Coadministration of probenecid and cimetidine with mirogabalin in healthy subjects: A phase 1, randomized, open-label, drug–drug interaction study

AIMS
The primary aim of this study was to assess the individual effects of probenecid and cimetidine on mirogabalin exposure.

METHODS
This phase 1, open-label, crossover study randomized healthy adults to receive three treatment regimens, each separated by ≥5-day washout: a single oral dose of mirogabalin 15 mg on day 2, mirogabalin 15 mg on day 2 plus probenecid 500 mg every 6 h from days 1 to 4, and mirogabalin 15 mg on day 2 plus cimetidine 400 mg every 6 h from days 1 to 4.

RESULTS
Coadministration of mirogabalin with probenecid or cimetidine increased the maximum and total mirogabalin exposure. The geometric mean ratios of Cmax and AUC(0-t) (90% CI) with and without coadministration of probenecid were 128.7% (121.9–135.7%) and 176.1% (171.9–180.3%), respectively. The geometric mean ratios of Cmax and AUC(0-t) (90% CI) with and without coadministration of cimetidine were 117.1% (111.0–123.6%) and 143.7% (140.3–147.2%), respectively. Mean (standard deviation) renal clearance of mirogabalin (l h⁻¹) was substantially slower after probenecid [6.67 (1.53)] or cimetidine [7.17 (1.68)] coadministration, compared with mirogabalin alone [11.3 (2.39)]. Coadministration of probenecid or cimetidine decreased mirogabalin mean (standard deviation) apparent total body clearance [10.5 (2.33) and 12.8 (2.67) l h⁻¹, respectively, vs. 18.4 (3.93) for mirogabalin alone].

CONCLUSIONS
A greater magnitude of change in mirogabalin exposure was observed when coadministered with a drug that inhibits both renal and metabolic clearance (probenecid) vs. a drug that only affects renal clearance (cimetidine). However, as the increase in exposure is not clinically significant (>2-fold), no a priori dose adjustment is recommended.
WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
• Mirogabalin is a substrate for organic anion transporters 1 and 3 (OAT1/3), organic cation transporter 2 (OCT2), and multidrug and toxin extrusion (MATE) transporter
• The US Food and Drug Administration guidance for drug interaction studies recommends that in vivo human drug–drug interaction studies are performed with probenecid, a uricosuric drug and an OAT1/3 and uridine 5'-diphospho-glucuronosyltransferase inhibitor (UGT); and cimetidine, an H2-receptor antagonist antihistamine and an OCT2 and MATE inhibitor

WHAT THIS STUDY ADDS
• This study clinically evaluates the effect of a UGT and OAT inhibitor, probenecid and an OCT and MATE inhibitor, cimetidine on mirogabalin pharmacokinetics
• This study demonstrates that a greater magnitude of change in mirogabalin exposure is observed when coadministered with probenecid, a drug that inhibits both metabolic and renal elimination, vs. cimetidine, a drug that only affects renal elimination of mirogabalin
• The increase in mirogabalin exposure with cimetidine was similar to the increase observed in patients with mild renal impairment, for whom mirogabalin dose adjustments are not considered necessary. Additionally, the effect of probenecid on mirogabalin was not clinically significant (>2-fold); therefore, a dose adjustment may not be necessary with concomitant administration of a UGT and OAT inhibitor

Introduction
Pain associated with the neurological conditions of diabetic peripheral neuropathic pain (DPNP) and postherpetic neuralgia (PHN) may profoundly impact function and quality of life [1]. DPNP is a common complication of diabetes affecting up to 50% of patients with diabetic neuropathy in the USA [2]. PHN, a common complication of herpes zoster (shingles), affects up to 20% of patients with herpes zoster [3].

Neuropathic pain has been linked to the upregulation of the αδ-1 subunit of voltage-dependent calcium channels in the central nervous system [4]. In addition to a pore-forming α1 subunit, voltage-dependent calcium channels are composed of an intracellular β subunit, a disulfide-linked dimer of α2 and δ subunits (α2δ), and a transmembrane γ subunit in some types [5]. Ligands of the α2δ-1 subunit exert analgesic effects by preventing its trafficking to presynaptic terminals, decreasing presynaptic calcium influx, and thereby, reducing neurotransmitter release [4]. Mirogabalin monobenzenesulfonate (referred to herein as mirogabalin; Daiichi Sankyo Co., Ltd., Tokyo, Japan) is a preferentially selective α2δ-1 ligand that is intended for the treatment of DPNP and PHN (NCT02318706, NCT02318719).

In a phase 2 study in patients with DPNP, mirogabalin was well tolerated in doses of up to 30 mg day⁻¹, and significantly reduced average daily pain scores compared with placebo when administered at 15 mg day⁻¹, 20 mg day⁻¹ or 30 mg day⁻¹ [6]. Mirogabalin is eliminated primarily as the parent drug through renal excretion after oral administration in animals and humans; approximately 20% is eliminated by glucuronidation, followed by generation of a lactam metabolite (A204–4455; unpublished data on file, Daiichi Sankyo). The US Food and Drug Administration (FDA) guidance for drug interaction studies recommends that investigational drugs with significant renal clearance are evaluated to determine whether they are a substrate of renal transporters—namely organic anion transporters 1 and 3 (OAT1/3)—and organic cation transporter 2 (OCT2) [7]. In vitro data indicate that mirogabalin is a substrate for OAT1/3, OCT2, and the multidrug and toxin extrusion (MATE) transporter (unpublished data on file, Daiichi Sankyo) [8–10]. The FDA guidance for drug interaction studies further recommends that in vivo human drug interaction studies are performed with probenecid, a uridine 5'-diphospho-glucuronosyltransferase (UGT) inhibitor for drugs which are metabolized by the UGT pathway. Probenecid is also an OAT1/3 inhibitor. Additionally, cimetidine is the recommended OCT2 and MATE inhibitor [7, 11–13]. Therefore, a drug–drug interaction study was conducted in healthy subjects to determine the effects of probenecid and cimetidine on mirogabalin exposure. The secondary objectives of this study were to assess the safety and tolerability of mirogabalin and additional PK parameters of mirogabalin when administered alone or with probenecid or cimetidine. The PK of a lactam metabolite of mirogabalin (A204–4455) was also evaluated, since this is a measure of UGT-mediated metabolism of mirogabalin and, therefore, its exposure may be altered by the coadministration of UGT inhibitor probenecid.

Methods

Study design
This was a phase 1, randomized, open-label, three-period, crossover study in which healthy adults received the following three treatments: a single oral dose of mirogabalin 15-mg tablet on day 2 (treatment A), mirogabalin 15 mg on day 2 plus probenecid 500-mg tablet every 6 h from days 1 to 4 (treatment B), mirogabalin 15 mg on day 2 plus cimetidine 400-mg tablet every 6 h from days 1 to 4 (treatment C); each separated by a ≥5-day washout period (Figure 1). Subjects fasted overnight for at least 10 h prior to mirogabalin administration and for at least 4 h after dosing. Mirogabalin was administered with approximately 240 ml of water. Subjects
received one of six possible treatment sequences (i.e. ABC, ACB, BAC, BCA, CAB or CBA).

The study was approved by an Institutional Review Board and was performed in accordance with the Declaration of Helsinki and International Conference on Harmonization guidelines. All subjects provided written informed consent before participation.

**Study population**

Healthy participants were eligible to enroll if they were aged 18 to 60 years and with a body mass index (BMI) of 18 to 30 kg m⁻². Healthy participants were determined by medical history, physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory tests at screening. Women were either of nonchildbearing potential or of childbearing potential (ECGs), and clinical laboratory tests at screening. Women were 3 months prior to study. Men agreed to use barrier contraception and using nonhormonal methods of contraception for at least 6 months prior to participation.

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**Sample collection and bioanalytic methods**

Blood samples were collected to assess the PK of mirogabalin and inactive lactam metabolite over days 2 to 5 of each treatment period at predose (h 0) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48, 54, 60 and 72 h postdose. Urine samples were collected for the assessment of mirogabalin and its lactam metabolite over days 2 to 5 of each treatment period at predose (h 0) and at 0 to 6 h, 6 to 12 h, 12 to 24 h, 24 to 48 h and 48 to 72 h postdose. Blood samples were collected to assess the PK of cimetidine and probenecid on day 1, prior to the morning dose and prior to the doses at 6, 12 and 18 h; on day 2, prior to the morning dose, at 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 h after the morning dose, and prior to the doses at 6 and 12 h; on days 3 and 4, prior to the morning dose and prior to the doses at 6 and 12 h; and on day 5, 6 h after the last dose.

Plasma concentrations of free-base mirogabalin were analyzed at Celerion (Lincoln, NE, USA) using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method. Plasma samples containing analyte and internal standard (d₅-mirogabalin, A206–04632; Daiichi Sankyo Pharma Development, Basking Ridge, NJ, USA) were extracted using an Oasis® HLB solid-phase extraction plate (Waters Inc., Milford, MA, USA). Extracted samples were analyzed on a Zorbax 300-SCX column (50 mm length, 3.0 mm internal diameter, 5 μm particle size, Agilent Technologies, Santa Clara, CA, USA) at ambient temperature with a mobile phase of 80:20 (v/v) acetonitrile: 20 mmol l⁻¹ ammonium formate, pH 2.5 with formic acid, at a flow rate of 1.0 ml min⁻¹. Mirogabalin and internal standard were detected using an AB Sciex API 4000™ triple quadrupole mass spectrometer (Sciex, Framingham, MA, USA). The calibration curves for mirogabalin (1/concentration squared-weighted linear regression) ranged from 1 to 500 ng ml⁻¹. The intra- and interassay precision (coefficient of variation, CV) values in validation were within 1.1% to 14.6% and 2.0% to 11.7%, respectively; the intra- and interassay accuracy values were –16.3% to 3.1%, and –7.1% to 1.9%, respectively. Dilution integrity was verified at a concentration up to 20 000 ng ml⁻¹.

The plasma concentrations of probenecid were analyzed using a validated LC–MS/MS method by Worldwide Clinical Trials (Austin, TX, USA). Plasma samples (50 μl) were mixed with internal standard (probenecid-d14, SynFine Research, Richmond Hill, ON, Canada). Samples were extracted via methanol-mediated protein precipitation. The 100 μl sample was removed and diluted with 0.800 ml of 20% acetonitrile in water. Up to 10 μl of extracted sample was injected onto an Onyx C-18, 2.0 × 500 mm (Phenomenex, Inc., Torrance, CA, USA), which was connected to an API 4000 triple quadrupole mass spectrometer (Sciex). Analyte was eluted using a gradient mobile phase comprised of water, formic acid, ammonium acetate (1000:0.5:0.385) and 2-propanol, acetonitrile, formic acid, ammonium acetate (200:800:0.5:0.385). The flow rate was 0.500 ml min⁻¹ with a total run time of 4.8 min. The plasma concentrations of probenecid were analyzed using a validated LC–MS/MS method by Worldwide Clinical Trials (Austin, TX, USA). Plasma samples (50 μl) were mixed with internal standard (probenecid-d14, SynFine Research, Richmond Hill, ON, Canada). Samples were extracted via methanol-mediated protein precipitation. The 100 μl sample was removed and diluted with 0.800 ml of 20% acetonitrile in water. Up to 10 μl of extracted sample was injected onto an Onyx C-18, 2.0 × 500 mm (Phenomenex, Inc., Torrance, CA, USA), which was connected to an API 4000 triple quadrupole mass spectrometer (Sciex). Analyte was eluted using a gradient mobile phase comprised of water, formic acid, ammonium acetate (1000:0.5:0.385) and 2-propanol, acetonitrile, formic acid, ammonium acetate (200:800:0.5:0.385). The flow rate was 0.500 ml min⁻¹ with a total run time of 4.8 min.

**Figure 1**

Study design. Treatment A (a single oral dose of mirogabalin 15 mg on day 2), Treatment B (mirogabalin 15 mg on day 2 plus probenecid 500 mg every 6 h from days 1–4), Treatment C (mirogabalin 15 mg on day 2 plus cimetidine 400 mg every 6 h from days 1–4). Treatment regimens were separated by a ≥5-day washout period.
The plasma concentrations of cimetidine were also analyzed using a validated LC-MS/MS method by Worldwide Clinical Trials (Austin, TX, USA). Plasma samples (50 μl) were mixed with the internal standard (cimetidine-d3, SynFine Research; Richmond Hill, ON, Canada). Samples were extracted via acetonitrile-mediated protein precipitation. Up to 5 μl of the extracted sample was injected onto a Kinetex PFP, 2.6 μm, 2.1 × 50 mm (Phenomenex, Inc.), which was connected to an API 5000 triple quadrupole mass spectrometer (Sciex). The analyte was eluted using a gradient mobile phase comprised of 5 mmol L⁻¹ ammonium formate in water and acetonitrile in water (900:100). The flow rate was 0.400 ml min⁻¹ with a total run time of 2.6 min. Quantitation was performed using weighted linear LS regression analyses generated from calibration standards prepared fresh daily. The method was validated for a range of 10 to 10 000 ng ml⁻¹ cimetidine. The intra- and interassay precision and accuracy (CV) values were within 7.2% and 8.5%, respectively, at LLOQ; the intra- and interassay accuracy values were within 4.2% and 5.3%, respectively, at other concentrations.

The plasma concentrations of the lactam metabolite of mirogabalin were analyzed at Celerion using a validated LC–MS/MS method. Plasma samples containing analyte and internal standard (d5-labeled analyte, A212™-OGY 2017/18 [15], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [15].

Results

Patient demographics and characteristics
All 30 subjects randomly assigned to one of three treatment sequences completed the study. Approximately 46.7% (14/30) of subjects were women and the subjects were predominantly White (56.7%; 17/30) or Black or African American (40.0%; 12/30). Mean (standard deviation, SD) age was 37.8 (7.81) years and mean (SD) BMI was 26.4 (2.56) kg m⁻² in this study population. Demographics were similar among patients in all treatment sequences.

Effects of probenecid and cimetidine on the single-dose pharmacokinetics of mirogabalin

The arithmetic mean (SD) concentration–time profiles of mirogabalin, when administered alone or in combination with probenecid or cimetidine, are shown in Figure 2A and 2B. The PK parameters of mirogabalin are summarized in Table 1, and a comparison between treatments administered mirogabalin alone or in combination with probenecid or cimetidine are shown in Table 2.

Coadministration of mirogabalin and probenecid or cimetidine resulted in an increase in maximum and total
mirogabalin exposure: the geometric mean ratios of C\textsubscript{max} and AUC\textsubscript{(0-t)} coadministered with and without probenecid were 128.7% (90% CI, 121.9–149.7%) and 176.1% (90% CI, 171.9–180.3%), respectively. The geometric mean ratios of C\textsubscript{max} and AUC\textsubscript{(0-t)} coadministered with and without cimetidine were 117.1% (90% CI, 111.0–123.6%) and 143.7% (90% CI, 140.3–147.2%), respectively (Table 2). Median t\textsubscript{max} of mirogabalin occurred at 1 h after dose, irrespective of the treatment (Table 1). Mean percentage of dose of mirogabalin excreted in the urine (Ae, % dose) was similar after probenecid coadministration (55.9%) compared with mirogabalin alone (61.5%; Table 1). Mean (SD) CLR for mirogabalin was substantially slower after probenecid [6.67 (1.53) l h\textsuperscript{-1}] or cimetidine [7.17 (1.68) l h\textsuperscript{-1}] coadministration, compared with mirogabalin alone [11.3 (2.39) l h\textsuperscript{-1}; Table 1]. Reduction in total clearance of mirogabalin when coadministered with probenecid was much larger than when mirogabalin was coadministered with cimetidine.

Mean plasma concentrations of the lactam metabolite of mirogabalin were lower with probenecid than when mirogabalin was administered alone. By contrast, mean plasma concentrations of the lactam metabolite of mirogabalin were slightly higher when mirogabalin was coadministered with cimetidine than with mirogabalin alone (Figure 3). Based on geometric means, C\textsubscript{max} and AUC\textsubscript{(0-t)} of the lactam metabolite of mirogabalin decreased by approximately 46% and 33%, respectively, in the presence of probenecid, compared with mirogabalin alone. C\textsubscript{max} and AUC\textsubscript{(0-t)} of the lactam metabolite of mirogabalin increased by approximately 24% and 58%, respectively, in the presence of cimetidine compared with mirogabalin alone. However, based on AUC, when coadministered with probenecid, the mean metabolite to parent ratio (MPR%) reduced by >50% (alone: 15.4% vs. coadministered with probenecid: 6.1%). There was only a small increase in mean MPR%, when coadministered with cimetidine (alone: 15.4% vs. coadministered with cimetidine: 17.2%).

Steady state was attained for both probenecid and cimetidine before mirogabalin administration and during coadministration of mirogabalin and probenecid or cimetidine (Figures S1 and S2).

Safety
There were no clinically significant changes in vital signs or ECGs. There were no deaths, serious AEs or TEAEs that led to discontinuation. Thirteen subjects (43.3%) reported 23 TEAEs during the study. All TEAEs were mild to moderate and resolved without sequelae. Constipation was the most common TEAE, reported by one subject (3.3%) in the mirogabalin alone group, one subject (3.3%) in the mirogabalin + probenecid group, and four subjects (13.3%) in the mirogabalin + cimetidine group. Dizziness, headache and somnolence were each reported by two subjects (6.7%) following mirogabalin and probenecid coadministration; dizziness was also reported by one subject (3.3%) in the mirogabalin alone group and two subjects (6.7%) following mirogabalin and cimetidine coadministration.

Discussion
Plasma exposure to mirogabalin was increased when a single 15-mg dose of mirogabalin was administered in combination with either probenecid or cimetidine, compared with mirogabalin alone. This increase was more pronounced with probenecid compared with cimetidine. When coadministered with probenecid, a known OAT1/3 and UGT inhibitor, mirogabalin C\textsubscript{max} and AUC\textsubscript{(0-t)} increased by approximately 29% and 76%, respectively. When coadministered with cimetidine, a known OCT2 and MATE inhibitor, mirogabalin C\textsubscript{max} and AUC\textsubscript{(0-t)} values increased by approximately 17% and 44%, respectively. Mean renal clearance for mirogabalin was substantially slower after probenecid or cimetidine coadministration compared with mirogabalin alone. Therefore, the observed increases in mirogabalin exposure with reduced renal clearance are likely a result of reduced renal secretion of mirogabalin caused by cimetidine-induced inhibition of renal transporters (OCT2 and/or MATE) or probenecid-induced inhibition of renal transporters (OAT1/3). Additionally, probenecid decreased total clearance of mirogabalin (>7.91 l h\textsuperscript{-1}) more than it did renal clearance (>4.6 l h\textsuperscript{-1}; Table 1), suggesting that it decreases not only...
renal but also nonrenal (i.e., metabolic) clearance of mirogabalin. These results are consistent with the decreased level of lactam metabolite of mirogabalin (which originates from a glucuronide metabolite) in the presence of probenecid. As probenecid inhibits both UGT and OAT1/3, this observation is specific to dual inhibition of OAT1/3 and UGT by probenecid. This also explains the greater increase in mirogabalin exposure when coadministered with probenecid due to the inhibition of both metabolic and renal clearance of mirogabalin—as compared with mirogabalin coadministered with cimetidine, which inhibits only the renal clearance of mirogabalin.

The unbound plasma concentration of cimetidine attained in this study was approximately 9.1 μmol l\(^{-1}\), with approximately 20% of cimetidine bound to human plasma [16]. The FDA guidance for drug interaction studies recommends that in vivo human drug–drug interaction studies are performed with cimetidine for OCT2 [7]; however, comparison of the inhibition constant (K\(\text{i}\)) values for cimetidine previously reported for OCT2 (K\(\text{i} = 95–146 \text{ μmol l}^{-1}\)), MATE1 (K\(\text{i} = 1.1–3.8 \text{ μmol l}^{-1}\)) and MATE2-K (K\(\text{i} = 2.1–6.9 \text{ μmol l}^{-1}\)) with the observed maximum unbound plasma concentration (9.1 μmol l\(^{-1}\)) suggests that the inhibition of MATE1 and/or MATE2-K, and not OCT2, is the likely

### Table 1

|                  | Mirogabalin 15 mg Alone (n = 30) | Mirogabalin 15 mg + probenecid 500 mg (n = 30) | Mirogabalin 15 mg + cimetidine 400 mg (n = 30) |
|------------------|---------------------------------|---------------------------------------------|---------------------------------------------|
| **Plasma parameters** |                                 |                                             |                                             |
| \(C_{\text{max}}\) (ng ml\(^{-1}\)) | 227 (55.0)                      | 290 (58.9)                                  | 265 (60.3)                                  |
| Geometric mean (CV%) | 221 (25.5)                      | 284 (21.4)                                  | 259 (22.6)                                  |
| \(t_{\text{max}}\) (h) | 1.00 (0.50, 2.50)               | 1.00 (0.50, 3.00)                           | 1.00 (0.50, 2.00)                           |
| \(AUC_{(0-t)}\) (ng·h ml\(^{-1}\)) | 840 (178)                      | 1480 (306)                                  | 1200 (239)                                  |
| Geometric mean (CV%) | 822 (21.6)                      | 1450 (21.5)                                  | 1180 (20.5)                                  |
| \(t_{\text{90}}\) (h) | 2.93 (0.486)                    | 4.62 (0.726)                                 | 3.92 (0.569)                                 |
| CL/F (l h\(^{-1}\)) | 18.4 (3.93)                     | 10.5 (2.33)                                 | 12.8 (2.67)                                 |
| **Urinary parameters** |                                 |                                             |                                             |
| \(f_{\text{e}}\) | 0.615 (0.044)                   | 0.636 (0.055)                               | 0.559 (0.056)                               |
| \(Ae, \% \text{dose}\) | 61.5 (4.37)                     | 63.6 (5.54)                                 | 55.9 (5.60)                                 |
| CL\(_R\) (l h\(^{-1}\)) | 11.3 (2.39)                     | 6.67 (1.53)                                 | 7.17 (1.68)                                 |

Shown as arithmetic mean (standard deviation), unless otherwise noted

\(Ae\), percentage of drug in urine; \(AUC_{(0-t)}\), area under the plasma concentration vs. time curve from time 0 to the last quantifiable dose; CL/F, apparent total body clearance; CL\(_R\), renal clearance; \(C_{\text{max}}\), maximum plasma concentration; CV, coefficient of variation; \(f_{\text{e}}\), fraction of dose excreted in urine; \(t_{\text{90}}\), terminal elimination half-life; \(t_{\text{max}}\), time to reach maximum plasma concentration

### Table 2

| Pharmacokinetic parameters | Geo LS mean mirogabalin + probenecid (Treatment B) | Geo LS mean mirogabalin alone (Treatment A) | Ratio (%; B/A) (90% CI) |
|---------------------------|---------------------------------------------------|---------------------------------------------|-------------------------|
| \(C_{\text{max}}\) (ng ml\(^{-1}\)) | 284                                               | 221                                         | 129 (122–136)           |
| \(AUC_{(0-t)}\) (ng·h ml\(^{-1}\)) | 1448                                              | 822                                         | 176 (172–180)           |
| \(AUC\) (ng·h ml\(^{-1}\)) | 1458                                              | 834                                         | 175 (171–179)           |

| Pharmacokinetic parameters | Geo LS mean mirogabalin + cimetidine (Treatment C) | Geo LS mean mirogabalin alone (Treatment A) | Ratio (%; C/A) (90% CI) |
|---------------------------|---------------------------------------------------|---------------------------------------------|-------------------------|
| \(C_{\text{max}}\) (ng ml\(^{-1}\)) | 259                                               | 221                                         | 117 (111–124)           |
| \(AUC_{(0-t)}\) (ng·h ml\(^{-1}\)) | 1181                                              | 822                                         | 144 (140–147)           |
| \(AUC\) (ng·h ml\(^{-1}\)) | 1192                                              | 834                                         | 143 (140–146)           |

\(AUC\), area under the plasma concentration vs. time curve at infinity; \(AUC_{(0-t)}\), area under the plasma concentration vs. time curve from time 0 to the last quantifiable dose; CI, confidence interval; \(C_{\text{max}}\), maximum plasma concentration; Geo LS mean, geometric least squares mean
mechanism underlying the drug–drug interaction between mirogabalin and cimetidine [17]. Similarly, comparison of the $K_i$ value of probenecid previously reported for OAT1/3 ($<4 \mu\text{mol l}^{-1}$) with the observed maximum unbound trough plasma concentration of $28 \mu\text{mol l}^{-1}$ just before dosing of mirogabalin is consistent with the hypothesis that the inhibition of OAT1/3 is the mechanism underlying the drug–drug interaction between mirogabalin and probenecid.

A single 15-mg dose of mirogabalin was well tolerated with no serious AEs, or AEs leading to discontinuation when administered alone or in combination with probenecid or cimetidine.

A limitation of this study is that the inhibitors tested in combination with mirogabalin affect multiple transporters. This is due to lack of inhibitors specific for each transporter. Therefore, the results of this study should be evaluated cautiously, and future studies or physiologically-based PK modeling are needed to determine the effects of specific transporters. Another limitation of this study is that it did not evaluate the effects of these drug–drug interactions in the target patient population. Diabetes is frequently complicated by renal and hepatic impairment [18, 19]. Since the metabolism and clearance of drugs may be different in patients with renal and hepatic impairment, future studies are needed to evaluate the PK and safety of mirogabalin coadministered with probenecid or cimetidine in these patients.

Finally, although this was a single-dose study, no significant accumulation of mirogabalin was observed over multiple therapeutic doses and mirogabalin has a linear PK [20, 21]. Therefore, effect of probenecid and cimetidine on mirogabalin PK from this study can be utilized for multiple dose settings.

**Conclusion**

There was a greater magnitude of change in mirogabalin exposure when coadministered with a drug that inhibits both renal and metabolic clearance (probenecid) vs. a drug that only affects renal clearance (cimetidine). The increase in mirogabalin exposure with cimetidine is similar to the increase observed in patients with mild renal impairment, for whom mirogabalin dose adjustments are not considered necessary [22]. Additionally, since the effect of probenecid on mirogabalin is not significant (>2-fold), mirogabalin dose adjustments may not be necessary with concomitant probenecid. Future studies or analyses should explore the combined effects of physiological changes, organ impairment, and drug interactions in the target population.

**Competing Interests**

M.T., N.Y., C.H., V.W., L.H. and H.Z. are full-time employees of the Sponsor, Daiichi Sankyo. V.D. was a full-time employee of Daiichi Sankyo at the time of the study.

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**Contributors**

M.T., C.H. and H.Z. designed the present studies. M.T., G.J.A., L.H., V.W. and V.D. conducted the research. M.T., N.Y., G.J.A., C.H. and H.Z. analysed the data. All authors critically revised the manuscript and the final version of the manuscript was approved by all authors.

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**Figure 3**

Mean (standard deviation) plasma mirogabalin lactam metabolite concentration–time profiles after administration of mirogabalin alone or when coadministered with probenecid or cimetidine: (A) linear scale; (B) semilogarithmic scale. Plasma mirogabalin lactam metabolite concentrations that are below the lower limit of quantification were not included in the plots.
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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13674/supinfo

Figure S1 Mean (standard deviation) plasma probenecid concentration-time profiles after coadministration of mirogabalin and probenecid. (A) Linear scale; (B) semilogarithmic scale

Figure S2 Mean (standard deviation) plasma cimetidine concentration-time profiles after coadministration of mirogabalin and cimetidine. (A) Linear scale; (B) semilogarithmic scale