Research Paper

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Mirogabalin for the management of postherpetic neuralgia: a randomized, double-blind, placebo-controlled phase 3 study in Asian patients

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Abstract

This study investigated the safety and efficacy of mirogabalin, a novel, potent, selective ligand of the $\alpha_2\delta$ subunit of voltage-dependent Ca^{2+} channels, for the treatment of postherpetic neuralgia (PHN). In this multicenter, double-blind, placebo-controlled phase 3 study, Asian patients ≥20 years with PHN were randomized 2:1:1:1 to placebo or mirogabalin 15, 20, or 30 mg/day for up to 14 weeks (NCT02318719). The primary efficacy endpoint was the change from baseline in average daily pain score at week 14, defined as a weekly average of daily pain (0 = "no pain" to 10 = "worst possible pain," for the last 24 hours). Of 765 patients randomized, 763 received ≥ 1 dose of the study drug and were included in the analysis; 303, 152, 153, and 155 received placebo, mirogabalin 15, 20, or 30 mg/day, respectively. A total of 671 (87.7%) patients completed the study. At week 14, the difference in average daily pain score least squares mean vs placebo was −0.41, −0.47, and −0.77, respectively; all mirogabalin groups showed statistical significance. The most common treatment-emergent adverse events were somnolence, nasopharyngitis, dizziness, weight increase, and edema, and all of them were mild or moderate in severity. Mirogabalin was superior to placebo in all groups for relieving PHN and appeared well tolerated.

Keywords: Pain, Postherpetic neuralgia, Pain medicine, α2δ-ligand

1. Introduction

Neuropathic pain has many causes, including neuropathy due to diabetes mellitus or to herpes zoster and spinal cord injury. Symptoms of postherpetic neuralgia (PHN) include spontaneous pain, hyperalgesia, and allodynia.

Multiple factors play a role in neuropathic pain, including the involvement of voltage-dependent sodium and calcium channels.[11] Animal studies support the role of voltage-dependent Ca^{2+} channels (VDCCs) in neuropathic pain signaling. In animal studies, the $\alpha_2\delta$ subunit of VDCCs enhances the activity of VDCCs by enabling increased trafficking to the membrane, leading to increased peripheral and central neuron excitability that is believed to contribute to neuropathic pain.[2,16,17] Although the mechanism of action is not fully understood, it is believed that $\alpha_2\delta$ ligands alleviate neuropathic pain by reducing the enhanced Ca^{2+} influx and neuronal excitability mediated by the $\alpha_2\delta$ subunit.[2,16,17]

Current options for managing neuropathic pain include anticonvulsants, tricyclic antidepressants, and serotonin/norepinephrine reuptake inhibitors. No single class of medication has shown efficacy for all neuropathic pain patients, and studies estimate the effect size reported in meta-analyses of pharmacotherapy for neuropathic pain may have been overestimated.[12] Many patients take multiple medications for neuropathic pain, which increases the risk of adverse events (AEs).[3] Current guidelines issued by the Japanese Society of Pain Clinicians for the management of neuropathic pain recommend the use of pharmacologic therapies as the best treatment strategy for neuropathic pain that focuses on the improvement of pain and quality of life (QoL).[24] Therefore, there is an unmet medical need for a management option with less AEs and high efficacy.

Mirogabalin monobenzenesulfonate (herein referred to as mirogabalin, Daiichi Sankyo Co, Ltd, Tokyo, Japan) is a novel, selective oral $\alpha_2\delta$ ligand being developed for the treatment of PHN and diabetic peripheral neuropathic pain (DPNP). In contrast to pregabalin, a standard $\alpha_2\delta$ ligand, mirogabalin showed higher binding affinities in human and rat $\alpha_2\delta$ subunits; furthermore, it had a slower dissociation rate for the $\alpha_2\delta$-1 subunit than the $\alpha_2\delta$-2 subunit. When studied in experimental neuropathic pain models, partial sciatic nerve ligation rats, and streptozotocin-induced diabetic rats, mirogabalin showed more potent and longer-lasting analgesic effects.[5] A phase 2 trial of mirogabalin has proven the drug's effectiveness in reducing sleep disturbances and improving pain scores associated with DPNP.[19,25,26]

This phase 3, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of mirogabalin in Asian patients with PHN.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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2. Research design and methods

2.1. Study design

This was a multicenter, double-blind, placebo-controlled, 14-week, parallel group study for the treatment of PHN (NCT02318719) in Asian patients, conducted between January 23, 2015, and January 9, 2017. This study followed the Declaration of Helsinki and the International Council for Harmonisation Consolidated Guideline E6 for Good Clinical Practice. There were approximately 200 study sites in Japan, Korea, Taiwan, Singapore, Malaysia, and Thailand, and the study was approved by the institutional review board, or equivalent, for each site before beginning. Before enrollment, informed consent was obtained from all patients. Safety was periodically monitored by an independent Data Safety Monitoring Board.

To be eligible for the study, patients had to meet all the following criteria: Asian ≥20 years of age with PHN (defined as persistent pain after 3 months from the disappearance of the herpes zoster rash); able to give written informed consent for study participation, understand procedures of this study, and complete patient-reported questionnaires adequately; a pain scale of ≥40 mm on visual analogue scale (VAS) of Short-form McGill Pain Questionnaire (SF-MPQ) at screening and randomization; and an average daily pain score (ADPS) of ≥4 on the 11-point numeric rating scale (NRS) over the past 7 days.

Patients were excluded if they met any of the following criteria: pain scale ≥90 mm on VAS of SF-MPQ at screening and randomization, or their daily pain score was ≥9 during observation period; previous use of a neurolytic block or neurosurgical therapy for current PHN; severe pain or neurologic disorder at screening or randomization not related to PHN; major psychiatric disorder at screening or randomization; use of prohibited concomitant drugs or prohibited concomitant therapies within 7 days or change of restricted concomitant drugs within 14 days before screening; presence of a skin condition that could complicate the assessment of PHN pain; previous use of pregabalin ≥300 mg/day or gabapentin ≥1200 mg/day with lack of effect or known hypersensitivity; creatinine clearance <60 mL/minute using the Cockcroft–Gault equation; malignancy other than basal cell carcinoma within the past 2 years before screening; clinically significant unstable neurologic, ophthalmologic, hepatobiliary, respiratory, or hematologic illness or unstable cardiovascular disease within 12 months before screening; clinically significant electrocardiogram findings at screening; history of pernicious anemia, untreated hypothyroidism, or HIV infection; known immunocompromised status or history of positive hepatitis B antigen or hepatitis C antibody; in women, pregnancy, potential pregnancy, or breastfeeding; or male or female unwilling to take reliable contraceptive measures during and for 4 weeks after the study; participation in another clinical study within 30 days before informed consent, or participation in any clinical study where mirogabalin was received; abuse of illicit drugs or alcohol within 1 year of screening; "yes" response to any question on the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or randomization in relation to events occurring within past year; previous treatment with a drug that could cause irreversible retinal degeneration; clinical laboratory values exceeding specified study limits at screening; or a "yes" response to the suicidality question on the Major Depressive Episode Module or to any question of B1b, B3-B11c, B13, or B14 in the Suicidality Module on the Mini-International Neuropsychiatric Interview at screening.

After informed consent, but before the screening visit, patients who received any of the following prohibited concomitant medications underwent a 7-day washout period: pregabalin; antiepileptics; hypnotics and anxiolytics; opioids; tramadol and any of its combination drugs; Neurotropin; N-methyl-D-aspartate receptor antagonists; muscle relaxants; topical capsaicin, steroids, prostaglandins, or local anesthetics, except as topical products for a nondisease site of PHN; sodium channel blockers; centrally acting sympatholytics; vitamin B1 or B12; α-lipoic acid; evening primrose oil; nefopam; immunosuppressants; drugs that could cause irreversible retinal degeneration; and study drugs in other studies. The patients could not resume these medications during the study. Patients could continue taking antidepressants, ultrashortacting hypnotics, nonsteroidal anti-inflammatory drugs, and Chinese herbal medications during the study provided the dosage had not changed for 14 days before screening, and the dosage was not changed and the drug was not stopped unless safety problems were observed.

After informed consent but before the screening visit, patients who received any of the following prohibited concomitant therapies underwent a 7-day washout period: nerve blocks; iontophoresis; laser therapy; acupuncture; spinal cord stimulation; surgery that could confound PHN assessment; transcutaneous electrical nerve stimulation; and other forms of pain reduction therapy for PHN except psychological, mental, and physical therapy. These therapies could not be resumed during the study. Patients could continue psychological, mental, or physical therapies provided the frequency of therapy had not changed from 14 days before the screening visit, and the therapy was not started after the screening visit.

After a 7-day observation period, patients were randomized 2:1:1:1 to 1 of 4 treatment groups: placebo, or mirogabalin 15 mg once daily, 10 mg twice daily, or 15 mg twice daily in accordance with the randomization schedule securely maintained in Interactive Web Response System (Bell Medical Solutions, Inc, Tokyo, Japan). Randomization was stratified by dichotomized baseline ADPS (<6 vs ≥6). The randomization schedule was generated and securely kept by the independent biostatistician of Bell Medical Solutions, Inc, throughout the study to maintain the blinding.

The study consisted of a 1-week observation period, followed by a 1- to 2-week dose titration period, a 12- to 13-week fixed-dose period, and a 1-week follow-up period, where patients were monitored after treatment (**Fig. 1**). For the mirogabalin 15 mg/day group, 5 mg/day was administered for the first week (once daily at bedtime), followed by 10 mg/day (10 mg once daily) during the second week of the titration period. For the mirogabalin 20- and 30-mg/day groups, 10 mg/day was administered (5 mg twice daily; once in the morning and at bedtime) during the first week of the titration period. On the second week, mirogabalin was administered 20 mg/day (10 mg twice daily; once in the morning and at bedtime) to the 30 mg/day group (15 mg twice daily; once in the morning and once at bedtime). Patients who were randomized to the 15 mg/day group received a matching placebo tablet in the morning. During the study, acetaminophen was permitted as rescue medication, up to the maximum dose in the package insert, as needed; patients were instructed to record in the electronic patient diary the dose of acetaminophen used.

2.2. Efficacy assessments

The primary efficacy endpoint was the change from baseline in ADPS at week 14, a weekly average of daily patient ratings recorded in an electronic diary. The patient was instructed to rate the pain over the past 24 hours on an NRS (0 = "no pain" to 10 = "worst possible pain") every morning upon awakening, before taking the study drug.

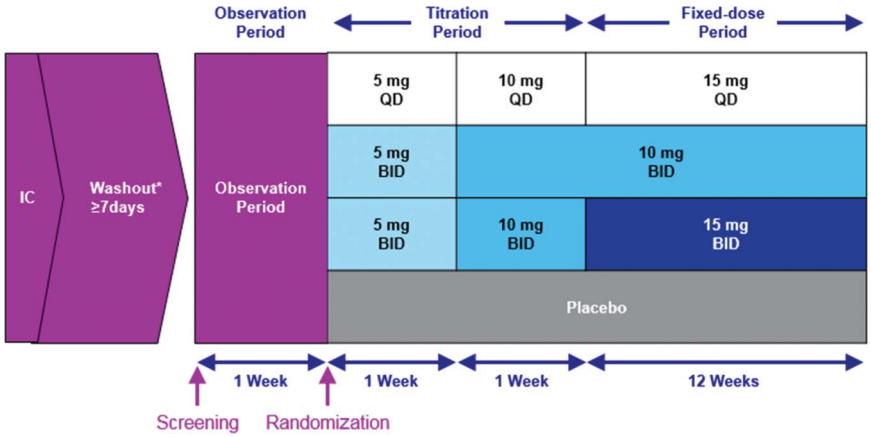

Figure 1. Study design. Mirogabalin treatment arms are shown in color. Randomization was stratified with factors of baseline average daily pain scores (<6.0 vs ≥6.0). *Patients who were under treatment with the prohibited concomitant medications or therapies underwent a washout period of 7 days or more.

Secondary efficacy endpoints included responder rate, defined as the percentage of patients with ≥30% and ≥50% reduction from baseline in ADPS; patient-rated pain on the VAS of SF-MPQ; and average daily sleep interference score (ADSIS). The ADSIS was the weekly average of sleep interference as recorded by patients in electronic diaries rated every morning on an NRS of 0 = "pain did not interfere with sleep" to 10 = "pain completely interfered with sleep" over the last 24 hours. 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.

Other secondary endpoints included SF-MPQ (other than VAS), brief pain inventory-short form, medical outcomes study sleep scale, hospital anxiety and depression scale (HADS), 36-item short form health survey (SF-36), and assessment of allodynia and hyperalgesia by the investigator on a 2-point scale (1 = "present," 2 = "absent"). Allodynia was evaluated by stroking the skin with a brush, and hyperalgesia was evaluated by pressing the skin with a bamboo cooking stick.

2.3. Safety assessments

Adverse events (AEs) were monitored throughout the study and classified according to the Medical Dictionary for Regulatory Activities, version 17.1. Patients had a total of 11 visits over the 14 weeks, including screening and randomization (week 0). At each visit, clinical laboratory evaluations, physical examinations, and vital signs were monitored. Suicidal behavior and ideation were monitored at each visit using the C-SSRS. In addition, a neurological examination and an electrocardiogram were performed at screening and at the end of treatment or at early termination, and included assessment of muscle strength (0–5 rating; ankle dorsiflexion) and gait/station.

2.4. Statistical analysis

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

The modified intent-to-treat analysis set, defined as patients who were randomized and received ≥1 dose of the study drug, was used for efficacy analysis. For the primary endpoint (change from baseline in ADPS at week 14 between each group), 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 covariates was used to produce a monotone missing data pattern first. 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 (AE, lack of efficacy, or other) and was applied to the imputed weekly ADPS data by regression with predictive mean matching to impose penalty on the study discontinuation under a missing not-at-random mechanism.[15] To compare change from baseline in ADPS at week 14 between each group receiving ≥ 1 dose of mirogabalin and the placebo group, a mixed-effect model with repeated measures (MMRM) was used for the imputed data sets.[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 the MMRM analyses were combined using Rubin's rule.[22] The following gatekeeping procedure was prespecified to adjust for multiplicity of comparisons between each of mirogabalin groups and placebo[4]; mirogabalin 20 and 30 mg/day, which have been evaluated and demonstrated efficacy trend in the phase 2 study, were tested against placebo at a significance level of 0.025. If both were statistically significant, 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, responder rates (≥30% and ≥50% improvement in ADPS) for mirogabalin groups were compared with the placebo group using a logistic regression model with the treatment group as a factor and baseline ADPS as a covariate. In the analysis, patients who discontinued the study were considered nonresponders 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. 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. For the other secondary endpoints, analysis of covariance model with the baseline value as a covariate was used for continuous variables, and a logistic

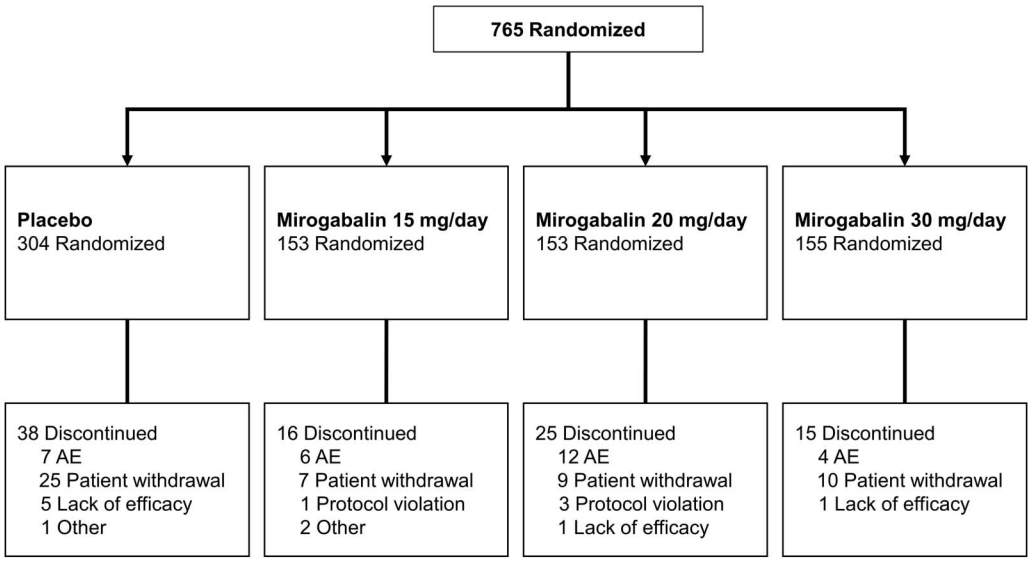

Figure 2. Patient disposition. AE, adverse event.

Table 1

Demographics and baseline disease characteristics.

Parameter	Placebo, N = 304	Mirogabalin, 15 mg/day*, N = 153	Mirogabalin, 20 mg/day†, N = 153	Mirogabalin, 30 mg/day‡, N = 155	Total, N = 765
Mean age§, y	66.2	66.6	68.9	64.5	66.5
Age at informed consent					
≥18–<65 y	102 (33.6)	47 (30.7)	39 (25.5)	64 (41.3)	252 (32.9)
≥65–<75 y	153 (50.3)	82 (53.6)	72 (47.1)	66 (42.6)	373 (48.8)
≥75 y	49 (16.1)	24 (15.7)	42 (27.5)	25 (16.1)	140 (18.3)
Sex					
Male	177 (58.2)	97 (63.4)	91 (59.5)	96 (61.9)	461 (60.3)
Female	127 (41.8)	56 (36.6)	62 (40.5)	59 (38.1)	304 (39.7)
Country					
Japan	245 (80.6)	122 (79.7)	121 (79.1)	124 (80.0)	612 (80.0)
Korea	41 (13.5)	24 (15.7)	22 (14.4)	21 (13.5)	108 (14.1)
Taiwan	11 (3.6)	4 (2.6)	5 (3.3)	5 (3.2)	25 (3.3)
Malaysia	2 (0.7)	1 (0.7)	3 (2.0)	4 (2.6)	10 (1.3)
Thailand	3 (1.0)	2 (1.3)	2 (1.3)	0	7 (0.9)
Singapore	2 (0.7)	0	0	1 (0.6)	3 (0.4)
Weight, kg, mean (SD)	62.1 (10.6)	62.8 (10.5)	62.0 (9.9)	62.2 (10.5)	62.3 (10.4)
CrCl‖, mL/minute, mean (SD)	85.4 (22.3)	83.0 (18.7)	80.3 (18.1)	85.8 (21.0)	84.0 (20.7)
ADPS, mean (SD)	5.75 (1.13)	5.69 (1.04)	5.70 (1.02)	5.65 (1.03)	5.71 (1.07)
VAS of SF-MPQ¶, mean (SD)	59.4 (10.6)	58.4 (10.8)	59.3 (9.8)	59.0 (10.7)	59.1 (10.5)
Duration of PHN, mo, median	15.0	18.0	22.0	21.0	18.0
Site of PHN					
Trigeminal segment area	72 (23.7)	25 (16.3)	46 (30.1)	52 (33.5)	193 (25.2)
Cervical segment area	49 (16.1)	26 (17.0)	16 (10.5)	26 (16.8)	118 (15.4)
Thoracic segment area	141 (46.4)	75 (49.0)	69 (45.1)	66 (42.6)	351 (45.9)
Lumbar segment area	43 (14.1)	22 (14.4)	22 (14.4)	16 (10.3)	103 (13.5)
Sacral segment area	11 (3.6)	9 (5.9)	3 (2.0)	4 (2.6)	28 (3.7)

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; PHN, postherpetic neuralgia; SD, standard deviation; SF-MPQ, short-form McGill Pain Questionnaire; VAS, visual analogue scale.

regression model with treatment group as a covariate was applied for categorical variables. Statistical analysis was performed using Statistical Analysis Software (Version 9.3).

All safety data were summarized on the safety analysis set including patients who received 1 dose of study drug. Treatment-emergent AEs (TEAEs) were summarized as a frequency table.

3. Results

3.1. Patients

A total of 765 patients were randomized to placebo (N = 304) and mirogabalin 15 mg/day (N = 153), 20 mg/day (N = 153), and 30 mg/day (N = 155) (**Fig. 2**). A total of 763 patients were included in the modified intent-to-treat analysis set population, and 671 (87.7%) patients completed the study. A total of 94 patients (12.3%) discontinued the study; 38 (12.5%) in the placebo group, 16 (10.5%) in the 15 mg/day group, 25 (16.3%) in the 20 mg/day group, and 15 (9.7%) in the 30 mg/day group. The most common reasons for discontinuation were patient withdrawal (25 patients in the placebo group, 7 patients in the 15 mg/day group, 9 patients in the 20 mg/day group, and 10 patients in the 30 mg/day group) and AEs (7 patients in the placebo group, 6 patients in the 15 mg/day group, 12 patients in the 20 mg/day group, and 4 patients in the 30 mg/day group). Randomized patients were mostly male (60.3%) and Japanese (80.0%), with a mean age of 66.5 years (**Table 1**). Across all treatment groups, the most common site of PHN (45.9%) was the thoracic segment area. The mean ADPS and VAS of the SF-MPQ at baseline were 5.71 and 59.1, respectively.

3.2. Efficacy

The ADPS gradually decreased through week 14 in all treatment groups, and all mirogabalin groups had a greater and more rapid decrease of ADPS compared with placebo starting at week 1 (**Fig. 3**). As the daily dose of mirogabalin increased, there was a greater decrease in least squares (LS) mean ADPS compared with placebo. At week 14, the LS mean change from baseline in ADPS was −1.20, −1.61, −1.68, and −1.97 for the placebo and mirogabalin 15, 20, and 30 mg/day groups, respectively. A statistically significant difference in mean change in ADPS from baseline for all mirogabalin groups vs placebo occurred at week 14; the LS mean vs placebo was −0.41 (95% confidence interval [CI] −0.74 to −0.07, $P = 0.0170$), −0.47 (95% CI −0.81 to −0.14, $P = 0.0058$), and −0.77 (95% CI −1.10 to −0.44, $P < 0.0001$) for mirogabalin 15, 20, and 30 mg/day groups, respectively.

The proportion of patients with a ≥30% reduction from baseline in ADPS was 35.0%, 45.4%, 45.1%, and 49.7% for the placebo and mirogabalin 15, 20, and 30 mg/day groups, respectively, with all groups being significantly higher than placebo (**Table 2** and **Fig. 4**). The proportion of patients with a ≥50% reduction from baseline in ADPS was 19.8%, 23.0%, 26.8%, and 29.0% for the placebo and mirogabalin 15, 20, and 30 mg/day groups, respectively, with the 30 mg/day group being significantly higher than placebo (odds ratio 1.63 [95% CI 1.04–2.56], $P = 0.0336$). The LS mean change from baseline to week 14 in VAS of the SF-MPQ and the ADSIS was significantly greater in all mirogabalin groups compared with placebo (**Table 2**).

Significantly more patients treated with mirogabalin 15 mg/day vs placebo reported a PGIC of "much improved or better (score ≤2)" at week 14 (36.2% vs 26.4%, $P = 0.0318$), and significantly more patients treated with mirogabalin 20 and 30 mg/day vs placebo reported a PGIC score of "minimally improved or better (score ≤3)" (69.3% and 69.0% vs 54.5%, respectively; $P = 0.0025$ and 0.0028, respectively) (**Fig. 5**).

At week 14, the changes from baseline in the SF-MPQ (excluding VAS) showed greater improvement in all mirogabalin groups vs placebo. For the SF-MPQ subscales (sensory score, affective score, total score, and present pain intensity), the LS mean differences in change from baseline at week 14 were significantly greater in all mirogabalin groups vs placebo.

The changes from baseline in the brief pain inventory-short form subscales at week 14 showed greater improvement in all mirogabalin groups vs placebo. The LS mean differences in change from baseline for worst pain, average pain, and pain right now were statistically significant for all mirogabalin groups vs placebo, with the greatest difference seen in the mirogabalin 30 mg/day group. The LS mean difference in change from baseline for impact on daily function vs placebo was statistically significant in the mirogabalin 20 mg/day and 30 mg/day group vs placebo.

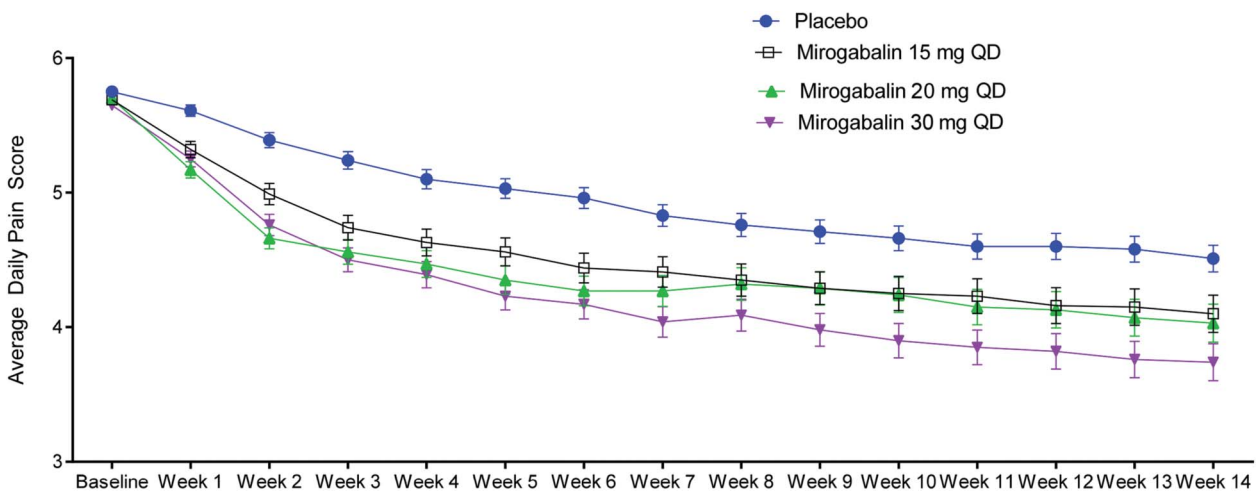

Figure 3. Average daily pain score shown as the time course of the least squares mean with standard error. Data are presented for the modified intent-to-treat analysis set. The multiple imputation method was applied using the pattern mixture model with different shift parameters based on reason for discontinuation. The mixed-effect model with repeated measures was performed for the imputed data sets, including treatment, week, and treatment-by-week as fixed effects; week as a repeated measure; and baseline ADPS as a covariate. ADPS, average daily pain score; QD, once daily.

Table 2

Averaged daily pain score, visual analog pain scores, averaged daily sleep interference scores, and responder rate.

	Baseline	LS mean change from baseline	Difference vs placebo (95% CI)	*P*
ADPS				
Placebo*	5.75	−1.20	—	—
Mirogabalin 15 mg/day†	5.69	−1.61	−0.41 (−0.74, −0.07)	0.0170
Mirogabalin 20 mg/day‡	5.70	−1.68	−0.47 (−0.81, −0.14)	0.0058
Mirogabalin 30 mg/day§	5.65	−1.97	−0.77 (−1.10, −0.44)	<0.0001
	Baseline	**Mean change from baseline ± SD**	**Difference vs placebo (95% CI)**	***P***
VAS of SF-MPQ, mm				
Placebo*	59.4	−13.6 ± 20.13	—	—
Mirogabalin 15 mg/day†	58.5	−18.7 ± 18.37	−5.1 (−8.8 to −1.4)	0.0076
Mirogabalin 20 mg/day‡	59.3	−19.3 ± 18.37	−5.7 (−9.4 to −1.9)	0.0030
Mirogabalin 30 mg/day§	59.0	−21.4 ± 18.50	−7.8 (−11.5 to −4.1)	<0.0001
ADSIS				
Placebo*	3.41	−0.95 ± 1.54	—	—
Mirogabalin 15 mg/day†	3.70	−1.45 ± 1.64	−0.50 (−0.81 to −0.19)	0.0014
Mirogabalin 20 mg/day‡	3.60	−1.38 ± 1.65	−0.48 (−0.79 to −0.17)	0.0027
Mirogabalin 30 mg/day§	3.65	−1.69 ± 1.62	−0.76 (−1.07 to −0.45)	<0.0001
		n (%)	**Odds ratio (95% CI)**	***P***
ADPS responder rate (≥30%)				
Placebo*	—	106 (35.0)	—	—
Mirogabalin 15 mg/day†	—	69 (45.4)	1.54 (1.03−2.29)	0.0363
Mirogabalin 20 mg/day‡	—	69 (45.1)	1.52 (1.02−2.27)	0.0405
Mirogabalin 30 mg/day§	—	77 (49.7)	1.81 (1.21−2.69)	0.0035
ADPS responder rate (≥50%)				
Placebo*	—	60 (19.8)	—	—
Mirogabalin 15 mg/day†	—	35 (23.0)	1.20 (0.75−1.93)	0.4526
Mirogabalin 20 mg/day‡	—	41 (26.8)	1.48 (0.93−2.34)	0.0964
Mirogabalin 30 mg/day§	—	45 (29.0)	1.63 (1.04−2.56)	0.0336
PGIC (score ≤2)				
Placebo*	—	80 (26.4)	—	—
Mirogabalin 15 mg/day†	—	55 (36.2)	1.58 (1.04−2.40)	0.0318
Mirogabalin 20 mg/day‡	—	51 (33.3)	1.39 (0.91−2.13)	0.1233
Mirogabalin 30 mg/day§	—	53 (34.2)	1.45 (0.95−2.20)	0.0830
PGIC (score ≤3)				
Placebo*	—	165 (54.5)	—	—
Mirogabalin 15 mg/day†	—	95 (62.5)	1.39 (0.94−2.08)	0.1025
Mirogabalin 20 mg/day‡	—	106 (69.3)	1.89 (1.25−2.85)	0.0025
Mirogabalin 30 mg/day§	—	107 (69.0)	1.86 (1.24−2.81)	0.0028

* n = 303.
† 15 mg once daily (n = 152).
‡ 10 mg twice daily (n = 153).
§ 15 mg twice daily (n = 155).
ADPS, average daily pain score; ADSIS, average daily sleep interference score; CI, confidence interval; LS, least squares; PGIC, patient global impression of change; SD, standard deviation; SF-MPQ, Short-form McGill Pain Questionnaire; VAS, visual analogue scale.

At week 14, the LS mean differences in change from baseline vs placebo for the medical outcomes study subscales of sleep disturbance and sleep somnolence increased improvement as the daily dose of mirogabalin increased.

The changes from baseline for the HADS subscales of depression and anxiety at week 14 were greater in all mirogabalin groups vs placebo. The LS mean differences in change from baseline were statistically significant vs placebo in all mirogabalin groups for the anxiety subscale and in the 15 mg/day group for the depression subscale.

The LS mean changes from baseline at week 14 for the SF-36 subscales of physical functioning, role-physical, bodily pain, general perception of health, vitality, social functioning, role-emotional, and mental health were greater in all mirogabalin groups vs placebo.

No notable differences were found in the percentage of patients with allodynia and those with hyperalgesia at week 14 between the treatment groups.

3.3. Safety and tolerability

The most common TEAEs (≥5%) are summarized in **Table 3**. The most common TEAEs were somnolence, dizziness, weight increase, and edema; all occurred more frequently in all mirogabalin groups than in the placebo group. The incidence of somnolence, dizziness, and edema increased as the daily dose of mirogabalin increased. Overall, the majority of the most common TEAEs were mild or moderate, and all resolved without treatment. Forty-eight patients (6.3%) had ≥ 1 TEAE leading to treatment discontinuation; 12 (4.0%) in the placebo group, 8 (5.3%) in the 15 mg/day group, 16 (10.5%) in the 20 mg/day group, and 12 (7.7%) in the 30 mg/day group. Fifteen patients, 5 in the 15 mg/day group, 2 in the 20 mg/day group, 3 in the 30 mg/day group, and 5 in the placebo group, had a serious TEAE. No specific serious TEAEs were reported more frequently in any treatment group, and overall, the incidence of serious TEAEs was low. Three

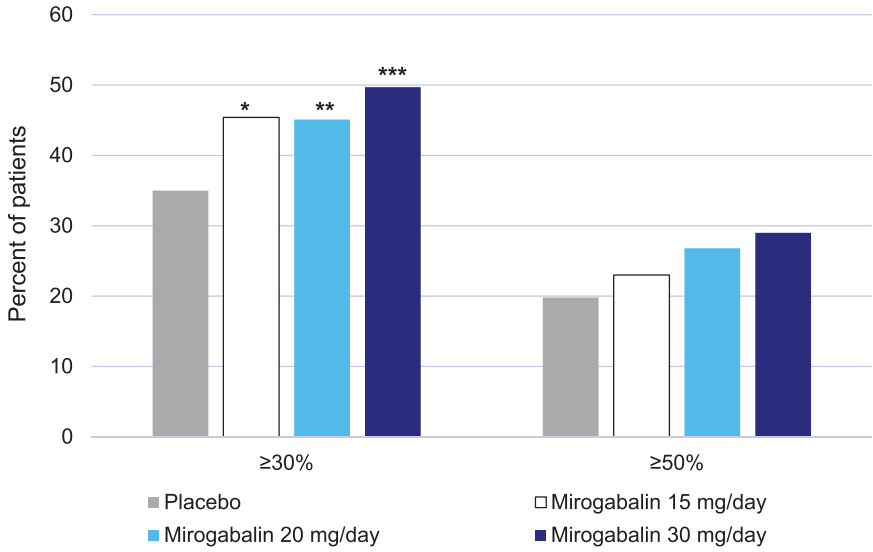

Figure 4. Responder rates for ≥30% and ≥50% reduction in baseline ADPS. *P = 0.0363; **P = 0.0405; ***P = 0.0035 ADPS, average daily pain score.

patients, 2 in the mirogabalin 30 mg/day group and 1 in the placebo group, had a severe TEAE of increased blood creatine phosphokinase; all resolved without treatment. Other severe TEAEs included Meniere disease, acute myocardial infarction, and radius fracture in the placebo group; pneumonia, rib fracture, and femur fracture in the 15 mg/day group; erectile dysfunction, fracture, and upper-limb fracture in the 20 mg/day group; and memory impairment, altered state of consciousness, cerumen impaction, and electrocardiogram change in the 30 mg/day group.

No notable changes were observed in electrocardiograms, vital signs, neurological examination, hematology, blood chemistry, or urinalysis. No patients answered "yes" to any question in C-SSRS regarding suicidal behavior and ideation.

4. Discussion

The findings reported here demonstrate that mirogabalin is effective and well tolerated for the management of PHN in Asian patients. In a large UK database of primary care records, approximately 5.8% of patients with herpes zoster developed PHN; of Japanese adults aged 50 years and older with herpes zoster, approximately 20% developed PHN.[13,23] There are 2 possible reasons for this difference. The first reason is the difference in the age of study patients. The data from the study in Japan include patients older than 50 years, whereas the data from the UK study include patients younger than 50 years. The other possible reason for the epidemiologic difference is the late implementation of the herpes zoster vaccine in Japan. The

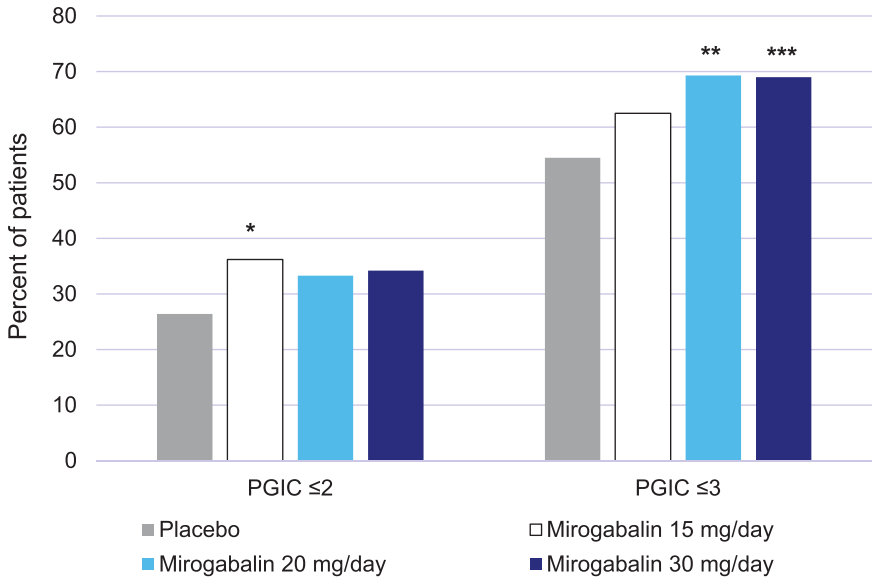

Figure 5. Changes in PGIC at week 14. Significantly more patients treated with mirogabalin 15 mg/day vs placebo reported a PGIC of "much improved or better (score ≤2)," 36.2% vs 26.4%, P = 0.0318. Significantly more patients treated with mirogabalin 20 and 30 mg/day vs placebo reported a PGIC of "minimally improved or better (score ≤3)," 69.3% and 69.0% vs 54.5%, respectively; P = 0.0025 and 0.0028, respectively. *P = 0.0318; **P = 0.0025; ***P = 0.0028. PGIC score ≤2 "much improved or better;" PGIC ≤3 "minimally improved or better." PGIC, patient global impression of change.

Table 3

Most frequent treatment-emergent adverse events (≥5%).

	Placebo, N = 303	Mirogabalin, 15 mg/day*, N = 152	Mirogabalin, 20 mg/day†, N = 153	Mirogabalin, 30 mg/day‡, N = 155
Nasopharyngitis	26 (8.6)	13 (8.6)	16 (10.5)	20 (12.9)
Somnolence	11 (3.6)	20 (13.2)	26 (17.0)	37 (23.9)
Dizziness	10 (3.3)	10 (6.6)	15 (9.8)	24 (15.5)
Edema	2 (0.7)	2 (1.3)	6 (3.9)	11 (7.1)
Weight increase	1 (0.3)	7 (4.6)	8 (5.2)	8 (5.2)

Data are presented as n (%). Results are from the safety analysis set.

* 15 mg once daily.

† 10 mg twice daily.

‡ 15 mg twice daily.

herpes zoster vaccine for persons older than 50 years became available in Japan in 2016, compared with 2013 in the United Kingdom.

Mirogabalin doses of 15 to 30 mg/day were well tolerated. All mirogabalin groups demonstrated a statistically significant improvement in ADPS vs placebo, and the improvements were greater as the daily dose of mirogabalin was increased, but the difference between the daily doses were not statistically significant. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials II and IV consensus recommends that ≥30% reduction in pain intensity from baseline can be considered a clinically important difference when measured on an NRS in a chronic pain clinical trial.[8,10] In this study, the NRS reduction rate from baseline of placebo was approximately 20%; mirogabalin 15 and 20 mg/day had a reduction rate from baseline of approximately 30%; and mirogabalin 30 mg/day had a reduction rate of approximately 35% in this study. A total of 45% to 50% of patients achieved a ≥30% reduction in ADPS across all mirogabalin treatment groups. Sleep dysfunction is a common comorbidity in patients with PHN[6] and is associated with worse pain outcomes. All doses of mirogabalin significantly improved the ADSIS.

In this study, the baseline total ADPS was 5.71, which is lower than previous clinical trials of gabapentinoids.[7,21] We excluded patients who reported extreme pain as a method to improve the assay sensitivity,[9] particularly, 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. This exclusion possibly contributed to the lower baseline total ADPS, which in turn may correlate with the lower efficacy of mirogabalin.

Patients with PHN also often have difficulty with activities of daily living and a decreased QoL.[6,14] Mirogabalin demonstrated statistically significant improvements in the ADPS, ADSIS, and PGIC scores vs placebo, indicating a possible improvement in activities of daily living and QoL. The mean ADPS for mirogabalin at week 14 decreased compared with baseline in all treatment groups vs placebo, and the results of the secondary analyses were consistent with the efficacy seen in the primary analyses.

For the handling of missing data for some of the secondary endpoints, the LOCF approach, which is no longer generally appropriate for clinical trials of chronic pain disease, was applied. We agree that a more appropriate approach should have been applied; however, if a more appropriate approach had been applied, we believe that the impact on the results would be limited because of the small number of discontinued subjects for each treatment group and small number of differences in discontinued subjects between treatment groups in our study.

The most common AEs were somnolence, dizziness, and weight increase, which were expected based on the mechanism of action of mirogabalin, and a similar result was reported in the phase 2 DPNP study of 5 weeks in the United States.[26] In the phase 2 study by Vinik et al.,[26] mirogabalin 30 mg/day had a higher incidence of somnolence (12.3% vs 8.0%) and dizziness (15.8% vs 6.0%) vs pregabalin 300 mg/day. To reduce AEs, this study adopted more gradual titration of mirogabalin compared with the US phase 2 study. When indirectly comparing the current phase 3 TEAEs with the treatment-related AEs reported for pregabalin 300 mg/day in the phase 3 study of Japanese patients with PHN, the incidence of somnolence was similar with mirogabalin 30 mg/day vs pregabalin 300 mg/day (23.9% vs 24.7%), but the incidence of dizziness and weight increase were lower (15.5% vs 30.3%, 5.2% vs 16.9%, respectively).[20] Peripheral edema, a common AE in the pivotal studies of pregabalin for DPNP and PHN, also occurred at lower incidence in mirogabalin 30 mg/day group compared with pregabalin 300 mg/day (2.6% vs 12.4%). This result supports the use of mirogabalin as an alternative therapeutic option for PHN.

Mirogabalin can be flexibly selected depending on individual patient response and tolerability in a dose range from 15 to 30 mg/day. In this study, there was a titration period for each mirogabalin group; mirogabalin 5 or 10 mg/day was administered for the first week, then increased in a step-wise manner. The step-wise increase in dosing for $\alpha_2\delta$ ligands helps increase patient tolerance and decrease AEs; the Japanese Society of Pain Clinicians recommend starting pregabalin at initial doses of 25 to 150 mg/day and increasing by 25 to 150 mg/day every 3 to 7 days.[24]

For the ideal dosing frequency, because elimination half-life of mirogabalin is estimated to be about 3 hours, plasma concentration of mirogabalin reaches baseline approximately 12 hours after administration. Thus, twice-daily dosing is the reasonable dosing frequency.

In addition, the incidence of somnolence and dizziness (common AEs of gabapentinoids) are correlated with the maximum plasma concentration (C_{max}) with internal assessment; this leads us to believe that the incidence of somnolence and dizziness will be lower when administered twice daily vs once daily (data will be published later). Regarding more frequent doses, such as 3 times daily, we did not try this regimen from the viewpoint of drug compliance and patient convenience.

This study has a few limitations. First, only Asian patients were enrolled in the study; studies have shown there may be difference in pain intensity between ethnic groups.[1] However, the phase 2 DPNP study was conducted in the United States, with 72.3% of patients being white and 24.1% of patients being black, and had favorable results for mirogabalin, which suggest mirogabalin might be efficacious in patients of different ethnicities.[26] Second, all patients met the inclusion criteria of creatine clearance of ≥60 mL/minute as determined by the Cockcroft–Gault equation, so efficacy in patients with PHN and renal impairment cannot be

determined from this analysis. Further studies are needed to determine the appropriate doses for these patients.

An additional limitation of this study is that the patients who received the 15-mg/day dose only received the medication at night. This could lead to decreased AEs during the day, including decreased daytime somnolence. The decrease in daytime AEs for the 15 mg/day group and also for the group that received placebo could result in potential unintended unblinding for the investigators.

The abuse liability of mirogabalin was not evaluated in this study; 2 randomized, double-blind, placebo-controlled studies using either pregabalin or diazepam as positive controls were undertaken; and the results will be reported in a separate publication.

In summary, mirogabalin has demonstrated a well-balanced profile of efficacy and safety and may provide an alternative therapeutic option for the treatment of PHN.

Conflict of interest statement

E. Murayama, M. Sugihara, N. Matsui, S. Ohwada, and Y. Kakehi are employees of Daiichi Sankyo Co, Ltd. J. Kato reports personal fees from Daiichi Sankyo Co, Ltd, during the conduct of the study; and personal fees from Pfizer Japan Inc; Eisai Co, Ltd; and Mochida Pharmaceutical Co, Ltd.

Parts of these study results were presented at the 52nd Annual Meeting of the Japan Society of Pain Clinicians, July 19–21, 2018, Tokyo, Japan.

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