Errata to FDA AC Briefing Document

The following revisions pertain to FDA AC Briefing document. The deletions are noted with a ~~strikethrough~~ and the additions are underlined.

1. Section 8 Appendix, Table 31: Narratives of CIC Patients Treated with Prucalopride with Standard MACE

2	Cardiovascular Death	81-year-old Caucasian male, with a history of ischemic heart disease and TIA (1998), started prucalopride (unknown dose) in an open-label study on (b) (6). Note that this subject rolled over from a 4-week double-blind study, where he was randomized to ~~placebo~~ prucalopride 4 mg. Total duration of treatment 272 days. On (b) (6), the subject discontinued intake of the study medication. On (b) (6), the subject died due to myocardial infarction (MI) (67 days after discontinuing prucalopride). The subject was not hospitalized prior to his death. No other TEAEs were reported for this subject during the open-label study. No additional information is available. The investigator considered the MI as not related to the study medication. He considered the event to be related to the subject's prior ischemic heart disease. The adjudication committee classified this event as: cardiovascular death.

3	Nonfatal Stroke	70-year-old Caucasian female started prucalopride at a dose of 2 mg twice daily in an open-label study on (b) (6). Note that this subject rolled over from a 12-week double-blind study, where she was randomized to prucalopride. Total duration of treatment 190 days in the open-label study. During the study, the subject had the AEs of hypertension and blood cholesterol increased reported after 61 days of treatment. Her screening cholesterol and triglycerides levels were elevated at 286 (0-220) and 212 (50-190), respectively, and her blood pressure was 140/90 mm Hg. The subject was treated with pravastatin and propranolol. Her blood pressure at the month 3 (day 100) visit was 168/92 mm Hg and at the month 6 (day 183) visit was 162/90 mm Hg. After 190 days of treatment with prucalopride, cerebrovascular accident (verbatim: small stroke shown on a computed tomography image) was reported as a TEAE. This event was considered moderate in intensity. No concomitant treatment was administered for the TEAE and no action was taken towards the study medication. The TEAE was considered resolved the same day. No further details are available. The investigator considered the TEAE not related to the study medication. The adjudication committee classified this event as: nonfatal stroke.

4	Nonfatal MI	71-year-old Caucasian female started prucalopride (unknown dose) treatment in an open label study on (b) (6) (per clinical study report). Note that this subject rolled over from a 12-week double-blind study, where she was randomized to placebo. In December 1998, the subject was diagnosed with a torn rotator cuff. On (b) (6) (112 days of treatment), the subject was hospitalized and had the cuff repaired. The intake of study medication was temporarily interrupted (4 mg prucalopride). While in the hospital, the subject started experiencing chest pain. She also experienced shortness of breath, palpitations, and diaphoresis. An ECG was performed and revealed anterior T-wave inversions. The subject was diagnosed with a MI. Troponin and myoglobin levels were elevated. The subject was started on intravenous heparin and topical nitrates. This event was reported as a serious TEAE, considered severe in intensity. On (b) (6), the subject underwent a diagnostic cardiac catheterization that showed the circumflex coronary artery was 85% stenosed. The subject was treated with heparin sodium and on (b) (6), a stent was inserted. The subject recovered with sequelae. The investigator considered MI as unrelated to the study medication. The adjudication committee classified this event as: nonfatal MI.

6	Nonfatal Stroke	64-year-old Caucasian male, with a history of hypercholesterolemia, also being treated with flecainide and atenolol for unreported conditions, started prucalopride at a dose of 2 mg in an open-label study on (b) (6). Note that this subject rolled over from a 4-week double-blind study, where he was randomized to prucalopride. In 1998 (per case report form), 860 days after the first intake of study medication in the open-label study, the subject was hospitalized with retinal artery thrombosis, resulting in 80% blindness. This TEAE was considered severe in intensity. He was treated with acetylsalicylic acid and dipyridamole. The TEAE was still ongoing at the end of the study. The event was not yet resolved at the end of the study. The investigator considered retinal artery thrombosis to be unrelated to the study medication. The adjudication committee classified this event as: nonfatal stroke.

2. Section 6.4 Deaths, page 22:
    a. A 56-year-old male with a history of cardiomyopathy, atrial fibrillation, hypertension, hypercholesterolemia, non-insulin dependent diabetes, and cardiovascular accident died of an MI on day 48 of the open-label study while on prucalopride ~~2~~ 4 mg (total prucalopride exposure 75 days; previously treated with prucalopride 2, 3, and 4 mg in the open-label trial, and 4 mg in a 4-week double-blind trial). The investigator deemed this event to be not related to the study drug.

3. Page 48, Table 25. As shown below, FDA amends the MACE adjudication procedure for GePaRD from ~~Reason hospitalized~~ to Not applicable.

Table 25. SPD555-802 Data Sources Compared

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

4. Page 50, Lines 3-4. ~~Three~~ "Two data sources (CPRD~~,~~ and THIN~~, and GePaRD~~) adjudicated lower quality clinical information."

5. Page 53, Figure 5 caption. "MACE Incidence (Per1000 Patient-Years) in Matched ~~and Trimmed~~ Cohorts (before trimming)*"

6. Page 53, Figure 5, LEGEND. "~~Prucalopride~~ Polyethylene glycol 3350 group shown with solid diamond symbol and ~~polyethylene glycol 3350~~ prucalopride group shown with open diamond symbol."

7. Page 54, Second bullet. As indicated by the lead-in sentence, this bullet presents results from a sensitivity analysis, which pooled results from U.K. data sources only. A sensitivity analysis pooling Swedish and U.K. data sources found 39 PRU and 341 PEG events, with MACE risk during current or past use estimated at SIRR 0.65, 95% CI 0.45 to 0.92.

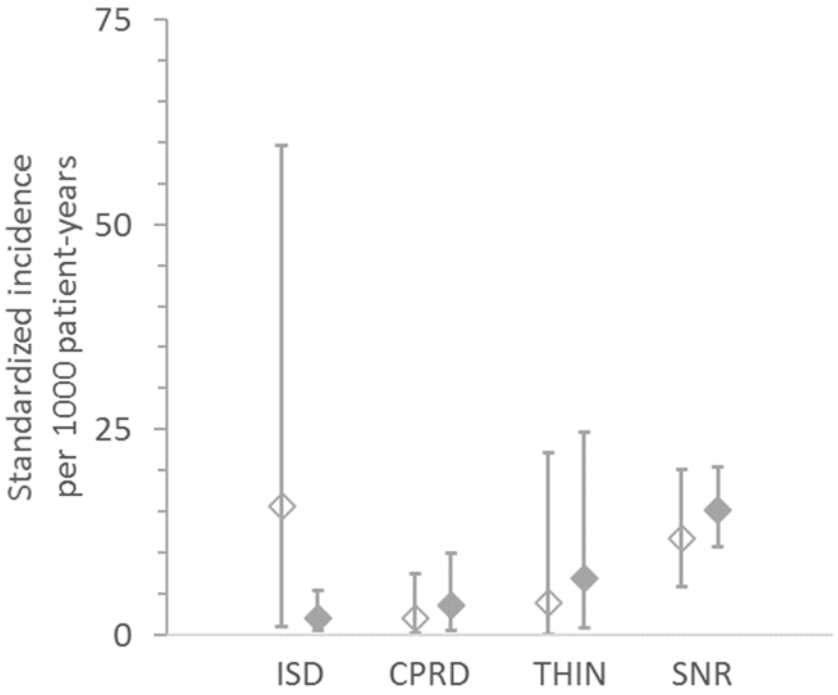
8. Pages 49-50 refer to a recently discovered programming error and a plan to provide relevant updates after FDA receives additional information. Additional information, received by FDA on September 19, requires the following changes to numeric results shown in the Briefing Documents for SPD555-802.

   a. Section 7.4.1 SPD555-802 Overview, Page 47. "This primary analysis estimated MACE incidence in PRU versus PEG with a standardized incidence rate ratio (SIRR) of 0.64, 95% confidence interval (CI) 0.36 to ~~1.13~~ 1.14. Subgroup lysis in ≥55-year-old men estimated risk from prucalopride at a SIRR 2.57, 95% CI 0.71 to ~~9.29~~ 9.26."

   b. Section 7.4.3. SPD555-802 Results Summary.

i. Page 53, Figure 5. Value shown for PEG in SNR changed from SIRR 16.1, 95% CI 11.5-21.7 to SIRR 15.1, 95% CI 10.6-20.4. Figure with the corrected SIRR appears below.

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



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

ii. Page 53. "Pooling results from SNR, ISD, CPRD, and THIN, SPD555-802 reported results from the primary analysis for MACE (nonfatal AMI, nonfatal stroke, or in-hospital cardiovascular death) in PRU versus PEG as SIRR 0.64, 95% CI 0.36 to ~~1.13~~ 1.14."

iii. Page 54, Table 28 amendments shown below.

Table 28. Results Integrating Four Data Sources

Result	Events, N PRU	Events, N PEG	SIRR	95% CI
MACE				
U.K. and SNR (Primary)	18	~~74~~ 73	0.64	~~0.36 1.13~~ 0.36-1.14
United Kingdom (U.K.[1)]	4	9	0.68	0.19-2.38
Sweden (SNR)	14	~~65~~ 64	0.63	~~0.33 1.19~~ 0.33-1.20
Secondary Analyses				
nonfatal AMI	~~8~~ 7	~~22~~ 21	~~1.06~~ 0.95	~~0.44 2.57~~ 0.38-2.39
nonfatal stroke	~~9~~ 8	~~39~~ 35	~~0.58~~ 0.54	~~0.25 1.31~~ 0.23-1.29
in-hospital CV death	3	19	0.47	0.13-1.67
Subgroup Analyses (MACE)				
18-54 year-old women	1	8	0.22	0.03-1.90
≥55 year-old women	13	~~54~~ 53	~~0.70~~ 0.71	~~0.36 1.36~~ 0.37-1.37
18-54 year-old men	0	1		
≥55 year-old men	4	11	2.57	~~0.71 9.27~~ 0.71-9.26

iv. Page 54, first paragraph after Table 28. "Pooling results from Swedish and U.K. data sources, one sensitivity analysis evaluated the effect of adding out-of-hospital cardiovascular death to the outcome definition. With 18 PRU and ~~120~~ 119 PEG events, this sensitivity analysis estimated MACE risk (including out-of-hospital cardiovascular death) in PRU versus PEG at SIRR 0.43, 95% CI 0.25 to 0.73."