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# A Review of the Cardiovascular Safety of Prucalopride in Patients With Chronic Idiopathic Constipation

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**Prokinetic agents, specifically 5-hydroxytryptamine type 4 (5-$HT_4$) receptor agonists, have been shown to provide relief in chronic idiopathic constipation (CIC). The first-generation 5-$HT_4$ agonists were initially withdrawn from use owing to associations with serious cardiovascular (CV) events. This review summarizes CV safety data for prucalopride, a high-affinity 5-$HT_4$ agonist approved in the United States in 2018 for adults with CIC. No significant effects of prucalopride on CV safety were observed in animal models or early-phase clinical studies, including a thorough QT study at therapeutic (2 mg) or supratherapeutic (10 mg) doses. Among 1,750 patients with CIC who received prucalopride (2–4 mg) in 5 phase 3 studies, no trends in CV adverse events, electrocardiogram parameters, or blood pressure were documented; ≤1.0%–2.0% of patients had prolonged QT interval corrected for heart rate (HR) using Fridericia formula after placebo or prucalopride treatment, and low HR occurred in ≤6.1% and ≤3.3% of these patients, respectively. In two 24-month observational studies among 2,468 patients, changes in electrocardiogram parameters over time were minor, except at occasional time points when significant changes from baseline were reported for HR or QT interval. In a real-world European CV safety study among 35,087 patients (prucalopride, 5,715; polyethylene glycol 3350 [PEG3350], 29,372), results were consistent for no evidence of increased risk of major adverse CV events among patients treated with prucalopride vs PEG3350 (incidence rate ratio = 0.64; 95% confidence interval 0.36–1.14). Studies to date have not raised concerns regarding the impact of prucalopride treatment on CV parameters.**

**KEYWORDS:** chronic idiopathic constipation (CIC); 5-hydroxytryptamine (serotonin) type 4 (5-$HT_4$) receptor agonists; prucalopride; cardiovascular safety; prolonged QT interval; arrhythmia

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/AJG/C907

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## INTRODUCTION

Globally, approximately 14% of adults experience chronic idiopathic constipation (CIC), with women and the elderly individuals disproportionately affected (1–3). For those who do not respond to initial therapies (dietary/lifestyle changes and over-the-counter medications), US Food and Drug Administration (FDA)–approved treatments include prokinetics such as 5-hydroxytryptamine type 4 (5-$HT_4$) receptor agonists (3–7).

The first-generation 5-$HT_4$ receptor agonists, cisapride and tegaserod, enhanced gastrointestinal motility but were nonselective (Figure 1) and associated with increased cardiovascular (CV) adverse events (AE). Cisapride, introduced globally in the 1990s, was reported to prolong the QT interval and increase the risk of arrhythmia, particularly at high plasma levels (8). Consequently, cisapride was withdrawn worldwide in July 2000 (8,9). In response, the International Conference on Harmonization (ICH) published 2 guidelines in 2005 to provide recommendations to sponsors developing new drugs on how to assess their effect on cardiac repolarization (see Supplemental Digital Content 1, http://links.lww.com/AJG/C907) (10,11). Tegaserod, approved in 2002 by the US FDA for chronic irritable bowel syndrome and chronic constipation (CC) (12), was withdrawn in 2007 owing to an increased risk of ischemic AE (8,13). In 2019, tegaserod was reintroduced in the United States for women younger than 65 years who have irritable bowel syndrome with constipation (14,15) but was later withdrawn from the US market based on a business decision (16).

The association between the benefit–risk profile of 5-$HT_4$ receptor agonists and their selectivity prompted the development of more selective agonists, for example, prucalopride (13). Prucalopride is a selective, high-affinity 5-$HT_4$ receptor agonist approved in Europe for symptomatic treatment of CC in adults in whom laxatives fail to provide adequate relief (2009 for women; 2015 for men) (17,18) and in the United States in 2018 for adults with CIC (19). A systematic review (up to 2011) reported no CV safety concerns with newer, more selective 5-$HT_4$ agonists, including prucalopride (8). Furthermore, an extensive CV safety

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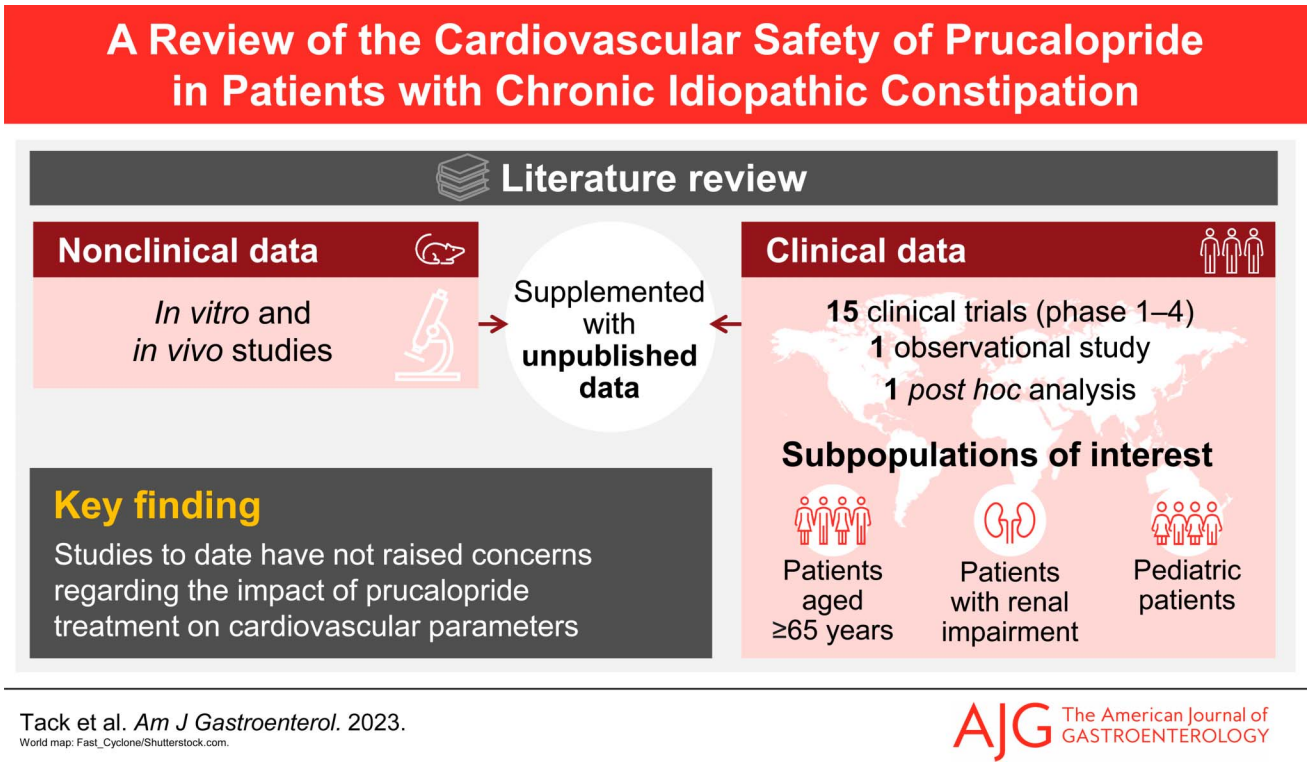


program has been conducted for prucalopride, and these data are discussed in this study. The literature review methodology and a summary of studies included are provided in Supplemental Digital Content 2 (http://links.lww.com/AJG/C907).

## NONCLINICAL STUDIES

*In vitro* and *in vivo* studies showed no significant effects of prucalopride on CV safety parameters (20,21) (see Supplemental Digital Content 3, http://links.lww.com/AJG/C907).

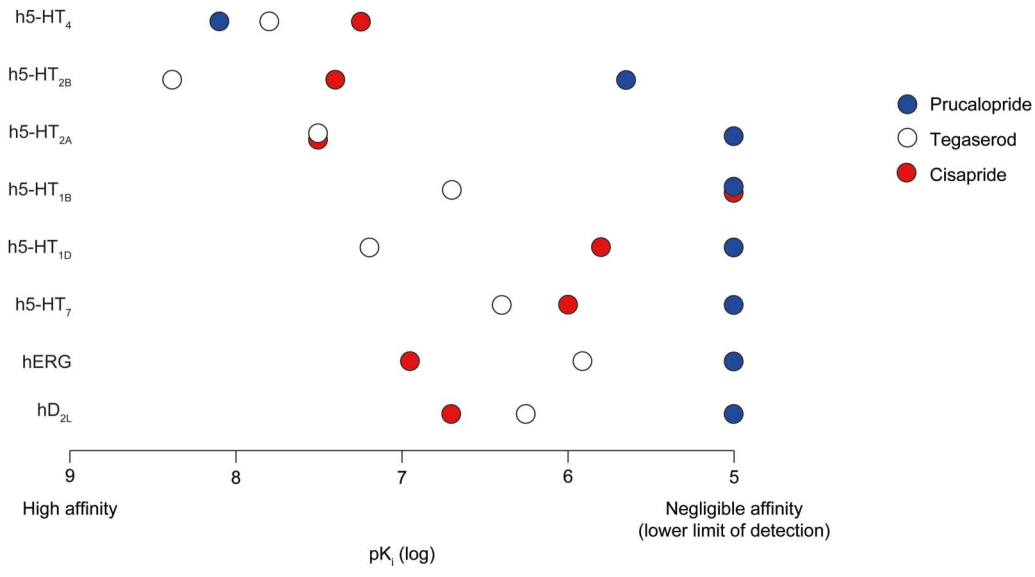


**Figure 1.** Binding affinities of prucalopride, tegaserod, and cisapride for 5-HT and other receptors (13,38). 5-HT, 5-hydroxytryptamine; h5-HT, human 5-hydroxytryptamine; $hD_{2L}$, human dopamine (2L); hERG, human Ether-à-go-go; $pK_i$, measure of binding affinity expressed on a logarithmic scale. $5\text{-}HT_4$ value for prucalopride is based on the lowest pKi estimate from competitive binding experiments with a radiolabeled agonist (13). $5\text{-}HT_4$ value for cisapride is based on the pKi estimate from a single competitive binding experiment with a radiolabeled agonist (13). $5\text{-}HT_4$ value for tegaserod is based on the lowest pKi estimate from competitive binding experiments with a radiolabeled antagonist (13). $5\text{-}HT_{2B}$ value for tegaserod is based on the highest pKi estimate provided (13). Data sourced from De Maeyer et al (13) and McKinnell et al (38).

## CLINICAL SAFETY DATA

### Early-phase clinical studies

Two phase 1 studies of prucalopride examined CV parameters (Supplemental Digital Content 2, http://links.lww.com/AJG/C907) (22,23). The first study (PRU-GBR-10; NCT00488215), conducted before the publication of the ICH E14 guideline, was a placebo-controlled crossover study assessing CV safety outcomes at the maximum tolerated dose of prucalopride in 32 healthy participants (2 mg once daily; 24 participants were titrated up to 20 mg once daily) (22) (unpublished). The second (M0001-C102; NCT00903747) was a double-blind, placebo-controlled and active-controlled, thorough QT study that assessed study-specific heart rate (HR)–corrected QT interval (QTcSS) in 120 healthy participants receiving 2–10 mg of prucalopride once daily (23).

In the first trial, an increase in mean HR vs baseline was observed at 3 hours postdose on days 1–13 during both prucalopride and placebo treatment periods, with the greater increase with prucalopride (range: +5.2 to +10.6 beats per minute [bpm]) vs placebo (range: +3.5 to +7.2 bpm). At steady state (day 13), the mean difference in HR between the prucalopride and placebo treatment periods was +6.3 bpm (95% confidence interval [CI] 3.08–9.52). Consistent with these data, decreases in QT interval were observed at 3 hours postdose on days 1–13 during both treatment periods (prucalopride, range: −31.1 to −21.7 milliseconds; placebo, −22.7 to −12.9 milliseconds), and despite an increase in prucalopride dose (days 2–13), the mean difference in QT interval between treatments remained stable (range: −14.7 to −2.0 milliseconds). Mean changes from baseline in QT interval corrected for HR using Fridericia formula (QTcF) at 3 hours on days 1–13 were comparable between prucalopride and placebo treatment periods (data not shown) (unpublished).

In the second trial (23), mean changes in QTcSS with a prucalopride therapeutic dose of 2 mg (measured on day 5 over 24 hours) and supratherapeutic dose of 10 mg (measured on day 13 over 48 hours) were both similar to those with placebo over the testing duration. The estimated mean difference in QTcSS time-matched change from baseline was <5 milliseconds between prucalopride and placebo for both doses. Differences in time-matched changes in HR from baseline between prucalopride (day 5) and placebo did not exceed 6 bpm after a 2 or 10 mg dose of prucalopride. No ventricular arrhythmias or electrocardiogram (ECG) AE were recorded (23). Early-phase studies showed no significant effects of prucalopride on CV safety in healthy participants at therapeutic and supratherapeutic doses.

### Late-phase clinical studies

CV safety was assessed in 5 phase 3, randomized, efficacy and safety studies where patients with CIC received prucalopride 2 mg or 4 mg, or placebo once daily for 12 weeks (Supplemental Digital Content 2, http://links.lww.com/AJG/C907). Electrocardiography was conducted at baseline and at 4-week and 12-week visits for all studies, except in 1 study where 12-lead ECG recordings were performed at baseline, weeks 8 and 12, or at early withdrawal (24–28).

In 3 trials (PRU-INT-6 [NCT00488137], PRU-USA-11 [NCT00483886], and PRU-USA-13 [NCT00485940]), which randomized 660 patients with CC to 2 mg of prucalopride, 657 patients to 4 mg of prucalopride, and 665 patients to placebo, there were similar incidences of prolonged HR-corrected QT interval (QTc) and abnormalities of HR, PR interval, and QRS duration in both prucalopride and placebo arms (24–26) (Supplemental Digital Content 4, http://links.lww.com/AJG/C907). There were no clinically significant CV AE, apart from in PRU-USA-11 where 1 patient (1/207 [0.5%]) with known mitral valve prolapse and a history of supraventricular tachycardia experienced these conditions with 2 mg of prucalopride, along with heart palpitations and hypokalemia; these serious AE were deemed related to the study drug, which was subsequently discontinued (24) (unpublished). A further 2 patients discontinued because of AE related to the study drug that included CV events; 1 patient had atrial arrhythmia (moderate severity; probably related), and 1 patient had palpitations (moderate severity; possibly related) (24).

A 4th study (PRU-CRC-3001; NCT01116206 [Asia-Pacific]) that randomized 249 and 252 patients to 2 mg of prucalopride and placebo, respectively, reported similar HR, blood pressure (BP), and ECG parameters between treatment groups (Supplemental Digital Content 4, http://links.lww.com/AJG/C907) (27). With placebo, an abnormally low postbaseline HR (4 patients, 1.7%) and prolonged PR interval (3 patients, 1.3%) occurred; these were not observed with prucalopride. Only 1 patient (1/249 [0.4%]) in the prucalopride group discontinued because of possible study drug–related signs of myocardial ischemia (mild severity; no treatment) (27).

In the 5th study (SPD555-302; NCT01147926 [Europe]), the efficacy and safety of prucalopride (n = 184) vs placebo (n = 186) were evaluated in men with CIC (28). While there were no reports of CV-related treatment-emergent AE (TEAE) affecting >2% of patients, serious CV-related AE occurred with prucalopride in a patient (1/184 [0.5%]) with a history of atrial fibrillation (AF) who experienced a moderate AF episode and with placebo in 1 patient (1/186 [0.5%]) with a history of angina pectoris, arterial hypertension, and ischemic heart disease who had myocardial ischemia of mild severity; both events resolved and patients completed the study (28) (unpublished). One patient receiving placebo discontinued because of a CV AE (palpitations and BP increase), which resolved without treatment after withdrawal (unpublished). Generally, mean changes in ECG parameters were small and nonsignificant (Supplemental Digital Content 4, http://links.lww.com/AJG/C907). However, in the prucalopride group, 1 patient (0.5% [1/184]) had a prolonged QT interval from baseline at week 4 (QT interval corrected for HR using Bazett formula [QTcB]: 496 milliseconds; QTcF: 472 milliseconds), which had returned to normal at week 12 scheduled measurements (QTcB: 438 milliseconds; QTcF: 435 milliseconds); this event was considered treatment related, but mild in severity and did not require treatment discontinuation (28). Late-phase studies of prucalopride, including 1 study in men, demonstrated no significant impact on CV AE, ECG parameters, or BP.

### Open-label and postmarketing studies

A global trial (PRU-INT-10; NCT01070615, Supplemental Digital Content 2, http://links.lww.com/AJG/C907) enrolled patients who had completed two phase 3 studies to continue prucalopride treatment for 24 additional months (29). Among 693 patients, changes from baseline in ECG parameters (HR, QT interval, QTc, PR interval, and QRS duration) were small; furthermore, the proportion of patients with changes in ECG parameters considered by the investigator to be clinically significant was low (<5%). QT intervals were not prolonged significantly from baseline, although statistically significant decreases from baseline were

 

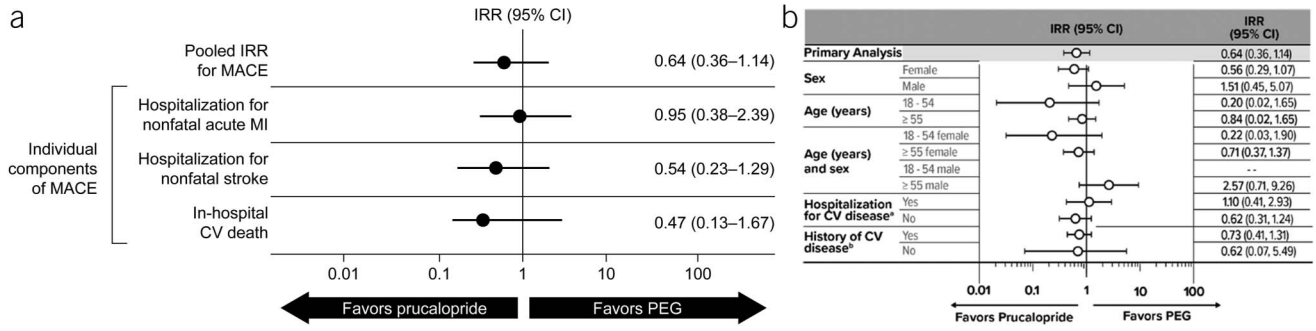


**Figure 2.** Results from the EUPAS9200 study, an observational population-based cohort study conducted in Germany, Sweden, and the UK to assess CV safety using real-world data generated from the clinical use of prucalopride to treat symptoms of CC. (**a**) Pooled-adjusted IRR for MACE and individual components of MACE in adults initiating prucalopride (N = 5,715) compared with those initiating PEG3350 (N = 29,372) (17) and (**b**) IRR in population subgroups (17). CC, chronic constipation; CI, confidence interval; CV, cardiovascular; IRR, incidence rate ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; PEG, polyethylene glycol. [a]Defined as a history of hospitalization for acute MI, stroke, transient ischemic attack, ischemic heart disease, or peripheral vascular disease (17). [b]Defined as a history of acute MI, stroke, hypertension, smoking, hyperlipidemia, diabetes mellitus, aged older than 55 years, or a body mass index >30 kg/m$^2$ (17). Panel (**a**): Data sourced from Gilsenan et al (17). Panel (**b**): © 2022. Reproduced with permission of Springer Nature from Cardiovascular safety of prucalopride in patients with chronic constipation: a multinational population-based cohort study. Gilsenan et al. Drug Saf 2019;42:1179–90. Source (https://link.springer.com/content/pdf/10.1007/s40264-019-00835-0.pdf). This work is licensed under a CC BY-NC 4.0 licence (https://creativecommons.org/licenses/by-nc/4.0/).

observed at 3, 6, 12, and 15 months for QT (range: −6.1 to −19.8 milliseconds), at 3, 6, and 15 months for QTcF (range: −3.8 to −19.8 milliseconds), and at 15 months for QTcB (−20.0 milliseconds). PR interval and QRS duration decreased from baseline (except at 9 months for PR interval), and these decreases were statistically significant at several time points (PR range: −2.9 to −8.5 milliseconds; QRS duration range: −1.6 to −7.3 milliseconds). These mean changes in ECG parameters, however, were not clinically meaningful. One patient (0.1% [1/693]) had a fatal myocardial infarction (MI) 67 days after prucalopride treatment was stopped, which was not considered related to study medication, and another patient had a nonfatal serious AE of severe nodal rhythm noted on ECG 182 days after starting treatment, which was considered related to the study drug by the investigator. However, no relevant changes were found at the next ECG, 11 days later (unpublished).

A total of 1,775 patients from 7 US studies (PRU-USA-22; NCT00987844, Supplemental Digital Content 2, http://links.lww.com/AJG/C907), eligible to continue prucalopride treatment for ≤24 months, received 1 mg prucalopride tablets and were allowed to self-titrate up to a maximum dose of 4 mg once daily (30). According to the safety report (unpublished), bradycardia (low HR; ≤60 bpm) was the most commonly reported CV-related abnormality, occurring in 6.9% of patients. Mean changes from baseline in ECG parameters were small, with significant ($P < 0.05$) changes in HR (2.9 and 2.6 bpm) and QT intervals (−4.6 and −3.7 milliseconds) at 3 and 6 months, respectively; however, these changes were not clinically meaningful. Fewer than 2% of patients had prolonged PR interval or QRS duration. Prolongation of QTcB and/or QTcF was uncommon: in patients with normal baseline values, QTcB prolongation occurred in 1.1% (14/1,314), 0.7% (7/938), and 2.2% (1/45) of patients at 3, 6, and 12 months, respectively; QTcF prolongation occurred in 0.6% (9/1,426), 0.5% (5/1,019), and 0% (0/47) of patients at 3, 6, and 12 months, respectively. No patient demonstrated prolonged QTcB or QTcF at 18 months irrespective of baseline classification.

Treatment with 2 mg of prucalopride was assessed for 24 weeks in a phase 4, randomized, efficacy and safety study in adults with CC (SPD555-401; NCT01424228, Supplemental Digital Content 2, http://links.lww.com/AJG/C907) (5). Analysis of CV safety end points found no clinically significant changes in ECG parameters, including QTc, with prucalopride vs placebo (5). One patient with preexisting QT interval prolongation receiving prucalopride was reported to have experienced serious TEAE of ECG QT interval prolonged (possibly treatment related) and decreased BP (unlikely related to treatment). These events (mild severity) resolved after temporary (days 123–126) treatment discontinuation (unpublished).

An observational population-based cohort study (EUPAS9200; Supplemental Digital Content 2, http://links.lww.com/AJG/C907), conducted in Germany, Sweden, and the UK, assessed CV safety using real-world data (17). Data from Germany were subsequently excluded from the pooled analysis because patients' comorbidities were markedly different from those in other countries (17). Country-specific and pooled-adjusted incidence rates (IR) and IR ratios (IRR) for major adverse cardiovascular events (MACE), defined as the composite of hospitalization for nonfatal acute MI, hospitalization for nonfatal stroke, and in-hospital CV death, were estimated in patients who had initiated prucalopride (N = 5,715; mean duration 175 days) or polyethylene glycol (PEG) 3350 (N = 29,372; mean duration 82 days). The study set a prespecified safety threshold of 3.00 (2-sided 95% CI for adjusted IRR of MACE, prucalopride vs PEG3350). In the primary analysis, pooled standardized IR per 1,000 person-years of MACE was 6.57 (95% CI 3.90–10.39) among patients initiating prucalopride, vs 10.24 (95% CI 6.97–14.13) among patients initiating PEG3350 (17). Moreover, the pooled adjusted IRR of MACE was 0.64 (95% CI 0.36–1.14), and the upper limit of the 95% CI excluded the prespecified safety threshold, thus demonstrating evidence consistent with a finding of no increased risk of MACE associated with use of prucalopride vs PEG3350 among patients treated for CC (Figure 2a) (17). Generally, *post hoc* subgroup analyses were consistent with the primary result, apart from the subgroup of men aged 55 years or older, for whom a pooled adjusted IRR of 2.57 (95% CI 0.71–9.26) was observed (Figure 2b); however, the subgroup was small with few events resulting in imprecise estimates (17).

An extensive *post hoc* evaluation of 19 placebo-controlled trials and 6 open-label studies investigated the incidence of MACE in patients with CIC who received 2 mg or 4 mg of prucalopride (Supplemental Digital Content 2, http://links.lww.com/AJG/C907) (31). Overall, 0.1% of placebo-treated patients (2/2,019) experienced 2 MACE (1 CV death and 1 nonfatal stroke), and 0.3% of prucalopride-treated patients (15/4,476) experienced 16 MACE (2 CV deaths, 2 nonfatal MI, 5 nonfatal strokes, and 7 occasions of unstable angina requiring hospitalization). After correcting for exposure time, the incidence of standard MACE (CV mortality, nonfatal MI, and nonfatal stroke) per 1,000 patient-years was 3.3 and 5.2 for prucalopride and placebo, respectively. The incidence of extended MACE (standard MACE plus events of unstable angina requiring hospitalization) per 1,000 patient-years was 5.4 and 5.2 for prucalopride and placebo, respectively (31). Further analyses of baseline characteristics demonstrated 89% and 100% of patients with standard MACE and 93% and 100% of those with extended MACE in the prucalopride and placebo groups, respectively, fulfilled the criteria for ≥1 of the predefined high-risk ischemic heart disease (IHD) groups (age older than 65 years, a history of IHD, or ≥2 other CV risk factors, and an IHD history with reduced creatinine clearance and/or peripheral vascular disease) (31,32). Longer-term data (≤24 months) and real-world data published to date have identified no unexpected CV safety issues with prucalopride.

### CV safety of prucalopride in selected subpopulations

Studies have examined CV safety in various subpopulations as detailed further, although these data are potentially limited by small population sizes and/or short study duration (Supplemental Digital Content 2, http://links.lww.com/AJG/C907).

***Patients aged 65 years and older.*** The safety of 0.5–2 mg of prucalopride was assessed over 28 days in a phase 2 placebo-controlled study (PRU-USA-26; NCT00627692) including 89 nursing home residents aged 65 years or older with CIC (33). Most of them had a history of CV disease (87.7%) and were being treated for an active CV condition (77.5%) (33). Compared with placebo, there were no differences in BP, PR interval, or HR with prucalopride (33). No consistent treatment-related differences were recorded in QT interval. Although increases in QTcF >60 milliseconds (limited to 1 or 2 time points only) were reported in 5 prucalopride-treated patients (vs none in the placebo group), values remained within the normal range (<430 milliseconds for men, <450 milliseconds for women) in 4 patients receiving 1 mg or 2 mg of prucalopride (33). The 5th patient, who had a pacemaker, active AF, and a history of CV disease, had received 0.5 mg of prucalopride and showed a prolonged QTcF (473 milliseconds) (33). There were no significant differences between treatments in arrhythmic or supraventricular events. However, on day 7, the incidence of nonsustained ventricular tachycardia was significantly higher in the placebo group than in the prucalopride 2 mg group (30.8% vs 0.0%; $P = 0.014$). Five patients recorded tachycardia at rest during prucalopride treatment; however, all 5 patients had medical conditions that would make them susceptible to developing arrhythmias (33).

In a placebo-controlled study of 300 patients aged 65 years or older receiving 1–4 mg of prucalopride daily for 4 weeks (PRU-INT-12; NCT00487422), the incidence of abnormalities in HR, PR interval, and QRS duration was low and similar between treatments (34). QTcF prolongation abnormalities were also comparable, with an increase in QTcF >60 milliseconds reported in 3, 1, and 2 patients in the prucalopride 4 mg, prucalopride 1 mg, and placebo groups, respectively (34).

***Patients with renal impairment.*** A phase 1 renal impairment study (PRU-USA-6; NCT01674192, Supplemental Digital Content 2, http://links.lww.com/AJG/C907) included 34 patients aged 18–75 years with varying degrees of renal function (35). Patients received a single oral dose of 2 mg of prucalopride. ECG results identified no CV safety concerns, and increases in QT interval reflected physiological baseline variations (35).

***Pediatric patients.*** Prucalopride was well tolerated in a phase 3 trial of 215 children aged 0.5–18 years with functional constipation (SPD555-303; NCT01330381, Supplemental Digital Content 2, http://links.lww.com/AJG/C907) (36). The incidence of abnormal changes in ECG parameters (HR, PR interval, QRS duration, and QT interval) vs baseline was minimal and similar between treatment groups, with no reports of clinically meaningful changes in QTcB or QTcF. One prucalopride-treated patient (1.1%) recorded an increased HR during the double-blind phase, while 2 PEG4000-treated patients (2.3%) had an ECG-related TEAE of first-degree atrioventricular block and QT interval prolongation during the open-label period; all events were nonserious and mild (36).

In a phase 1 study (PRU-USA-24; NCT01670669, Supplemental Digital Content 2, http://links.lww.com/AJG/C907) of 38 children aged 4–12 years with functional constipation who received prucalopride for 8 weeks, there were no reports of clinically meaningful changes in HR, QRS duration, or QT interval (37). Although 2 children had a QTcB increase of >30 milliseconds, their QTcB values were classified as normal (37).

In patients aged 65 years and older, patients with renal impairment, or pediatric patients, no significant effect of prucalopride on CV parameters was observed; however, further research is warranted in these populations.

## CONCLUSIONS

In summary, *in vitro*, *in vivo*, and early-phase trial data showed no significant effects of prucalopride on CV safety. Later-phase studies demonstrated a consistent CV safety profile in men and women, and a pooled analysis of long-term phase 3 data showed there was no increased risk associated with prucalopride vs PEG3350 for MACE or its individual components. These results were also consistently observed in populations of clinical interest. Long-term data were generally consistent with the primary data from these studies, suggesting no long-term CV risk in patients with CIC receiving prucalopride. Despite the innate limitations of literature reviews and the inclusion of *post hoc* or pooled analyses, this review provides robust evidence regarding the CV safety of prucalopride and its value as a treatment for patients with CIC who currently have limited therapeutic options.

### CONFLICTS OF INTEREST

**Guarantor of the article:** Jan Tack, MD, PhD.

**Specific author contributions:** All authors were involved in the planning and conduct of this review; all authors were involved in the collection and interpretation of data and drafting of the manuscript. All authors approved the final draft submitted.

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