A Randomized, Placebo-Controlled, Double-Blind Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Repeated Doses of Mirogabalin in Healthy Asian Volunteers

Mendel Jansen¹,⁎, Steven Warrington², Victor Dishy³,⁎, Shoichi Ohwada⁴, Lisa Johnson¹,⁎, Karen Brown³,⁎, and Hitoshi Ishizuka⁴

Abstract

Mirogabalin is a novel, preferentially selective α₂δ-1 ligand under investigation to treat neuropathic pain. The purpose of this study was to evaluate the safety, tolerability, and pharmacokinetics of various doses of mirogabalin in healthy subjects of different ethnicities. This randomized, placebo-controlled, double-blind, sequential, ascending-dose study evaluated single (10-40 mg) and repeated (10, 15 mg twice a day) doses of mirogabalin in Japanese subjects, and a single dose of mirogabalin in Korean, Chinese, and white subjects. Mirogabalin was rapidly absorbed, with a median time to maximum plasma concentration of 1 hour, and rapidly eliminated, with a mean elimination half-life of 2 to 3 hours. Single-dose mirogabalin pharmacokinetic parameters were comparable between Asian and white subjects. Exposure increased proportionally as mirogabalin dose increased in Japanese subjects. Mean mirogabalin steady-state clearance and volume of distribution values were comparable across dose levels. No accumulation of mirogabalin was observed on repeated dosing in Japanese subjects. Mirogabalin had an acceptable safety and tolerability profile in Asian and white subjects at doses up to 15 mg twice a day for 7 days. The most common treatment-emergent adverse events (somnolence, headache, and dizziness) were consistent with the known mechanism of action and safety profile of mirogabalin.

Keywords

ethnic differences, mirogabalin, pharmacodynamics, pharmacokinetics, safety

Mirogabalin monobenzenesulfonate (herein called mirogabalin) (Daiichi Sankyo Co, Ltd, Tokyo, Japan) is a novel, preferentially selective α₂δ-1 ligand¹ that is in phase 3 development in Asia for the treatment of neuropathic pain conditions, including diabetic peripheral neuropathic pain and postherpetic neuralgia (Figure 1). In neuropathic pain models there is significant upregulation of the calcium (Ca²⁺) channel subunit α₂δ-1.²³ Nonclinical studies suggest that neuropathic pain symptoms may be due to changes in the protein content of membranes of injured neurons, which can lead to a lowered threshold for action potential generation. This decreased threshold results in abnormal and spontaneous firing in peripheral and primary afferent and dorsal root ganglionic neurons. The α₂δ-1 ligands are believed to act by repressing abnormal neurotransmission mainly in the dorsal horn of the spinal cord. The therapeutic effect of α₂δ-1 ligands is believed to be due to reduction of Ca²⁺

¹Daiichi Sankyo Development Ltd, Gerrards Cross, Buckinghamshire, UK
²Hammersmith Medicines Research, London, UK
³Daiichi Sankyo Pharma Development, Basking Ridge, NJ, USA
⁴Daiichi Sankyo Co Ltd, Hiromachi, Shinagawa-ku, Tokyo, Japan

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Corresponding Author:
Steven Warrington, Chief Medical Adviser, Hammersmith Medicines Research Ltd, Cumberland Avenue, London NW10 7ES, United Kingdom (e-mail: swarrington@hmrlondon.com)

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influx through voltage-dependent Ca\textsuperscript{2+} channels. This decrease in Ca\textsuperscript{2+} reduces the release of excitatory neurotransmitters such as glutamate, norepinephrine, and substance P.\textsuperscript{2} Because it can decrease abnormal neurotransmitter release, the \(\alpha_2\beta-1\) subunit is an important therapeutic target in the treatment of neuropathic pain.\textsuperscript{4,5}

Mirogabalin is rapidly absorbed, and elimination occurs mainly via renal excretion (61% to 72%).\textsuperscript{6,7} Owing to its renal elimination, a reduction in the dose of mirogabalin is recommended for patients with moderate or severe renal impairment.\textsuperscript{8,9} Following oral administration of doses ranging from 3 to 75 mg in healthy volunteers, the peak and total exposure to mirogabalin increases proportionally with increasing doses.\textsuperscript{6} The time of peak plasma concentration of mirogabalin is 1 hour with a mean half-life ranging from 3.0 to 4.9 hours.\textsuperscript{6}

Mirogabalin has shown efficacy in randomized, double-blind, placebo- and active comparator-controlled phase 2 studies in patients with diabetic peripheral neuropathic pain.\textsuperscript{10} Results of single ascending-dose and repeated ascending-dose studies in healthy subjects in the United States indicated that mirogabalin was well tolerated at doses up to 30 mg/d. The most common treatment-emergent adverse events (TEAEs), dizziness and somnolence,\textsuperscript{11} were expected based on the mechanism of action of mirogabalin. In previous studies (\(N = 96\)), most of the subjects were white or black (91.7%), with only 2 subjects (2.1%) of Asian ethnicity.\textsuperscript{6,12} However, drug exposure, safety, and tolerability in Asian subjects might differ from those of other ethnic groups.\textsuperscript{13} The current study was designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of various doses of mirogabalin in healthy subjects of different races and ethnicities before the design and commencement of the phase 2 studies.

**Methods**

**Study Design and Treatment**

This single-center study was performed at Hammersmith Medicines Research, and the study protocol was approved by the North London Research Ethics Committee 1. The study was conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonisation, consoli-
1 to 6 (a morning dose after overnight fasting and an evening dose approximately 2 hours after a meal) and as a single morning dose on day 7. Subjects remained in the clinic through 72 hours after the last dose, and returned to the clinic for a final follow-up visit 8 days after the last dose of the study drug.

Japanese subjects who participated in the single-dose phase of the study could also participate in the repeated-dose phase after a ≥96-hour washout period; randomization to mirogabalin or placebo was performed independently in the single- and repeated-dose phases for these subjects.

One subject treated with a single 20-mg dose of mirogabalin (cohort 5) experienced a severe AE of orthostatic hypotension. This AE met a protocol-defined stopping criterion; therefore, escalation to mirogabalin or placebo was performed independently in the single- and repeated-dose phases for these subjects.

Subjects
Healthy Japanese, Korean, Chinese, and white men and women 20 to 45 years of age with a body mass index of 19.0 to 30.0 kg/m² were enrolled if they had no history of clinically relevant illness and if physical and laboratory findings were normal. Japanese, Korean, and Chinese subjects were required to have both parents and all 4 grandparents of equivalent descent; Japanese subjects could not have lived outside of Japan for more than 5 years before study entry. Subjects were excluded if they displayed suicidal tendencies, as judged by the Columbia-Suicide Severity Rating Scale; had a history of severe adverse drug reaction; had a history of drug or alcohol abuse; used tobacco- or nicotine-containing products within the past 6 months; or were women who were pregnant, breastfeeding, or not using reliable contraceptive methods.

Blood Sampling and Bioanalytics
In the single-dose phase, blood samples for PK analysis were taken before dosing and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours postdose. Urine samples for PK were collected before dosing and over prespecified intervals for 72 hours postdose. In the repeated-dose phase, blood and urine samples were collected daily, as well as serial blood and urine sample collection pre- and postdose on study days 1 and 7.

Blood samples were collected into prechilled 4-mL tubes that were filled to a specified collection volume. The tube was gently inverted ≥9 times to thoroughly mix and then was placed in a coolbox with ice water. The samples were centrifuged within 30 minutes of collection, for approximately 10 minutes. Within 60 minutes of blood sampling, plasma samples were stored in darkness at −20°C until shipment, on dry ice, to CelerionMDS (Lincoln, Nebraska) for mirogabalin analysis. Urine samples were stored and shipped in the same manner to CelerionMDS.

Mirogabalin is rapidly converted to its predominant circulating free-base form, A200-0700, which was targeted for PK analysis of mirogabalin. The A200-0700 concentration was measured by liquid chromatography tandem mass spectrometry (lower limit of quantitation: plasma, 1.00 ng/mL; urine, 0.100 μg/mL; dialysate, 0.100 ng/mL). The mass transitions were 210.1-133.1 m/z for mirogabalin and 215.1-138.1 m/z for the internal standard. The linear calibration range was 1-1000 ng/mL for the plasma samples and 0.100-100 μg/mL for the urine samples.

Mirogabalin and its deuterated internal standard (d₅ form of A200-0700) were extracted from a 0.050-mL plasma sample using a 96-well solid-phase extraction plate conditioned with 0.5 mL of methanol and 0.5 mL of water. The plate was washed with 0.5 mL of water and 0.75 mL of 5% methanol in water and eluted with 0.2 mL of an 80:20 mixture of acetonitrile and 20 mmol/L ammonium formate in water (pH 2.5) for the mobile phase. Chromatographic separation was performed using a Zorbax 300-SCX column (Agilent Technologies, Santa Clara, California; 50 × 3.0 mm, 5 μm) with a mirogabalin assay flow rate of 1.0 mL/min. Detection was performed by a Sciex API 4000 tandem mass spectrometer (Sciex, Framingham, Massachusetts) with TurboIonSpray source in the positive ion mode and multiple-reaction monitoring for mirogabalin and the internal standard. The coefficients of variation (CV) for the intraday and interday precision of the plasma quality control samples for mirogabalin were 1.1% to 14.6% and 2.0% to 11.7%, respectively.

Mirogabalin and its internal standard were extracted from a 0.025-mL urine sample using a 96-well solid-phase extraction plate conditioned with 0.5 mL of methanol and 0.5 mL of water. The plate was washed with 0.5 mL of ultrapure water and 0.75 mL of 5% methanol in water and eluted with 0.3 mL of an 80:20 mixture of acetonitrile and 20 mmol/L ammonium formate in water (pH 2.5) for the mobile phase; 0.5 mL of 0.1% formic acid in water was added to the wells; and 0.8 mL of 0.1% formic acid in water was added to all urine samples. Chromatographic separation was performed using an Agilent Zorbax 300-SCX column (50 × 3.0 mm, 5 μm) with a mirogabalin assay flow rate of 1.0 mL/min. Detection was performed by a Sciex API 4000 tandem mass spectrometer with TurboIon-Spray source in the positive ion mode and multiple-reaction monitoring for mirogabalin and the internal standard. The mirogabalin intraday and interday
precision CV for the urine quality control samples were 0.8% to 18.3% and 2.7% to 12.8%, respectively.

Blood samples (3 mL) for plasma A200-0700 were collected before mirogabalin administration and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 24, 36, and 48 hours after administration. Urine samples (20 mL) for urine A200-0700 concentration measurement were collected before mirogabalin administration and accumulated during the following periods: from 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours after administration.

**Psychometric Assessments**

Pharmacodynamic variables in the single- and repeated-dose phases were selected to elucidate the central nervous system–related tolerability profile of mirogabalin. Any findings from these tests that were clinically relevant were entered as AEs and evaluated with other primary safety data.

Sedation was analyzed in both single- and repeated-dose studies using the Line Analog Rating Scale (LARS). The LARS is a standard measure of sedation that consists of a series of lines 10 cm in length labeled as drowsy, tired, happy, sad, relaxed, anxious, clumsy, dizzy, alert, depressed, and energetic. The subject made a mark corresponding to their present state, assuming the midpoint of the line represented their normal condition before treatment. To assess sedation, the individual scores for “drowsy,” “tired,” “alert,” and “energetic” were determined by measuring the distance in millimeters from the “less drowsy,” “less tired,” “more alert,” or “more energetic” ends of the lines. The scores were then averaged to get a total score; a higher score indicates a greater degree of sedation.

The Profile of Mood States (POMS) questionnaire was used to evaluate mood disturbances, including fatigue. The subject responded with an answer of 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, or 4 = extremely. Responses were totaled to produce raw scores.

Attention was analyzed using the Digit Symbol Substitution Test (DSST), which is adapted from the Wechsler Adult Intelligence Scale, a well-established measure of diffuse brain impairment. The score is based on the number of symbols the subject is able to associate with the appropriate digit according to an association key, within a set time. The test consisted of digit-symbol pairs followed by a list of digits; under each digit, the subject wrote down the corresponding symbol as fast as possible. The number of correct symbols within 90 seconds was the main outcome measure.

The Vertigo Symptom Scale Short Form (VSS-SF) was used to analyze dizziness. The questionnaire was modified for this study to ask the subject how often in the past day he/she had experienced a given list of symptoms. The analysis variables for the VSS-SF were the VSS-SF total and 2 subscales, 1 summarizing symptoms related to vertigo-balance and 1 summarizing autonomic/anxiety-related symptoms.

Ataxia was analyzed using the Brief Ataxia Rating Scale (BARS). The BARS was developed from a validated ataxia-rating scale to allow assessment of ataxia in a clinical setting without specialized equipment or procedures. Subjects were rated on the items related to gait, knee-tibia test, finger-to-nose test, dysarthria, and oculomotor abnormalities. The analysis variable for the BARS was the total score.
Safety Analysis
Safety was assessed by the frequency and severity of TEAEs, clinical laboratory testing, physical examination and electrocardiography. In addition, in accordance with recommendations set out by the US Food and Drug Administration on the development of centrally acting analgesics, subjects were assessed for suicidal ideation and behavior using the Columbia-Suicide Severity Rating Scale.

Statistical Analysis
The population for PK analysis included all subjects who had received at least 1 dose of mirogabalin and had sufficient plasma concentration data for PK characterization. The PD analysis population included all subjects who had received at least 1 dose of mirogabalin and had at least 1 postdose PD assessment. The safety population included all subjects who had received at least 1 dose of the study drug. All quantitative PK, PD, and safety data were tabulated with descriptive summary statistics.

Plasma and urine concentration-time data were analyzed by noncompartmental methods using WinNonlin, version 4.0 (Pharsight Corporation, Sunnyvale, California). Arithmetic mean and CV percentages were provided for peak concentration and area under the concentration-time curves. Frequency tables were provided for categorical data.

Results
Subject Disposition and Demographics
A total of 53 subjects were randomly assigned to receive treatment, and all subjects completed the study. In the single-dose phase, 6 subjects (all Japanese) received mirogabalin 10 mg, 22 subjects (5 Japanese, 6 Korean, 5 Chinese, 6 white) received mirogabalin 20 mg, and 9 subjects (3 Japanese, 2 each Korean, Chinese, and white) received placebo. The repeated-dose phase included 16 Japanese subjects (2 groups of 6 each received mirogabalin 10 mg twice daily and 15 mg twice daily [instead of the planned 20 mg twice daily]; 4 received placebo). Demographic data are provided in Table 1.

Pharmacokinetics
Single-Dose Phase. PK data indicated that mirogabalin was rapidly absorbed (Figure 2A), with a median time to peak concentration of approximately 1 hour or less, and rapidly eliminated, with a mean elimination
Table 2. Plasma and Urinary Pharmacokinetic Parameters

| Single-Dose Phase | Mirogabalin Cohort |
|-------------------|--------------------|
|                   | Japanese, 10 mg (n = 6) | Japanese, 20 mg (n = 5) | Korean, 20 mg (n = 6) | Chinese, 20 mg (n = 5) | White, 20 mg (n = 6) |
| Plasma PK parameters, study day 1 | | | | |
| $T_{\text{max}}$, h, median [range] | 0.79 [0.5–1.0] | 0.55 [0.5–1.0] | 0.50 [0.5–2.0] | 1.00 [0.5–1.6] | 1.25 [0.5–2.0] |
| $C_{\text{max}}$, ng/mL | 239 (51.5) | 439 (72.7) | 346 (34.3) | 398 (193) | 358 (127) |
| AUC$_{\text{last}}$, ng·h/mL | 627 (117.9) | 1185 (166.3) | 1060 (201.7) | 1282 (226.9) | 1170 (230.2) |
| AUC$_{0-\text{inf}}$, ng·h/mL | 641 (119.8) | 1215 (182.0) | 1076 (199.7) | 1302 (237.2) | 1201 (232.5) |
| $t_1/2$, h | 2.3 (0.3) | 2.4 (0.3) | 2.9 (0.7) | 2.6 (0.7) | 2.6 (0.4) |
| CL/F, mL/min | 16.1 (2.9) | 16.7 (2.2) | 19.1 (3.6) | 15.8 (2.7) | 17.1 (3.0) |
| Urinary PK parameters, study day 1 | | | | |
| $Ae_0-72$, mg | 7.5 (0.5) | 13.5 (2.4) | 14.9 (1.6) | 14.1 (1.2) | 15.0 (1.3) |
| $F_{\text{co}}$, day 1 | 0.75 (0.05) | 0.67 (0.12) | 0.74 (0.08) | 0.70 (0.06) | 0.75 (0.07) |
| CLr, mL/min | 200.3 (43.5) | 188.5 (46.3) | 235.5 (40.1) | 185.1 (35.5) | 211.0 (24.9) |
| Repeated-Dose Phase | Japanese, 10 mg BID (n = 6) | Japanese, 15 mg BID (n = 6) |
| Plasma PK parameters, study day 7 | | |
| $T_{\text{max ss}}$, h, median [range] | 1.5 [0.5–2.0] | 0.5 [0.5–1.5] |
| $C_{\text{max ss}}$, ng/mL | 210 (39.4) | 381 (88.0) |
| AUC$_{\tau}$, ng·h/mL | 601.0 (63.7) | 1057 (142.2) |
| $t_1/2_{\text{ss}}$, h | 2.4 (0.5) | 2.8 (0.7) |
| CLss/F, L/h | 16.8 (1.8) | 14.4 (2.1) |
| $R_{\text{obs}}$ | 1.0 (0.1) | 1.0 (0.1) |
| Urinary PK parameters, study days 1 and 7 | | |
| $Ae_0-12$, mg, day 1 | 6.4 (1.2) | 9.7 (0.9) |
| $F_{\text{co}-12}$, day 1 | 0.64 (0.12) | 0.65 (0.06) |
| $Ae_0$, mg, day 7 | 6.4 (0.7) | 11.0 (1.3) |
| $F_{\text{co}-7}$, day 7 | 0.64 (0.07) | 0.73 (0.09) |
| CLr, mL/min | 179.6 (29.1) | 175.4 (24.9) |

Data are expressed as arithmetic mean (SD) unless otherwise specified. Only Japanese subjects participated in the repeated-dose phase of the study. Ae, amount of parent drug excreted in urine during each collection interval; $Ae_0-T$, amount of parent drug excreted unchanged up to $T$; AUC$_{\text{last}}$, area under the concentration-time curve extrapolated to infinity; AUC$_{\text{inf}}$, area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; AUC$_{\tau}$, area under the concentration-time curve from time 0 to $\tau$ (12 hours); BID, twice daily; CLr ss, renal clearance (at steady state); CLss/F, apparent total body clearance after oral administration (at steady state); $C_{\text{max ss}}$, maximum observed concentration in plasma (at steady state); $C_{\text{max ss}}$, maximum observed concentration in plasma (at steady state); Fe, cumulative fraction of the dose excreted as unchanged parent in urine during each collection interval; $F_{\text{co}-Tss}$, fraction of the dose excreted measured over the dosing interval at steady state; PK, pharmacokinetics; $R_{\text{obs}}$, observed accumulation ratio during multiple dosing, calculated as AUC$_{0-\tau}$ (day 7)/AUC$_{0-12}$ (day 1); ss, steady state; $t_1/2$, terminal half-life (at steady state); $T_{\text{max ss}}$, time of maximum observed concentration (at steady state).

half-life of 2 to 3 hours (Table 2). Single-dose PK parameters were similar among ethnic groups (Table 2). Urinary parameters, volume of distribution, and clearance values were similar between the dose levels in Japanese subjects and were similar across the ethnic groups.

Repeated-Dose Phase. Exposure seemed to increase proportionally as mirogabalin dose increased in Japanese subjects (Figure 2B and 2C; Table 2). Mean mirogabalin steady-state clearance and volume of distribution values were comparable across dose levels: mean estimates of apparent total body clearance after oral administration at steady state for 10 mg and 15 mg BID regimens were 16.8 and 14.4 L/h, respectively (Table 2). Mean fraction of the dose excreted as unchanged parent mirogabalin over the 12-hour dosing interval and mean renal clearance rates were similar across dose levels (Table 2). There was no accumulation of mirogabalin over a twice-daily 7-day dosing regimen.

Pharmacodynamics

No appreciable effects of mirogabalin were noted on the LARS, POMS, DSST, VSS-SF, or BARS scores (data not shown).
Table 3. Treatment-Emergent Adverse Events

| AEs, n (%)                      | Mirogabalin Cohort                                                                 |
|--------------------------------|-----------------------------------------------------------------------------------|
|                                | Japanese, 10 mg (n = 6)               | Japanese, 20 mg\(^a\) (n = 5)               | Korean, 20 mg (n = 6)               | Chinese, 20 mg (n = 5)               | White, 20 mg (n = 6)               | Overall Placebo (n = 9)               |
| Single-Dose Phase              |                                   |                                  |                                  |                                   |                                   |                                  |
| Any TEAE                       | 1 (16.7)                           | 3 (60.0)                          | 4 (66.7)                          | 5 (100.0)                         | 3 (50.0)                          | 1 (11.1)                          |
| At least 1 study drug related  | 1 (16.7)                           | 3 (60.0)                          | 4 (66.7)                          | 5 (100.0)                         | 3 (50.0)                          | 1 (11.1)                          |
| TEAE                           | At least 1 SAE resulting in withdrawal | 0                             | 0                                | 0                                | 0                                | 0                                |
| Most common TEAEs in ≥2 subjects in any dose cohort |                                   |                                  |                                  |                                   |                                   |                                  |
| Somnolence                     | 1 (16.7)                           | 3 (60.0)                          | 3 (50.0)                          | 0                                | 0                                | 0                                |
| Headache                       | 1 (16.7)                           | 0                                | 1 (16.7)                          | 1 (20.0)                         | 1 (16.7)                          | 1 (11.1)                          |
| Dizziness                      | 0                                 | 1 (20.0)                          | 2 (33.3)                          | 1 (20.0)                         | 0                                | 0                                |
| Repeated-Dose Phase            | Japanese, 10 mg BID (n = 6)         | Japanese, 15 mg BID\(^b\) (n = 6) | Japanese Placebo (n = 4)          |                                   |                                   |                                  |
| Any TEAE                       | 6 (100.0)                          | 6 (100.0)                         | 2 (50.0)                          |                                   |                                   |                                  |
| At least 1 study drug–related  | 5 (83.3)                           | 6 (100.0)                         | 1 (25.0)                          |                                   |                                   |                                  |
| TEAE                           | At least 1 SAE resulting in withdrawal | 0                             | 0                                | 0                                | 0                                | 0                                |
| Most common TEAEs in ≥2 subjects in any dose cohort |                                   |                                  |                                  |                                   |                                   |                                  |
| Somnolence                     | 5 (83.3)                           | 5 (83.3)                          | 0                                |                                   |                                   |                                  |
| Headache                       | 2 (33.3)                           | 1 (16.7)                          | 1 (25.0)                          |                                   |                                   |                                  |
| Dizziness                      | 1 (16.7)                           | 4 (66.7)                          | 0                                |                                   |                                   |                                  |
| Nausea                         | 0                                 | 3 (50.0)                          | 0                                |                                   |                                   |                                  |
| Diarrhea                       | 0                                 | 2 (33.3)                          | 0                                |                                   |                                   |                                  |

\(^a\)One subject experienced a severe AE of orthostatic hypotension.  
\(^b\)Due to the severe AE experienced in the single-dose study, mirogabalin 20 mg twice daily was replaced by 15 mg.

Safety

There were no deaths, serious or severe AEs, or discontinuations because of AEs. Overall, across both single- and repeated-dose phases, the most frequently reported TEAEs, which were mild to moderate in severity, were somnolence (n = 17/53, 32%), headache (n = 11/53, 21%), and dizziness (n = 9/53, 17%). The primary TEAEs were expected based on the mechanism of action of mirogabalin.\(^6\)

In the single-dose phase, TEAEs most commonly involved nervous system disorders and were most frequently reported after the mirogabalin 20-mg dose (Table 3). All nervous system TEAEs were either mild or moderate in severity. The onset of the most frequently occurring TEAEs was delayed relative to the time of peak concentration. All other TEAEs (nausea and diarrhea) were mild or moderate in severity, with the exception of a single case of severe orthostatic hypotension in a Chinese patient receiving mirogabalin 20 mg. This event resolved approximately 2 hours after onset, without any intervention.

In the repeated-dose phase, mirogabalin 15 mg twice daily was associated with an increased incidence of nervous system disorders, as well as nausea and diarrhea, although the latter were only mild to moderate in severity (Table 3). Most nervous system AEs developed tolerance within 4 to 5 days of the start of dosing.

There were no reports of suicidal ideation or behavior during the study.

Discussion

Single-dose mirogabalin PK parameters were similar between Asian subjects and those of other ethnicities. There were no major differences in single-dose mirogabalin PK parameters among healthy Japanese, Korean, Chinese, and white subjects. The PK parameters in this study are similar to results seen in previous studies. Although there were modest differences in...
body weight among ethnic groups (mean body weight in the Japanese 20-mg single-dose cohort vs white 20-mg single-dose cohort [SD] were 52.2 kg [4.6] and 65.4 [14.2], respectively), these variations did not result in significant differences in mirogabalin exposure. No accumulation of mirogabalin was observed on repeated dosing in Japanese subjects.

Mirogabalin has an acceptable safety and tolerability profile in Japanese subjects at doses up to 15 mg BID for 7 days, and in Korean and Chinese subjects at a single dose of up to 20 mg. The most common TEAEs were consistent with previous reports and known mechanism of action of mirogabalin. After single doses of mirogabalin, Japanese and Korean subjects appeared to have a higher incidence of dizziness and somnolence than white subjects; however, ethnic subgroups in this study were small, and investigation is required to further define the tolerability profile in these subgroups. Tolerability in the white group was comparable to the safety profile noted in other studies with 20-mg dosing. One severe TEAE occurred at the 20-mg mirogabalin dose and met the protocol-stopping criteria for dose escalation.

Although repeated doses of mirogabalin 15 mg BID were tolerated in Japanese subjects, the incidence of central nervous system AEs was higher than that observed with mirogabalin 10 mg BID. Tolerance to nervous system AEs developed after the first few days of treatment. None of the psychometric scales, including LARS, POMS, DSST, VSS-SF, and BARS, detected symptoms with greater sensitivity than AE reports.

Disclosures

H.I. and S.O. are full-time employees of Daiichi Sankyo Co, Ltd. S.W. reports grants from Daiichi Sankyo to his employer as payment for conduct of the study. K.B. was an employee of Daiichi Sankyo and owned stock in the company at the time the study was conducted. V.D., M.J., and L.J. were employees of Daiichi Sankyo at the time the study was conducted.

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