ORIGINAL RESEARCH ARTICLE

Open-Label Single-Dose Study to Assess the Effect of Mild and Moderate Hepatic Impairment on the Pharmacokinetics of Mirogabalin

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Abstract

Background and Objectives Mirogabalin is an $\alpha_2\delta$ ligand being developed to treat neuropathic pain. A small fraction of mirogabalin is metabolized by the liver, where hepatic impairment may affect exposure. The objective of this phase I, open-label single-dose study was to determine if mild or moderate hepatic impairment alters the pharmacokinetics of mirogabalin.
Methods Serial blood samples were collected for determination of maximum observed concentration, time to maximum concentration, and area under the concentration–time curve until the last quantifiable concentration of the active free form (A200-700) and inactive lactam metabolite (A204-4455) of mirogabalin.
Results The A200-700 maximum observed concentration was similar in subjects with mild hepatic impairment but lower in subjects with moderate hepatic impairment vs. control subjects. The A204-4455 maximum observed concentration was lower in subjects with mild and moderate hepatic impairment vs. control groups. The A200-700 area under the concentration–time curve until the last quantifiable concentration was slightly lower in subjects with mild hepatic impairment and slightly higher in subjects with moderate hepatic impairment vs. control subjects. Peak A204-4455 levels were approximately 22% and 31% lower for subjects with mild and moderate hepatic impairment vs. control individuals, respectively. Exposure to A204-4455 was approximately 37% lower in subjects with mild hepatic impairment but unaffected in subjects with moderate hepatic impairment vs. control groups. Two subjects in the mild hepatic impairment group reported a treatment-emergent adverse event of mild somnolence. No serious or severe treatment-emergent adverse events, discontinuations as a result of treatment-emergent adverse events, or deaths were reported.
Conclusions Mild hepatic impairment resulted in lower A200-700 and A204-4455 exposure, while moderate hepatic impairment did not affect A200-700 exposure. Overall, mild-to-moderate hepatic impairment did not have a significant effect on mirogabalin exposure. A single 15-mg dose of mirogabalin was well tolerated by subjects with mild or moderate hepatic impairment.

Key Points

In this phase I trial, mild hepatic impairment resulted in lower systemic exposure to the free form of mirogabalin and its inactive lactam metabolite, while moderate hepatic impairment had no effect on exposure to the free form of mirogabalin.

A single 15-mg dose of mirogabalin was well tolerated by patients with mild and moderate hepatic impairment.

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1 Introduction

Mirogabalin monobenzenesulfonate (herein called mirogabalin) is a novel, preferentially selective $\alpha_2\delta$ ligand [1] in phase III development in Asia for the treatment of pain associated with neuropathic pain conditions, including diabetic peripheral neuropathic pain and post-herpetic neuralgia. Neuropathic pain models demonstrate significant upregulation of $\alpha_2\delta$-1 subunit, which is thought to increase calcium (Ca^{2+}) influx and sensitize the spinal cord to pain [2, 3]. Non-clinical studies suggest changes in the protein content of membranes of injured neurons can lead to a lowered threshold for action potential generation. This lowered threshold can result in abnormal and spontaneous firing in peripheral and primary afferent and dorsal root ganglion neurons. Thus, the $\alpha 2\delta$-1 subunit is an important therapeutic target in the treatment of neuropathic pain [4, 5]. The $\alpha_2\delta$-1 subunits exert their therapeutic effect by reducing Ca^{2+}

influx through voltage-dependent Ca^{2+} channels through an unknown mechanism and this represses abnormal neurotransmission mainly in the dorsal horn of the spinal cord [2]. Decreasing Ca^{2+} influx reduces the release of neurotransmitters, including glutamate, norepinephrine, and substance P [6].

Mirogabalin was effective in treating diabetic peripheral neuropathic pain in phase II studies in the USA [7] and Asia. Following oral administration of doses ranging from 3 to 75 mg in healthy volunteers, the peak and total exposure of mirogabalin increases proportionally with increasing doses [8]. The time of peak plasma concentration (T_{max}) of mirogabalin is 1 h with a mean elimination half-life ranging from 3.0 to 4.9 h [8]. Mirogabalin is rapidly converted to the free form of mirogabalin, A200-700, which is the predominant, active circulating chemical form. Mirogabalin is eliminated mainly unchanged (61%–72%) via renal excretion by filtration and active secretion, [8] but a small fraction (13%–20%) is also metabolized by hepatic
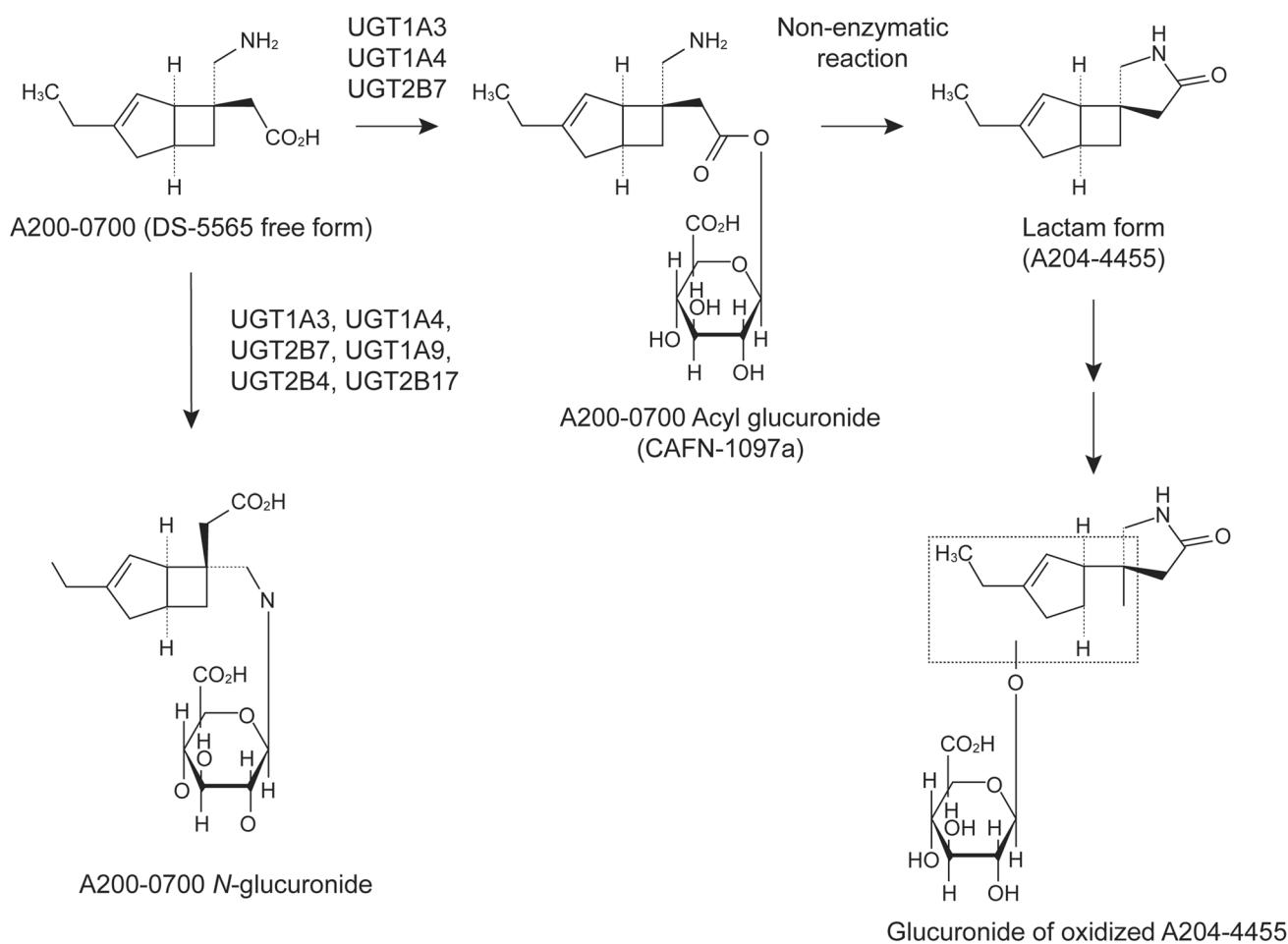

Fig. 1 Proposed metabolic pathway of mirogabalin in humans (Daiichi Sankyo, Inc.). The metabolic pathway of mirogabalin was determined from in vitro studies using human liver microsomes and complementary deoxyribonucleic acid (cDNA)-expressed human uridine 5′-diphospho-glucuronosyltransferase (UGT) enzyme systems. A204-4455 was produced by UGT1A3, UGT1A4, and UGT2B7

uridine 5′-diphospho-glucuronosyltransferase (UGT) isoforms (Fig. 1). In-vitro data indicate that mirogabalin is a substrate for organic anion transporter 1/3, organic cation transporter 2, and the multi-drug and toxin extrusion transporter [9–11].

One of the metabolites of mirogabalin, A204-4455 (the inactive lactam metabolite of mirogabalin), is generated by glucuronidation. In-vitro pharmacological studies show the biological effect of A204-4455 is insignificant. In humans, approximately 1.2% of the mirogabalin dose is excreted in feces [12]. Subjects with diabetes mellitus, who are at risk for diabetic peripheral neuropathic pain, have a higher risk of hepatic impairment (HI) from multiple etiologies [13–15]. The primary objective of the study was to evaluate the effect of mild and moderate HI on the pharmacokinetic parameters of A200-700 after a single oral 15-mg dose of mirogabalin compared to healthy control individuals. The secondary objectives included assessing the safety and tolerability of mirogabalin and evaluating the pharmacokinetic parameters of A204-4455 in subjects with mild and moderate HI compared to healthy control individuals.

2 Methods

This phase I, open-label single-dose study consisted of eight subjects with mild HI paired with eight healthy control individuals, and eight subjects with moderate HI paired with eight healthy control individuals, for a total of 32 subjects. For each level of HI, eight subjects were enrolled with the expectation that at least seven subjects would complete the study. As per the US Food and Drug Administration Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function, eight subjects in the moderate HI arm and the control group is a sufficient number of subjects to provide evaluable data [16]. The sample sizes were not based on statistical considerations, but rather the number of subjects considered sufficient to achieve the study objectives.

The subjects with HI and the healthy control individuals were matched in a 1:1 ratio according to sex, age (± 10 years), and body mass index (± 15%). The Child–Pugh score, a method of assessing the prognosis of chronic liver disease based on serum total bilirubin, albumin, prothrombin time, presence of ascites, and hepatic encephalopathy, was used to assess the severity of HI [17]. A Child–Pugh classification of A (5–6 points) was considered mild HI, and a Child–Pugh classification of B (7–9 points) was considered moderate HI. The healthy matched control individuals were recruited and enrolled after all HI subjects received the study drug.

2.1 Study Population

Subjects for the study included adults 18 to 65 years of age, with a body mass index of 18 to 40 kg/m^2, inclusive. All subjects had to be in good health at screening, outside of HI, as determined by medical history, physical examination, vital signs, and clinical laboratory tests. Subjects with HI were required to have a documented history of chronic liver disease or a history of chronic hepatitis B or hepatitis C infection, a Child–Pugh A or B classification score, and normal or non-clinically significant findings at physical examination with the exception of findings consistent with HI. Female subjects were required to either be of non-childbearing potential or agree to use an acceptable means of contraception. Male subjects had to agree to use an acceptable means of contraception and not donate sperm for at least 6 weeks' post-dose.

Exclusion criteria for all subjects included any history of dizziness or vertigo or inner ear problems, history of clinically significant hypotension, or history of any psychotic mental illness. Other exclusion criteria included concomitant use of any central nervous system depressant drug within 7 days before dosing or the use of medications known to affect the elimination of serum creatinine or inhibitors of renal tubular secretion within 60 days. Any subject who had a positive response on the Columbia Suicide Severity Rating Scale or an estimated glomerular filtration rate of < 70 mL/min was also excluded from the study. Additional exclusion criteria for the matched healthy subjects included any clinically relevant abnormality identified on physical examination, electrocardiogram, vital signs, or clinical laboratory tests at screening; a clinically unstable, uncontrolled medical condition; liver function tests above the upper limit of normal at screening and on day −2; and the use of prescription or over-the-counter medications, with the exception of acetaminophen, stool softeners, and topical hydrocortisone cream, within 14 days prior to receiving the study drug.

2.2 Study Design

The screening visit was performed within 21 days prior to study drug administration, and all subjects were admitted to the clinical unit on study day −2. All subjects received 15 mg of mirogabalin orally on day 1 with approximately 240 mL of water after an overnight fast of at least 10 h. This dose was considered to be safe in subjects with HI because mirogabalin (Tarlige; Daiichi Sankyo, Co., Ltd., Tokyo, Japan) is mainly cleared by renal elimination, is minimally metabolized, and doses of 15 mg daily or twice daily are currently being tested in phase III studies.

2.3 Study Assessments

2.3.1 Blood Sampling

Serial samples of 4 mL of venous blood for pharmacokinetic assessments of A200-700 and A204-4455 were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, 48, and 72 h post-dose. An additional 4-mL venous blood sample to assess the binding of A200-700 to plasma proteins was collected 1 h post-dose.

Blood samples were collected into pre-chilled, 4-mL K_2EDTA vacutainer tubes to the specified collection volume. The tube was gently inverted eight or more times to thoroughly mix with the anticoagulant, and then was placed in an ice bath. The samples were centrifuged within 30 min of collection, for approximately 10 min at $1500 \times g$, to obtain plasma and then stored in darkness at -20 °C until shipment, on dry ice, to Celerion MDS (Lincoln, NE, USA).

2.3.2 Bioanalytical Assay

All plasma samples were assayed for A200-700 and A204-4455 concentrations using a validated liquid chromatography-tandem mass spectrometry method (Celerion). A200-0700 and its internal standard were extracted from a 0.050-mL plasma sample, after mixing with 0.2 mL of 0.1% (v/v) formic acid (Mallinckrodt, Center Valley, PA, USA), using a 96-well solid-phase extraction plate conditioned with 0.5 mL of methanol (EMD Millipore, Burlington, MA, USA) and 0.5 mL of ultrapure water. The plate was washed with 0.5 mL of water and 0.75 mL of 5% methanol in water and eluted with mobile phase solution, 0.2 mL of an 80:20 (v/v) mixture of acetonitrile (EMD Millipore) and 20 nM ammonium formate in water (pH 2.5) [Acros, Bridgewater, NJ, USA]. Chromatographic separation was performed using a Zorbax 300-SCX (Agilent Technologies; Santa Clara, CA, USA) column (50×3.0 mm, 5-μm particle size) and isocratic elution at a 1.0 mL/min flow rate. Detection was performed by a Sciex API 4000 (Sciex, Framingham, MA, USA) tandem mass spectrometer with a TurboIonSpray source in the positive ion mode and multiple-reaction monitoring for mirogabalin and the internal standard. The lower limit of quantitation was 1.00 ng/mL.

For A204-4455, plasma samples containing an analyte and internal standard were mixed with equal-volume ammonium acetate (250 mM) and extracted with n-Butyl chloride in a 96-well plate. Extracted samples were analyzed on an ACE C18 column (50-mm length, 3.0-mm internal diameter, 5-μm particle size; Advanced Chromatography Technologies, Aberdeen, Scotland, UK) at an ambient temperature, with a mobile phase of 40:60:0.1 (v/v) acetonitrile:water:formic acid and a flow rate of 1.0 mL/min. The lactam metabolite of mirogabalin and the internal standard were detected using an AB Sciex API 4000™ triple quadrupole mass spectrometer (Sciex). The calibration curve for the analyte (1/concentration^2 weighted linear regression) ranged from 0.1 to 50 ng/mL. The intra- and inter-assay precision (coefficient of variation) values in validation were 1.9% to 17.3% and 3.4% to 14.2%, respectively; the intra- and inter-assay accuracy values were -9.2% to 10.0%, and -4.7% to 1.3%, respectively. Dilution integrity was verified at a concentration of 200 ng/mL. The lower limit of quantitation was 1.00 ng/mL.

For the protein-binding analysis, equilibrium dialysis was performed to measure the amount of A200-0700 bound to a plasma protein. Free A200-0700 was dialyzed using a rapid equilibrium dialysis device (Pierce Biotechnology, Waltham, MA, USA) through a membrane until its concentration across the membrane was at an equilibrium between the plasma and buffer chambers. The time to equilibrium was approximately 12 to 20 h on an orbital shaker at 500 rpm at 37 °C. Following dialysis, the plasma chamber sample was diluted 1:1 with blank buffer (phosphate-buffered saline) and the buffer chamber sample was diluted 1:1 with control plasma (i.e., pooled blank plasma).

2.3.3 Pharmacokinetic Analysis

Pharmacokinetic parameters were estimated from the plasma concentrations using standard methods of non-compartmental analysis using WinNonlin software version 6.3 (Pharsight Inc., Mountain View, CA, USA). Estimated parameters for A200-700 and A204-4455 included maximum observed concentration (C_{max}), T_{max}, area under the concentration–time curve until the last quantifiable concentration (AUC_{last}) as calculated by the logarithm-linear trapezoidal method, area under the concentration–time curve from time 0 to infinity (AUC_{inf}), elimination half-life, total apparent clearance, and volume of distribution in the terminal phase.

Actual time was used for pharmacokinetic parameter estimation. If the first value below the level of quantitation was at the beginning, it was considered as a zero. If a below the level of quantitation value was flanked by two non-zero concentrations, it was treated as a missing value. All other cases of values that were below the level of quantitation were treated as zero.

2.3.4 Safety Assessment

The safety measures assessed include laboratory tests, physical examination, vital signs, 12-lead electrocardiogram, Columbia Suicide Severity Rating Scale, and evaluation of any suspected treatment-emergent adverse events (AEs). All AEs recorded were coded according to the Medical Dictionary for Regulatory Activities (Version 17.1) terminology. Increased suicidal behavior and ideation or increased hepatic transaminases were treated as AEs of special interest.

2.3.5 Statistical Analysis

The safety analysis set included all subjects who received one dose of the study medication. The pharmacokinetic analysis set included all subjects who received one dose of the study drug and had enough plasma concentrations over time to characterize pharmacokinetic parameters. The pharmacokinetic parameters were summarized by subject group, analyte, and nominal time point using descriptive statistics.

The geometric least-square means and geometric mean coefficient of variation were calculated for C_{max}, AUC_{last}, and AUC_{inf}. For A200-700 C_{max}, AUC_{last}, and AUC_{inf}, each HI group was compared with the corresponding matched control group using a mixed-effect analysis of variance with subject groups as fixed effects on the logarithm-transformed C_{max}, AUC_{last}, and AUC_{inf}. For A204-4455, the C_{max}, AUC_{last}, and AUC_{inf} were assessed by descriptive statistics for each HI group and matched control group. Although the study was not powered as a bioequivalence trial, the 90% confidence interval of the ratio of the log-transformed AUC and C_{max} of each HI group to the matched control individuals had to fall completely within the range of 80% to 125% to be considered bioequivalent. Statistical significance of protein-binding differences between the mild and moderate HI groups was determined using a student's *t* test.

3 Results

3.1 Subjects

Thirty-two subjects were enrolled into the study with a mean (standard deviation) age of 56.6 ($\pm$ 6.37) years. The majority of subjects were male (68.8%) and white (71.9%) (Table 1).

All enrolled subjects completed the study and were included in the analysis.

In the subjects with mild HI, five subjects had a history of chronic hepatitis B or C, two subjects had hepatic cirrhosis, and one subject had a combination of hepatitis C infection and cirrhosis. Six of the eight subjects with moderate HI had a combination of chronic hepatitis infection and hepatic cirrhosis and the other two subjects had alcohol-induced cirrhosis.

3.2 Pharmacokinetics

3.2.1 A200-700

After administration of a single 15-mg dose of mirogabalin, the mean plasma concentrations of A200-700 were similar in subjects with mild HI and normal hepatic function. The mild HI and the normal hepatic function groups had a similar mean C_{max}, with a median T_{max} of 1.0 h (Fig. 2, Table 2). The mean AUC_{last} and AUC_{inf} were slightly lower in subjects with mild HI vs. subjects with normal hepatic function, with an approximate 12% decrease in the geometric mean (Table 2).

After administration of mirogabalin, subjects with moderate HI had a slightly lower mean C_{max} and slightly higher mean AUC_{last} compared with subjects with normal hepatic function (Fig. 2). In subjects with moderate HI, the mean geometric ratio for C_{max} was approximately 15% lower and for AUC the mean geometric ratio was approximately 10% higher compared with subjects with normal hepatic function. The median T_{max} was 1.0 h for both groups (Table 2). Even though the mean exposure is slightly lower for the moderate HI group, there was considerable overlap of the exposures between the mild and moderate HI groups; therefore, the exposure was considered to be similar between these groups.

Table 1 Subject demographics

Characteristic	Mild HI ($N=8$)	Mild control group ($N=8$)	Moderate HI ($N=8$)	Moderate control group ($N=8$)
Age, y	56.1 (8.7)	56.0 (6.7)	59.3 (4.0)	55.1 (5.7)
Sex, *n* (%)				
Male	6 (75)	6 (75)	5 (62.5)	5 (62.5)
Female	2 (25)	2 (25)	3 (37.5)	3 (37.5)
Race, *n* (%)				
White	7 (87.5)	3 (37.5)	5 (62.5)	8 (100)
Black/African American	1 (12.5)	4 (50)	3 (37.5)	0 (0)
American Indian or Alaska native	0 (0)	1 (12.5)	0 (0)	0 (0)
BMI (kg/m^2)	27.0 (5.1)	28.2 (2.7)	29.2 (4.6)	28.8 (2.2)

Results are reported as mean (standard deviation), unless specified otherwise
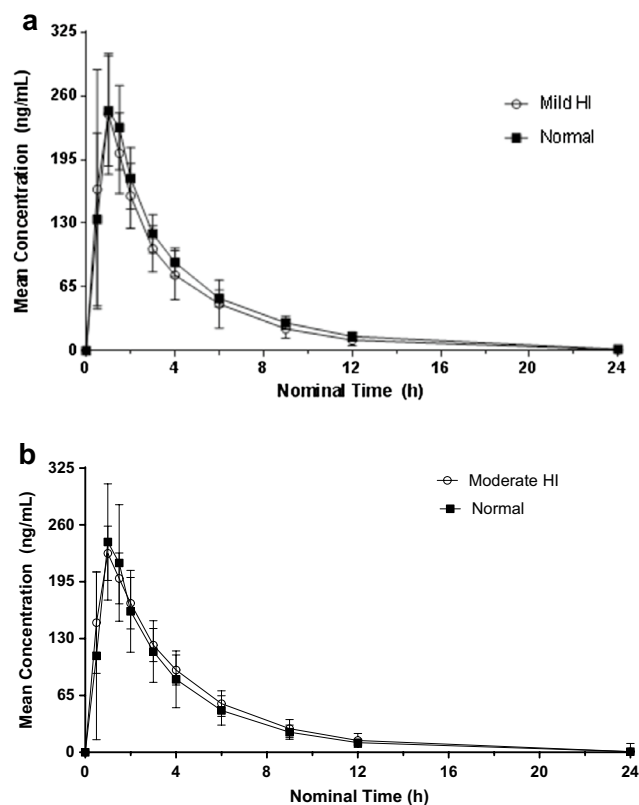
BMI body mass index, *HI* hepatic impairment

Fig. 2 Mean (SD) concentration of A200-700 over time after administration of 15 mg of mirogabalin to subjects with (**a**) mild hepatic impairment (HI) and normal hepatic function, and (**b**) moderate HI and normal hepatic function

3.2.2 A204-4455

Subjects with mild HI had lower plasma concentrations of A204-4455 after administration of a single 15-mg dose of mirogabalin vs. subjects with normal hepatic function (Fig. 3). The mean C_{max} was lower for subjects with mild HI vs. subjects with normal hepatic function, and occurred at a median T_{max} of 3.0 h in both groups. Subjects with mild HI had an approximately 22% lower geometric mean ratio for C_{max}. The geometric mean ratio for AUC_{last} was approximately 37% lower, and AUC_{inf} was approximately 33% lower in subjects with mild HI vs. subjects with normal hepatic function (Table 3).

Similarly, for subjects with moderate HI, lower plasma concentrations of A204-4455 were observed after a single 15-mg dose of mirogabalin vs. subjects with normal hepatic function (Fig. 3). The mean C_{max} was approximately 31% lower in subjects with moderate HI, and occurred at a slightly later median T_{max} compared with healthy subjects (2.5 vs. 2.0 h, respectively). The geometric mean ratio for AUC_{last} and AUC_{inf} was approximately 7% lower in subjects with moderate HI vs. subjects with normal hepatic function (Table 3).

3.3 Protein Binding

Subjects with mild HI and normal hepatic function had similar mean plasma protein binding of A200-700 (26%),
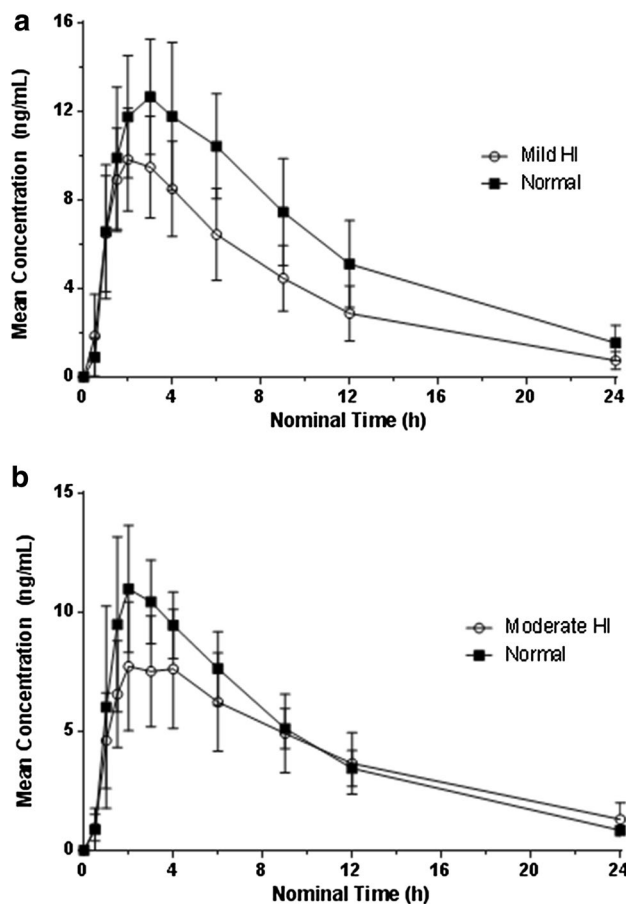
Table 2 Pharmacokinetics of A200-700 in subjects after a single 15-mg dose of mirogabalin

Parameter	Mild HI ($N=8$)	Mild control group ($N=8$)	Moderate HI ($N=8$)	Moderate control group ($N=8$)
T_{max} (h)[a]	1.0 (0.5–1.5)	1.0 (1.0–1.5)	1.0 (1.0–1.5)	1.0 (0.5–1.5)
$t_{1/2}$ (h)	3.2 (0.7)	3.5 (0.8)	2.9 (0.7)	3.3 (1.2)
CL/F (L/h)	17.4 (2.5)	15.3 (1.9)	15.8 (2.5)	17.5 (3.3)
V_z/F (L)	79.0 (17.9)	76.9 (16.9)	65.2 (13.1)	81.1 (31.2)
C_{max} (ng/mL)	274.4 (63.8)	260.6 (42.1)	228.3 (31.1)	272.8 (56.6)
Geometric LSM (% CV)	267.5 (25.0)	258.0 (15.0)	226.4 (13.5)	266.7 (24.1)
Ratio (90% CI)	103.7 (86.8–123.9)		84.9 (71.6–100.7)	
AUC_{last} (ng·h/mL)	866.3 (169.3)	980.7 (139.0)	939.9 (169.7)	872.5 (219.8)
Geometric LSM (% CV)	854.3 (17.2)	972.6 (13.6)	927.4 (17.5)	852.2 (22.6)
Ratio (90% CI)	87.8 (76.7–100.6)		108.8 (91.3–129.8)	
AUC_{inf} (ng·h/mL)	886.0 (168.0)	997.8 (136.5)	971.6 (164.9)	891.5 (211.6)
Geometric LSM (% CV)	874.3 (16.8)	990.1 (13.1)	960.1 (16.5)	873.0 (21.3)
Ratio (90% CI)	88.3 (77.4–100.7)		110.0 (93.2–129.8)	

Reported as mean (standard deviation) unless specified otherwise

AUC_{inf} area under the concentration–time curve from 0 to infinity, AUC_{last} area under the plasma concentration–time curve from 0 to time of the last quantifiable concentration, *CI* confidence interval, *CL/F* total apparent clearance, C_{max} maximum observed concentration, *CV* coefficient of variation, *HI* hepatic impairment, *LSM* least squares mean, T_{max} time to reach C_{max}, $t_{1/2}$ terminal elimination half-life, *Vz/F* volume of distribution in the terminal phase

[a]Median (range)

Fig. 3 Mean (SD) concentration of A204-4455 over time after administration of 15 mg of mirogabalin to subjects with (**a**) mild hepatic impairment (HI) and normal hepatic function, and (**b**) moderate HI and normal hepatic function

while subjects with moderate HI had slightly lower plasma protein binding (22.1%). Mean (standard deviation) protein binding for the moderate HI group (22.1% [3.6]) was statistically significantly lower vs. the mild HI group (25.9% [1.6]), $p = 0.0154$.

3.4 Safety

There were no deaths; no moderate, serious, or severe AEs; and no discontinuations from the study as a result of an AE. Two (25%) of the subjects in the mild HI group reported mild somnolence as the only AE, and was considered to be related to the study drug. No action was taken for the AE and both subjects recovered on the same day. There were no clinically significant changes in clinical laboratory test results, electrocardiograms, or physical examination findings, or positive responses on the Columbia Suicide Severity Rating Scale.

4 Discussion

Overall, a single 15-mg dose of mirogabalin appeared to be well tolerated by subjects with mild and moderate HI and healthy subjects. Two of the 32 enrolled subjects (6.25%) experienced a treatment-emergent AE, and both of these AEs were considered mild.

After administration of a single 15-mg dose of mirogabalin, the geometric mean ratios for A200-700 exposure parameters were within 20% for both mild and moderate HI compared to subjects with normal hepatic function. For A204-4455, the C_{max} geometric mean values were 22% and 31% lower for subjects with mild and moderate HI compared

Table 3 Summary of A204-4455 pharmacokinetic results in subjects after a single 15-mg dose of mirogabalin

Parameter	Mild HI ($N=8$)	Mild control group ($N=8$)	Moderate HI ($N=8$)	Moderate control group ($N=8$)
C_{max} (ng/mL)[a]	9.8	12.6	7.7	11.1
Ratio (90% CI)	78.4 (63.4–96.8)		69.2 (53.0–90.5)	
T_{max} (h)[b]	3.0 (2.0–4.0)	3.0 (2.0–4.0)	2.5 (2.0–4.0)	2.0 (1.5–3.0)
$t_{1/2}$ (h)[c]	5.4 (1.0)	6.4 (1.0)	7.3 (2.0)	5.8 (0.9)
AUC_{last} (ng·h/mL)[a]	88.9	141.7	98.8	106.1
Ratio (90% CI)	62.7 (47.9–82.2)		93.1 (70–124)	
AUC_{inf} (ng·h/mL)[a]	95.6	143.6	100.5	107.6
Ratio (90% CI)	66.5 (50.8–87.1)		93.4 (70.3–124.1)	

AUC_{inf} area under the concentration–time curve from 0 to infinity, AUC_{last} area under the plasma concentration–time curve from 0 to time of the last quantifiable concentration, *CI* confidence interval, C_{max} maximum observed concentration, *HI* hepatic impairment, T_{max} time to reach C_{max}, $t_{1/2}$ terminal elimination half-life

[a]Geometric least-squares mean

[b]Median (range)

[c]Arithmetic mean (standard deviation)

with healthy subjects, respectively. The AUC_{last} and AUC_{inf} values for A204-4455 were 37% and 33% lower, respectively, for subjects with mild HI, but similar in subjects with moderate HI, compared to healthy control individuals. While the mild HI group had a C_{max} for A200-700 that was within the 90% confidence interval, the other exposure parameters for A200-700 fell outside of the 90% confidence interval for both the mild and moderate HI groups. However, this finding was not unexpected owing to the small sample size in the study.

Metabolism via glucuronidation is less affected by mild-to-moderate hepatic dysfunction compared with metabolism by cytochrome P450 isoenzymes [18–20]. A potential mechanism responsible for preserving glucuronidation may be an upregulation of UGT enzyme content in remaining viable hepatocytes as a response to liver injury, especially in those with cirrhosis [19]. Extrahepatic glucuronidation, as well as the deeper location of glucuronosyltransferases within the microsomal membrane, may also help preserve metabolism via glucuronidation [18, 21]. One notable example of this is morphine; studies have shown that the glucuronidation of morphine remains preserved and the plasma clearance of morphine was not changed in subjects with cirrhosis [18]. The reduced A204-4455 AUC_{inf} and AUC_{last} in the mild HI group may be owing to the diminished activity of several UGT enzymes (specifically 1A3, 1A4, and 2B7) secondary to the chronic hepatitis, rather than cirrhosis, which was more prevalent in the moderate HI group.

The plasma protein binding of A200-700 was relatively low and not affected by mild HI, but was statistically significantly lower in subjects with moderate HI compared with the mild HI group. Subjects with mild HI had lower exposure for A204-4455 compared with subjects with normal hepatic function. A204-4455 does not have pharmacological activity, thus the lower levels will not have any impact on the therapeutic activity of mirogabalin. Overall, it does not appear that the dose of mirogabalin should be altered in subjects with mild or moderate HI, relative to the dose and regimen for subjects with normal hepatic function.

5 Conclusion

Overall, mild-to-moderate HI did not have a significant effect (> two-fold) on mirogabalin exposure and was well tolerated as a single dose of 15 mg in subjects with mild-to-moderate HI.

Author Contributions KD was the study lead, VW was the study manager, GS was the medical monitor, and JL was the study statistician. TM and KL were study investigators. HZ was the clinical pharmacology lead and was also responsible for the study design, data analysis, and interpretation. All authors contributed to the development of the manuscript.

Compliance with Ethical Standards

Conflict of interest Thomas Marbury reports grants from the Orlando Clinical Research Center during the conduct of the study and is an equity owner of the Orlando Clinical Research Center. Giorgio Senaldi, Vance Warren, and Hamim Zahir were employees of Daiichi Sankyo at the time the study was conducted. Kenneth Duchin is a consultant to Daiichi Sankyo and has no other conflicts of interest to report. Kenneth Lasseter has no conflicts of interest that are directly relevant to the contents of this article.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate All subjects provided written informed consent prior to enrollment.

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