 Objectives/Aims/Scope	Estimate a Standardized Incidence Rate Ratio (SIRR), with 95% Confidence Interval (CI), for Major Adverse Cardiovascular Events (MACE), comparing patients starting treatment with prucalopride or polyethylene glycol 3350 (PEG).
1.2.1 Design for the Primary Analysis	
1.2.1.1 Type	Retrospective cohort study
1.2.1.2 Data Sources	Swedish National Registers (SNR): • Swedish Prescribed Drug Register (PDR) • National Patient Register (NPR) • Swedish Cancer Register (SCR) • Causes of Death Register (CDR) • Population Registers of Statistics Sweden
1.2.1.3 Study period	2012-2015, period for assessing study exposures and outcomes
1.2.1.4 Criterion (Selection) Standards	Inclusion criteria: • Two cohorts separately identified by first (index) prescription filled during study period for (1) prucalopride (PRU) or (2) PEG Exclusion criteria: • <12 months data available before index date, as defined by dispensing date for index prescription • Age <18 years on index date • PEG patient with index prescription supplying ≤4 days of treatment • PRU patient, filling before index date, a prucalopride prescription • PEG patient filling, before index date, a PEG prescription supplying >4 days of treatment • PRU or PEG patient filling, within 12 months + 10 days before index date, a PEG prescription supplying ≤4 days of treatment • Patient filling, on PRU index date, a prescription for PEG • Patient filling, on PEG index date, a prescription for prucalopride • PRU patient with prucalopride-exposed time completely covered by treatment with PEG • PEG patient with PEG-exposed time completely covered by treatment with prucalopride
1.2.1.5 Protected Health Information	Anonymized data analyzed by (b) (4) with personal identifying information retained by National Board of Health and Welfare
1.2.2 Setting	Swedish resident population

1.2.3 Exposure for primary analysis	Prucalopride exposure defined by treatment time (in days) covered uniquely by prucalopride prescriptions, with 7-day gaps allowed between a sequence of prescriptions, 7-day extension added to last prescription in a sequence, and follow-up terminated on first switch to PEG, as indicated by first post-PRU-index PEG prescription supplying >4 days of treatment PEG exposure defined by treatment time (in days) covered uniquely by PEG prescriptions supplying >4 days of treatment, with 7-day gaps allowed between a sequence of prescriptions, 7-day extension added to last prescription in a sequence, and follow-up terminated on first switch to prucalopride, as indicated by first post-PEG-index prucalopride prescription FOOTNOTES: • Prescriptions stockpiled, *i.e.*, days of supply remaining from previous prescriptions added to days supplied by a current prescription • Overlapping exposure ignored, *i.e.*, time covered by prescriptions for both PRU and PEG • At exposure level (PRU or PEG), follow-up censored on first event • At patient level, follow-up censored on death, second switch, prescription filled for PRU and PEG on same date, emigration, or end of study period
1.2.4 Outcome	First MACE, *i.e.*, non-fatal acute myocardial infarction, non-fatal stroke, or in-hospital cardiovascular death (**APPENDIX 2**)
1.2.5 Covariates	Confounder control achieved through matching on, • Sex • Calendar year of index date • Closest year of birth (±10 years allowed) • Recent hospitalization (APPENDIX **3**) • Prescriber specialty (four categories) Propensity scores modeled with 35 covariates (APPENDIX **3**) in eight domains, • Demographic factors • Prescription opioid history • History of gastrointestinal problems • History of cardiovascular hospitalization • History of cardiovascular procedure • Prescription drug history • Medical history • Health care utilization

1.2.6 Sample Size	Primary matched analysis: N=3,194 PRU and N=16,769 PEG with 1,327 and 3,682 patient-years, respectively (Table 12 in Supplemental Full Results File)
1.2.7 Statistical Analyses	Steps for controlled analysis, • Form cohorts, five PEG for every PRU, matched on five factors. • Estimate propensity scores. • Trim cohorts (*i.e.*, exclude patients with extreme propensity scores). • Calculate crude MACE Incidence Rate (IR) as the number of events per 1000 patient-years. • To compare MACE in PRU *vs.* PEG, - Calculate MACE IRs in each of ten propensity-score strata. - Calculate Standardized Incidence Rates (SIRs) as weighted averages of the stratum-specific IRs. - Calculate SIRR as the ratio between the SIRs for PRU and PEG.
1.2.8 Study Results	From Table 14a in Full Supplemental Results File PRU: 14 MACE (crude IR 10.6 per 1000 patient-years) PEG: 64 MACE (crude IR 17.4 per 1000 patient-years) SIRR (95% CI): 0.63 (0.33-1.20)

APPENDIX 2: MACE in Swedish National Registers

Non-fatal Acute Myocardial Infarction (AMI): Defined by hospital code, providing death not recorded within 30 days of event. See FOOTNOTES 1 and 2.

ICD-10	Description
I21	Acute myocardial infarction

Non-fatal Stroke: Defined by hospital code, providing death not recorded within 30 days of event. See FOOTNOTES 1 and 2.

ICD-10	Description
H34.1	Central retinal artery occlusion
I60	Nontraumatic subarachnoid hemorrhage
I61	Nontraumatic intracerebral hemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction

In-hospital Cardiovascular Death: Defined by underlying cause of death on death certificate, with death occurring during hospitalization or within three days after hospital discharge. See FOOTNOTE 1.

ICD-10	Description
Death due to Acute Myocardial Infarction (AMI)	
I21	Acute myocardial infarction
I22	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
I23	Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period)
I24.1	Dressler's syndrome
I25.3	Aneurysm of heart
Sudden Cardiac Death	
I44.2	Atrioventricular block, complete
I46.1	Sudden cardiac death, so described
I46.9	Cardiac arrest, cause unspecified
I47.0	Re-entry ventricular arrhythmia
I47.2	Ventricular tachycardia
I49.0	Ventricular fibrillation and flutter
R09.2	Respiratory arrest
R96.0	Instantaneous death
R96.1	Death occurring less than 24 hours from onset of symptoms, not otherwise explained
R98	Unattended death
Death due to Heart Failure	
I11.0	Hypertensive heart disease with heart failure
I13.0	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease
I50	Heart failure
J81	Pulmonary edema
Death due to Stroke	
G45	Transient cerebral ischemic attacks and related syndromes
H34.1	Central retinal artery occlusion
I60	Nontraumatic subarachnoid hemorrhage

ICD-10	Description
I61	Nontraumatic intracerebral hemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
I69.0	Sequelae of nontraumatic subarachnoid hemorrhage
I69.1	Sequelae of nontraumatic intracerebral hemorrhage
I69.3	Sequelae of cerebral infarction
I69.4	Sequelae of stroke, not specified as haemorrhage or infarction
Death due to Cardiovascular Hemorrhage	
I31.2	Hemopericardium, not elsewhere classified
I62	Other and unspecified nontraumatic intracranial hemorrhage
I69.2	Sequelae of other nontraumatic intracranial hemorrhage
I71.0	Dissection of aorta
I71.1	Thoracic aortic aneurysm, ruptured
I71.3	Abdominal aortic aneurysm, ruptured
I71.5	Thoracoabdominal aortic aneurysm, ruptured
I71.8	Aortic aneurysm of unspecified site, ruptured
Death due to Other Cardiovascular Causes	
B33.2	Viral carditis
F01	Vascular dementia
I01	Rheumatic fever with heart involvement
I02.0	Rheumatic chorea with heart involvement
I05	Rheumatic mitral valve diseases
I06	Rheumatic aortic valve diseases
I07	Rheumatic tricuspid valve diseases
I08	Multiple valve diseases
I09	Other rheumatic heart diseases
I10	Essential (primary) hypertension
I11.9	Hypertensive heart disease without heart failure
I12	Hypertensive chronic kidney disease
I13.1	Hypertensive heart and chronic kidney disease without heart failure
I13.9	Hypertensive heart and renal disease, unspecified
I15	Secondary hypertension
I20	Angina pectoris
I24.0	Acute coronary thrombosis not resulting in myocardial infarction
I24.8	Other forms of acute ischemic heart disease
I24.9	Acute ischemic heart disease, unspecified
I25	Chronic ischemic heart disease
I26	Pulmonary embolism
I27	Other pulmonary heart diseases
I28	Other diseases of pulmonary vessels
I30	Acute pericarditis
I31.0	Chronic adhesive pericarditis
I31.1	Chronic constrictive pericarditis
I31.3	Pericardial effusion (noninflammatory)
I31.8	Other specified diseases of pericardium
I31.9	Disease of pericardium, unspecified
I32	Pericarditis in diseases classified elsewhere
I33	Acute and subacute endocarditis
I34	Nonrheumatic mitral valve disorders

ICD-10	Description
I35	Nonrheumatic aortic valve disorders
I36	Nonrheumatic tricuspid valve disorders
I37	Nonrheumatic pulmonary valve disorders
I38	Endocarditis, valve unspecified
I39	Endocarditis and heart valve disorders in diseases classified elsewhere
I40	Acute myocarditis
I41	Myocarditis in diseases classified elsewhere
I42	Cardiomyopathy
I43	Cardiomyopathy in diseases classified elsewhere
I44.0	Atrioventricular block, first degree
I44.1	Atrioventricular block, second degree
I44.3	Other and unspecified atrioventricular block
I44.4	Left anterior fascicular block
I44.5	Left posterior fascicular block
I44.6	Other and unspecified fascicular block
I44.7	Left bundle-branch block, unspecified
I45	Other conduction disorders
I47.1	Supraventricular tachycardia
I47.9	Paroxysmal tachycardia, unspecified
I48	Atrial fibrillation and flutter
I49.1	Atrial premature depolarization
I49.2	Junctional premature depolarization
I49.3	Ventricular premature depolarization
I49.4	Other and unspecified premature depolarization
I49.5	Sick sinus syndrome
I49.8	Other specified cardiac arrhythmias
I49.9	Cardiac arrhythmia, unspecified
I51	Complications and ill-defined descriptions of heart disease
I52	Other heart disorders in diseases classified elsewhere
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67	Other cerebrovascular diseases
I68	Cerebrovascular disorders in diseases classified elsewhere
I70	Atherosclerosis
I71.2	Thoracic aortic aneurysm, without rupture
I71.4	Abdominal aortic aneurysm, without rupture
I71.6	Thoracoabdominal aortic aneurysm, without rupture
I71.9	Aortic aneurysm of unspecified site, without rupture
I72	Other aneurysm
I73	Other peripheral vascular diseases
I74	Arterial embolism and thrombosis
I77	Other disorders of arteries and arterioles
I78.0	Hereditary hemorrhagic telangiectasia
I78.8	Other diseases of capillaries
I78.9	Disease of capillaries, unspecified
I79	Disorders of arteries, arterioles and capillaries in diseases classified elsewhere
I98.8	Other specified disorders of circulatory system in diseases classified elsewhere
I99	Other and unspecified disorders of circulatory system
R57.0	Cardiogenic shock

REFERENCE: Appendix C, Operational Definitions of Study Endpoints, Table C-1, Page C-41, in (b) (4) (b) (4) October 2, 2017, Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator (SPD555-802): Full Study Data Development Plan, Version 7.0, submitted to NDA 210166 (eCTD 0001) on December 21, 2017.

FOOTNOTES:

1. Event date defined by date of hospitalization.
2. Diagnosis code in primary or secondary position of a National Patient Register (NPR) hospital record. Responding to uncertainty in DEPI, Shire confirmed that SNR identified AMI and stroke endpoints "from primary and secondary hospital discharge diagnoses." See Clinical Information Amendment, eCTD 0037, page 5.

APPENDIX 3: Key covariates in Swedish National Registers.

Demographic variables (assessed on last day of year before index year)	**Coding**
1. Sex by Age	26 levels
2. Education	3 levels
3. Income	4 levels
Outpatient prescription opioid history	**Coding**
4. Recent opioid – ≥1 ATC N02A outpatient prescription filled during 6-month pre-index period (including index date)	yes/no
5. Chronic opioid – ≥2 ATC N02A outpatient prescriptions filled during 12-month pre-index period (including index date)	yes/no
History of gastrointestinal problem (2001 through index date)	**Coding**
6. Outpatient encounters with IBS diagnosis – ICD-10 K58.0 or K58.9 (FOOTNOTE 2)	0, 1, ≥2
7. Gastrointestinal diagnostic classes associated with an outpatient encounter (FOOTNOTE 3)	0, 1, 2-12
8. Constipation inpatient diagnosis – ICD-10 K59.0	yes/no
9. Other inpatient gastrointestinal diagnosis – ICD-10 K20-K31, K35-K38, K40-K46, K50-K52, K55-K67, or K90-K93	yes/no
History of cardiovascular hospitalization (2001 through index date)	**Coding**
10. Acute myocardial infarction – ICD-10 I21	yes/no
11. Stroke – ICD-10 I60-I66, I69.3, or I69.4	yes/no
12. Transient ischemic attack – ICD-10 G45 or G46	yes/no
13. Ischemic heart disease – ICD-10 I20, I21, I22, I23, I24 (except I24.1), or I25 (except I25.2, I25.3, or I25.4)	yes/no
14. Peripheral vascular disease – ICD-10 I70, I73.9, or I74	yes/no
History of inpatient or outpatient cardiovascular procedure (2001 through index date)	**Coding**
15. Any coronary revascularization procedure – KVÅ FNA, FNB, FNC, FND, FNE, FNF, or FNG (FOOTNOTE 3)	yes/no
16. Any peripheral revascularization procedure – KVÅ PAE, PAF, PAH, PAP, PAQ, PBE, PBF, PBH, PBP, PBQ, PCE, PCF, PCH, PCP, PCQ, PDE, PDF, PDH, PDP, PDQ, PEE, PEF, PEH, PEP, PEQ, PFE, PFF, PFH, PFP, or PFQ (FOOTNOTE 3)	yes/no
Outpatient prescription drug history (2006 through day before index date)	**Coding**
17. Agents acting on renin-angiotensin system – ATC C09	yes/no
18. Anticoagulants – ATC B01AA, B01AB, B01AE, B01AF, or B01AX	yes/no
19. Antidiabetics – ATC A10	yes/no
20. Aspirin and other platelet aggregation inhibitors – ATC B01AC	yes/no
21. Beta-blocking agents – ATC C07	yes/no
22. Calcium-channel blockers – ATC C08	yes/no
23. Diuretics – ATC C03	yes/no
24. HMG CoA reductase inhibitors (*i.e.*, statins) – ATC C10AA	yes/no
25. Other anti-hypertensives [vasodilators, alpha-blockers, and central agents] – ATC C02C, C02D, C02AC01, or C02AC05	yes/no
Medical history (2001 through index date, inpatient or outpatient diagnosis, except where indicated)	**Coding**
26. Asthma – ICD-10 J45 or J46	yes/no

27.	Bronchitis, emphysema, and COPD – ICD-10 J40-J44	yes/no
28.	Cancer – outpatient ICD-10 C00-C97 (FOOTNOTE 4)	yes/no
29.	Chronic kidney disease – ICD-10 N18	yes/no
30.	Diabetes – ICD-10 E10, E11, E12, or E13	yes/no
31.	Hyperlipidemia – ICD-10 E78	yes/no
32.	Hypertension – ICD-10 I10, I11, I12, I13, or I15	yes/no
33.	Obesity – ICD-10 E65 (FOOTNOTE 5)	yes/no
Health care utilization		**Coding**
34.	Recent hospitalization – discharged from hospital in two-week pre-index period (excluding index date)	yes/no
35.	Number of outpatient visits during 12-month pre-index period (excluding index date)	0, 1, 2, ≥3

ABBREVIATIONS: ATC, Anatomical Therapeutic Chemical; COPD, Chronic Obstructive Pulmonary Disease; IBS, Irritable Bowel Syndrome; ICD-10, International Classification of Disease, 10th Revision

REFERENCE: Appendix D, Operational Definitions of Covariates, Table D-4, Pages D-52 to D-58, in (b) (4) (b) (4) October 2, 2017, Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator (SPD555-802): Full Study Data Development Plan, Version 7.0, submitted to NDA 210166 (eCTD 0001) on December 21, 2017.

FOOTNOTES:

1. **APPENDIX 3** lists covariates available to SNR propensity score models. See Data Development Plan, Table 20, pages 80-81.
2. ICD-10 K58.0 and K58.9 define Irritable bowel syndrome with diarrhea and Irritable bowel syndrome without diarrhea, respectively. DEPI recognizes ICD-10 K58.x as a more suitable code. ICD-10 K58.x includes K58.1, Irritable bowel syndrome with constipation.
3. Twelve diagnostic classes, as defined by ICD-10 codes for esophagus (K20-K23), stomach or duodenum (K25-K31), appendix (K35-K38), hernia (K40-K46), other diseases of intestine (K52, K55-K57, K59.1-K59.4, K59.8-K59.9, or K60-K64), peritoneum (K65-K67), liver (K70-K77), biliary system (K80-K83), pancreas (K85-K87), gastrointestinal hemorrhage (K92.0-K92.2), intestinal malabsorption (K90), and inflammatory bowel disease (K50-K51).
3. KVÅ refers to the Swedish National Board of Health and Welfare classification system for surgical and medical procedures. See http://www.socialstyrelsen.se/klassificeringochkoder/laddaner/Sidor/kodtextfiler.aspx?utm_campaign=20171121&utm_medium=email&utm_source=apsis, accessed on July 19, 2018.
4. Using data from the Swedish Cancer Register. See Clinical Information Amendment, eCTD 0037, page 6.
5. ICD-10 E65 defines Localized adiposity. DEPI recognizes ICD-10 E66, Overweight and obesity, as the correct code.

APPENDIX 4: Key covariates in Information Services Division of Scotland.

Demographic variables (assessed on index date)	**Coding**
1. Sex	2 levels
2. Age (<55 *vs.* ≥55 years)	2 levels
3. Calendar time (2013-2016 *vs.* 2010-2012)	2 levels
4. Socioeconomic level (deprivation index)	5 levels
Outpatient prescription opioid history	**Coding**
5. Recent opioid – ≥1 outpatient prescription filled during 6-month pre-index period	yes/no
6. Chronic opioid – ≥2 outpatient prescriptions filled during 12-month pre-index period (including index date)	yes/no
History of gastrointestinal problem (2009 through index date)	**Coding**
7. IBS inpatient diagnosis – ICD-10 K58	yes/no
8. Other inpatient gastrointestinal diagnosis – ICD-10 K50-K52, K55-K57, K59.1, K59.2, K59.3, K59.4, K59.8, K59.9, K60-K63	yes/no
History of cardiovascular hospitalization (2009 through index date)	**Coding**
9. Acute myocardial infarction – ICD-10 I21-I23, I24.1, I51.0, I51.1, I51.2, I51.3	yes/no
10. Stroke – ICD-10 I60-I61, I63-I64	yes/no
11. Transient ischemic attack – ICD-10 G45	yes/no
12. Ischemic heart disease – ICD-10 I20, I21, I22, I23, I24, or I25	yes/no
13. Peripheral vascular disease – ICD-10 I70.2, I73, or I79.2	yes/no
History of inpatient cardiovascular procedure (2009 through index date)	**Coding**
14. Any coronary revascularization procedure – OPCS4 K40, K41, K42, K43, K44, K45, K46, K49, K50.1, K50.8, K75	yes/no
15. Any peripheral revascularization procedure – OPCS4 I50, I51, I52, I532, 158, L59, L601, L602, L622, L261, L262, L263, L268, L269, L311, L318, L319, L391, L392, L393, L398, L399, L431, L432, L433, L438, L439, L471, L472, L478, L479, L541, L542, L548, L549, L631, L632, L633, L638, L639, L71	yes/no
Outpatient prescription drug history (2009 through day before index date)	**Coding**
16. Anticoagulants – BNF Chapter 2.8 (except 'detection strips')	yes/no
17. Antidiabetics – BNF Chapter 6.1	yes/no
18. Antihypertensive – BNF Chapters 2.2.1, 2.4 (except 'sotalol'), 2.5, or 2.6.2 containing 'dipine' or 'diltiazem' or 'verapamil'	yes/no
19. Aspirin and other platelet aggregation inhibitors – BNF Chapter 2.9	yes/no
20. HMG CoA reductase inhibitors (*i.e.*, statins) – BNF Chapter 2.12 containing 'statin'	yes/no
Medical history (2009 through index date, inpatient diagnosis, except where indicated)	**Coding**
21. Cancer – Any pre-index Scottish Cancer Registry record for ICD-10 C00-C97, except C44 (Other and unspecified malignant neoplasm of skin)	yes/no
22. COPD – ICD-10 J41, J42, J43, or J44	yes/no
23. Diabetes – ICD-10 E10, E11, E12, E13, or E14	yes/no
24. Hyperlipidemia – ICD-10 E78	yes/no
25. Hypertension – ICD-10 I10-I16	yes/no
Health care utilization	**Coding**
26. Recent hospitalization – discharged from hospital in two-week pre-index period (excluding index date)	yes/no

ABBREVIATIONS: BNF, British National Formulary; COPD, Chronic Obstructive Pulmonary Disease; IBS,

Irritable Bowel Syndrome; ICD-10, International Classification of Disease, 10th Revision; OPCS4, Office of Population Censuses and Surveys Classification of Interventions and Procedures

REFERENCE: Appendix D, Operational Definitions of Covariates, Table D-4, Pages D-10 to D-14, in (b) (4) (b) (4) October 2, 2017, SPD555-802 Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator: Full Study Data Development Plan, Version 7.0, submitted to NDA 210166 (eCTD 0001) on December 21, 2017.

FOOTNOTES:

1. **APPENDIX 4** lists covariates available to ISD propensity score models. See Data Development Plan, Table 20, pages 80-81.

APPENDIX 5: Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) Assessment

The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

Version 19 September 2016

ROBINS-I tool (Stage I): At protocol stage

Specify the review question

Participants	Adults with chronic idiopathic constipation (CIC)
Experimental intervention	Prucalopride (PRU)
Comparator	PEG (conceived as placebo proxy)
Outcomes	MACE

List the confounding domains relevant to all or most studies

sex, age, calendar time, medical history (ischemic vascular disease, diabetes, etc.), behavioral risk factor (smoking, etc.)

List co-interventions that could be different between intervention groups and that could impact on outcomes

alternative treatments for CIC (diet modification, exercise, fiber, chloride channel activators, guanylate cyclase C agonists, tricyclic antidepressants, antispasmodics, SSRIs)

ROBINS-I tool (Stage II): For each study

Specify a target randomized trial specific to the study

Design	Randomized
Participants	Adults
Experimental intervention	PRU initiated
Comparator	PEG initiated

Is your aim for this study…?

☐ to assess the effect of *assignment to* intervention

X to assess the effect of *starting and adhering to* intervention

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

First Major Adverse Cardiovascular Event (MACE), a composite of non-fatal acute myocardial infarction, non-fatal stroke, or in-hospital cardiovascular death

Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

SIRR 0.64, 95% CI 0.36-1.14

Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

(i) Confounding domains listed in the review protocol				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?* (Note: Assessed in SNR, the dominant data source)	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?
sex	female sex	No (patient-years in SNR, matched, before trimming, percent female in PRU vs. PEG, 94.6% vs. 91.8%)	Yes	Observed SIRR < True SIRR
age	Age 18-54 years	No (patient-years in SNR, matched, before trimming, percent aged 18-54 years in PRU vs. PEG, 50.5% vs. 39.7%)	Yes	Observed SIRR < True SIRR
calendar time	2010-2012	Yes (patient-years in SNR, matched, before trimming, percent 2010-2012 in PRU vs. PEG, 9.9% vs. 7.5%)	Yes	
medical history	diagnostic code for diabetic mellitus and selected diabetic complications	Yes (patient-years in SNR, matched, before trimming, percent diabetic in PRU vs. PEG, 9.5% vs. 10.4%)	Yes	
medical history	diagnostic code for hypertensive disease	No (patient-years in SNR, matched, before trimming, percent hypertensive in PRU vs. PEG, 18.0% vs. 25.4%)	Yes	Observed SIRR < True SIRR
medical history	diagnostic code for disorder of lipid metabolism	No (patient-years in SNR, matched, before trimming,	Yes	Observed SIRR < True SIRR

		percent with lipid disorder in PRU vs. PEG, 5.6% vs. 8.0%)		
medical history	drug code for insulin and other anti-diabetics	Yes (patient-years in SNR, matched, before trimming, percent treated for diabetes in PRU vs. PEG, 10.3% vs. 11.3%)	Yes	
medical history	drug code for anti-hypertensives	Yes (patient-years in SNR, matched, before trimming, percent treated for hypertension in PRU vs. PEG, 48.2% vs. 51.3%)	Yes	
medical history	drug code for statin	Yes (patient-years in SNR, matched, before trimming, percent treated with statin in PRU vs. PEG, 21.7% vs. 25.2%)	Yes	
medical history	diagnostic code for myocardial infarction, stroke, or other cardiovascular disease	Yes (patient-years in SNR, matched, before trimming, percent with history of cardiovascular disease in PRU vs. PEG, 5.8% vs. 7.9%)	Yes	
behavioral risk factor	overweight and obesity	No	No	Unpredictable
behavioral risk factor	cigarette smoking	No	No	Unpredictable

(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?

Healthcare Utilization	Recent hospitalization	Yes (patient-years in SNR, matched, before trimming, percent with recent hospitalization in PRU vs. PEG, 1.8% vs. 2.1%)	Yes	

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

(i) Co-interventions listed in the review protocol		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator
Not applicable (i.e., not investigated by study authors)		

(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator
Over-the-counter aspirin	No	Unpredictable

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Signalling questions	Description	Response options
Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	Observational (non-randomized) study design creating potential for confounding.	YES
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.	A PRU patient switched to PEG could be selected as a PEG control. However, exposed time defined solely by cohort assignment.	NO
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)		NOT APPLICABLE

Questions relating to baseline confounding only		
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Stratifying patients by propensity score decile did not balance patient-years in PRU vs. PEG for confounding variables.	PROBABLY NO
1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NOT APPLICABLE
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?		NO
Questions relating to baseline and time-varying confounding		
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Stratifying patients by propensity score decile did not balance patient-years in PRU vs. PEG for baseline confounding variables.	PROBABLY NO
1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NOT APPLICABLE
Risk of bias judgement	See Responses to Items 1.4, above. Assessment also informed by (1) low confidence in PEG control, (2) major uncontrolled imbalance between PRU and PEG with respect to pre-index GI diagnoses, and (3) channeling demonstrated in GePaRD.	SERIOUS
Optional: What is the predicted direction of bias due to confounding?		Observed SIRR < True SIRR

Bias in selection of participants into the study		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4	Patient selection determined by index date defined by first prescription for PRU or PEG in patients with ≥12 months of pre-index data available.	NO
2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?		NOT APPLICABLE
2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NOT APPLICABLE
2.4. Do start of follow-up and start of intervention coincide for most participants?	Follow-up begins on index date.	YES
2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?		NOT APPLICABLE
Risk of bias judgement		LOW
Optional: What is the predicted direction of bias due to selection of participants into the study?		

Bias in classification of interventions		
3.1 Were intervention groups clearly defined?	Intervention defined by time covered by prescriptions for PRU or PEG, with ambiguity created by missing information for the number of days supplied.	PROBABLY YES
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Information about intervention (exposure status) fixed in real time by prescriptions filled by pharmacies or written by physicians (and recorded in electronic health records).	YES
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Information about intervention (exposure status) collected through purely administrative channels independent of the research study.	NO
Risk of bias judgement		LOW
Optional: What is the predicted direction of bias due to classification of interventions?		

Bias due to deviations from intended interventions		
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?		NOT APPLICABLE
4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?		NOT APPLICABLE
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
4.3. Were important co-interventions balanced across intervention groups?		NO INFORMATION
4.4. Was the intervention implemented successfully for most participants?	Prescriptions, filled or written, viewed as a proxy for patient use.	NO INFORMATION
4.5. Did study participants adhere to the assigned intervention regimen?	Prescriptions, filled or written, viewed as a proxy for patient use.	NO INFORMATION
4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	MACE risk referenced against patient-years.	NOT APPLICABLE
Risk of bias judgement	Non-adherence to intervention plausible. Unmeasured co-intervention (e.g., over the counter aspirin) assessed as not critical to risk of bias judgment.	AT LEAST MODERATE
Optional: What is the predicted direction of bias due to deviations from the intended interventions?		Unpredictable. Extent of non-adherence plausibly different in PRU and PEG.

Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?	Outcome partially defined by medical charts (ISD), physician questionnaires (CPRD), or links to external databases (CPRD). Charts available for nearly all events in ISD. For CPRD, physician questionnaire missing in ≈60% and database links in ≈50%.	NO
5.2 Were participants excluded due to missing data on intervention status?	Patients not excluded from analysis because of missing data about exposure.	NO
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Study eligibility required ≥12 months of pre-index data coverage. Patients not excluded from analysis because of missing data about other variables.	NO
5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?		NO INFORMATION
5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?		NO INFORMATION
Risk of bias judgement	Missing outcome data not applicable to SNR, a dominant data source.	LOW
Optional: What is the predicted direction of bias due to missing data?		

Bias in measurement of outcomes		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Medical decision making and medical record documentation procedures probably unrelated to exposure, PRU or PEG.	PROBABLY NO
6.2 Were outcome assessors aware of the intervention received by study participants?	In ISD, treatment outcomes determined by blinded clinical review of medical record abstracts assembled by research nurses possibly aware of PRU or PEG status. In CPRD and THIN, treatment outcomes determined by blinded clinical review of physician questionnaires (CPRD only), notations in electronic health records (THIN only), and electronically generated patient profiles (CPRD and THIN).	PROBABLY NO
6.3 Were the methods of outcome assessment comparable across intervention groups?	Standardized procedures used to assess outcomes.	YES
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Choice of diagnostic code (used to determine treatment outcomes in SNR) possibly related to exposure (PRU or PEG), either directly or indirectly through a confounding variable.	PROBABLY NO
Risk of bias judgement	SNR outcome (based only on diagnostic and cause-of-death codes) assessed as probably unbiased (internally valid per ROBINS-I)	LOW
Optional: What is the predicted direction of bias due to measurement of outcomes?		

Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from...		
7.1. ... multiple outcome *measurements* within the outcome domain?	Pre-specified outcomes, including primary MACE composite, reported.	NO
7.2 ... multiple *analyses* of the intervention-outcome relationship?	Presentation of results aligning with pre-specified protocol and statistical analysis plan.	NO
7.3 ... different *subgroups*?	Important subgroup analyses reported (age by sex and baseline history of cardiovascular disease).	NO
Risk of bias judgement	Risk of bias in selection of reported result judged as low despite analytic data files unavailable to FDA and missing sensitivity analyses.	LOW
Optional: What is the predicted direction of bias due to selection of the reported result?		

Overall bias		
Risk of bias judgement	Overall risk-of-bias judgement driven by confounding domain. Otherwise, study professionally conducted and responsibly reported.	SERIOUIS
Optional: What is the overall predicted direction of bias for this outcome?		Observed SIRR < True SIRR

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/

JOEL L WEISSFELD
10/25/2018

PATRICIA L BRIGHT
10/25/2018

SUKHMINDER K SANDHU
10/25/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: September 6, 2018 **Date Consulted:** December 22, 2017

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne Yao, MD, Director
Division of Pediatric and Maternal Health

To: Andrew Kelleher, Regulatory Project Manager (RPM)
Division of Gastroenterology and Inborn Error Products (DGIEP)

Drug: Motegrity (prucalopride succinate)

NDA: 210166

Indication: Treatment of Chronic Idiopathic Constipation in adults

Applicant: Shire Development LLC

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- NDA 210166 submitted on December 21, 2017.
- Applicant's literature review and case summary submitted April 20, 2018

Consult Question: DGIEP requests DPMH assistance with the PLLR labeling review for this new molecular entity (NME).

INTRODUCTION

On December 21, 2017, the applicant, Shire Development LLC, submitted a new NDA (210166) for a new molecular entity (NME), Motegrity (prucalopride). On December 22 2017, DGIEP consulted DPMH to provide input on the proper format and content of the *Pregnancy* and *Lactation* subsections of Motegrity labeling to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

REGULATORY HISTORY

- Prucalopride is a selective 5-hydroxytryptamine type 4 (5-HT_4) serotonin receptor agonist with a proposed indication to treat chronic idiopathic constipation in adults.
- Prucalopride (Tradenames: Resolor, Restorans, and Resotran) has been approved and marketed since 2009 for the treatment of chronic idiopathic constipation in several regions including the European Union (EU), Switzerland, Canada, China, and Japan.
- The Agency had safety concerns related to cardiovascular signals observed in another 5-HT4 agonist, tegaserod (approved in 2002 but withdrawn from the U.S. market in 2007). To better understand any cardiovascular risks with prucalopride prior to approval, the Agency required the applicant to conduct additional safety studies.
- On March 23, 2018, the Agency sent the applicant an information request (IR) to provide a review and summary of the published literature specific to prucalopride use in pregnancy, lactation, and females and males of reproductive potential. The Agency also requested narratives for the cases of adverse maternal and/or fetal outcomes in the pregnancies during clinical trials.
- On April 20, 2018, the Applicant submitted the requested supporting information which was found to be adequate for this PLLR review.

BACKGROUND

Drug Characteristics[1]

- *Drug Class:* selective (5-HT_4) serotonin receptor agonist
- *Mechanism of action:* gastrointestinal prokinetic agent that stimulates colonic peristalsis increasing bowel motility
- *Dosage and Administration:* 2 mg tablet taken orally once daily
- *Half-life:* 1 day
- *Molecular weight:* 485 Daltons
- *Plasma protein binding:* 30%
- *Bioavailability:* >90%
- *Adverse reactions:* headache, nausea, diarrhea, abdominal pain

Reviewer's Comment

The applicant noted in the clinical overview that first generation 5-HT4 receptor agonists (i.e., cisapride and tegaserod) are nonselective and interact with other receptors. Both have been associated with rare cardiovascular events (cisapride: QT prolongation, torsade de pointes, ventricular arrhythmias, and sudden death; tegaserod: unstable angina, heart attack, and stroke). However, available data from published literature suggest the cardiovascular adverse events are related to nonselective binding to receptors other than 5HT4.

[1] Motegrity (NDA 210166) proposed prescribing information

REVIEW

PREGNANCY

Nonclinical Experience

In oral embryofetal development studies in rats and rabbits, prucalopride was administered to pregnant animals at doses of 5, 20, and 80 mg/kg/day throughout the period of organogenesis. No adverse embryofetal developmental effects were observed in either rats or rabbits up to the highest oral dose of 80 mg/kg/day (390 times and 780 times the recommended human dose of 2 mg/day). For more details, refer to the Nonclinical Review by Babtunde Akinshola, PhD.

Review of Published Literature

-Applicant's Review: The applicant searched the following database for published literature specific to prucalopride use in pregnancy: Embase (1973 to present), Medline (1946 to present), International Pharmaceutical Abstracts (1970 to present), and Biosis (1993 to present).

- A total of 372 articles were identified (mostly nonclinical literature)
- No articles specific to the effects of 5-HT_4 use in human pregnancy were identified
- Relevant publications regarding 5-HT are summarized below:
    - Serotonin 5-HT increases contraction of uterine smooth muscle (myometrium) in the rabbit, rat, guinea pig, and human; decreased myometrium contractions were observed in the pig.[2,3,4,5,6]
    - Pregnant human myometrium expresses 5-HT_{2A} and 5-HT_3 receptors that are coupled to pathways that stimulate uterine contractions.[7,8]

Reviewer's Comment

The applicant concluded based on literature review, "there is no evidence to suggest a mechanism in which 5-HT_4 agonists cause myometrium contraction."

-DPMH's Review: PubMed, Embase, Micromedex[9], TERIS[10], Reprotox[11], and Briggs[12] were searched using "prucalopride" AND "pregnancy," "pregnant women," "birth defects,"

[2] Freyburger, et al. The pharmacology of 5-hydroxytryptamine (serotonin). Journal of Pharmacology and Experimental Therapeutics, The, 105, 80-6.

[3] Woolley, et al. 1958. A probable mechanism of action of serotonin. Proceedings of the National Academy of Sciences of the United States of America, 44, 197-201.

[4] Contractor, et al. 1968. The response of the human myometrium to 5HT and oxytocin and it's MOA activity during gestation. Journal of Physiology, The, 195, 16P-17P.

[5] Kitazawa, et. Al. 1998 Involvement of 5-HT7 receptors in inhibition of porcine myometrial contractility by 5-HT. British Journal of Pharmacology, 123, 173-182.

[6] Kitazawa, et al. 2001. 5-HT7 receptor and beta (2)-adrenoceptor share in the inhibition of porcine uterine contractility in a muscle layer-dependent manner. European Journal of Pharmacology, 433, 187-197.

[7] Cordeaux, et al. 2009. Characterization of Serotonin Receptors in Pregnant Human Myometrium. Journal of Pharmacology and Experimental Therapeutics, The, 328, 682-691.

[8] Li, et al. 2016. Stimulation of contractions in pregnant human myometrium is associated with 5-HT3 receptors. International Journal of Obstetric Anesthesia, 28, 28-33.

[9] Truven Health Analytics information, http://www micromedexsolutions.com/Accessed 7/25/18.

[10] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 7/25/18.

[11] Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 7/25/18.

[12] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

"congenital malformations," "stillbirth," "spontaneous abortion," and "miscarriage." Additional relevant literature not cited by the applicant was identified as described below:

- **Micromedex** pregnancy rating: "fetal risk cannot be ruled out." Available data is inconclusive or inadequate to assess the fetal risk. It is unknown if prucalopride crosses the placenta. Due to the lack of human safety data, weigh the potential benefits versus potential risks of drug treatment.

Clinical Trials

The applicant's clinical trials for prucalopride consisted of 93 total studies including 14 completed phase 3 studies and 2 completed phase 4 studies. Pregnant women were excluded from clinical trials. Serum pregnancy tests were performed prior to enrollment and women of reproductive potential were advised to use effective birth control.

- A total of 36 pregnancies occurred during clinical trials
- Outcomes in the prucalopride treatment group (n=30) included:
    - **Live birth (n=8)**
        - *1 Congenital Malformation*: malposition of the intestines with partial obstruction requiring surgical intervention.
            - ✓ Prucalopride exposure: 1st trimester (for ~12 days duration at 3-4 weeks gestation).
            - ✓ Concomitant medications: valcyclovir, piroxicam, ketoprofen, promethazine, ondansetron, hydrocodone/acetaminophen, paracetamol
            - ✓ Underlying maternal conditions: polycystic ovarian syndrome, herpes simplex virus
    - **Stillbirth (n=1)**
        - *Twin Pregnancy (1 stillbirth; 1 live birth)*
            - ✓ Prucalopride exposure: 8 weeks prior to pregnancy.
            - ✓ Concomitant medications: carbamazepine, heparin
            - ✓ Underlying maternal conditions: seizure, deep vein thrombosis
    - **Spontaneous abortion (n=7)**
    - **Pregnancy termination (n=1)**
    - **Unspecified abortion (n=1)**
    - **Ectopic (n=1)**
    - **Unknown (n=12)**
- Outcomes in the placebo group (n=6) included:
    - **Spontaneous abortion (n=2)**
    - **Unknown (n=4)**

Reviewer's Comment

The available pregnancy data from prucalopride clinical trials are limited in quantity and quality. Furthermore, prucalopride exposures (dose range 2-4 mg) occurred during the early 1st trimester only in most cases because the clinical trial protocol excluded pregnant women. Additional data limitations include: small sample size, lack of randomization, and the inability to control for confounders such as underlying maternal disease and maternal use of concomitant

medications. Moreover, nearly half of the pregnancies during prucalopride clinical trials had unknown outcomes.

Overall, the limited available pregnancy data from clinical trials do not suggest any drug associated risks of adverse pregnancy outcomes. First, the rate of spontaneous abortion (SAB) in the prucalopride treated group (23%) is consistent with the reported rate in the general population. Second, advanced maternal age compliciated 4 of the 7 pregnancies with SAB. Finally, the rate of congenital malformations in the prucalopride treated group (3%) is consistent with the reported rate of congenital malformations in the general population.

Regarding the GI malformation case, the applicant noted that major development of the mid-gut occurs during 6-10 weeks gestation; whereas the pregnant woman discontinued prucalopride at 4 weeks gestation. Similarly, the cause of the stillbirth is unclear but unlikely related to prucalopride. Prucalopride use occurred prior to pregnancy (8 weeks preconception)in the stillbirth case and the reporter noted both twins were alive 30 minutes prior to birth.

Pharmacovigilance Database

The applicant estimated the total number of postmarketing exposures to prucalopride as 282,535 person-years. The Shire Global Safety System (SGSS) database was searched cumulatively through October 14, 2017 for reported pregnancy cases related to all formulations and dosage forms of prucalopride approved outside the U.S. The applicant used the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for pregnancy to identify all reports including: spontaneous, regulatory authority, literature, solicited, and postmarketing studies.

- 22 unique pregnancy cases were identified with 24 total adverse events as follows:
    - **Exposure during pregnancy (n=22)**
        - Unknown outcome in 18 cases
    - **Induced abortion for malformations (n=1)**
        - Propafenone and other laxatives used for constipation at 6-15 weeks of pregnancy (dose and regimen unknown)
        - Maternal history of ulcerative colitis in remission treated with sulfasalazine during pregnancy (dose and regimen unknown)
        - Fetal malformations: bilateral multicystic renal dysplasia, severe oligohydramnios, encephalocele (suspected Meckel-Gruber Syndrome)
    - **Spontaneous abortion (n=1)**

Reviewer's Comment
The applicant's search for reported pregnancy cases from the global safety database appears adequate. The postmarketing pregnancy cases above do not suggest an increased risk of adverse pregnancy outcomes related to prucalopride. The cause of fetal malformations in the case above is unclear. Multiple factors may have contributed including: genetics, underlying maternal disease, or the maternal use of concomitant medications during pregnancy.

Overall, the available pregnancy data for prucalopride from published literature, clinical trials, and postmarketing experience have not identified any drug associated risks of miscarriage, congenital malformations, or other adverse maternal or fetal outcomes.

LACTATION

Nonclinical Experience

In an oral pre-and post-natal development study in rats, prucalopride was administered at doses of 5, 20, and 80 mg/kg/day. At the 80 mg/kg dose (about 390 times the recommended human dose of 2 mg/day), a slight decrease in the survival rate of pups on day 7 was observed, which could be related to maternal toxicity. For more details, refer to the Nonclinical Review by Babtunde Akinshola, PhD.

Review of Published Literature

-Applicant's Review: The applicant searched the following database for published literature specific to prucalopride use in lactation: Embase (1973 to present), Medline (1946 to present), International Pharmaceutical Abstracts (1970 to present), and Biosis (1993 to present).

- No articles specific to the effects of 5-HT_4 use in lactation were identified

-DPMH's Review: PubMed, Embase, Micromedex[13], TERIS[14], Reprotox[15], and Briggs[16], *Medications and Mother's Milk*[17], and LactMed[18] were searched using "prucalopride" AND "breastfeeding" or "lactation." Additional relevant articles not cited by the applicant include:

- *Medications in Mother's Milk* lactation rating: "No Data-Probably Compatible." The author notes no data are available on the transfer of prucalopride into human milk. Caution is advised; however, no pediatric concerns have been reported in the literature in breastfed infants. Infant monitoring for diarrhea is recommended.

- **Micromedex** lactating rating: "Infant risk cannot be ruled out."

Clinical Trials

Lactating patients were excluded from prucalopride clinical trials. The only exposures during lactation were reported in a single phase 1 lactation study as described below:

- *Objective:* Evaluate the transfer of prucalopride into breast milk of lactating women
- *Methods:* Open-label study in 8 healthy lactating women who took 2 mg prucalopride once daily for 4 consecutive days. Plasma and milk concentrations were assessed on Day 4. Steady state milk:plasma ratios and the relative infant dose were determined.
- *Inclusion criteria:* Healthy lactating females (age 18 to 45) no longer breastfeeding

[13] Truven Health Analytics information, http://www.micromedexsolutions.com/Accessed 8/13/18
[14] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 8/13/18
[15] Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 8/13/18
[16] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[17] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas. Hale Publishing.
[18] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. LactMed is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare providers and nursing women. LactMed provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 8/13/18

- *Exclusion criteria:* Subject who wanted to continue breastfeeding while taking prucalopride, history of substance abuse, history of underlying chronic medical conditions, or history of concomitant medication (except oral contraceptives, paracetamol, and postpartum medication).
- *Results:*
    - Pharmacokinetics:
        - Mean time to reach peak prucalopride concentration in plasma was 2.4 hours with a median time of 2 hours (range 1-4 hours).
        - Mean time to reach peak prucalopride concentration in breastmilk was 3.7 hours with a median time of 4 hours (range 2-8 hours).
        - Mean prucalopride concentration in breast milk was 2.65 times the plasma concentration
        - Based on the average steady-state milk concentration in the mother, and assuming a daily milk intake of 150 mL/kg by the infant, the average daily amount passed to the infant was estimated to be 1.74 µg/kg (or ~6% of the body weight adjusted maternal dose).
    - Safety:
        - Adverse events: 3 lactating women reported moderate headaches which were considered related to prucalopride treatment.

For more details, refer to the Clinical Pharmacology Review by Shin Li, PharmD.

Reviewer's Comment
A limitation of the above data is the lactating women were in the weaning stage rather than in the stage of full milk production. Milk composition, milk volume, and drug concentration can vary depending on the stage of lactation studied. In addition, no data was collected regarding the effects of prucalopride on the breastfed infant considering women that desired to continue breastfeeding were excluded.

Pharmacovigilance Database
The applicant searched the Shire Global Safety System (SGSS) database cumulatively through October 14, 2017 for reported lactation cases related to all formulations and dosage forms of prucalopride approved outside the U.S. The applicant used the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for lactation to identify all reports including: spontaneous, regulatory authority, literature, solicited, and postmarketing studies.

- 1 lactation case identified (exposure via breast milk) with no associated adverse events.

Reviewer's Comment
The applicant provided an adequate review of the available lactation data for prucalopride. Overall, the available lactation data suggest prucalopride is present in milk at low levels and RID < 10% is considered safe for breastfeeding.[19] Nonetheless, data from one small lactation study performed during the weaning stage is insufficient to clearly determine the expected concentration of prucalopride in breastmilk during the stage of full milk production.

[19] Sachs HC, et al. The transfer of drugs and therapeutics into human breast milk: An update on selected topics. Pediatrics. Volume 132, Number 3, September 2013.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Nonclinical studies in rats did not indicate adverse drug effects on male or female fertility at doses up to 20 mg/kg. Secondary rodent-specific effects due to prolactin-mediated toxicity (increased pre-coital interval and pre-implantation loss) was observed at 80 mg/kg (highest dose tested). For more details, refer to the Nonclinical Review by Babtunde Akinshola, PhD.

Pharmacovigilance Database

The applicant searched the Shire Global Safety System (SGSS) database cumulatively through October 14, 2017 for reported fertility disorder cases related to all formulations and dosage forms of prucalopride approved outside the U.S. The applicant used the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for fertility disorders to identify all reports including: spontaneous, regulatory authority, literature, solicited, and postmarketing studies.

- 4 fertility disorder cases identified as follows:
  - **Female infertility (n=2)**
  - **Amenorrhea (n=2)**

Reviewer's Comment

Limitations of the above postmarketing fertility data include: small sample size, insufficient information provided to draw clinically meaningful conclusions, and the inability to control for confounders such as underlying disease or concomitant medication use.

Review of Published Literature

-Applicant's Review: The applicant searched the following database for published literature specific to prucalopride and effects on fertility: Embase (1973 to present), Medline (1946 to present), International Pharmaceutical Abstracts (1970 to present), and Biosis (1993 to present).

- No relevant articles were identified.

-DPMH's Review: PubMed, Embase, Reprotox[11] were searched using, "prucalopride" AND "fertility," "infertility," "contraception," and "oral contraceptives." Additional relevant literature not cited by the applicant is described below:

- A randomized, open-label, phase 1 clinical trial[20] evaluated the effects of single-dose and the effect of 5 or 6 days of treatment with prucalopride 2 mg on the pharmacokinetics of an oral contraceptive (ethinyl estradiol and norethisterone) in 16 healthy women. Author's conclusion: co-administration of prucalopride with an oral contraceptive was not associated with any clinically meaningful drug-drug interactions or safety concerns.

Reviewer's Comment

The applicant provided an adequate review of the available fertility data for prucalopride. The limited available human and animal data do not suggest prucalopride adversely effects fertility.

[20] Van de Velde, et al. Effect of prucalopride on the pharmacokinetics of oral contraceptives in healthy women. Drugs R D (2013) 13:43-21.

DISCUSSION AND CONCLUSIONS

Pregnancy

DPMH recommends subsection 8.1 of labeling for Motegrity define the available pregnancy data from cases reported during prucalopride clinical trials and postmarketing experience outside the U.S. Overall, the available pregnancy data have not identified any drug-associated risks for miscarriage, birth defects, or other adverse maternal or fetal outcomes. In addition, no adverse embryofetal developmental effects were observed in pregnant rats and rabbits at prucalopride exposures well above the anticipated clinical dose.

Lactation

DPMH recommends subsection 8.2 of labeling for Motegrity contain the risk/benefit statement for lactation. Available data from one small clinical lactation study suggest prucalopride is present in breast milk but at low levels (6% of the weight adjusted maternal dose). No data are available regarding the effects of prucalopride on the breastfed infant or the effects on milk production. Nonetheless, no adverse events in lactating women or breastfed infants have been reported to the applicant's global pharmacovigilance database following almost 9 years of postmarketing experience outside of the U.S.

(b) (4)

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR. The labeling recommendations below reflect input from both the Nonclinical and Clinical Pharmacology Review Teams. DPMH discussed our labeling recommendations with DGIEP on August 30, 2018. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Motegrity Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports with prucalopride use in pregnant women (b) (4) any drug associated risks of miscarriage, major birth defects, or adverse maternal or fetal outcomes. In animal reproduction studies, no adverse developmental effects were observed with prucalopride administration during the period of organogenesis to pregnant rats and rabbits at doses up to approximately (b) (4) times and 780 times, respectively, the recommended human dose of 2 mg/day *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

In oral embryofetal development studies in rats and rabbits, prucalopride was administered to pregnant animals at doses of 5, 20, and 80 mg/kg/day throughout the period of organogenesis. No adverse embryofetal developmental effects were observed in either rats or rabbits up to the highest oral dose of 80 mg/kg/day (about 390 times and 780 times the recommended human dose of 2 mg/day, respectively, based on body surface area).

In an oral pre-and post-natal development study in rats, prucalopride was administered at doses of 5, 20, and 80 mg/kg/day. At the 80 mg/kg dose (about 390 times the recommended human dose of 2 mg/day, based on body surface area), a slight decrease in overall survival rate of pups after 7 days was observed, which could be due to maternal toxicity observed at this dose.

8.2 Lactation

Risk Summary

Prucalopride is present in breastmilk *(see Data).* There are no data on the effects of prucalopride on the breastfed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Motegrity and any potential adverse effects on the breastfed child from Motegrity or from the underlying maternal condition.

Data

In an open-label study in 8 healthy lactating women in the weaning stage, plasma and milk samples were collected at predose (day 1 and 4), and then 2, 4, 8, 12, and 24 hours (day 4) after a 2 mg dose of prucalopride was administered once daily for 4 days. Prucalopride is excreted in breast milk with a milk to plasma AUC ratio of 2.65:1; the average amount passed to the infant was estimated to be 1.74 mcg/kg, which is about 6% of the maternal dose, adjusted for body weight. The propafenone concentration detected in breast milk during weaning may not reflect the propafenone concentration in breast milk during full milk production.

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/s/

KRISTIE W BAISDEN
09/06/2018

TAMARA N JOHNSON
09/07/2018

LYNNE P YAO
09/10/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Elizabeth L. Durmowicz, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Drug Evaluation IV (ODE IV)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
John J. Alexander, MD, MPH, Deputy Director
DPMH, ODE IV, OND

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)
Office of Drug Evaluation III, OND

Subject: Pediatric Labeling Recommendations

Sponsor: Shire Development, LLC

Drug: Motegrity ™[1] (prucalopride succinate/SPD555)

Indication (approved): None

Indication (proposed): Chronic Idiopathic Constipation (CIC) in adults

[1] DMEPA communicated to the sponsor that the proposed proprietary name, Motegrity, submitted for review as part of this NDA application, is conditionally acceptable on March 20, 2018.

Dosage Form: Oral tablet (1 mg, 2 mg)

Consult Request:

DGIEP requested DPMH provide recommendations on pediatric labeling for this new drug application (NDA) and assist with activities related to review by the Pediatric Review Committee (PeRC).

Materials Reviewed:

- Applicant's Proposed Draft Labeling. Module 1.14.1.3 submitted to NDA 210166 on March 26, 2018 (eCTD Sequence Number: 0018)
- Proposed Pediatric Study Request (PPSR) submitted to IND 55078 on December 8, 2017 (eCTD Sequence Number: 0060)
- Agreed initial Pediatric Study Plan (iPSP) Letter (which includes the Agreed iPSP document) issued to the sponsor under IND 55078 on September 26, 2017
- Clinical Review of the iPSP. DARRTS entry under IND 055078 on April 14, 2017

Brief Regulatory History of NDA 210166

The applicant, Shire, submitted NDA 210166 on December 21, 2017 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) seeking approval for use of prucalopride for the treatment of CIC in adults.

The applicant included the agreed upon iPSP outlining the applicant's plan for meeting Pediatric Research Equity Act (PREA) requirements in the NDA submission. The applicant requested a partial waiver in patients (b) (4) (because necessary studies are impossible or highly impracticable), and a deferral in pediatric patients (b) (4) (because the product is ready for approval in adults).

DPMH Comment:

(b) (4)

(b) (4) *DPMH recommends requiring studies under PREA in patients 6 months of age and older with FC. Please see the DPMH Prucalopride PPSR Review for a full discussion of recommended PREA required studies.*[3]

Prucalopride was evaluated in pediatric patients based on the studies described in the agreed upon Pediatric Investigation Plan (PIP), and was approved by the European Medicines Agency (EMA) on October 15, 2009 "for symptomatic treatment of chronic constipation in adults in whom laxatives fail to provide adequate relief." The EMA has not labeled prucalopride for use in pediatric patients.

Pediatric Development of Prucalopride for FC

In addition to the clinical trials submitted in the NDA to support adult approval for CIC, the applicant submitted study reports from the following three completed clinical trials of prucalopride for the treatment of FC in pediatric patients: two Phase 1 trials in pediatric patients 4 years to 12 years of age, and one Phase 3 trial in patients 6 months to less than 18 years of age. The Phase 3 trial was conducted outside the United States (U.S.) and failed to establish efficacy (see Appendix: Pediatric Prucalopride Development).

DPMH Comment:

Although the study reports from the pediatric development program were submitted in the NDA, given that the applicant is not pursuing a pediatric indication, DGIEP is not formally reviewing the pediatric clinical trial data as part of this NDA review. High level review of the clinical data by the DGIEP Clinical Reviewer during FDA's review of the iPSP[4] *did not identify any unique pediatric safety concerns that would preclude studying this drug in pediatric patients or a subpopulation of pediatric patients.*

Per my personal correspondence with the Pharmacology/Toxicology Reviewer (Babatunde Akinshola, PhD, April 6, 2018, and August 15, 2018), the nonclinical juvenile animal data did not identify a unique pediatric safety risk relevant to humans. The applicant's proposed labeling describes a carcinogenicity study in neonatal mice under the Carcinogenicity subheading in the Carcinogenesis, Mutagenesis, Impairment of Fertility Subsection (13.1) of the Nonclinical Toxicology Section (13) that was conducted by the applicant to clarify the mechanism of prucalopride genotoxicity. Data from this study do not have relevance to the safety of prucalopride use in pediatric patients and information from this study should remain in subsection 13.1 as proposed by the applicant (b) (4)

[3] See DPMH PPSR Prucalopride Review (DARRTS entry April 6, 2018 under IND 055078)

[4] Clinical Review of iPSP, DARRTS entry under IND 055078 on April 14, 2017

Summary and Discussion of Pediatric Prucalopride Labeling

Because the applicant is not seeking a pediatric indication, DGIEP did not formally review the pediatric clinical data as part of this submission and will not be granting the applicant a pediatric indication. As such, an appropriate pediatric use statement, such as "The safety and effectiveness of MOTEGRITY have not been established in pediatric patients," should be placed as the first statement in the Pediatric Use subsection (8.4).[5]

(b) (4) Unless DGIEP identifies data suggesting a unique safety issue in pediatric patients compared to adults, no additional information should be included in the Pediatric Use subsection (8.4) or in other sections of labeling to avoid misleading prescribers that this product is approved for use in pediatric patients.

Applicant Proposed Labeling and DPMH Labeling Recommendations:

DPMH recommends changes to the Pediatric Use (8.4) and Clinical Pharmacology (12.3) subsections of labeling. The recommendations are based on DPMH correspondence with the Pharmacology/Toxicology Reviewers and the Clinical Pharmacology Reviewers.

Excerpts from the applicant's proposed labeling[6] with proposed FDA revisions by DPMH are followed by the DPMH-Pediatric team's comments. This review identifies the FDA revisions by underlining the text of proposed additions and by striking-through the text of proposed deletions.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The (b) (4) safety and effectiveness of MOTEGRITY (b) (4) have not been established in pediatric patients (b) (4)

(b) (4)

[5] See 21 CFR 201.57(c)(9)(iv)(E) or (F)

[6] Labeling submitted by the applicant on March 26, 2018 (eCTD Sequence Number: 0018)

(b) (4)

DPMH Comment:

The proposed language (b) (4) *should be removed* (b) (4)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Use in Specific Populations

(b) (4)

DPMH Comment:

(b) (4)

DPMH participated in the Filing Meeting, and monthly Review Team meetings and plans to participate in the Pediatric Review Committee (PeRC) meeting discussion of the PREA requirements for this product and relevant labeling meetings.

Appendix: Pediatric Prucalopride Development

Pediatric Nonclinical and Clinical Trials[7]

Completed Nonclinical Studies			
A comprehensive program of nonclinical studies has been conducted with prucalopride (see Section 7). These data include 1-month oral juvenile studies in both rats and dogs, a further study in juvenile rats with subcutaneous dosing from PND 7-55 and detailed information on 5-HT_4 receptor density and distribution. Since no relevant differences in 5-HT_4 expression are to be expected from 1 month after birth onwards, no further nonclinical studies are planned.			
Completed Clinical Pharmacokinetic, Effectiveness, and Safety Studies			
Age Group	**Type of Study**	**Comments**	**Deferral Request Planned for the Study (Y/N)**
< 6 months	NA	NA	N
≥ 6 months and < 18 years	Single-dose PK study in subjects with functional fecal retention (PRU-USA-12)	Subjects with functional fecal retention [a] aged ≥4 to ≤12 years	N
	Open-label follow-up study to PRU-USA-12 (PRU-USA-24)	Subjects with functional fecal retention [a] aged ≥4 to ≤12 years	N
	A study consisting of an 8-week double-blind placebo-controlled part to evaluate efficacy, safety, tolerability, and PK of prucalopride, followed by a 16-week open-label comparator (PEG) controlled part to document safety and tolerability up to 24 weeks (SPD555-303)	Subjects with functional constipation [b], aged ≥6 months to <18 years	N
Planned Clinical Effectiveness and Safety Studies			
Age Group	**Type of Study**	**Comments**	**Deferral Request Planned for the Study (Y/N)**
≥ 4 to ≤ 17 years	Randomized, double-blind, placebo-controlled, parallel-group study to determine the safety and efficacy of prucalopride in subjects with functional constipation (based on the Rome IV criteria)	Subjects with functional constipation aged ≥ 4 to ≤ 17 years	Y

[a] Functional fecal retention was defined as a minimum 2 month history of fecal impactation plus at least one of the following: < 3 bowel movements per week at the toilet and/or a history of soiling.
[b] Chronic constipation in children based on the Rome III criteria (Drossman et al., 2006)
5-HT_4 = 5-hydroxytryptamine type 4; N = no; NA = not applicable; PEG = polyethylene glycol; PK = pharmacokinetics; PND = post-natal day

Brief Summary of Completed Pediatric Trials[8]

- PRU-USA-12 (NCT01674166): a single dose pharmacokinetic (PK) study in pediatric patients four years to 12 years of age (n=38) with functional fecal

[7] Table 5 from the sponsor's PPSR submitted December 8, 2017 (eCTD Sequence Number: 0060)

[8] Brief summary from this reviewer.

retention conducted in the U.S. The study report is dated August 29, 2000 and included in Module 5.3.3.3

- PRU-USA-24 (NCT01670669): an open-label, eight week follow on study to Study PRU-USA-12 in 37 pediatric patients four years to 12 years of age during which parents could adjust prucalopride dosing conducted in the U.S. The study report is dated July 23, 2001 and included in Module 5.3.3.3

- SPD555-303 (NCT01330381): a two-part trial in pediatric patients six months to less than 18 years with functional constipation. The first part of the trial was an eight-week, double-blind, placebo-controlled, PK, safety and efficacy evaluation of prucalopride, and the second part of the trial was a 16-week, open-label period with a comparator arm (i.e., polyethylene glycol (PEG) to evaluate safety and tolerability of prucalopride up to 24 weeks conducted in eight European countries. The study report is dated August 16, 2013 and included in Module 5.3.5.1.

The applicant also conduced PK modeling studies, and includes population PK study reports in Module 5.3.3.5

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/s/

ELIZABETH L DURMOWICZ
08/29/2018

JOHN J ALEXANDER
09/05/2018

Clinical Inspection Summary

Date	August 24, 2018
From	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Charles Line, M.D., Medical Officer, DGIEP
NDA #	210166
Applicant	Shire Development LLC.
Drug	Prucalopride Succinate
NME	Yes
Division Classification	Constipation
Proposed Indication	Chronic Idiopathic Constipation
Consultation Request Date	March 2, 2018
Summary Goal Date	September 4, 2018
Action Goal Date	December 7, 2018
PDUFA Date	December 21, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

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

Two of the clinical trials submitted in support of the application, Studies PRU-USA-11 and PRU-USA-13, were conducted from 1998 to 1999 by Janssen Research Foundation (JRF). 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 preNDA discussions with FDA, Shire stated that source data from only 29% of sites in PRU-USA-11 and 22% of sites in PRU-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. For Studies SPD555-302 and PRU-CRC-3001 data from 88% and 87% of the sites were available. Data for three of the top ten enrolling sites in Studies SPD555-302 and all of the top ten enrolling sites for PRU-CRC-3001 were available for inspection. FDA stated that the ability to verify data for these studies would be assessed in the overall review of the application.

There was a lack of source data at most clinical sites from PRU-USA-11 and PRU-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 JRF indicate that these studies were adequately conducted at the sites inspected and can be used in support of the application. (see also "Rationale for site selection" on the following page.) OSI recommends that the review division conduct additional statistical analyses, such as a comparison of the results of the data from the sites with missing source records to sites with available source records to further evaluate safety and effectiveness of the product.

The data from Studies SPD555-302 and PRU-CRC-3001 is consider reliable. The reliability of the data from Studies PRU-USA-11 and PRU-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 studies.

II. BACKGROUND

The sponsor submitted this NDA for prucalopride for the indication of treatment of chronic idiopathic constipation (CIC) in adults. Prucalopride is a selective, high affinity 5-HT4 receptor antagonist. The product was approved by the EMA, in 2009 but development in the U.S. had been stalled because of cardiovascular safety concerns.

Drug: prucalopride

Studies– Protocol numbers and titles for all studies that were inspected

1. Protocol SPD555-C302 entitled, "A 12-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy, quality of life, safety and tolerability of prucalopride in male subjects with chronic constipation"

Number of subjects: 374 subjects
Number of sites: 66 sites
Number of countries where subjects were enrolled: 10 countries
Dates that study was conducted: September 2010 to October 2013
Efficacy endpoint: the proportion (%) of subjects with an average of ≥3 spontaneous complete bowel movements (SCBM)/week over the entire treatment period

2. Protocol PRUCRC3001 entitled "A Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Prucalopride (Resolor®) Tablets in Subjects with Chronic Constipation"

Number of subjects: 501 subjects
Number of sites: 46 sites
Number of countries where subjects were enrolled: 5 countries
Dates that study was conducted: April 2010 to March 2011
Efficacy endpoint: percentage of subjects with an average of 3 or more SCBMs per week during the entire 12-week double-blind treatment phase (i.e., responders).

3. Protocol PRU-USA-11 entitled "A Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Prucalopride (Resolor®) Tablets in Subjects with Chronic Constipation" was conducted by Janssen Research Foundation (JRF)

Number of subjects: 628 subjects
Number of sites: 38 sites
Number of countries where subjects were enrolled: U.S. only
Dates that study was conducted: April 1998 to May 1999
Efficacy endpoint: the proportion of patients who had an average of ≥3 SCBM (spontaneous or non-laxative induced, complete BM)/week at time points Weeks 1 through 4 and weeks 1 through 12

4. Protocol PRU-USA-13 entitled "A Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Prucalopride (Resolor®) Tablets in Subjects with Chronic Constipation" was conducted by Janssen Research Foundation (JRF)

Number of subjects: 651 subjects
Number of sites: 41 sites
Number of countries where subjects were enrolled: U.S. only
Dates that study was conducted: from March 1998 to May 1999
Efficacy endpoint: Efficacy endpoint: the proportion of patients who had an average of ≥3 SCBM (spontaneous or non-laxative induced, complete BM)/week at time points Weeks 1 through 4 and weeks 1 through 12

Note: Protocols PRU-USA-11 and PRU-USA-13 are identical.

Rationale for Site Selection and notes on feasibility of inspections: Sites were chosen based on enrollment and efficacy results as well as history of previous inspections.

For Studies PRU-USA-11 and PRU-USA-13, only 29% and 22% of sites respectively had source data available and, of the sites with available data, only three sites in each study ranked in the top ten of high enrollers. For lower ranking sites, many of the sites had a previous history of BIMO inspections conducted by FDA, so it was determined that effort would be focused on the sponsor inspection. Two sites were chosen for inspection for PRU-USA-11 and, of these two, Site 13 that enrolled 23 subjects no longer had the source documents available. No clinical sites were chosen for inspection of PRU-USA-13.

An additional feasibility issue for inspections for this application concerned sites originally chosen for SPD555-C3001 in China. The Chinese sites could not be inspected in a timely manner due to issues with visas and site availability, therefore, sites in South Korea were chosen instead.

III. RESULTS (by site):

Name and Type of Inspected Entity/Address	Protocol #/ Site #/ # of Subjects randomized	Inspection Dates	Classification*
CI: Julian Copaci, M.D. Spitalul Universitar de Urgenta Militar Central "Dr. Carol Davila" Str. Mircea Vulcanescu nr. 88 Bucuresti, sector 1, Romania	SPD555-C302 Site #350015 Subjects: 22	June 4 to 7, 2018	NAI
CI: Anne-Sofie Krogsaa, M.D. Center for Clinical and Basic Research Ballerup, 2750, Denmark	SPD555-C302 Site #530001 Subjects: 28	June 11 to 14, 2018	NAI
CI: Hyo Jong Kim, M.D. Kyung Hee University Medical Center 23, Kyung Hee Dae-ro Dongdaemun-gu, Seoul, 02447, Korea	SPD555-C3001 Site 10375 Subjects: 20	August 6 to 10, 2018	NAI *
CI: Jae Hee Cheon, M.D. Yonsei University Hospital (Severance Hospital) 50-1, Yonsei-ro, Seodaemun-gu Seoul, 03722, Korea	SPD555-C3001 Site 10382 Subjects: 10	June 13 and 14 and June 16 and 17, 2018	NAI *
CI: Terry Klein, M.D. 7602 E. Harry Street Wichita, KS 67208	PRU-USA-11 Site 28Subjects: 17	June 18 to 20, 2018	NAI
Applicant: Shire Development LLC 300 Shire Way Lexington, MA 02421	Protocol SPD555-C302 374 subjects Protocol SPD555-C3001 501 Subjects Protocol PRU-USA-11 628 Subjects Protocol PRU-USA-13 651 Subjects	July 9 to 25, 2018	VAI

Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data may be unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Julian Copaci, M.D.
   Spitalul Universitar de Urgenta, Militar Central "Dr. Carol Davila"
   Bucuresti, sector 1, 010825, Romania

For Protocol SPD555-C302 at this site, 26 subjects were screened, and 22 subjects were enrolled and completed the study. Review of 100% of all enrolled subject records was conducted for informed consent process, staff training, test article accountability, efficacy parameters, protocol deviations, concomitant medications, eligibility criteria, and adverse events. Source documents for protocol adherence and data verification were compared to line listings from the NDA. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

2. Anne-Sofie Krogsaa, M.D.
   Center for Clinical and Basic Research, Ballerup, 2750, Denmark

For Protocol SPD555-C302 at this site, 42 subjects were screened, and 28 subjects were enrolled, and 23 subjects completed the study. Review of 100% of enrolled subject records was conducted for informed consent process, staff training, test article accountability, efficacy parameters, protocol deviations, concomitant medications, eligibility criteria, and adverse events. Source documents for protocol adherence, data verification, and test article accountably records were compared to line listings from the NDA. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

3. Hyo Jong Kim, M.D.
   Kyung Hee University Medical Center, Seoul, 02447, Korea

Note: Observations below for this clinical investigator (CI) inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

At this site, for Protocol SPD555-C3001, a total of 29 subjects was screened, 20 subjects enrolled in the study, and 18 subjects completed the study. A total of 15 subject records were reviewed. The data in the line listings was compared with the

source documents. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events. There were minor deviations to the protocol such as out of window visits and missing laboratory values. The deviations were documented and submitted to the IRB.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

4. Jae Hee Cheon, M.D.
   Yonsei University Hospital (Severance Hospital), Seoul, 03722, Korea

Note: Observations below for this CI inspection are based on review of the Form FDA 483 and communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

At this site, for Protocol SPD555-C3001, a total of 15 subjects was screened, 10 subjects enrolled in the study, and 7 subjects completed the study. Fifteen subject records were reviewed. The data in the line listings was compared with the source documents. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events. There were minor deviations to the protocol such as out of window visits and missing laboratory values. The deviations were documented and submitted to the IRB.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

5. Terry Klein, M.D.
   7602 E. Harry Street, Wichita, KS 67208

At this site, for Protocol PRU-USA-11, a total of 27 subjects were screened, 17 subjects enrolled, and 16 subjects completed the study. Janssen Research Foundation was the sponsor and the monitor at the time this study was conducted. All subject records were reviewed. The data in the line listings was compared with the source documents. There was no evidence of under reporting of adverse events and all efficacy endpoint data was verifiable.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

6. Shire Development LLC
   300 Shire Way, Lexington, MA 02421

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of Studies SPD555-C302, PRUCRC3001, conducted by Shire and Studies PRU-USA-11, and PRU-USA-13 conducted by Janssen Research Foundation (JRF) and acquired by Shire. The reviews included oversight of monitoring, selection and oversight of contract research organizations (CROs), financial disclosure, FDA Form 1572s, quality assurance (QA), and handling of data, review of general correspondence and study master files, and handling of adverse events and other sponsor/monitor related activities. Investigational product areas including drug accountability, stability, and expiration dates were also covered. Review of monitoring records from eleven sites for the four studies was conducted. The sites included those chosen for inspection and some sites that were unable to be inspected because of feasibility (China sites participating in PRUCRC3001) or for lack of source documents (Studies PRU-USA-11 and PRU-USA-13). A Form FDA 483 was issued for the following violations:

1. Failure to notify FDA of the ending, for cause, of an investigator's participation in an investigation. Specifically, for Study PRU-US-11, Site 22 supervised by Dr. Gordon Ohning was closed in April 1999 because all research at the Veterans Administration (VA) of Greater Los Angeles Health Care Systems was being shut down. The Institutional Review Board (IRB) at the VA system had failed an audit by the National Institutes of Health and was being reconstituted, so it was decided to close all research until the IRB could be reconstituted.

Reviewer note: Although this may be a violation, there is no indication that monitoring was not adequate for this study. In fact, there is an instance in which a CI was terminated, FDA was notified and inspected, and issued a VAI letter. This occurred in January 2000 when JRF notified FDA that it had terminated Dr. Steven Krumholz. Dr. Krumholz was subsequently inspected by FDA and a VAI letter was issued to him on July 27, 2001. In their response of August 13, 2018, Shire acknowledged that there had not been procedures in place to review study records of an acquired study and this was an oversight. They have since revised their procedures.

2. Monitors not qualified by experience and training were selected to monitor the progress of a clinical investigation. Specifically, there was no documentation provided during the inspection of the qualifications and training of the monitors for PRU-USA-11 and PRU-USA-13. These monitors were employees of the sponsor.
3. Failure to ensure proper monitoring of the study. Specifically, there were no monitoring reports for the last 4 of the 10 interim monitoring visits, as well as for the final close out visit for Study PRU-US-11 Site 28 (Klein).

Reviewer note: In their response, Shire acknowledged that there had not been procedures in place to ensure that study records of an acquired study were complete, and this was an oversight. They have since revised their procedures. The above, although technically a violation, does not appear to have an impact on data integrity.

The studies appear to have been conducted adequately and the data generated by this sponsor may be used in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm.
Review Division /Acting Division Director/Dragos Roman
Review Division /Medical Team Leader/Juli Tomaino
Review Division /Project Manager/Andrew Kelleher
Review Division/Medical Officer/Charles Line
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Susan D. Thompson
OSI/DCCE/GCP Reviewer/ Susan Leibenhaut
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

SUSAN LEIBENHAUT
08/27/2018

SUSAN D THOMPSON
08/27/2018

KASSA AYALEW
08/27/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 16, 2018
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 210166
Product Name and Strength:	Motegrity (prucalopride) tablets, 1 mg and 2 mg
Applicant/Sponsor Name:	Shire
FDA Received Date:	June 29, 2018 & July 31, 2018
OSE RCM #:	2018-86-1
DMEPA Safety Evaluator:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMORANDUM

Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised container and carton labeling for Motegrity (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and sample carton labeling for Motegrity are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Barlow M. Label and Labeling Review for Motegrity (NDA 210166). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 18. RCM No.: 2018-86.

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/s/

MATTHEW J BARLOW
08/16/2018

SARAH K VEE
08/16/2018

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		

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/s/

SHILA S NKAH
08/02/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Memorandum

Date:	June 29, 2018
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Team Leader:	Patricia L. Bright, MSPH PhD Division of Epidemiology I
Deputy Director:	Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Drug Name:	prucalopride (Motegrity®)
Subject:	A Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort (SPD555-802)
Application Type/Number:	NDA 210166
Applicant/sponsor:	Shire Pharmaceuticals
OSE RCM #:	2017-2646, 2018-622

1 INTRODUCTION

To inform a review of NDA 210166 by the Division of Gastroenterology and Inborn Error Products (DGIEP), the Division of Epidemiology I and Division of Biometrics VII prepared language, which requests additional information, from the NDA sponsor (Shire Pharmaceuticals), about SPD555-802, *A Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort*.

2 RECOMMENDATIONS

2.1 Recommendations for DGIEP

Please send Shire Pharmaceuticals a communication, which includes the language shown below.

2.2 Information Requested from the Sponsor

Please respond to the following requests for additional information about SPD555-802, *A Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort*.

- By our count, the SPD555-802 Study Protocol specified three secondary analyses and nine sensitivity analyses. We located results for three secondary analyses and two sensitivity analyses in the Final Study Report (FSR) or Supplemental Full Results File for SPD555-802. We acknowledge your disclosure of a departure from planned analyses, as found in FSR Section 9.8.5.1, which reads, "Only those sensitivity analyses mentioned in the protocol that could be conducted in all applicable data sources have been performed." For transparency, please provide the specific reasons missing sensitivity analyses could not be conducted. Our list of missing sensitivity analyses appears below.
  - Exclude patients with earlier PEG prescriptions from the prucalopride cohort and patients with earlier prucalopride prescriptions from the PEG cohort.
  - Exclude patients with a history of cancer.
  - Extend allowed prescription gap from seven to thirty days.
  - Consider first episodes of use only.
  - Add time at risk from past use.
  - Include overlapping time during switches to the comparator.
  - Exclude patient-time associated with hospitalizations unrelated to MACE (Major Adverse Cardiovascular Event).
- We recognize that the number of outcome events available in SPD555-802 might limit the feasibility or meaningfulness of some sensitivity analyses. However, one planned sensitivity analysis appears feasible and possibly meaningful. This analysis appears on the list directly above as "add time at risk from past use." A description of this analysis appears on page 30 of the SPD555-802 Study Protocol. If possible, please provide results for this sensitivity analysis, which includes "all observation time meeting criteria for time at risk from current

use or time at risk from past use." If unable to provide results pooled from all data sources, please provide results for data sources able to conduct this analysis.

- As shown in the shell table, below, please provide counts of the number of patients in the matched prucalopride (PRU) and PEG cohorts (before propensity-score trimming) with (1) ≥1 MACE during current or past use and (2) ≥1 MACE during current use.

	SNR		U.K.	
	PRU	PEG	PRU	PEG
Patients with ≥1 MACE during current or past use				
Patients with ≥1 MACE during current use				

LEGEND:
MACE: Major Adverse Cardiovascular Event, confirmed or definite
SNR: Swedish National Registers
U.K.: CPRD, THIN, and ISD, combined
PRU: prucalopride
PEG: polyethylene glycol 3350

- Please clarify several details about analyses conducted in Swedish National Registers (SNR).
  - Page C-40 in Appendix C to the Data Development Plan Version 7.0 for SPD555-802 contains the SNR narrative definitions for non-fatal acute myocardial infarction (AMI) and non-fatal stroke. These narratives require "hospitalization with a *main* (*emphasis added*) hospital discharge diagnosis" of AMI and stroke, respectively. Page 40 in the FSR for SPD555-802, as amended on 25 May 2018, states, (1) "AMI and stroke endpoints were identified from hospital discharge diagnoses (*primary and secondary*; *emphasis added*)" and (2) "*all cases* (*emphasis added*) identified in Sweden were considered confirmed." Please clarify, after consultation (b) (4) the procedure used to define confirmed non-fatal AMI and confirmed non-fatal stroke in SNR. To complete our understanding of SNR, please complete the shell table, as shown below, with the number of patients, in the matched SNR prucalopride (PRU) and PEG cohorts (before propensity-score trimming), who experienced AMI and stroke during current use.

	PRU		PEG	
Number of patients with ≥1 hospital discharge	NON-FATAL	FATAL	NON-FATAL	FATAL
AMI in primary position				
AMI in secondary position				
AMI in primary or secondary position				
Stroke in primary position				
Stroke in secondary position				
Stroke in primary or secondary position				

NOTES: Fatal events defined by death recorded within 30 days of hospital admission.

  - Page 46 in the FSR for SPD555-802, as amended on 25 May 2018, lists the Swedish Cancer Register as one for five registers used by SNR for SPD555-802. After consulting

[redacted] (b) (4) please describe the contributions from the Swedish Cancer Register to analyses completed for SPD555-802.

- For each data source, use patient-level data to fit a Poisson regression modeling incidence rate as function of treatment indicator (prucalopride or PEG) using propensity score stratification by deciles. Check model assumptions and provide the relative risk and 95% confidence interval estimates. The data sources to provide results for are CPRD, THIN, ISD, SNR, and GePaRD.

CC: Pinheiro S / Sandhu S / Hua W / Bright P / Iannacone M / Jackson S / Calloway P (OSE)

Korvick J / Tomaino J / Line C / Kelleher A (DGIEP)

Kim C / Tran T (DB VII)

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/s/

JOEL L WEISSFELD
06/29/2018

PATRICIA L BRIGHT
06/30/2018

SUKHMINDER K SANDHU
06/30/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 18, 2018
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	NDA 210166
Product Name and Strength:	Motegrity (prucalopride) tablets, 1 mg and 2 mg
Product Type:	Single Ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Shire
FDA Received Date:	December 21, 2017
OSE RCM #:	2018-86
DMEPA Safety Evaluator:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review is in response to DGIEP's request for DMEPA to evaluate the proposed carton and container labeling and prescribing information (PI) submitted by Shire on December 21, 2017. The Applicant submitted the proposed labels and labeling under NDA 210166.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Shire submitted the proposed carton and container labeling and prescribing information on December 20, 2017 under NDA 210166. We performed a risk assessment of the submitted labels and labeling for areas of vulnerability that may lead to medication errors. We note areas of the proposed labels and labeling that can be revised to improve clarity and understanding of important information. We note the lot number and expiration date information is not present on the proposed carton and container labeling, which should be added to align with current regulations. Additionally, we note the barcode is not currently present on the proposed labels and labeling, which should be added to align with current regulations. Also, we note the net quantity statement could be moved away from the usual dose statement to promote the safe and effective use of this product.

4 CONCLUSION & RECOMMENDATIONS

We note areas of the proposed labels and labeling that can be revised to improve clarity and understanding of important information and promote the safe and effective use of this product.

4.1 RECOMMENDATIONS FOR SHIRE

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels and Carton Labeling)
   a. The lot number statement and expiration date statement are required per 21 CFR 201.10(i)(1) and 21 CFR 201.17. We recommend ensuring the lot number is clearly differentiated from the expiration date[a].
   b. We recommend relocating the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement[b].

B. Container Labels
   a. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual container label as required per 21CFR 201.25(c)(2).

[a] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

[b] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Motegrity received on December 21, 2017 from Shire.

Table 2. Relevant Product Information for Motegrity	
Initial Approval Date	N/A
Active Ingredient	Prucalopride
Indication	indicated for the treatment of chronic idiopathic constipation (CIC) in adults
Route of Administration	Oral
Dosage Form	Tablets
Strength	1 mg and 2 mg
Dose and Frequency	Recommended adult dosage is 2 mg taken once daily. The recommended dosage for geriatric patients or patients with renal impairment is 1 mg once daily.
How Supplied	MOTEGRITY tablets 1 mg are white to off-white, round, biconvex film-coated tablets debossed with "PRU 1" on one side and no debossing on the other side. They are supplied as: •NDC 54092-546-01: HDPE bottle of 30 tablets, with child-resistant closure. MOTEGRITY tablets 2 mg are pink, round, biconvex film-coated tablets debossed with "PRU 2" on one side and no debossing on the other side. They are supplied as: •NDC 54092-547-01: HDPE bottle of 30 tablets, with child-resistant closure
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F) [see USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 25, 2018, we searched DMEPA's previous reviews using the terms, Motegrity. Our search identified no previous relevant reviews.

APPENDIX C. HUMAN FACTORS STUDY—N/A

APPENDIX D. ISMP NEWSLETTERS—N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)—N/A

APPENDIX F.—N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Motegrity labels and labeling submitted by Shire.

- Container label received on December 21, 2017
- Carton labeling received on December 21, 2017
- Professional Sample Container labels received on December 21, 2017
- Professional Sample Carton Labeling received on December 21, 2017
- Prescribing Information (Image not shown) received on December 21, 2017

G.2 Label and Labeling Images

Container Labels

(b) (4)

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MATTHEW J BARLOW
05/18/2018

SARAH K VEE
05/21/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 17, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Andrew Kelleher, RPM
DGIEP

Subject: QT-IRT Consult to NDA 210166

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 02/09/2018 regarding the label proposed by the sponsor. The QT-IRT reviewed the following materials:

- Previous QT-IRT review under IND 55078 dated 12/27/2013 in DARRTS;
- Day 74 Letter dated 03/02/2018 in DARRTS;
- Information request dated 03/12/2018 in DARRTS;
- Sponsor's response to IR submitted to Sequence #0014 dated 03/19/2018; and
- Sponsor's proposed label submitted to Sequence #0001 dated 12/13/2017.

1. QT-IRT Responses to the Division

Question: DGIEP kindly requests your expertise in assessing the language in the proposed label, section 12.2 Cardiac Electrophysiology. We note that in your review of the Thorough QT Study, dated 12/27/2013, you determined that no significant QTc prolongation effect was detected in the TQT study but that assay sensitivity was not established. Please comment on whether the language in the label is supported by available data.

QT-IRT's response: We have previously reviewed the TQT study report for prucalopride under IND 55078 (DARRTS 12/27/2013) and concluded that prucalopride does not cause significant QTc prolongation, however, we had concerns about assay sensitivity in the study. The concern with assay sensitivity was due to limited ECG data submitted (only 1 through 6 h post-dose) and that we could therefore not confirm the time-course of the QT effects of moxifloxacin. We requested submission of additional ECG data from the sponsor, however, the sponsor has responded that the data are not available. To mitigate the lack of sufficient moxifloxacin data, we have undertaken a QT bias analysis by comparing the sponsor submitted QT measurements to the fully automatic measurements in the ECG warehouse. This analysis suggested an overall absence of bias, but a slight difference between placebo and active treatment was observed. To assess the impact of this slight difference, we evaluated the time-course and concentration-QTc relationship for the fully-automated measurements and did not observe any significant differences to the sponsor submitted results. Altogether, the TQT study submitted for prucalopride is acceptable and supports excluding small mean increases (i.e. 10 ms) in the QTc interval for prucalopride.

Because the thorough QT study is negative, we suggest using the labeling language proposed in the clinical pharmacology labeling guidance as was also suggested in the 74-day letter:

The Sponsor included the following language in the proposed label:

12.2 Pharmacodynamics

(b) (4)

[redacted]

The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

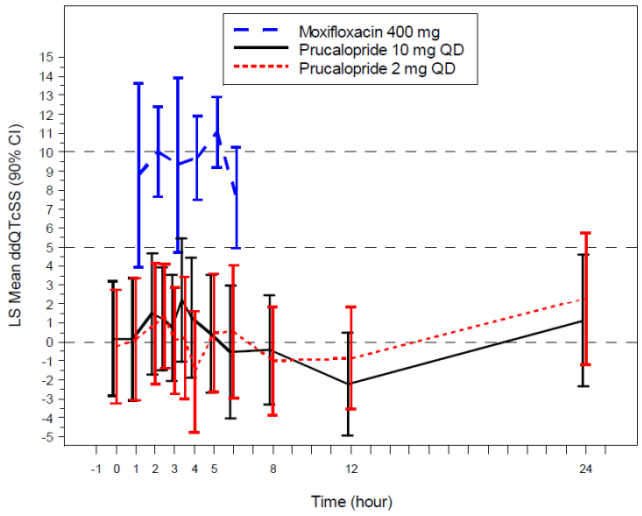
At a dose 5 times the maximum approved recommended dose, MOTEGRITY does not prolong the QT interval to any clinically relevant extent.

2. BACKGROUND

Prucalopride is a serotonin type (5-HT4) receptor agonist with the proposed indication of treatment of chronic idiopathic constipation in adults. We have previously reviewed the TQT study for prucalopride under IND 55078 (DARRTS 12/27/2013) and concluded that the study did not suggest clinically relevant QTc prolongation for prucalopride, but that assay sensitivity was not demonstrated due to limited QT data for moxifloxacin (1 through 6 h post-dose). While,

the limited ECG data showed a mean effect of moxifloxacin like that of other TQT studies, we could not conclude that the time-course of moxifloxacin had been demonstrated (Figure 1).

Figure 1: Mean and 90% CI for ΔΔQTcSS Timecourse



Source: QT-IRT review for IND 55078 (DARRTS 12/27/2013), Figure 4

An information request has been sent to the sponsor requesting submission of ECGs before 1 and after 6 h to allow for assessment of the moxifloxacin time-profile. The sponsor has responded that the data is not readily available and that they consider assay sensitivity to have been demonstrated based on the mean effect observed.

To confirm this, the QT-IRT has performed a QT bias analysis by comparing the QT measurements submitted by the sponsor to automatic QT measurements available in the ECG warehouse. The result of this analysis is the slope of the difference between sponsor and ECG warehouse vs the mean of the two, i.e. a Bland-Altman slope. This analysis was conducted for QT and QTcF independently. The objective of this analysis is to confirm the absence of negative bias overall, i.e. as QT is prolonged it is under-read, as well as absence of bias between different treatments, e.g. between placebo and active treatment. The results of the bias analysis are presented in Table 1 for QT and Table 2 for QTcF. Both tables show an absence of overall negative QT bias, however, a difference in the slope was observed for both QT and QTcF when comparing active to placebo, suggesting that placebo was read longer as QT/QTcF was prolonged compared to active.

Table 1: QT bias analysis

Treatment	# of ECGs	mean (sd)	Slope [95% CI]
ALL	15083	-3 (11.56) ms	4.26 [3.56 to 4.96] ms per 100 ms
Active	4606	-3.16 (12.21) ms	1.17 [-0.19 to 2.52] ms per 100 ms
Control	1080	-3.27 (10.19) ms	3.37 [1.08 to 5.66] ms per 100 ms
Placebo	5080	-2.74 (11.03) ms	9.1 [7.87 to 10.33] ms per 100 ms
Undefined	4317	-3.09 (11.75) ms	2.67 [1.4 to 3.94] ms per 100 ms

Table 2: QTcF bias analysis

Treatment	# of ECGs	mean (sd)	Slope [95% CI]
ALL	15083	-3.18 (12.02) ms	-2.54 [-3.53 to -1.54] ms per 100 ms
Active	4606	-3.35 (12.75) ms	-6.49 [-8.43 to -4.55] ms per 100 ms
Control	1080	-3.5 (10.66) ms	-4.19 [-7.48 to -0.9] ms per 100 ms
Placebo	5080	-2.91 (11.46) ms	1.55 [-0.22 to 3.33] ms per 100 ms
Undefined	4317	-3.24 (12.17) ms	-2.23 [-4.02 to -0.44] ms per 100 ms

The impact of the difference in the bias slopes between placebo and active arm was evaluated further by evaluating the time-course of QTcF (sponsor) and QTcF (ECG warehouse) (Figure 2) as well as the concentration-QTc relationship for both (Figure 3). Neither of these analyses revealed any significant differences between the two QT measurements and we therefore conclude that the study is interpretable and supports excluding QT prolongation for prucalopride.

Figure 2: Time-course of prucalopride PK (top panel), ΔΔQTcF (sponsor) and ΔΔQTcF (ECG warehouse)

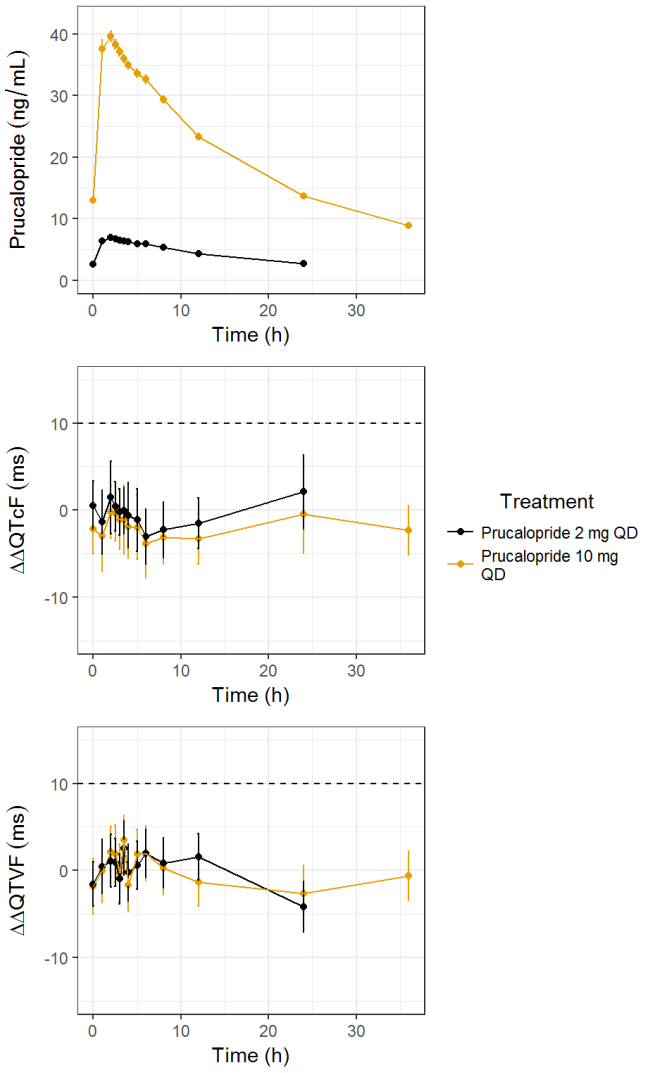
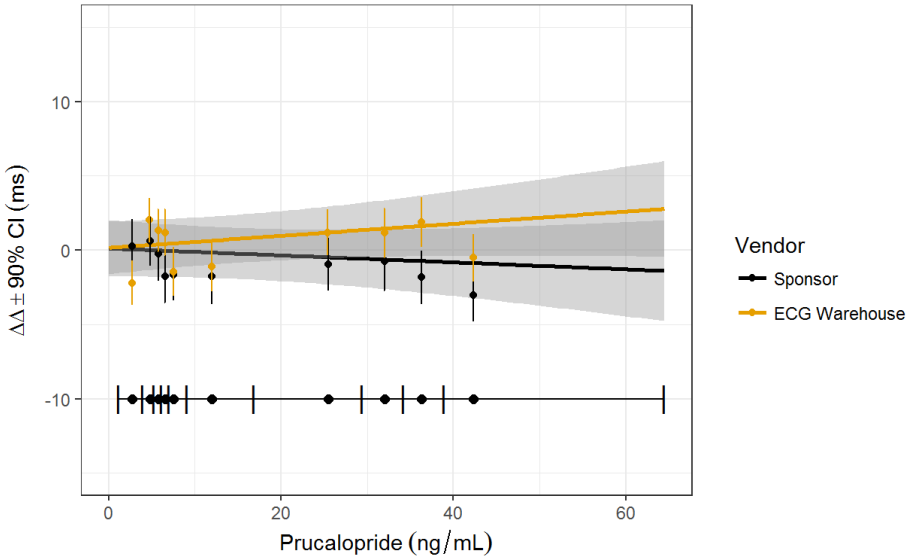


Figure 3: Comparison of concentration-QTc of sponsor's QTcF (black) and ECG warehouse (orange)



Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

LARS JOHANNESEN
04/17/2018

JOSE VICENTE RUIZ
04/17/2018

CHRISTINE E GARNETT
04/17/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

MEMORANDUM

Date:	February 16, 2018
Reviewer:	Patricia L. Bright, MSPH, PhD Epidemiology Team Lead, Division of Epidemiology I (DEPI-I), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)
Deputy Director:	Sukhminder K. Sandhu, PhD, MPH, MS DEPI-I, OPE, OSE
Subject:	Request for additional data to support DEPI-I review of a postmarketing epidemiology study (SPD555-802) for Motegrity (prucalopride)
Drug Name(s):	Motegrity (prucalopride)
Application Type/Number:	IND 055078 / NDA 210166
Applicant/sponsor:	Shire Development LLC.
OSE RCM #:	2018-355

MEMORANDUM

This Division of Epidemiology-I (DEPI-I) Memorandum documents a DEPI-I request for additional data to support a DEPI-I review of postmarketing safety data relevant to Motegrity (prucalopride), NDA 210166, and corresponding to a non-interventional epidemiologic study (SPD555-802). The DEPI-I review of Motegrity (prucalopride) will assist the Office of New Drugs (OND), Division of Gastroenterology and Inborn Error Products (DGIEP), in evaluating safety data included in the submission from a non-interventional epidemiologic study conducted to estimate the adjusted incidence ratio and 95% CI for MACE in prucalopride compared to polyethylene glycol (PEG).

BACKGROUND:

The sponsor submitted a NDA for prucalopride, a high affinity 5-HT4 receptor agonist that stimulates or enhances propulsive motor patterns in the gastrointestinal tract, for the proposed indication of Chronic Idiopathic Constipation. [1]

The agency requested that the sponsor assess the cardiovascular safety of prucalopride:

> "While the sponsor reports no cardiovascular risks among prucalopride users, the Food and Drug Administration (FDA) is concerned by cardiovascular signals observed in similar 5-HT4 agonists, including tegaserod, which was withdrawn from the U.S. market in 2007. The Division of Gastroenterology and Inborn Errors Products (DGIEP), Office of New Drugs (OND), allowed the sponsor to address the potential cardiovascular risks prior to approval using a pharmacoepidemiologic observational study from existing data in European databases." [2]

The epidemiologic study (SPD555-802) supporting the cardiovascular safety assessment of prucalopride is described in brief below:

> "…(A) retrospective study completed in five European electronic healthcare data sources, (1) Clinical Practice Research Datalink (CPRD), (2) The Health Improvement Network (THIN), (3) Information Services Division for Scotland (ISD), (4) German Pharmacoepidemiological Research Database (GePaRD), and (5) Swedish National Health Registers (SNHR). SPD555-802 compares the frequency of major adverse cardiovascular events (MACE) in patients who receive a new prescription, after January 1, 2010, for prucalopride or polyethylene glycol 3350 (PEG). SPD555-802 defines two cohorts, (1) new users of prucalopride and (2) new users of PEG, 5:1 individually matched to prucalopride cohort members according to data source, sex, age, and calendar period." [3]

To respond to an FDA request, the Sponsor discussed the process required for FDA to receive patient-level data from the epidemiology study (SPD555-802) in a Nov 2013 meeting. This Sponsor summarized this November 2013 discussion with the FDA in their June 29, 2017, Type B Meeting, Pre-NDA Briefing Book:

> "During the November 2013 meeting between Shire and the United States (US) Food and Drug Administration (FDA) to discuss study SPD555-802, the FDA

requested that Shire "clarify whether patient-level data from the proposed study SPD555-802 will be provided to the FDA for review." Shire agreed to provide "de-identified medical information (e.g., demographics, diagnosis codes, concomitant medications, cardiovascular history) for all potential cases of major adverse cardiovascular events (MACE) to the FDA, as permitted by local authorities or database governing policies." [1]

The June 29, 2017, Briefing Book also provided information on:

> "…(T)he ability of each data partner to provide detailed information on MACE cases, as well as their ability to share patient-level data with the FDA so the FDA can validate information submitted with the New Drug Application (NDA) submission." [1]

In Appendix 3, of the June 29, 2017, Pre-NDA Briefing submission, the sponsor clarified the availability and process for accessing patient-level data in each data source. Table 3 stated that patient-level data could be sent out of the host country for two data sources (CPRD and THIN), but not for three of the data sources (ISD, GePaRD, and SNHR). Appendix 3 also clarified that the process for obtaining CPRD data would involve FDA signing a data use agreement with CPRD. Appendix 3 further clarified that to obtain data from THIN would require FDA signing a research agreement with Quintiles IMS Health and completing the necessary training.

DEPI-I is interested in pursuing strategies to access the patient-level data for CPRD and THIN that would allow for the review of the detailed safety data and which will help assess the integrity of the aggregate data included in the NDA submission.

RECOMMENDATION:

DEPI-I is requesting that DGIEP send the following Information Request (IR) to the Sponsor:

- In your IND 55,078, submission to the FDA of SPD555 (Prucalopride Succinate Tablets 1 mg and 2 mg), Type B Meeting, Pre-NDA Briefing Book, dated 29 June 2017, Appendix 3 included information related to availability of patient-level data for the submission. FDA is interested in obtaining the patient-level data to support your application from the following two of the five data sources: CPRD and THIN.

  The Appendix 3 clarification included the following (summarized to only reflected responses relevant to the CPRD and THIN data sources.):

Table 1.

Ability of Each Data Source to Share Detailed Descriptions and Small Cell Counts of Cases

Data Source	Produce Line Listing Available for Confidential Review by FDA or Small Cell Counts in Report to FDA
CPRD	Yes, but not for public disclosure
THIN	Yes, but not for public disclosure

Table 3.

Availability and Process for Accessing Patient-Level Data in Each Data Source

Data Source	Patient-Level Data Can be Sent Out of Country	Process for Access to Patient-Level Data
CPRD	Yes	FDA signs data use agreement with CPRD
THIN	Yes	FDA signs research agreement with Quintiles IMS Health and completes necessary training

FDA requests that you help facilitate this transaction by contacting your associated data source contacts within CPRD and THIN and requesting the documents that would require FDA's signed agreement, along with the details describing who to submit these documents to, and any reference numbers/identifiers that correspond to the patient-level data that supports your submission. Alternatively, provide the contact information for each person associated with the data sources who would be directly responsible for assisting with this transaction and the reference numbers/identifiers that correspond to the patient-level data that supports your submission. Please provide any other information (such as how the data will be transmitted) that would expedite this request to receive the patient-level data from CPRD and THIN in order to support your submission.

cc:

Calloway P/Weissfeld J/Iannacone M/Sandhu S/Pinheiro S/Zhou E/Puigbo J/Hua W/DEPI-I
Tran T/Kim C/DB7
Kelleher A/Line C/Tomaino J/Korvick J/DGIEP
Jackson S/OSE

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[1] IND 55,078, Sponsor submission to the FDA of SPD555 (Prucalopride Succinate Tablets 1 mg and 2 mg), Type B Meeting, Pre-NDA Briefing Book, dated June 29, 2017, eCTD 0054).

[2] Taylor, L. Review of sponsor's study synopsis and submitted questions, DARRTS upload April 11, 2013, Reference ID: 3292064.

[3] Weissfeld, Joel. Table Formats for Presenting Results from SPD555-802, IND-055078, DARRTS upload March 7, 2017, Reference ID: 4065787.

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/s/

PATRICIA L BRIGHT
02/16/2018

SUKHMINDER K SANDHU
02/16/2018