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CLINICAL TRIAL

Long-term safety and efficacy of mirogabalin in Asian patients with diabetic peripheral neuropathic pain

Masayuki Baba[1], Norimitsu Matsui[2], Masanori Kuroha[2], Yosuke Wasaki[3], Shoichi Ohwada[4]

[1]Aomori Prefectural Central Hospital, Aomori, Japan, [2]Clinical Development Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan, [3]Asia Development Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan, and [4]Biostatistics and Data Management Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan

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***Correspondence**
Masanori Kuroha
Tel.: +81-3-5740-3781
Fax: +81-3-5740-3605
E-mail address:
kuroha.masanori.kh@daiichisankyo.co.jp

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Clinical Trial Registry
DS-5565 Phase III Study for Diabetic Peripheral Neuropathic Pain
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ABSTRACT

Aims/Introduction: Diabetic peripheral neuropathic pain (DPNP) affects the functionality, mood and sleep patterns of patients with diabetes. Mirogabalin, an $\alpha_2\delta$ ligand with a slower dissociation for $\alpha_2\delta$-1 versus $\alpha_2\delta$-2 subunits, showed efficacy and safety in a randomized, double-blind, placebo-controlled, 14-week study in Asian patients with DPNP. This open-label extension study evaluated the long-term safety and efficacy of mirogabalin in Asian patients with DPNP.

Material and Methods: This 52-week open-label extension study was carried out in Japan, Korea and Taiwan in patients with DPNP. Patients received mirogabalin, initiated at 5 mg twice daily and increased to a flexible maintenance dosage of 10 or 15 mg twice daily. Adverse events were monitored throughout the study. Patients provided a self-assessment of pain using the Short-Form McGill Pain Questionnaire.

Results: Of the 214 patients who entered the study, 172 (80.4%) completed the extension study. Of 172 patients who completed the study, 149 received the highest dosage of mirogabalin (15 mg twice daily). The most common treatment-emergent adverse events were nasopharyngitis, diabetic retinopathy, peripheral edema, somnolence, diarrhea, increased weight and dizziness. Most treatment-emergent adverse events were mild or moderate in severity. The incidence of treatment-emergent adverse events leading to treatment discontinuation was 13.1%. The visual analog scale and all other Short-Form McGill Pain Questionnaire subscales (sensory score, affective score, total score and present pain intensity) generally decreased over time from baseline until week 52.

Conclusions: This extension study showed the safety and efficacy of a long-term flexible dosing regimen of mirogabalin 10 or 15 mg twice daily in patients with DPNP.

INTRODUCTION

Diabetic peripheral neuropathy is present in up to half of all patients with long-standing diabetes mellitus, and up to one-third will develop diabetic peripheral neuropathic pain (DPNP)[1–3] DPNP is a major cause of morbidity, often worsening quality of life, as well as being associated with a significant economic burden[1,4,5]. DPNP often results in sleep disturbance[5,6], and the constant tiredness from disturbed sleep and painful symptoms during the day leads to limitations in daily activities and work productivity[1,5,7]. DPNP symptoms are also frequently associated with depression and anxiety[8,9].

Mirogabalin is a novel, selective oral ligand of the $\alpha_2\delta$ calcium channel subunit. It has higher binding affinities for $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits than pregabalin, and a slower dissociation rate for $\alpha_2\delta$-1 than $\alpha_2\delta$-2[10]. Additionally, mirogabalin showed more potent and longer lasting analgesic effects in experimental models of neuropathic pain in rats (partial sciatic nerve ligation and streptozotocin-induced diabetic neuropathic pain)[10]. Furthermore, mirogabalin (10, 30 and 100 mg/kg) and pregabalin (30, 100 and 300 mg/kg) inhibited rotarod performance and locomotor activity in rats; however, the safety indices of mirogabalin were superior to those of pregabalin[10].

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Mirogabalin has shown efficacy in patients with DPNP[11,12]. Compared with placebo, mirogabalin significantly improved the average daily pain score in Asian patients with DPNP in a 14-week phase III study[13]. However, the long-term efficacy and safety of mirogabalin remains unclear. This 52-week open-label extension of the phase III study investigated the long-term safety and efficacy of flexible-dosage mirogabalin in Asian patients with DPNP.

METHODS

Study design

The multinational, open-label extension study of a previous phase III study (NCT02318706) was carried out between 2 May 2015 and 4 July 2017, in Asian patients with DPNP. This extension study was carried out at approximately 200 study sites in Japan, Korea and Taiwan.

The protocol for the phase III study has been described elsewhere[13]. Briefly, in the double-blind, placebo-controlled, parallel-group study, 834 patients were randomized to receive fixed-dosage mirogabalin 15, 20 or 30 mg/day, or placebo. The 14-week study included a 1- to 2-week titration period and a 12- to 13-week fixed-dosage period, followed by a 1-week follow-up period.

Eligible patients entered the open-label extension study at the end of week 14 of the phase 3 study. There was no washout period after the phase III study. The extension study consisted of an initial 4-week titration period, a 48-week flexible-dosage period and a 1-week follow-up period (Figure S1). Mirogabalin was administered twice daily (in the morning and at bedtime in the same manner as in the phase III study). During the titration period, mirogabalin was administered at a dosage of 5 mg twice daily for the first 2 weeks, and then 10 mg twice daily for the second 2 weeks. From the fifth week, the mirogabalin dosage was increased to 15 mg twice daily, if there were no safety issues. For the remainder of the study, the dosage could be changed to either 10 or 15 mg twice daily, depending on the safety findings at each visit.

Use of any concomitant medications or therapies during the study was documented, regardless of whether they were permitted. In particular, the concomitant use of pregabalin or gabapentin, and drugs that could cause irreversible retinal degeneration (e.g., phenothiazine antipsychotics, deferoxamine, quinine, quinidine, ethambutol, voriconazole etc.) were prohibited during the extension study.

The extension study was carried out in compliance with the Declaration of Helsinki, and was consistent with the Good Clinical Practice Guidelines of the International Council for Harmonization and applicable regulatory requirements. All participating clinical sites received institutional review board or independent ethics committee approval of the study protocol and study-related documents before patient enrolment. All patients provided written informed consent. The independent Data Safety Monitoring Board reviewed safety data in an ongoing manner.

Study population

Asian patients with DPNP who had completed 14 weeks of administration of mirogabalin in the phase III study were eligible for inclusion in the extension study. Patients were excluded if they had experienced a critical safety issue in the phase III study or had received previous treatment with drugs that could cause irreversible retinal degeneration. In addition, the following groups of patients were excluded from the extension study: compliance <80% in the phase III study; creatinine clearance <60 mL/min; known positive hepatitis B antigen or hepatitis C antibody; pregnant or breast-feeding women; or women who were likely to become pregnant or unwilling to take reliable contraceptive measures during the study and 4-week follow up.

Safety assessments

Throughout the study, adverse events (AEs) were recorded and classified according to the Medical Dictionary for Regulatory Activities version 17.1. AEs were defined as any unfavorable and unintended sign (including abnormal laboratory value or vital sign), symptom or disease that developed after study entry and up to 7 days after the last dose of the study drug, regardless of the relationship to the study drug. Any symptom that the investigator regarded as associated with diabetic peripheral neuropathy was evaluated as an efficacy variable and not regarded as an AE; however, if such a symptom was considered potentially related to the study drug, it was considered an AE. Pre-existing diseases, including diabetes mellitus, were coded as AEs if they worsened or were inadequately controlled during the study (as judged by the investigator). In addition, vital signs, physical examinations and clinical laboratory assessments were carried out. A 12-lead electrocardiogram was carried out during the titration period visit and at the end of treatment or early termination. Other safety end-points included bodyweight, physical examinations, evaluation of edema, a neurological examination, an ophthalmological examination, Columbia-Suicide Severity Rating Scale[14] assessment and the Hospital Anxiety and Depression Scale[15] assessment.

Efficacy assessment

Patients provided a self-assessment of pain using the Short-Form McGill Pain Questionnaire (SF-MPQ)[16] from the titration period visit to the end of treatment/early termination visit.

Statistical analysis

Safety and efficacy analysis sets included all patients who received at least one dose of the study medication. For the SF-MPQ (the sensory score, affective score, total score, visual analog scale [VAS] and the present pain intensity index), summary statistics were calculated for the measured value and the change from baseline at each scheduled visit (including last observation carried forward imputation and baseline observation carried forward imputation). Baseline values were defined as the last non-missing available values before the first dose of the extension study. All statistical analyses were carried out using

Table 1 | Patient disposition

Enrolled	Mirogabalin 5 mg twice daily† *n* = 4	Mirogabalin 10 mg twice daily† *n* = 35	Mirogabalin 15 mg twice daily† *n* = 175	Total *n* = 214
Completed	0	23 (65.7)	149 (85.1)	172 (80.4)
Discontinued	4 (100.0)	12 (34.3)	26 (14.9)	42 (19.6)
Reason for discontinuation				
Adverse event	2 (50.0)	6 (17.1)	13 (7.4)	21 (9.8)
Death	0	0	1 (0.6)	1 (0.5)
Lack of efficacy	0	0	1 (0.6)	1 (0.5)
Withdrawal by subject	2 (50.0)	6 (17.1)	11 (6.3)	19 (8.9)

Data presented as *n* (%). The percentage is calculated using the number of enrolled patients as the denominator. †The most frequent administered dose during the treatment period.

Statistical Analysis System® software (version 9.3 or higher; SAS Institute, Cary, NC, USA).

RESULTS

Patients

Of the 214 patients enrolled (all of whom provided informed consent), 172 (80.4%) completed the extension study (Table 1). A total of 42 patients (19.6%) discontinued the study, with the most common reasons for withdrawal being AEs (21 patients [9.8%]) and patient withdrawal (19 patients [8.9%]).

The demographics and baseline characteristics of the patients enrolled in the extension study are shown in Table 2. In the enrolled analysis set, the mean (standard deviation [SD]) age at informed consent was 58.9 (9.85) years. Overall, 72.0% (154/214) of the patients were male and 28.0% (60/214) were female. The mean bodyweight was 69.32 kg (SD 13.34 kg), and the mean body mass index was 25.47 kg/m^2 (SD 4.16 kg/m^2). The median duration of DPNP at randomization in the phase III study was 35.5 months (range 6.0–225.0 months). Overall, most of the patients (77.1%) were enrolled in Japan.

Safety

The treatment-emergent AEs (TEAEs) occurring in ≥5% of patients during the extension study are reported in Table 3. The incidence of TEAEs (percentage of patients with at least one TEAE) was 91.1%. The most common TEAEs (reported for ≥5% of patients) were nasopharyngitis (27.1%), diabetic retinopathy (11.7%), edema peripheral (11.2%), somnolence (9.3%), diarrhea (8.4%), increased weight (7.9%), dizziness (7.5%), edema (6.1%), diabetes mellitus, hypoglycemia, constipation (5.6% each) and back pain (5.1%).

Most of the TEAEs resolved without any treatment, and most were mild (57.5%) or moderate (26.2%) in severity. Of patients with diabetic retinopathy, 20 cases were mild, three were moderate (one needed laser therapy) and two were severe (one experienced a clinically significant decline in visual acuity, the other did not).

The incidence of severe TEAEs was 7.5% (16/214), and the incidence of serious TEAEs was 11.2% (24/214). The incidence of TEAEs leading to treatment discontinuation was 13.1% (28/214). Overall, the incidence of AEs considered to be related to the study drug was 27.6%, with the most frequent being somnolence (7.9%), dizziness (6.1%), edema peripheral (4.7%), edema (3.7%) and increased weight (2.8%). Most were mild-to-

Table 2 | Patient demographics and baseline characteristics

Parameter	Mirogabalin *n* = 214
Age (years)†	58.9 ± 9.9
Sex, *n* (%)	
Male	154 (72.0)
Female	60 (28.0)
Height (cm)†	164.72 ± 8.2
Weight (kg)	69.32 ± 13.3
BMI (kg/m^2)	25.47 ± 4.2
Creatinine clearance (mL/min)	105.2 ± 32.7
Type of diabetes mellitus, *n* (%)	
Type 1	12 (5.6)
Type 2	202 (94.4)
Duration of diabetes (years)†	
Median (range)	10.0 (0–46)
Duration of painful DPN (months)†	
Median (range)	35.5 (6–225)
HbA1c (%)	7.43 (1.01)
History of psychiatric disease, *n* (%)	
Yes	2 (0.9)
No	212 (99.1)
Medical and surgical history, *n* (%)	214 (100.0)
Country, *n* (%)	
Japan	165 (77.1)
Korea	27 (12.6)
Taiwan	22 (10.3)

Data presented as the mean ± standard deviation unless otherwise stated. Shown for the enrolled analysis set. The percentage for each categorical variable was calculated using the number of patients in a column heading as the denominator. Creatinine clearance was calculated by the Cockcroft–Gault equation. †At informed consent for extension study. BMI, body mass index; DPN, diabetic peripheral neuropathy; HbA1c, glycated hemoglobin; SD, standard deviation.

Table 3 | Treatment-emergent adverse events occurring in ≥5% of patients during the extension study

TEAE	Mirogabalin *n* = 214
Patients with at least one TEAE	195 (91.1)
Nasopharyngitis	58 (27.1)
Diabetic retinopathy	25 (11.7)
Edema peripheral	24 (11.2)
Somnolence	20 (9.3)
Diarrhea	18 (8.4)
Weight increased	17 (7.9)
Dizziness	16 (7.5)
Edema	13 (6.1)
Diabetes mellitus	12 (5.6)
Hypoglycemia	12 (5.6)
Constipation	12 (5.6)
Back pain	11 (5.1)

Data presented as *n* (%). Coded using the Medical Dictionary for Regulatory Activities Version 17.1. TEAE, treatment-emergent adverse event.

moderate in severity, and most resolved without any treatment. The incidence of serious AEs related to the study drug was 1.4% (3/214). Myocardial infarction, drowning and aspartate aminotransferase increase were reported in one patient each; all were considered severe. One death was reported; a woman aged 68 years treated with mirogabalin 15 mg twice daily who drowned. This event was considered related to the study drug by the investigator. Except for reported AEs, no notable abnormalities were reported in the laboratory evaluations. No notable changes were observed in electrocardiograms, vital signs, neurological examination results, ophthalmological examination, Columbia-Suicide Severity Rating Scale or Hospital Anxiety and Depression Scale.

Efficacy

The mean changes from baseline in the SF-MPQ subscales at week 52 of the extension study are shown in Table 4. For VAS, the mean change from baseline was −9.8 (SD 14.06) at week 52 of the extension study using the last observation carried forward imputation method. From baseline through week 8 of the extension study, the VAS gradually decreased, with the decrease in VAS then maintained throughout the remainder of the study (Figure 1). Other SF-MPQ subscales (total score, sensory score, affective score and present pain intensity) generally decreased from baseline to week 52 of the extension study (Table 4).

Table 4 | Short-Form McGill Pain Questionnaire; mean change from baseline† at week 52 of the extension study

	Baseline (*n* = 214)	Change from baseline at week 52 (*n* = 214)
Sensory score	5.0 ± 5.49	−1.2 ± 3.29
Affective score	0.9 ± 1.78	−0.3 ± 1.30
Total score	5.9 ± 6.94	−1.5 ± 4.31
VAS (mm)	42.1 ± 20.41	−9.8 ± 14.06
Present pain intensity	1.5 ± 0.83	−0.2 ± 0.69

Results analyzed using the last observation carried forward imputation method. Data presented as the mean ± standard deviation. †Baseline value was defined as the last non-missing available value prior to first dose of the extension study. VAS, visual analog scale.

DISCUSSION

Neuropathic pain has been linked to the upregulation of the $\alpha_2\delta$-1 subunit of voltage-gated Ca^{2+} channels in the nervous system.[17,18] The $\alpha_2\delta$-1 subunit has become a target of $\alpha_2\delta$ ligand analgesic drugs[17]. The $\alpha_2\delta$-1 ligands are thought to exert analgesic effects by preventing the trafficking of the $\alpha_2\delta$-1 unit to presynaptic terminals, decreasing presynaptic calcium influx and, consequently, reducing neurotransmitter release[17].

Mirogabalin has potent and selective binding affinities for human and rat $\alpha_2\delta$ subunits, and a slower dissociation rate for the $\alpha_2\delta$-1 versus $\alpha_2\delta$-2 subunit[10]. It shows potent and long-lasting analgesic effects in rat models for neuropathic pain and a wider safety margin for CNS side-effects[10]. In the preceding double-blind phase III trial in Asian patients with DPNP,

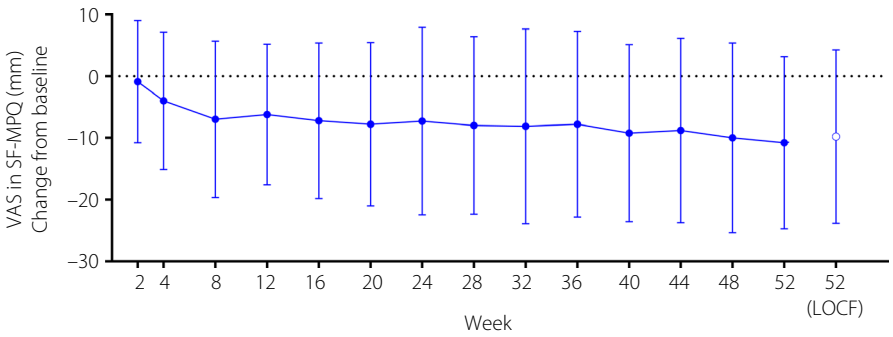

Figure 1 | Time course of mean change (±standard deviation) in visual analog scale in the Short-Form McGill Pain Questionnaire. Shown for the efficacy analysis set. LOCF, last observation carried forward imputation method used; SF-MPQ, Short-Form McGill Pain Questionnaire; VAS, visual analog scale.

mirogabalin 15–30 mg/day was well tolerated and relieved DPNP in a dose-dependent manner for up to 14 weeks[13]. In the present open-label extension study, the safety and efficacy of mirogabalin (administered using a flexible dosing of 10 or 15 mg twice daily) was shown over a longer period (52 weeks) in patients with DPNP, with >80% of the patients completing the extension study.

Mirogabalin was well tolerated in the extension study, with no notable safety concerns identified with the long-term flexible dosing regimen. Overall, the incidence of TEAEs was 91.1%. The most common TEAEs were nasopharyngitis (27.1%), diabetic retinopathy (11.7%), peripheral edema (11.2%), somnolence (9.3%), diarrhea (8.4%), increased weight (7.9%) and dizziness (7.5%). Most of the TEAEs of somnolence, dizziness, weight gain and edema resolved without treatment. The incidence of serious TEAEs (11.2% vs 4.7%), severe TEAEs (7.5% vs 3.0%) and TEAEs leading to treatment discontinuation (13.1% vs 5.5%) remained low with long-term (extension study) compared with short-term (double-blind study) administration of mirogabalin.

In terms of efficacy, improvements from baseline in SF-MPQ subscales (sensory score, affective score, total score, VAS and present pain intensity) occurred over the 52-week extension period, indicating the long-term efficacy of mirogabalin for pain relief in patients with DPNP. Tachyphylaxis was not observed, because the change in VAS from baseline through the eighth week showed a gradual decrease, and the decrease in VAS was maintained throughout the study period.

With this drug class, adverse drug reactions include fatigue, dizziness, sedation, somnolence and ataxia; peripheral edema and increased weight also are frequently reported[19–23]. In a long-term, open-label phase III extension trial in Japanese patients with DPNP treated with pregabalin, a similar adverse event profile to that observed in the mirogabalin extension study was reported. The most common TEAEs in the pregabalin study included somnolence (22.8%), increased weight (22.0%), dizziness (20.3%) and peripheral edema (15.4%)[23]. Given that most TEAEs in the mirogabalin extension study resolved without treatment, it is possible that patients developed tolerance to TEAEs over time. However, further studies would be required to confirm this.

The current study had a number of limitations that should be considered. Outcomes from this open-label extension study should be interpreted with caution due to the absence of a control arm. In addition, all enrolled patients were Asian (most were from Japan) and thus the outcomes in this study might not be transferable to other ethnicities. However, an analysis of pooled safety data from trials involving pregabalin (another $\alpha_2\delta$ ligand) found similar safety outcomes in patients from Japan and those from Western countries[21]. As mirogabalin is eliminated primarily as the parent drug through renal excretion, it is important to assess the efficacy and safety of mirogabalin in patients with renal impairment[24]. However, enrollment was restricted to patients with creatinine clearance of ≥60 mL/min at baseline in the open label phase; therefore, the impact of renal impairment on the efficacy and safety of long-term mirogabalin could not be assessed. In addition, patients had fewer restrictions on the use of concomitant medications during the open-label extension study than during the double-blind study; this might have impacted the safety profile and efficacy outcomes of long-term treatment with mirogabalin.

In conclusion, the present long-term extension study showed the safety and efficacy of a flexible dosing regimen of mirogabalin 10 mg or 15 mg twice daily in patients with DPNP.

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DISCLOSURE

MB has received consultancy fees and speaker fees from Daiichi Sankyo Co., Ltd. NM, MK, YW and SO are employees of Daiichi Sankyo Co, Ltd.

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SUPPORTING INFORMATION

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

Figure S1 | Study design of extension study.