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Safety assessment of prucalopride in elderly patients with constipation: a double-blind, placebo-controlled study

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Abstract *Chronic constipation is common among nursing home residents. The aim of this study was to evaluate safety, tolerability and pharmacokinetics of the selective 5HT$_4$ receptor agonist prucalopride in elderly, chronically constipated patients in nursing homes. A multicentre, phase II, randomized, double-blind dose-escalation study in 89 elderly constipated nursing home residents treated with placebo, 0.5, 1 or 2 mg prucalopride once daily for 28 days was analysed. Adverse events, vital signs, ECG, Holter monitor and pharmacokinetics were assessed (Clinicaltrials.gov identifier: NCT00627692). Patients' mean age was 83 years; 88% had a history of cardiovascular diseases. Most frequent adverse events, at least possibly related to prucalopride, were diarrhoea and abdominal pain. Relative to placebo, there were no differences in vital signs, ECG corrected QT interval, ECG morphology parameters, or incidence of supraventricular or ventricular arrhythmias on Holter monitoring. Plasma prucalopride concentrations increased proportionally with administered dose. Prucalopride up to 2 mg once daily for 4 weeks was safe and well-tolerated by constipated elderly patients, with no differences vs placebo in ECG or a range of Holter-monitoring parameters.*

Keywords *arrhythmia, cardiac, corrected QT interval, safety, satisfaction.*

Abbreviations: AE, adverse event; CPMP, Committee for Proprietary Medicinal Products; CYP, cytochrome P 450; hERG, human Ether-à-go-go Related Gene; QTc, corrected QT interval; QTcB, QTC Bazett; QTcF, QTc Fridericia; SAE, serious adverse event.

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INTRODUCTION

Chronic constipation is common among nursing home residents and may affect up to half of the residents.[1–3] Prucalopride is the first compound of a new class (dihydrobenzofurancarboxamide derivatives) of highly selective 5HT$_4$ receptor agonists, with strong enterokinetic activity.[4,5] A comprehensive set of data supports the efficacy of prucalopride in patients with chronic constipation in whom laxatives had not provided adequate relief. The affinity of prucalopride for other receptors, channels [including hERG (human Ether-à-go-go Related Gene) channels] or transporters is only detected at concentrations exceeding its 5-HT$_4$ receptor-affinity by at least 150-fold,[6] suggesting that the drug has a wide safety margin at therapeutic doses.

The efficacy of prucalopride has been demonstrated in phases II and III studies in constipated adults and in elderly patients.[7–13] Cardiovascular safety concerns with other, less-selective serotonergic prokinetic agents led to this study, designed to assess the cardiovascular safety of prucalopride in a patient population at potentially high risk of cardiovascular complications, that is elderly nursing home residents with chronic constipation, all taking concomitant medication and most having a history of cardiovascular disease.

Other serotonergic prokinetic agents, such as tegaserod and cisapride, are less selective for the 5HT$_4$ receptor and interact with other receptors at concentrations that are similar to those required for therapeutic effect. Cisapride has activity at the hERG encoded Ikr channel, a potassium ion channel that is responsible for the repolarizing I_{Kr} current in the cardiac action potential.[14–16] Cisapride treatment has

been associated with rare cardiovascular side effects, notably in those patients with predisposing conditions, such as cardiac disease or those taking concomitant medications that might inhibit the metabolism of cisapride through the cytochrome P450 CYP3A4 pathways.[17,18] Ischaemic cardiac effects have been reported with tegaserod; whether this finding is associated with the use of the drug or occurs spontaneously in an at-risk population is less clear.[19–22]

Prucalopride has been well-tolerated in all subject groups studied to date. The most frequent treatment-emergent adverse events (AEs) in all age groups are headache and gastrointestinal (GI) AEs (nausea, abdominal pain, diarrhoea), occurring most often on day 1 of treatment.[8,11–13] Over 24 month of follow-up in 693 patients revealed no new safety signals.[23]

Efficacy of prucalopride has been demonstrated in healthy elderly patients (≥65 years of age) with constipation in a phase III study. In this population, prucalopride 1 mg has comparable efficacy to 2 mg.[11] Steady-state plasma concentrations of prucalopride in healthy elderly subjects were nearly 30% higher than in younger subjects; this may be attributed to decreased renal function in the elderly.[24]

The primary objective of this study was to assess the safety, tolerability and pharmacokinetics of prucalopride in elderly patients with constipation who were resident in nursing homes. This clinical trial is registered at http://www.clinicaltrials.gov (NCT00627692).

MATERIALS AND METHODS

Study design

This was a multicentre, randomized, double-blind, phase II, placebo-controlled, dose-escalation study in elderly patients with constipation residing in a nursing facility. The study was conducted from February 1999 to May 2000. The clinical development programme was interrupted in 2001 because of the need to perform extra toxicology studies. These have been performed and support the long-term safety of the compound. Prucalopride was transferred to Movetis in 2007 as part of a portfolio of GI compounds that is now being further developed.

Eligible male and female patients were aged at least 65 years (no upper limit) and had a history of constipation, having received treatment for constipation at any time during the 4 weeks preceding entry into the study. Patients had to be able to reliably report AEs and provide informed consent, signed by the patient or by their legal representative. Patients with significantly impaired renal function or receiving cisapride or cancer chemotherapy, and those clinically unstable, were excluded.

The first cohort of patients was randomly assigned in a 4 : 1 ratio to receive either prucalopride 0.5 mg or placebo for 4 weeks. After 2 weeks of treatment, the safety and tolerability of this dose was evaluated by an independent safety committee. If approval was granted to proceed to a higher dose, a second cohort was randomly assigned in the same 4 : 1 ratio to receive either 1 mg prucalopride or placebo. A similar procedure was used for the third cohort to receive 2 mg prucalopride or placebo. All patient cohorts received the treatment for 4 weeks.

Patients received either prucalopride once daily as an oral solution or a visually matching placebo solution.

Safety and pharmacokinetics assessments

Safety was monitored by an external independent safety committee that was provided with copies of the case report form of each patient and had ongoing access to information regarding serious AEs (SAEs), premature discontinuation, laboratory test results, electrocardiogram (ECG) and Holter-monitoring data. The safety committee was allowed to reveal the treatment code for the patient only after the determination of safety/tolerability was made.

Patients were questioned about AEs 3 and 24 h after the first intake of study medication and then daily throughout the study.

Pharmacokinetic assessment Blood samples were taken at the screening visit, 3 h after the first intake of study medication on day 1 and again prior to and 3 h after study medication administration on days 4, 7 and 14 or at discontinuation. Blood samples were drawn just after the ECG was recorded.

Laboratory tests Blood and urine samples were taken at the screening visit, days 7, day 14, and at day 28 or at discontinuation.

Vital signs Pulse rate, systolic blood pressure and diastolic blood pressure (first supine, then upright) were recorded at screening, prior to, and 3 and 24 h after the first intake of study medication on day 1, and prior to and 3 h after the intake of study medication on days 4, 7, 14 and 28. On day 21, vital signs were recorded only prior to dosing.

Electrocardiogram parameters A resting 12-lead ECG was recorded immediately before and 3 h after the first intake of study medication at day 1, and again just prior to and 3 h after study medication administration on day 4, day 7, day 14, and day 28 or at discontinuation. Electrocardiograms were analysed centrally and all interpretations were validated by a single experienced cardiologist (who was blinded to group assignment of the patient). The cardiologist provided an interpretation of clinically relevant findings (within normal limits: yes/no/not applicable, clinically relevant changes: yes/no, change from baseline; no change, improved, deteriorated). Specific ECG intervals of interest (RR, PR, QRS and QT) were measured manually by the use of electronic calipers.

Quantitative ECG analyses The QT interval, measured as a mean value of minimally 3 beats, was corrected for HR according to corrected QT Bazett (QTcB) and corrected QT Fridericia (QTcF). The correction formulae used were:

$$QTcB = QT \times [HR/60]^{1/2}$$

$$QTcF = QT \times [HR/60]^{1/3}$$

Corrected QT Bazett and QTcF were classified as normal, borderline or prolonged according to the Committee for Proprietary Medicinal Products (CPMP) criteria.[25] Corrected QT intervals of <430 ms (men) and <450 ms (women) were considered normal; 430–450 ms (men) and 450–470 ms (women) were considered borderline; and >450 ms (men) and >470 ms (women) were

considered prolonged. Patients were also classified according to the change from baseline in QTcB or QTcF in following categories: <30, 30–60 and >60 ms.

Continuous Holter monitoring This study was conducted from 24 h before until 24 h after the first dose of the study medication (day 1) and for 24 h on days 7 and 14, starting immediately before the intake of study medication. The occurrence of arrhythmic events was evaluated qualitatively and quantitatively according to published criteria.[26] This included the assessment of atrial or ventricular dysrhythmias as well as the presence or absence of atrial fibrillation, supraventricular tachycardia, sustained and nonsustained ventricular tachycardia, ventricular fibrillation and torsades de pointes. In addition, the average number of episodes ('runs') of supraventricular tachycardia (any run, runs of ≥5 beats, runs of ≥10 beats) and the change from baseline in mean supraventricular premature beats per hour were analysed. The cardiologist characterized the results as normal or abnormal, and rated the results as clinically significant or not. He also rated the change from baseline as 'no change', 'improved' or 'deteriorated'.

Statistical analysis

All statistical analyses were performed using Statistical Analysis System® (SAS 6.12 by SAS Institute Inc., Cary, NC, USA. Copyright © 1989–1996). For analysis, placebo groups were pooled across the cohorts. Continuous demographic and baseline characteristic parameters were analysed using the Kruskal–Wallis test, while nominal parameters were analysed using Fisher's exact test.

Adverse events are presented with descriptive statistics and frequency tabulations, while changes in vital signs from baseline and between-group differences were analysed using Kruskal–Wallis and Wilcoxon signed-rank tests.

Between-group differences in ECG and Holter-monitoring measurements were analysed at each time point using Fisher's exact test. Changes from baseline in ECG and Holter monitoring parameters were analysed using the Wilcoxon rank-sum test.

RESULTS

Patients

One hundred patients were randomized, 11 did not receive double blind treatment because of early withdrawal. The remaining 89 patients received treatment as shown in Table 1. There were no meaningful differences between the treatment groups in terms of gender, age, race, height and weight.

All patients were in relatively good health; previous or current medical conditions were consistent with an elderly nursing home population, with no relevant differences between the treatment groups. Overall, 87.7% of the patients enrolled had a history of cardiovascular disease (active currently or in the past) and 77.5% were being concurrently treated for a cardiovascular condition. The most common active cardiovascular diseases were hypertension (51.7%), congestive heart failure (21.3%), atrial fibrillation (12.4%) and coronary heart disease (11.2%). None of these conditions was considered serious enough by the investigator at the study centre to require the exclusion of patients from participating in the study. Patients with unstable or uncontrolled cardiovascular disease were excluded.

Abnormalities in non-GI organ systems were reported as part of the past medical history, in ≥50% of patients as follows: musculoskeletal 82%, cardiovascular 79%, psychiatric 73%, genitourinary 52% and others 78%. All patients were taking at least one concomitant medication.

Table 1 Participant demographics and characteristics

	Placebo (n = 18)	Prucalopride 0.5 mg (n = 21)	Prucalopride 1 mg (n = 24)	Prucalopride 2 mg (n = 26)	P-value
Gender (M/F), n	5/13	3/18	7/17	9/17	0.46
Mean age (SE), years	85.4 (1.77)	84.4 (1.46)	82.6 (1.72)	81.7 (1.65)	0.52
Range (min–max)	71–98	75–98	69–96	65–94	
Age groupings, n (%)					
≥65 to <75	2 (11.1)	0	6 (25.0)	5 (19.2)	
≥75 to <85	7 (38.9)	12 (57.1)	7 (29.2)	9 (34.6)	
≥85	9 (50.0)	9 (42.9)	11 (45.8)	12 (46.2)	
Race, n (%)					
Caucasian	18 (100.0)	19 (90.5)	24 (100.0)	25 (96.2)	0.11
Black	0	2 (9.5)	0	0	
Hispanic	0	0	0	1 (3.8)	
Mean height (SE), cm	160.6 (2.9)	160.9 (3.6)	162.5 (2.5)	164.6 (2.9)	0.24
Mean weight (SE), kg	63.5 (3.6)	72.7 (3.0)	61.7 (2.9)	71.6 (4.9)	0.08
Discontinued, n (%)	4 (22.2)	3 (14.3)	3 (12.5)	2 (7.7)	
Adverse event	0	3 (14.3)	1 (4.2)	0	
Other	2 (11.1)	0	0	1 (3.8)	
Noncompliance	0	0	1 (4.2)	0	
Withdrawal of consent	2 (11.1)	0	1 (4.2)	1 (3.8)	
Patients being actively treated for cardiovascular conditions, n (%)	15 (83.3)	15 (71.4)	19 (79.2)	20 (76.9)	

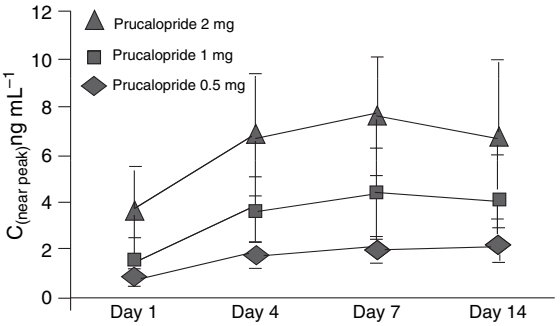

Figure 1 Mean plasma concentrations (ng mL^{-1}) of prucalopride (after once-daily oral administration of 0.5-, 1- and 2-mg doses), from day 1 until day 14. Mean near-peak plasma prucalopride concentrations ($C_{(near\ peak)}$, ng mL^{-1}, measured in blood samples drawn 3 h postdose) ± SD are shown. Steady state was attained between 4 and 7 days.

Pharmacokinetics

Steady state of prucalopride was reached between days 4 and 7 of treatment, and mean plasma concentrations increased proportionally with the administered dose (Fig. 1). Peak plasma concentrations of prucalopride were attained 2–3 h postdose (data not shown). This is consistent with observations in previous studies in younger adults (data on file, Movetis). There was no evidence that pharmacokinetics were altered by any concomitant medication.

Adverse events

Deaths There were two deaths during the study; neither was considered related to study medication by the site investigator. One patient in the 1 mg prucalopride treatment group died on day 13 of treatment due to lobar pneumonia. A patient in the 2-mg prucalopride treatment group was hospitalized for severe acute bronchitis secondary to *Staphylococcus aureus* on day 28 of treatment and died due to respiratory failure 3 days after the end of treatment.

Serious AEs Two patients in the prucalopride 0.5 mg group reported nonfatal SAEs:
A 75-year old female discontinued prucalopride treatment on day 12 because of moderate diarrhoea (which started on day 9, was considered possibly related and was treated with loperamide from days 9 to 12). The patient also reported three SAEs 4 days after the last intake of prucalopride: melaena, colitis and diverticulitis (all considered possibly related). Colitis and diverticulitis were treated with cefotaxime and resolved 5 days after onset.

A 77-year old man was hospitalized for urinary tract infection and skin ulceration on day 6 (not related to study medication) and discontinued the study because of these SAEs.

Discontinuations due to AEs In total, four patients discontinued the study due to AEs: three are described above. One additional patient in the 0.5-mg prucalopride group had nonsustained ventricular tachycardia on the Holter monitoring prior to drug administration (day −1; 4 beats at 116 bpm). The patient also had nonsustained ventricular tachycardia on the Holter monitor on Day 1 (8 beats at 135 bpm) and discontinued the study after 21 days of treatment (moderate severity, possibly related to study drug, duration 1 day).

Frequency of AEs Adverse events were reported by nine patients (50.0%) treated with placebo, 18 (85.7%) on 0.5 mg prucalopride, 17 (70.8%) on 1 mg prucalopride and 18 (69.2%) on 2 mg prucalopride. Analysis of AEs according to WHO system organ class indicated that the most commonly reported AEs were related to the GI and urinary systems (Fig. 2).

Overall, the incidence of AE was low. The most commonly reported AEs are shown in Table 2. The incidence of diarrhoea tended to increase with prucalopride dose and no diarrhoea was reported in the placebo group. Abdominal pain was reported more frequently in the placebo group than in the prucalopride groups. Headache was observed more frequently on prucalopride than placebo treatment, without evidence of a dose response. No events were serious, and they were generally short-lived and treated symptomatically.

Urinary tract infections, falls and injuries occurred both on placebo and prucalopride without evidence of dose response. The higher incidence of AEs in the prucalopride 0.5-mg group was largely due to a high incidence of urinary tract infection (Table 2).

Adverse event attribution and severity The majority of AEs [175 of 215 (81.4%) in the 89 patients] were assessed by the study site investigators as not related or doubtfully related to study medication. Only diarrhoea and abdominal pain were reported by investigators for more than one patient as being at least possibly related to the use of the drug. These AEs were transient and lasted 1 or 2 days. For one patient in the placebo treatment group, the AEs of fall and subsequent injury were considered related to the study drug by the investigator. No events of fall and injury occurring in the prucalopride treatment groups were considered related to treatment.

Most AEs were considered by the investigators to be mild or moderate in severity. In total, 25 severe AEs

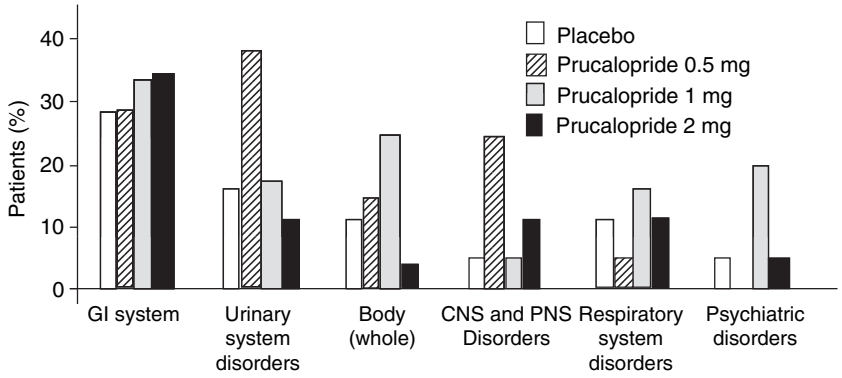

Figure 2 Treatment-emergent adverse events (organized by system organ class) reported by at least 10% patients in at least two treatment groups. Per cent of patients experiencing treatment-emergent events with prucalopride and placebo, over the 4 weeks of the study.

Table 2 Adverse events reported by >10% of patients in any treatment group

WHO preferred term, *n* (%)	Placebo (*n* = 18)	Prucalopride 0.5 mg (*n* = 21)	Prucalopride 1 mg (*n* = 24)	Prucalopride 2 mg (*n* = 26)
Diarrhoea	0	1 (4.8)	3 (12.5)	4 (15.4)
Abdominal pain	2 (11.1)	0	2 (8.3)	0
Headache	0	3 (14.3)	0	1 (3.8)
Urinary tract infection	3 (16.7)	7 (33.3)	1 (4.2)	1 (3.8)
Injury	1 (5.6)	1 (4.8)	4 (16.7)	0
Fall	1 (5.6)	1 (4.8)	3 (12.5)	1 (3.8)
Anaemia	0	0	0	4 (15.4)

were reported in the placebo (by 2 patients), prucalopride 0.5 mg (2 patients), 1 mg (2 patients) and 2 mg (1 patient) groups. One patient in the prucalopride 1 mg group reported 10 severe AEs.

Laboratory studies

There were no clinically relevant changes or dose-related effects in the clinical laboratory parameters.

Cardiovascular parameters

Vital signs There were no clinically relevant changes in supine pulse rate, systolic or diastolic blood pressure from baseline or between prucalopride and placebo treatment, and no dose relationship on prucalopride was observed.

Electrocardiogram parameters In both placebo and prucalopride treatment groups, increase in median HR was noted 3 h. Median change from baseline at 3 h postdose ranged from +2.00 to +8.50 bpm (placebo), 0.00 to +5.00 bpm (prucalopride 0.5 mg), −2.00 to +3.00 bpm (prucalopride 1 mg) and +3.00 to +4.50 bpm (prucalopride 2 mg). There was no clinically or statistically relevant difference between the prucalopride and placebo groups and no dose relationship was noted.

There were no consistent or clinically relevant treatment-related differences noted in PR, QT, QTcB or QTcF time intervals. None of the patients with normal QTcF values at baseline had QTcF values >500 ms during treatment (Table 3).

Increases in QTcF > 60 ms compared to baseline were observed in 0, 1, 3 and 1 patients during placebo and prucalopride 0.5, 1 and 2 mg treatment respectively. All had QTcF increases compared to baseline >60 ms at 1 or 2 time points only. Moreover, in four of these five patients (3 on 1 mg and 1 on 2 mg), QTc values remained within normal ranges (<450 ms for females, <430 ms for males) at all time points. A QTcF increase over baseline of >60 ms resulting in a prolonged QTcF value (473 ms) was observed in one female patient in the 0.5 mg prucalopride group. This patient had a pacemaker and an extensive history of cardiovascular disease, including currently active atrial fibrillation. In this patient, the ranges of HR, QTcB and QTcF were broad, both pretrial and during prucalopride treatment, and there were also decreases in QTcF > 60 ms *vs* baseline.

The incidence of QTcF increases between 30 and 60 ms was similar on placebo and prucalopride.

Electrocardiogram abnormalities The majority of ECG evaluations in these elderly patients were abnormal,

Table 3 Patients who had normal corrected QT interval (QTc) at baseline and developed QTc intervals that were borderline, prolonged and >500 ms during treatment period

Corrected QT interval	Treatment group	Total *n* in group	Number normal[a] at baseline	Borderline[b], *N* (%)	Prolonged[c], *n* (%)	>500 ms, *n* (%)
QTcF	Placebo	18	18	2 (11.1)	1 (5.6)	0
	Prucalopride 0.5 mg	21	19	3 (15.8)	1 (5.3)	0
	Prucalopride 1 mg	24	22	2 (9.1)	1 (4.5)	0
	Prucalopride 2 mg	26	26	1 (3.8)	0	0

QTcF, corrected QT Fridericia. [a]Normal: <430 (men), <450 (women). [b]Borderline: 430–450 (men), 450–470 (women). [c]Prolonged: >450 (men), >470 (women).

including those acquired at baseline. The percentage of patients for which the ECG abnormalities were considered deteriorated compared to baseline was higher in the placebo group (varying from 5.6% to 30.8% at different time points) than in the prucalopride groups (varying from 0% to 14.3%, 0% to 16.7% and 0% to 16.0% at different time points in the prucalopride 0.5-, 1- and 2-mg groups respectively). Over time, no change in the percentage of patients with clinically relevant abnormalities compared to baseline was detected in any of the treatment groups.

Holter monitoring: atrial and ventricular arrhythmias Holter monitoring revealed no statistically significant differences between the treatment groups in the incidence of possible arrhythmic or supraventricular events. There was no difference in the average number of premature supraventricular beats per hour or in the incidence of runs of supraventricular tachycardia (with HR ≥ 100 bpm). On day 7, there was a higher incidence of nonsustained ventricular tachycardia in the placebo group compared to the prucalopride 2-mg group (30.8% *vs* 0% respectively; $P = 0.014$, Fisher's exact test). There were no events of sustained ventricular tachycardia, ventricular fibrillation or torsades de pointes.

In two patients, the events of ventricular and supraventricular tachycardia on the Holter recordings during prucalopride treatment were reported as AEs. Three additional patients had unspecified tachycardia during prucalopride treatment, reported as an AE by the investigator (onset on days 8, 19 and 28 of treatment). All five patients had relevant medical conditions that would render them susceptible to the development of such arrhythmias, e.g. hypertension, chronic heart failure, coronary artery disease, nonsustained ventricular tachycardia, atrial fibrillation and sinus tachycardia at rest. Moreover, prior to and during the trial, all five patients were receiving at least two concomitant medications with the recorded cardiac dysrhythmia listed as a potential AE in the summary of product characteristics of the concomitant medications (amlodipine, digoxin, enalapril and different classes of antidepressants).

DISCUSSION

This double-blind, placebo-controlled trial was specifically conducted to study prucalopride safety, tolerability and AEs, with emphasis on cardiovascular parameters, in elderly patients with chronic constipation residing at a nursing home. As 88% had a history of cardiovascular disease, this was a relevant, susceptible population for assessing the potential cardiovascular safety in patients treated with prucalopride. Our study suggests that prucalopride is safe in an elderly constipated cohort with stable or controlled cardiovascular disease, based on in-depth analysis of vital sign, ECG, Holter monitor and laboratory assessments during 4 weeks of treatment in a dose escalation study.

The two deaths during the study (due to pneumonia and bronchitis leading to respiratory failure) were not related to study drug. There were two nonfatal SAEs and one AE that resulted in discontinuation of treatment, which would be expected considering the advanced age and medical histories of the patients. One SAE of melaena, colitis and diverticulitis occurred 4 days after the last intake of prucalopride and was not reported to have ischaemic aetiology. No cases of ischaemic colitis have been found in the prucalopride clinical database with more than 3000 treated patients encompassing an exposure to prucalopride of 406 and 2021 patient years, in the double-blind and open-label trials respectively.

The most commonly reported AEs in this elderly population were urinary tract infection, injury, fall, anaemia, headache, diarrhoea and abdominal pain. The last two were reported at least possibly related to the drug by the investigators. Headache and GI-related AEs (with the exception of abdominal pain) are reported with higher frequency in prucalopride than placebo groups.[8,12,13] The GI events were mostly of mild or

moderate severity and attributable to the drug's pharmacodynamic activity. The mechanism of headache is unknown.

When QT measurements were analysed according to CPMP-specified parameters for borderline or prolonged values and by gender,[25] there was no evidence of prucalopride-induced QT prolongation. Although five patients had a QTcF increase >60 ms at isolated time points, the QTc was still within the normal range for four of the five patients, and in the fifth patient who had several CV risk factors and atrial fibrillation at baseline, the QTcF is difficult to evaluate but the QTcF increase is unlikely drug-related. Corrected QT interval has a large diurnal variation of 19–95 ms in normal volunteers.[27–30]

QT interval prolongation is of particular interest as it has been associated with another GI prokinetic cisapride, was attributed to the high affinity of cisapride for the potassium hERG encoded Ikr channel, and occurred mainly in patients with cardiovascular medical history or use of concomitant medication inhibiting CYP3A4 metabolism.[14,16] Unlike cisapride, prucalopride has only affinity for the Ikr channel at concentrations that exceed its therapeutic concentration by at least 150-fold[31,32] and prucalopride is not metabolized by the CYP3A4 pathway,[24] and thus the potential increase in drug levels with inhibition of CYP3A4 by other drugs should not occur. Therefore, it is far less likely that prucalopride would present any clinical risk due to such drug interactions.

Given the high incidence of abnormalities in ECG at baseline in our study and the high incidence of underlying cardiovascular disease, it was expected that deterioration of the ECG would occur across a wide range of ECG parameters. Electrocardiogram analysis (including rate, rhythm and ischaemia parameters) showed that the percentage of patients with deterioration of ECG abnormalities was higher in the placebo than in the prucalopride groups. Cardiovascular ischaemic events were of interest due to recent withdrawal of tegaserod from the US market in 2007; this was the result of an analysis of the tegaserod clinical trials database, which revealed a number of patients reporting serious cardiovascular ischaemic events.[22] The mechanism has not been elucidated,[20,21] but it may be related to tegaserod's affinity for the 5-HT_1 receptor within the therapeutic range of the drug. Activation of these receptors results in vasoconstriction, e.g. of coronary and cerebral arteries.[20] However, a preliminary report of a large epidemiological study[19] identified a low number of cardiovascular ischemic events, similar in patients treated with tegaserod and matched untreated patients, and comparable to expected rates in a population of mostly premenopausal women. Thus, this large epidemiological study failed to confirm the differential event rate for cardiovascular ischaemia noted in the tegaserod clinical trial database, and it suggests that the higher cardiovascular event rate in the latter database might be due to chance. In contrast to tegaserod, prucalopride has only affinity for the 5-HT_1 receptor at concentrations exceeding its therapeutic range by at least 150-fold. Moreover, review of the prucalopride clinical database revealed no difference in the occurrence of cardiac, cerebral or peripheral ischaemic events between placebo and prucalopride treated patients (data on file at Movetis).

Holter-monitoring data did not reveal any proarrhythmic or supraventricular effects, and there were no events of sustained ventricular tachycardia, ventricular fibrillation or torsades de pointes. One patient discontinued prucalopride treatment because of nonsustained ventricular tachycardia; however, the incidence of this form of tachycardia on Holter monitoring was significantly higher in the placebo group than in the prucalopride 2 mg group. All patients with tachycardia reported as an AE (ventricular and/or supraventricular tachycardia observed on Holter or unspecified tachycardia reported by the investigator) had relevant medical histories and/or were using concomitant medications with a known side effect of arrhythmia and/or tachycardia. These clinical studies are also complemented by the recently published,[33] extensive *in vitro* studies showing that prucalopride induces only weak atrial inotropic contractile responses whereas it desensitizes the atrial response to 5-HT. In contrast, in the stomach prucalopride induced a strong increase in cholinergic contractions without desensitizing the response to 5-HT. These *in vitro* data add to the cardiac safety of prucalopride.[33]

Phase II studies have demonstrated increased stool frequency and decreased stool hardness with prucalopride 0.5–4 mg,[7,9,10] attributable to stimulation of intestinal motility and transit, particularly in the lower GI tract.[4,5,34] Phase III studies confirmed prucalopride's ability to normalize bowel function [mean of ≥3 spontaneous complete bowel movements (SCBM) per week] in up to 31% of patients receiving 2 mg prucalopride compared to 12% of patients receiving placebo.[8,12,13] Prucalopride also produced a clinically significant increase in the percentage of patients with an increase of ≥1 SCBM week^{-1} (47% *vs* 26% on placebo, $P < 0.001$), and improved other constipation-associated symptoms and quality of life.[8]

CONCLUSIONS

Prucalopride was safe and well-tolerated in a double-blind placebo-controlled, dose-escalation trial with a treatment of 4 weeks duration designed to assess cardiovascular safety in an elderly nursing home population with high incidence of underlying cardiovascular disease. Extensive ECG and Holter monitoring confirm that prucalopride does not induce QT prolongation, ventricular arrhythmias or torsades de pointes.[35] In addition, no evidence of drug-induced ischaemia or arrhythmia was found. Further safety studies over long-term treatment (mean 231 days, maximum 721 days) are currently in preparation for full publication.[36]

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DISCLOSURES AND COMPETING INTERESTS

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