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CLINICAL TRIAL

Mirogabalin for the treatment of diabetic peripheral neuropathic pain: A randomized, double-blind, placebo-controlled phase III study in Asian patients

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ABSTRACT

Aims/Introduction: This study evaluated the efficacy and safety of mirogabalin, a novel, potent, selective ligand of the $\alpha_2\delta$ subunit of voltage-dependent Ca^{2+} channels, for the treatment of diabetic peripheral neuropathic pain (DPNP).

Materials and Methods: During this double-blind, multisite, placebo-controlled phase III study, Asian patients aged ≥20 years with type 1 or 2 diabetes and DPNP were randomized 2:1:1:1 to a placebo, mirogabalin 15, 20 or 30 mg/day for up to 14 weeks, with a 1- to 2-week titration (NCT02318706). The primary endpoint was the change from baseline in average daily pain score (ADPS) at week 14, defined as a weekly average of daily pain (0 = no pain to 10 = worst possible pain, for the past 24 h).

Results: Of 834 randomized patients, 330, 164, 165 and 165 received placebo, mirogabalin 15, 20 or 30 mg/day, respectively, and were included in analyses (modified intention-to-treat population, n = 824); 755 (90.5%) completed the study. At week 14, the least squares mean average daily pain score change from baseline was −1.31, −1.34, −1.47 and −1.81, respectively, showing statistical significance for mirogabalin 30 mg/day versus placebo (P = 0.0027). The treatment-emergent adverse events observed were mostly mild-to-moderate in all mirogabalin doses, and the most frequent treatment-emergent adverse events were nasopharyngitis, somnolence, dizziness, peripheral edema and weight increase.

Conclusions: Mirogabalin relieved DPNP in a dose-dependent manner; mirogabalin 30 mg/day showed statistically significant pain relief (vs placebo) in Asian DPNP patients. All doses of mirogabalin tested were well tolerated.

INTRODUCTION

Approximately 20–30% of patients with diabetes mellitus experience diabetic peripheral neuropathic pain (DPNP)[1,2]. DPNP is associated with morbidity (e.g., depressive symptoms, anxiety and sleep disturbance), loss of work productivity, poor quality of life and significant economic burden[3–5]. Although pregabalin and gabapentin are first-line treatments for DPNP[6,7], they are not effective for all patients and are limited by side-effects[8–11]. Therefore, there is an unmet medical need for effective treatment options with an improved safety profile.

Mirogabalin monobenzenesulfonate (herein referred to as mirogabalin; Daiichi Sankyo Co., Ltd., Tokyo, Japan) is a novel, selective oral ligand for the $\alpha_2\delta$ subunit of the voltage-dependent Ca^{2+} channels being developed for the treatment of DPNP and postherpetic neuralgia. The $\alpha_2\delta$-1 subunit of voltage-dependent Ca^{2+} channels in the nervous system is the main target for the analgesic effect of $\alpha_2\delta$ ligands, such as pregabalin[12]. Although mirogabalin has a similar binding affinity for $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits compared with pregabalin, mirogabalin

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shows slower dissociation rates from $\alpha_2\delta$-1 than $\alpha_2\delta$-2 and, in particular, a slower dissociation rate from $\alpha_2\delta$-1 relative to pregabalin[13]. In a phase II study at sites in the USA, mirogabalin showed efficacy in reducing pain and associated sleep interference in patients with DPNP[14,15].

The present phase III, randomized, double-blind, placebo-controlled study evaluated the efficacy, tolerability and safety of mirogabalin, a ligand of the $\alpha_2\delta$ subunit, in Asian patients with DPNP.

METHODS

Study design

This was a randomized, double-blind, placebo-controlled, parallel-group study for treatment of DPNP (NCT02318706) carried out in multiple sites in Asia between 24 January 2015 and 29 June 2017. This study was carried out in compliance with the Declaration of Helsinki and the International Council for Harmonisation consolidated Guideline E6 for Good Clinical Practice; all patients provided informed consent before enrollment. Safety was periodically evaluated by an independent Data Safety Monitoring Board. A CONSORT checklist is included in the Supplemental Materials.

Eligibility criteria included age ≥20 years with type 1 or 2 diabetes mellitus and DPNP; painful distal symmetric polyneuropathy diagnosed at least 6 months before screening; a pain scale of ≥40 mm on the visual analog scale (VAS) of the Short-form McGill Pain Questionnaire (SF-MPQ) at randomization; and an average daily pain score (ADPS) of ≥4 on the 11-point numerical rating scale over the past 7 days.

Patients were excluded if their pain scale was ≥90 mm on the VAS of the SF-MPQ at screening or at randomization, or their daily pain score was ≥9 during the observation period. In addition, patients were excluded if they had glycated hemoglobin A1c >10.0% at screening (based on the National Glycohemoglobin Standardization Program)[16] or creatinine clearance <60 mL/min at screening (using the Cockcroft–Gault equation).

Eligible patients were randomized 2:1:1:1 to placebo or mirogabalin 15, 20 or 30 mg/day groups in accordance with the randomization schedule securely stored in the Interactive Web Response System (Bell Medical Solutions, Inc., Tokyo, Japan). Randomization was stratified by baseline ADPS (<6 vs ≥6).

The study consisted of a 1-week baseline observation period, a 1- to 2-week titration period, a fixed-dose period (12–13 weeks) and a 1-week follow-up period, whereby patients were monitored post-treatment (Figure S1). For the 15 mg/day group, patients received mirogabalin 5 mg/day (once daily at bedtime) during the first week of titration, 10 mg/day during the second week, then titrated up to 15 mg once daily for the fixed-dose period. The 15 mg/day group received a matching placebo tablet in the morning. For the 20 and 30 mg/day groups, mirogabalin was administered 10 mg/day (5 mg twice daily; in the morning and at bedtime) during the first week of the titration period. During the second week, mirogabalin was administered 20 mg/day (10 mg twice daily; in the morning and at bedtime) to both dosing groups; the 30 mg/day group was then titrated up to 15 mg twice daily the following week, while the 20 mg/day group remained at that dose.

Any concomitant medications or therapies administered to patients during the study were documented regardless of whether they were permitted. Prohibited medications included pregabalin, anti-epileptics, serotonin and norepinephrine reuptake inhibitors, hypnotics (except ultrashort acting; e.g., zolpidem) and anxiolytics, and opioids. Acetaminophen (as needed) was permitted as a rescue medication.

Efficacy assessments

The primary efficacy endpoint was the change from baseline in ADPS at week 14, a weekly average of daily pain scores on a numerical rating scale (0 = "no pain" to 10 = "worst possible pain" for the last 24 h) recorded in an electronic diary. The patient was instructed to rate the pain over the past 24 h on an numerical rating scale (0 = "no pain" to 10 = "worst possible pain") every morning on awakening, before taking the study drug. The secondary efficacy endpoints included the responder rate (defined as the proportion of patients who had a ≥50% improvement in ADPS vs baseline); patient-rated pain on the VAS of SF-MPQ; and the Average Daily Sleep Interference Score (ADSIS), which was the weekly average of patient-reported sleep interference (rated every morning on a numerical scale of 0 = "pain did not interfere with sleep" to 10 = "pain completely interfered with sleep" over the past 24 h). Another secondary endpoint was the Patient Global Impression of Change (PGIC), in which patients rated their improvement on a scale from 0 = "very much improved" to 7 = "very much worse" at the end of treatment.

Safety assessments

Adverse events were monitored throughout the study and classified according to the Medical Dictionary for Regulatory Activities version 17.1. Clinical laboratory evaluations, physical examinations and vital signs were carried out at each visit. In addition, a neurological examination and 12-lead electrocardiogram were carried out at screening and at the end of treatment or at early termination, and included assessment of ankle jerk, vibratory sensation, pain sensation (hyperalgesia, allodynia), muscle strength (0–5 rating; ankle dorsiflexion) and gait/station.

Statistical analysis

The sample size was determined to achieve 90% statistical power under the assumption of a 0.6 difference versus placebo in change from baseline in ADPS for all mirogabalin groups and a common standard deviation of 1.8. The power calculation was based on analysis of variance, and a gatekeeping procedure was applied to control the type I error rate at <0.05.

The modified intention-to-treat analysis set, defined as patients who were randomized and received one dose of study drug, was used for the efficacy analysis. For the primary endpoint, the change from baseline in ADPS, the multiple imputation method was used to handle missing weekly ADPS data. In the multiple imputation data generation, the Markov chain Monte Carlo method with treatment group, age, and sex as covariates was used first to produce a monotone missing data pattern. Subsequently, the regression with predictive mean matching with the same set of covariates was applied to the monotone missing data. A pattern mixture model with different shift parameters depending on reasons for study discontinuation (adverse event, lack of efficacy or the others) was applied to the imputed weekly ADPS data by regression with predictive mean matching to impose a penalty on the study discontinuation under a missing not-at-random mechanism[17]. To compare the change from baseline in ADPS at week 14 between each of the mirogabalin groups and placebo group, a mixed effects model with repeated measures (MMRM) was used for the imputed datasets[18]. The MMRM included treatment, week and treatment-by-week as fixed effects; week as a repeated measure; and baseline ADPS as a covariate. The results from MMRM analyses were combined using Rubin's rule[19]. The gatekeeping procedure was prespecified to adjust multiplicity for comparisons between each of the mirogabalin groups and placebo as follows[20]: The results for mirogabalin 20 and 30 mg/day, which have been evaluated and showed an efficacy trend in the phase II study, were tested against a placebo using a significance level of 0.025. If both were statistically significant, then mirogabalin 15 mg/day would be tested at a level of 0.05. If neither of them was statistically significant, mirogabalin 15 mg/day would not be tested. If either mirogabalin 20 or 30 mg/day was statistically significant, mirogabalin 15 mg/day would be tested at a level of 0.025.

For secondary endpoints, the responder rates (≥50% improvement in ADPS) for mirogabalin groups were compared with the placebo group using a logistic regression model with treatment group and baseline ADPS as covariates. In the analysis, patients who discontinued the study were considered non-responders and a last observation carried forward (LOCF) approach was used for the imputation for patients who completed the study, but did not have week 14 ADPS. For VAS on the SF-MPQ, the changes from baseline at week 14 (LOCF) were compared between treatments using the analysis of covariance model with treatment group and baseline value as covariates. The ADSIS was analyzed using MMRM with treatment, week and treatment-by-week as fixed effects; week as a repeated measure; and baseline ADSIS as a covariate. PGIC was analyzed using the logistic regression model with treatment group as a covariate.

All safety data were summarized on the safety analysis set including patients who received one dose of study drug. Treatment-emergent adverse events (TEAEs) were summarized as a frequency table. All statistical analyses were carried out using SAS software (version 9.3; SAS Institute; Cary, NC, USA).

RESULTS

Patients

A total of 834 patients were randomized to placebo (n = 334), mirogabalin 15 mg/day (n = 166), 20 mg/day (n = 168) and 30 mg/day (n = 166; Figure 1); of which, 824 patients were included in the modified intention-to-treat population and 755 (90.5%) completed the study. Of the 79 patients (9.5%) who discontinued the study, 25 (7.5%) were in the placebo group, 12 (7.2%) in the 15 mg/day group, 18 (10.7%) in the 20 mg/day group and 24 (14.5%) in the 30 mg/day group. The most commonly reported reasons for discontinuation were patient withdrawal (n = 31; 3.7%) and adverse events (AEs; n = 24, 2.9%, more detail in the Safety section). Randomized patients were mostly male (72.5%) and Japanese (72.3%), with a mean age of 61.4 years (Table 1). Most had type 2 diabetes (96.3%), with a mean glycated hemoglobin A1c of 7.5% at baseline. The median duration of DPNP was 36.0 months across treatment groups. At baseline, the mean ADPS was 5.59 across treatment groups (Table 1).

Efficacy

At week 14, the difference in ADPS least square mean (95% confidence interval [CI]; P-value) versus placebo was −0.03 (−0.35 to 0.30; P = 0.8773), −0.15 (−0.48 to 0.17; P = 0.3494) and −0.50 (−0.82 to −0.17; P = 0.0027) for mirogabalin 15, 20 and 30 mg/day groups, respectively. At week 14, the least square mean change from baseline in ADPS was −1.31, −1.34, −1.47 and −1.81 for the placebo and mirogabalin 15, 20 and 30 mg/day groups, respectively (Table S1). Figure 2 shows the time course of the change in ADPS by treatment group and the responder rate (≥30% and ≥50% improvement) for ADPS. For the mirogabalin treatment groups, the decrease in ADPS was greater than placebo from week 1, and further decreased through week 14 (Figure 2a; Table S1). ADPS decreased more rapidly for the mirogabalin 30 mg/day group versus placebo, especially during the first 3 weeks. There was a statistically significant difference in mean change in ADPS from baseline for mirogabalin 30 mg/day versus placebo as early as the first week. The 50% responder rate was significantly greater for mirogabalin 30 mg/day versus placebo (P = 0.0048; Figure 2b; Table S1).

The mean change from baseline to week 14 in VAS of the SF-MPQ was −16.6, −16.8, −18.1 and −22.5 for placebo, mirogabalin 15, 20 and 30 mg/day, respectively. The reduction in VAS was statistically significant for mirogabalin 30 mg/day versus placebo (P = 0.0018; Table S1). The mean change from baseline in ADSIS was −0.91, −1.06, −1.04 and −1.47 for placebo, mirogabalin 15, 20 and 30 mg/day, respectively (Table S1). The reduction in ADSIS was statistically significant for mirogabalin 30 mg/day versus placebo (P = 0.0001); the difference in least square mean (95% CI) change from baseline versus placebo was

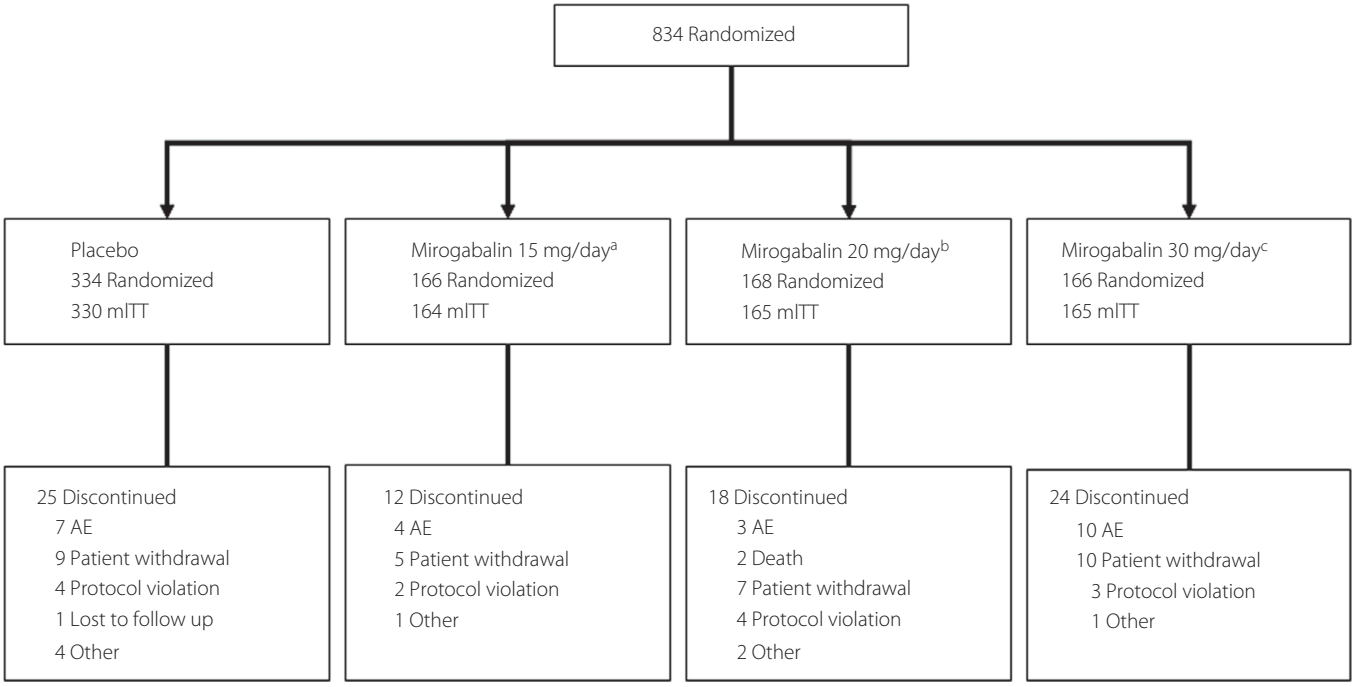

Figure 1 | Patient disposition. [a]15 mg once daily. [b]10 mg twice daily. [c]15 mg twice daily. AE, adverse event; mITT, modified intention-to-treat (patients who were randomized and received 1 dose of study drug).

Table 1 | Demographics and baseline disease characteristics

Parameter	Placebo *n* = 334	Mirogabalin 15 mg/day† *n* = 166	Mirogabalin 20 mg/day‡ *n* = 168	Mirogabalin 30 mg/day§ *n* = 166	Total *n* = 834
Mean age¶ (years)	61.0	61.9	61.2	61.8	61.4
Age¶ (years)					
≥18, <65	198 (59.3)	99 (59.6)	102 (60.7)	98 (59.0)	497 (59.6)
≥65, <75	110 (32.9)	57 (34.3)	51 (30.4)	54 (32.5)	272 (32.6)
≥75	26 (7.8)	10 (6.0)	15 (8.9)	14 (8.4)	65 (7.8)
Sex					
Male	241 (72.2)	113 (68.1)	121 (72.0)	130 (78.3)	605 (72.5)
Female	93 (27.8)	53 (31.9)	47 (28.0)	36 (21.7)	229 (27.5)
Mean weight (kg)	69.38	67.98	67.88	70.78	69.08
Mean CrCl†† (mL/min)	100.9	97.3	100.6	99.3	99.8
Mean ADPS	5.60	5.60	5.57	5.56	5.59
Mean VAS, in SF-MPQ‡‡ (mm)	58.6	58.1	57.4	58.9	58.3
Type of diabetes mellitus					
Type 1	12 (3.6)	6 (3.6)	6 (3.6)	7 (4.2)	31 (3.7)
Type 2	322 (96.4)	160 (96.4)	162 (96.4)	159 (95.8)	803 (96.3)
Median duration of DPN (months)	43.0	36.0	48.0	44.0	43.0
Median duration of painful DPN (months)	36.0	36.0	41.5	36.0	36.0
Mean HbA_{1c} (%)	7.57	7.45	7.51	7.42	7.50
Country					
Japan	242 (72.5)	119 (71.7)	121 (72.0)	121 (72.9)	603 (72.3)
Korea	47 (14.1)	25 (15.1)	29 (17.3)	29 (17.5)	130 (15.6)
Taiwan	36 (10.8)	15 (9.0)	11 (6.5)	11 (6.6)	73 (8.8)
Malaysia	9 (2.7)	7 (4.2)	7 (4.2)	5 (3.0)	28 (3.4)

Values are *n* (%) unless otherwise noted. Results are from the randomized set. †15 mg once daily. ‡10 mg twice daily. §15 mg twice daily. ¶Age at informed consent. ††Calculated using the Cockcroft–Gault equation. ‡‡At randomization. ADPS, average daily pain score; CrCl, creatinine clearance; DPN, diabetic peripheral neuropathy; HbA_{1c}, hemoglobin A1c; SF-MPQ, Short-form McGill Pain Questionnaire; VAS, visual analog scale.

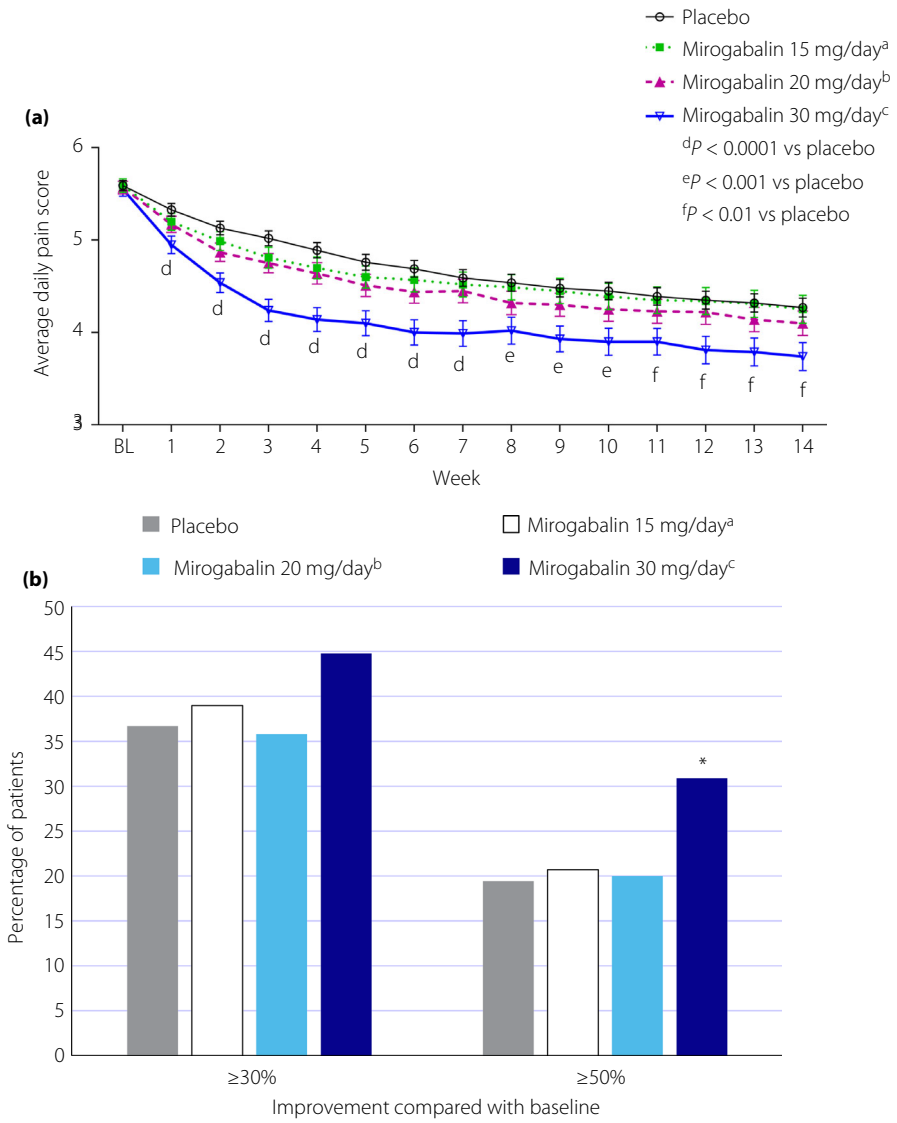

Figure 2 | Average daily pain score shown as (a) the time course of the least squares mean ± standard error and (b) responder rates (≥30% and ≥50% improvement). [a]15 mg once daily. [b]10 mg twice daily. [c]15 mg twice daily. *P = 0.0048 compared with placebo. Data is presented for the modified intention-to-treat analysis set. The multiple imputation method was applied, using a pattern mixture model with different shift parameters depending on reasons for discontinuation (adverse event, lack of efficacy or others). The mixed effects model with repeated measures was carried out for the imputed datasets. This model included treatment, week and treatment-by-week as fixed effects; week as a repeated measure; and baseline ADPS as a covariate. Rubin's rule was used to provide the least squares means and its standard errors for each week of each treatment. ADPS, average daily pain score; BL, baseline.

−0.60 (−0.90, −0.30). Significantly more patients treated with mirogabalin 30 mg/day versus placebo reported a PGIC of "minimally improved or better" (score ≤3, 70.3% vs 58.8%, P = 0.0129) or "much improved or better" (score ≤2, 40.0% vs 26.1%, P = 0.0016; Table S1).

Safety and tolerability

Treatment-emergent adverse events are summarized in Table 2. Most TEAEs were mild or moderate. Two patients (in the mirogabalin 15 mg/day group) reported severe dizziness or edema; both patients recovered without treatment and while on the study drug. One patient (in the mirogabalin 15 mg/day group) experienced a severe TEAE of increased alanine transferase and hepatic enzyme; the patient recovered without treatment or withdrawal of study drug. No severe TEAE was reported by more than one patient. Somnolence, dizziness, peripheral edema and weight increase occurred more frequently in the mirogabalin treatment groups compared with placebo. A total of 40 patients (4.9%) had at least one TEAE leading to treatment discontinuation; 13 (3.9%) in the placebo group, four

Table 2 | Most frequent treatment-emergent adverse events (≥5%) by preferred term

Preferred term	Placebo *n* = 330	Mirogabalin 15 mg/day† *n* = 164	Mirogabalin 20 mg/day‡ *n* = 165	Mirogabalin 30 mg/day§ *n* = 165
Nasopharyngitis	42 (12.7)	22 (13.4)	24 (14.5)	27 (16.4)
Somnolence	13 (3.9)	14 (8.5)	20 (12.1)	24 (14.5)
Dizziness	7 (2.1)	8 (4.9)	14 (8.5)	18 (10.9)
Edema peripheral	4 (1.2)	8 (4.9)	4 (2.4)	14 (8.5)
Weight increased	2 (0.6)	4 (2.4)	5 (3.0)	11 (6.7)
Contusion	6 (1.8)	2 (1.2)	3 (1.8)	9 (5.5)

Data are presented as *n* (%). Results are from the safety analysis set. Coded using the Medical Dictionary for Regulatory Activities version 17.1. †15 mg once daily. ‡10 mg twice daily. §15 mg twice daily.

(2.4%) in the 15 mg/day group, seven (4.2%) in the 20 mg/day group and 16 (9.7%) in the 30 mg/day group. The most common TEAEs leading to treatment discontinuation were dizziness (0.0% in the placebo group, 1 [0.6%] in the 15 mg/day group, 1 [0.6%] in the 20 mg/day group and 4 [2.4%] in the 30 mg/day group) and somnolence (1 [0.3%] in the placebo group, 1 [0.6%] in the 15 mg/day group, 1 [0.6%] in the 20 mg/day group and 2 [1.2%] in the 30 mg/day group). One patient in the placebo group experienced a mild TEAE of suicidal ideation, occurring 9 days after the last dose of the study drug. All TEAEs leading to discontinuation were mild or moderate, and most of them were resolved or resolving without any treatment.

Serious TEAEs were reported by 11 (3.3%) patients in the placebo group, four (2.4%) patients in the 15 mg/day group, eight (4.8%) in the 20 mg/day group and 11 (6.7%) in the 30 mg/day group. No serious TEAE was reported by more than one patient in any treatment group. Five severe serious TEAEs (perinephric abscess, hepatocellular carcinoma, acute myocardial infarction, lung disorder and comminuted fracture) were reported in the placebo group; three (diabetic retinopathy, glaucoma and humerus fracture) were reported in the 15 mg/day group; four (loss of consciousness, pneumothorax, death and drowning) were reported in the 20 mg/day group; and three (acute pyelonephritis, lacunar infarction and atrioventricular block second degree) were reported in the 30 mg/day group. Overall, reported serious TEAEs did not raise any specific concerns. As mentioned above, two patients in the 20 mg/day group died during the present study. One patient died of unknown causes, not considered to be related to the study drug by the investigator; this patient had a significant cardiac history. A second patient died from drowning – this event was also considered by the investigator to be unrelated to the study drug.

The most frequent AEs related to the study drug were somnolence (3.9, 7.9, 9.7 and 14.5%), dizziness (0.9, 4.3, 7.9 and 9.1%), vertigo (0.0, 0.0, 0.0 and 2.4%), peripheral edema (0.6, 1.8, 1.8 and 5.5%) and weight increase (0.0, 1.2, 1.8 and 5.5%) in the placebo, mirogabalin 15, 20 and 30 mg/day groups, respectively. Most were mild and resolved without treatment. Overall, most AEs related to the study drug were mild or moderate.

No notable changes were observed in electrocardiograms, vital signs, neurological examination results, hematology, blood chemistry or urinalysis.

DISCUSSION

In a 5-week, proof-of-concept, double-blind, randomized active comparator- and placebo-controlled phase II study in mainly White patients with DPNP, at week 5 mirogabalin at oral doses of 15, 20 and 30 mg/day provided significant pain relief versus placebo ($P < 0.05$), as measured by change from baseline in ADPS. In addition, mirogabalin 15- and 30-mg/day doses provided significantly greater pain relief than pregabalin 300 mg/day ($P < 0.05$)[15]. Across all mirogabalin doses tested, rates of AEs were low, and common AEs were those associated with the drug class[15].

In the present phase III, randomized, double-blind, placebo-controlled study, mirogabalin 15–30 mg/day was well tolerated by Asian patients with DPNP, and the difference in mean change in ADPS from baseline for mirogabalin versus placebo was greater numerically as the daily dose of mirogabalin increased for up to 14 weeks. The 30-mg/day dose of mirogabalin showed statistically significant pain relief compared with placebo. In the present study, the baseline total ADPS was 5.59, which is lower than previous clinical trials of gabapentinoids[6,21]. We excluded patients who reported extreme pain as a method to improve the assay sensitivity; in particular, patients with a pain scale ≥90 mm on VAS of SF-MPQ at screening and randomization, or a daily pain score ≥9 during the observation period[22]. This exclusion possibly contributed to the lower baseline total ADPS, which in turn might correlate with the lower efficacy of mirogabalin.

Sleep dysfunction is a common comorbidity in DPNP patients, and is associated with worse pain outcomes[4,23]. Mirogabalin 30 mg/day significantly improved sleep interference. In addition, PGIC was improved with mirogabalin 30 mg/day compared with placebo.

The most common AEs were dizziness and somnolence, which were expected based on the mechanism of action of mirogabalin. A similar result was reported in the USA phase II study in which the results showed that mirogabalin had a better balance of efficacy and safety than pregabalin[15]. When indirectly comparing the current phase III TEAEs with the treatment-related AEs reported for pregabalin 300 mg/day by Ogawa *et al.*, in Japanese DPNP patients, there was a lower incidence of somnolence (14.5% vs 20.9%) and dizziness (10.9% vs 19.4%) with mirogabalin 30 mg/day versus pregabalin 300 mg/day[24]. The present result indicates that mirogabalin could be an alternative therapeutic option for DPNP.

The present study had a few limitations. First, all patients enrolled in the study were Asian and most were from Japan. Second, as all patients randomized met the criteria of having creatinine clearance ≥60 mL/min,

efficacy was not assessed in DPNP patients with renal impairment. Future studies are required to confirm these results in DPNP patients with renal impairment and determine appropriate dose adjustments. Finally, although the present study had a longer follow-up period than the phase II mirogabalin trial (14 weeks vs 5 weeks), studies are required to assess whether these safety and efficacy results persist over longer periods.

Mirogabalin showed dose-dependent efficacy results in Asian patients. For the primary endpoint – the change from baseline in ADPS – mirogabalin 30 mg/day results were significantly different than placebo. Mirogabalin was well tolerated up to 30 mg/day. In summary, mirogabalin has a balanced efficacy versus safety profile, and may provide an alternative therapeutic option for the treatment of DPNP.

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DISCLOSURE

Masayuki Baba has received consultancy fees and speaker fees from Daiichi Sankyo Co., Ltd., Norimitsu Matsui, Masanori Kuroha, Yosuke Wasaki and Shoichi Ohwada 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.

Appendix S1 | Acknowledgments.
Table S1 | Average daily pain scores, visual analog pain scores, average daily sleep interference scores, and responder rate at baseline and week 14.
Figure S1 | Study design.
Data S1 | CONSORT 2010 checklist of information to include when reporting a randomized trial*.