

Mirogabalin in Japanese Patients with Renal Impairment and Pain Associated with Diabetic Peripheral Neuropathy or Post-Herpetic Neuralgia: A Phase III, Open-Label, 14-Week Study

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Purpose: Mirogabalin was recently approved in Japan for the treatment of peripheral neuropathic pain, based on data from clinical trials in diabetic peripheral neuropathic pain (DPNP) and post-herpetic neuralgia (PHN), common clinical conditions which cause intense distress for patients. We characterized the safety and tolerability of mirogabalin in Japanese patients with renal impairment.

Patients and Methods: This multicenter, open-label study (ClinicalTrials.gov identifier NCT02607280) enrolled renally impaired individuals aged ≥ 20 years diagnosed with DPNP or PHN, and with an average daily pain score (ADPS) of ≥ 4 over the 7 days prior to treatment initiation. Mirogabalin dosage was titrated for 2 weeks, followed by a fixed dose for 12 weeks according to degree of renal impairment: 7.5 mg twice daily for moderate impairment and 7.5 mg once daily for severe impairment. The primary endpoint was safety and tolerability of mirogabalin, evaluated via treatment-emergent adverse events (TEAEs). Secondary efficacy endpoints included change in ADPS from baseline to Week 14.

Results: Overall, 35 patients were enrolled (30 with moderate and 5 with severe renal impairment). Most TEAEs were mild or moderate in severity; the most commonly reported were nasopharyngitis (22.9%) and somnolence (11.4%). Only 4 patients (11.4%) discontinued treatment due to TEAEs. Mirogabalin significantly decreased ADPS from baseline in patients with renal impairment; least squares mean change from baseline at Week 14 was -1.9 (95% confidence interval: $-2.8, -1.0$).

Conclusion: Mirogabalin was well tolerated and significantly reduced pain levels when used to treat DPNP/PHN at a fixed dose of 7.5 mg once or twice daily in patients with renal impairment.

Keywords: peripheral neuropathic pain, mirogabalin, creatinine clearance, dose adjustment, safety, tolerability

Introduction

Neuropathic pain is a common clinical problem, affecting approximately 1 in 10 of the general population, and is associated with a number of underlying conditions, including diabetes mellitus, infection, surgery, and cancer.^{1,2} The symptoms may include burning pain, sensations of pressure, electric shock, or stabbing pain, and mechanical allodynia.³ Neuropathic pain causes intense distress for patients, and is commonly associated with depression, anxiety, and sleep disturbances.^{4,5}

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Despite the high prevalence of conditions such as diabetic peripheral neuropathic pain (DPNP) and post-herpetic neuralgia (PHN), treatment remains challenging and patient dissatisfaction is high.^{6,7} Current therapeutic recommendations include antidepressants (duloxetine), anticonvulsants (pregabalin, gabapentin), topical analgesics (lidocaine, capsaicin), and even opioids (tapentadol).^{2,8,9} However, not all of these agents are approved for treatment by regulatory authorities; of those that are approved, optimal administration may be compromised by the occurrence of adverse events (AEs), and efficacy is limited.^{10,11} Polypharmacy and off-label treatment is common,¹² but can be risky for patients, especially for the elderly, who may have additional comorbidities.¹³

Mirogabalin besylate (herein referred to as mirogabalin; Daiichi Sankyo Co., Ltd., Tokyo, Japan) was developed for the treatment of peripheral neuropathic pain (PNP), which includes DPNP and PHN, and was recently approved in Japan as monotherapy for adults with PNP.¹⁴ It is an orally administered gabapentinoid which acts via $\alpha_2\delta$ calcium channel subunits to modulate pain transmission and processing.¹⁵ In a Phase II study in patients with DPNP in the United States, mirogabalin provided statistically significant reductions in average daily pain score (ADPS) and a clinically meaningful effect, compared with placebo.¹⁶ In a recently published Phase III, randomized, controlled trial (RCT) in Asian patients with DPNP, mirogabalin (30 mg/day) provided significant pain relief vs placebo and was well tolerated.¹⁷ In a second Phase III RCT, in Asian patients with PHN, mirogabalin efficacy was superior to placebo at all doses tested (15, 20, or 30 mg/day), with no new safety signals.¹⁸

PNP is common in the elderly, with an increased prevalence of both DPNP and PHN associated with increasing age.^{19,20} Since renal function is also often impaired in elderly patients,^{21,22} mirogabalin could, potentially, be widely used by PNP patients with renal impairment. Findings from a single-dose clinical pharmacology study in healthy individuals with varying degrees of renal function indicated that mirogabalin was excreted primarily in the urine, and that the pharmacokinetic parameters were affected by renal function. The area under the plasma concentration–time curve up to the last quantifiable time (AUC_{last}) increased with the severity of renal impairment; compared with individuals with normal renal function, the geometric least squares mean was 1.9 and 3.6 for subjects with moderate and severe renal impairment, respectively.²³ Based on these data, a dose reduction of 50% to 75% was

deemed necessary in individuals with moderate or severe renal impairment. Thus, the objective of this study was to characterize the safety and tolerability of an adjusted dose of mirogabalin in patients with moderate or severe renal impairment.

Patients and Methods

Study Design

This was a multicenter, open-label study (ClinicalTrials.gov identifier NCT02607280) conducted at 35 centers in Japan between January 21, 2016, and March 1, 2017 (Figure 1). A full list of study investigators and institutions is provided as [Appendix 1](#). No randomization was performed, but patients were enrolled in this study using an interactive web response system according to degree of renal impairment. All study medication was supplied to patients by the investigator at each study site.

The study duration per patient was approximately 16 weeks (comprising a 1-week observation period, a 2-week titration period, a 12-week fixed-dose period, and a 1-week follow-up period) (Figure 2). Patients using prohibited concomitant medications or prohibited concomitant therapies were required to undergo a ≥ 7 -day washout period prior to screening.

Patients

Eligible patients were aged ≥ 20 years, with DPNP (defined as type 1 or type 2 diabetes mellitus at screening and painful distal symmetric polyneuropathy, diagnosed at least 6 months prior to screening) or PHN (defined as pain present for 3 months or more after herpes zoster skin rash at screening). The DPNP assessment was conducted in accordance with the simplified diagnostic criteria for diabetic neuropathy established in Japan, and the diagnosis was made by a trained physician. At screening, patients were required to have creatinine clearance (CL_{CR} ; Cockcroft-Gault equation²⁴) 15–59 mL/min, and a pain score of ≥ 40 mm but < 90 mm on the visual analog scale (VAS) of the short-form McGill Pain Questionnaire (SF-MPQ).²⁵ At initiation of study treatment, patients were required to have an SF-MPQ VAS score of ≥ 40 mm and < 90 mm, plus completion of at least 4 days of daily electronic patient diaries (for pain) and ADPS of ≥ 4 (on an 11-point numerical rating scale) over the prior 7 days.

Key exclusion criteria for patients with DPNP were glycosylated hemoglobin (HbA1c) $> 10.0\%$ at screening (in accordance with the National Glycohemoglobin Standardization Program); uncontrolled blood glucose that could necessitate

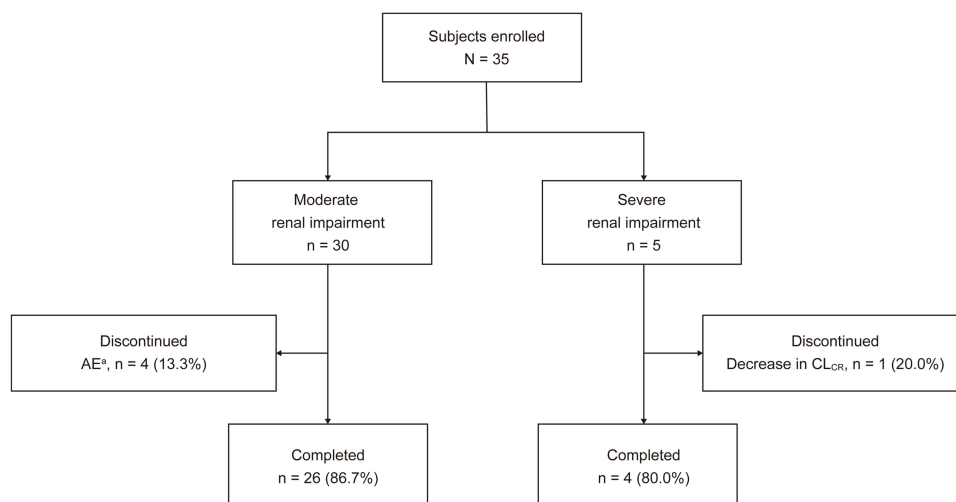


Figure 1 Patient disposition.

Note: ^aOne event each of angina pectoris, hepatitis E, myelitis, and somnolence.

Abbreviations: AE, adverse event; CL_{CR}, creatinine clearance.

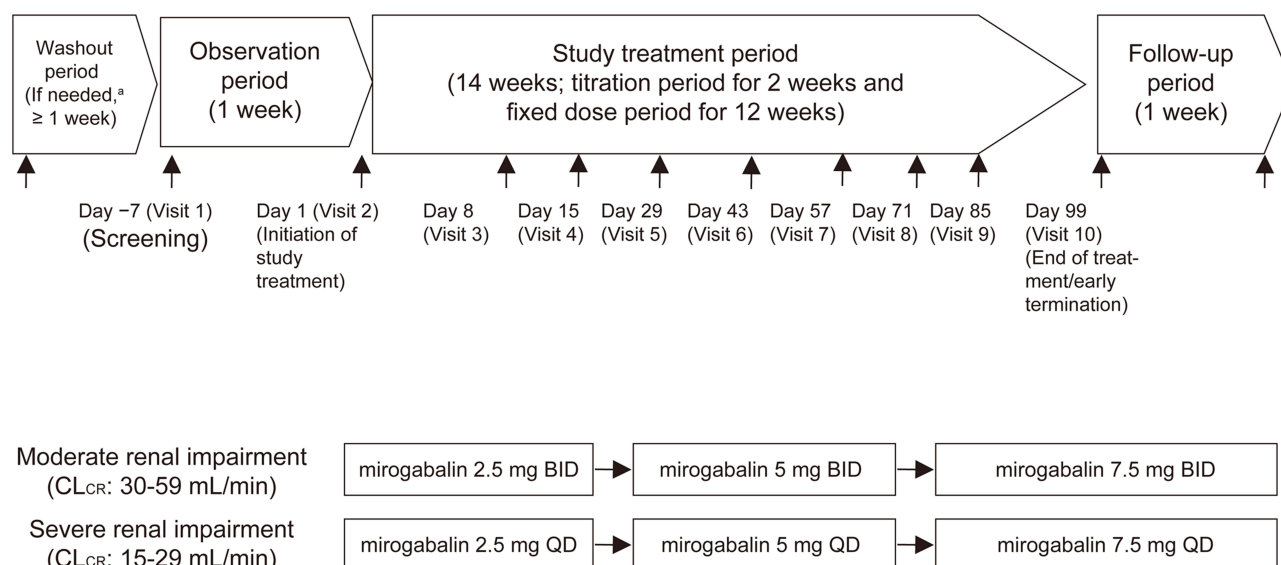


Figure 2 Study design.

Notes: ^aAfter obtaining informed consent, patients who were treated with prohibited concomitant medications (DPNP and PHN) or prohibited concomitant therapies (PHN) underwent a washout period of ≥7 days.

Abbreviations: BID, twice daily; CL_{CR}, creatinine clearance; DPNP, diabetic peripheral neuropathic pain; PHN, post-herpetic neuralgia; QD, once daily.

changes in diabetes treatment during the study; any lower limb amputation (with the exception of toes); and a change in restricted concomitant medications ([Appendix 2](#)) within 30 days prior to screening. Key exclusion criteria for patients with PHN were prior neurolytic block or neurosurgery for PHN; a change in restricted concomitant medications ([Appendix 2](#)) within 14 days prior to screening; and known immunocompromised status.

Additional exclusion criteria which applied to all patients were ADPS ≥9 during the observation period;

any non-DPNP/PHN-related severe pain or neurologic disorder, or skin conditions, that could confound the assessment of DPNP or PHN; hemodialysis, acute renal failure or a history of kidney transplant; suicidality (assessed using the Mini-international Neuropsychiatric Interview [MINI; version 6.0]²⁶ and the Columbia-Suicide Severity Rating Scale [C-SSRS]²⁷) at screening; current or previous history of major psychiatric disorder, malignancy (except for basal cell carcinoma), pernicious anemia, untreated hypothyroidism, or any other clinically significant illness;

hepatitis B or C or human immunodeficiency virus positive; prior treatment with drugs that could cause irreversible retinal degeneration; use of prohibited concomitant therapies ([Appendix 2](#)) within 7 days prior to screening; drug or alcohol abuse within 12 months prior to screening; participation in another clinical study within 30 days of screening or in any previous mirogabalin clinical study; hypersensitivity to, or previous lack of efficacy with, pregabalin or gabapentin; pregnancy, lactation, or unwillingness to use contraception; any other clinical or laboratory finding that rendered the subject ineligible at the discretion of the investigator.

Treatment

Mirogabalin dose levels are expressed as the free form. Patients with moderate renal impairment (CL_{CR} 30–59 mL/min) received mirogabalin 2.5 mg twice daily (BID) for the first week of the titration period and 5 mg BID for the second week, followed by a fixed dose of 7.5 mg BID for 12 weeks. Patients with severe renal impairment (CL_{CR} 15–29 mL/min) received mirogabalin 2.5 mg once daily (QD) for the first week of the titration period and 5 mg QD for the second week, followed by a fixed dose of 7.5 mg QD for 12 weeks. Based on the results of a prior study in healthy Japanese subjects individuals with varying degrees of renal function,²³ Phase III studies in Asian patients,^{17,18} plus modeling and simulation analyses,²⁸ the dosages of 7.5 mg BID in patients with moderate renal impairment and 7.5 mg QD in patients with severe impairment administered in this study were expected to produce exposures equivalent to 15 mg BID in patients with normal renal function.

Study Endpoints and Measurements

The primary endpoint was safety and tolerability of mirogabalin in patients with renal impairment. Evaluations included AEs; laboratory assessments, vital signs, and electrocardiogram; body weight; Hospital Anxiety and Depression Scale (HADS)²⁹ and C-SSRS;²⁷ and neurologic examination (gait/station and muscle strength).

Secondary study endpoints included the effect of mirogabalin on ADPS; ADPS responder rate (defined as the percentage of patients with $\geq 30\%$ and $\geq 50\%$ reduction from baseline to Week 14); results of pain questionnaires (SF-MPQ:²⁵ sensory, affective, and total subscales, VAS, present pain intensity); impact on sleep interference (based on the average daily sleep interference score [ADSIS]); and patient global impression of change (PGIC) in pain.³⁰

AEs were recorded throughout the duration of the study and follow-up period, regardless of perceived relationship to the study drug. AEs were coded using the Medical Dictionary for Regulatory Activities Version 17.1. Treatment-emergent AEs (TEAEs) were defined as any AE that emerged during study treatment (having been absent prior to treatment) or worsened relative to the pre-treatment state. Adverse drug reactions (ADRs; defined as TEAEs considered to be related to the study drug) were evaluated as any AE for which a causal relationship to the study drug could not be ruled out, according to the International Conference on Harmonisation Tripartite Guideline E2A. Pain and sleep interference were recorded in the electronic patient diary once daily (upon awakening, prior to receiving study drug) from the day after the screening visit to the end of treatment/early termination visit. The subject selected the number describing their pain over the past 24 hours on a scale of 0 (no pain) to 10 (worst possible pain); weekly mean ADPS was calculated using these scores. The subject selected the number describing how their pain had interfered with sleep over the past 24 hours on a scale of 0 (no interference) to 10 (complete interference); weekly mean ADSIS was calculated using these scores. Most other efficacy parameters were measured weekly.

Statistical Analysis

The sample size of 35 patients was determined to provide $>95\%$ probability that at least one AE of moderate/severe dizziness and somnolence was observed, assuming the true AE rate was 10%. Both the safety and efficacy analysis sets included all enrolled patients who received at least one dose of study drug.

TEAEs and ADRs were summarized as a frequency table. Missing weekly ADPS data were handled using the multiple imputation (MI) method. In the MI data generation, the Markov Chain Monte Carlo method with age, sex, and CL_{CR} group as covariates, was used to produce a monotone missing data pattern, followed by regression with predictive mean matching (REGPMM) with the same set of covariates applied to the monotone missing data. A pattern mixture model with different shift parameters according to reasons for study discontinuation (AE, lack of efficacy or other reason) was applied to the imputed weekly ADPS data by REGPMM to impose a penalty on the study discontinuation under a missing, not at random, mechanism.³¹ To estimate the change from baseline in ADPS at Week 14 for each CL_{CR} group, a mixed-effects

model with repeated measures (MMRM), which included CL_{CR} group, week and CL_{CR} group-by-week as fixed effects and baseline ADPS as a covariate, was used for the imputed datasets.³² The results of MMRM analysis from each imputed dataset were combined using Rubin's rule.³³ ADPS responder rates ($\geq 30\%$ and $\geq 50\%$ improvement in ADPS) at Week 14 were calculated. Those 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. Continuous responder analysis,³⁴ representing cumulative distribution of the percent reduction from baseline in ADPS, was provided. For SF-MPQ and ADSIS, the changes from baseline at Week 14 were summarized using the LOCF approach. PGIC was also tabulated.

All statistical analyses were performed using Statistical Analysis Software®, Version 9.3 (SAS Institute, Cary, NC, USA).

Results

Patients

Overall, 35 patients were enrolled (30 with moderate renal impairment and 5 with severe renal impairment), received at least one dose of study drug, and were included in the safety and efficacy analysis sets.

Subject disposition is shown in Figure 1. Four patients with moderate renal impairment discontinued treatment due to AEs: one event each of angina pectoris (severe, not deemed by the investigator to be related to the study drug), hepatitis E (mild, not related to the study drug), myelitis (mild, not related to the study drug), and somnolence (moderate, related to the study drug). All four AEs were reported as resolved/resolving subsequent to treatment cessation. One subject with severe renal impairment discontinued due to a decrease in CL_{CR} <15 mL/min (a prespecified discontinuation criterion); no patients in this group discontinued due to AEs.

Baseline demographic and clinical characteristics are shown in Table 1. Six patients (17.1%) had PHN, and 29 (82.9%) had DPNP. All patients with DPNP had type 2 diabetes, no patients with type 1 diabetes were enrolled. All patients with severe renal impairment had DPNP. Overall, the mean (standard deviation [SD]) age was 73.4 (7.3) years, and the majority (80.0%) of patients were male. Mean baseline ADPS was 5.7 (1.1) and mean SF-MPQ VAS scores at screening and at initiation of

treatment were 58.2 (9.4) and 59.6 (9.6), respectively. Characteristics were similar between the two renal impairment groups, with the exception of baseline CL_{CR}, which was 51.8 (9.6) mL/min in patients with moderate impairment and 22.0 (6.2) mL/min in patients with severe impairment.

Safety Outcomes

The median treatment duration was 98.0 days in patients with moderate renal impairment and 97.0 days in patients with severe renal impairment. The mean treatment compliance rate was high: 99.9% in patients with moderate renal impairment and 78.7% in patients with severe renal impairment (primarily due to the subject who discontinued treatment due to meeting a prespecified discontinuation criterion: a decrease in CL_{CR} <15 mL/min).

The overall incidence of TEAEs was 82.9% (29/35 patients) (Table 2); all were mild or moderate in severity with the exception of one severe TEAE (angina pectoris, considered unrelated to the study drug) reported in a subject with moderate renal impairment. Serious TEAEs were reported in one subject (3.3%; angina pectoris) with moderate renal impairment, but in no subject with severe impairment. Only four patients (11.4%) discontinued due to TEAEs; all were in the moderate renal impairment group. No deaths were reported during the study.

The most commonly reported TEAEs were nasopharyngitis (22.9% [8/35]), somnolence (11.4% [4/35]), and edema peripheral (8.6% [3/35]) (Table 2). ADRs occurred in 25.7% (9/35) of patients overall; this included 30.0% (9/30) of patients with moderate renal impairment and 0% of patients with severe impairment. The most common ADRs were somnolence (11.4% [4/35]) and dizziness (5.7% [2/35]). No suicide-related TEAEs were reported. At Week 14, no clinically significant changes from baseline were found in the HADS subscales of depression and anxiety. In addition, no clinically significant changes or trends over time were found in any physical or neurological examination data or laboratory test values.

Efficacy Outcomes

The mean baseline ADPS was 5.7 overall (5.7 and 6.0 in patients with moderate and severe renal impairment, respectively). The least squares mean change from baseline in the imputed ADPS at Week 14 for the 35 renally impaired

Table 1 Demographic and Other Baseline Characteristics (Safety Analysis Set)

Parameters	Moderate Renal Impairment (CL _{CR} 30–59 mL/min) n=30	Severe Renal Impairment (CL _{CR} 15–29 mL/min) n=5	Total N=35
Age (years), mean (SD)	73.8 (7.7)	71.0 (4.1)	73.4 (7.3)
<65 years, n (%)	3 (10.0)	0 (0)	3 (8.6)
65–<75 years, n (%)	12 (40.0)	4 (80.0)	16 (45.7)
≥75 years, n (%)	15 (50.0)	1 (20.0)	16 (45.7)
Sex, n (%)			
Male	24 (80.0)	4 (80.0)	28 (80.0)
Female	6 (20.0)	1 (20.0)	7 (20.0)
Body mass index (kg/m ²), mean (SD)	22.9 (3.0)	23.7 (4.3)	23.0 (3.1)
Primary disease, n (%)			
DPNP ^a	24 (80.0)	5 (100.0)	29 (82.9)
PHN	6 (20.0)	0 (0)	6 (17.1)
Duration of primary disease (months), median (range)			
DPNP	49.5 (9–139)	60.0 (12–156)	51.0 (9–156)
PHN	14.5 (10–87)	–	14.5 (10–87)
CL _{CR} (mL/min), mean (SD)	51.8 (9.6)	22.0 (6.2)	47.5 (13.9)
Baseline ADPS, mean (SD)	5.7 (1.0)	6.0 (1.3)	5.7 (1.1)
SF-MPQ VAS score, mean (SD)			
At screening	58.5 (9.4)	56.6 (10.1)	58.2 (9.4)
At treatment initiation	59.1 (9.1)	62.8 (13.4)	59.6 (9.6)

Notes: ^aAll patients with DPNP had type 2 diabetes, no patients with type 1 diabetes were enrolled. The percentage for each categorical variable was calculated using the “non-missing” n as the denominator. CL_{CR} was calculated by the Cockcroft-Gault equation. Baseline ADPS was defined as the average of up to 7 available pain scores in the prior 7 days at or before first study treatment.

Abbreviations: ADPS, average daily pain score; CL_{CR}, creatinine clearance; DPNP, diabetic peripheral neuropathic pain; PHN, post-herpetic neuralgia; SD, standard deviation; SF-MPQ, short-form McGill Pain Questionnaire; VAS, visual analog scale.

patients was -1.9 [95% confidence interval [CI] $-2.8, -1.0$]; by group, the changes were -1.8 (95% CI $-2.5, -1.1$) in patients with moderate renal impairment and -2.1 (95% CI $-3.8, -0.4$) in patients with severe renal impairment (Table 3). Most of the missing values of ADPS occurred due to AE-related discontinuations (four due to AEs and one due to reduction in CL_{CR} <15 mL/min). No trends were found related to the timing of discontinuations. Mirogabalin significantly decreased the ADPS at Week 14 from baseline in both renal impairment groups (Figure 3).

At Week 14, 42.9% (15/35) of patients achieved a $\geq 30\%$ reduction from baseline in ADPS; this equated to 43.3% (13/30) of patients with moderate renal impairment and 40.0% (2/5) of patients with severe renal impairment. At Week 14, 28.7% (10/35) of patients achieved a $\geq 50\%$ reduction from baseline in ADPS; this included 26.7% (8/30) of patients with moderate renal impairment and 40.0% (2/5) of patients with severe renal impairment (Table 3).

The results of the SF-MPQ are also shown in Table 3. For the VAS score, the mean (SD) changes from baseline at Week 14 were -20.8 (17.7) in patients with moderate impairment and -26.0 (22.8) in patients with severe impairment. For the total score, the mean (SD) changes from baseline at Week 14 were -6.1 (5.4) and -2.6 (2.7) in patients with moderate and severe impairment, respectively. The difference between groups was largely driven by changes in the sensory score.

At Week 14, the percentage of patients with a PGIC score of much improved or better (score ≤ 2) was 36.7% (11/30) in patients with moderate renal impairment and 20.0% (1/5) in patients with severe impairment. At Week 14, the percentage of patients with a PGIC score of minimally improved or better (score ≤ 3) was 76.7% (23/30) and 80.0% (4/5), respectively (Table 3).

The mean (SD) changes from baseline in ADSIS at Week 14 were -1.4 (1.6) in patients with moderate renal

Table 2 Summary of TEAEs and ADRs (Safety Analysis Set)

	Moderate Renal Impairment (CL _{CR} 30–59 mL/min) n=30	Severe Renal Impairment (CL _{CR} 15–29 mL/min) n=5	Total N=35
TEAEs			
All TEAEs	25 (83.3)	4 (80.0)	29 (82.9)
Serious TEAEs	1 (3.3)	0 (0)	1 (2.9)
Severe TEAEs	1 (3.3)	0 (0)	1 (2.9)
TEAEs leading to discontinuation	4 (13.3)	0 (0)	4 (11.4)
ADRs			
All ADRs	9 (30.0)	0 (0)	9 (25.7)
Serious ADRs	0 (0)	0 (0)	0 (0)
Severe ADRs	0 (0)	0 (0)	0 (0)
ADRs leading to discontinuation	1 (3.3)	0 (0)	1 (2.9)
Deaths	0 (0)	0 (0)	0 (0)
Most frequently reported TEAEs (≥5% overall) by preferred term			
Nasopharyngitis	6 (20.0)	2 (40.0)	8 (22.9)
Somnolence	4 (13.3)	0 (0)	4 (11.4)
Edema peripheral	2 (6.7)	1 (20.0)	3 (8.6)
Back pain	2 (6.7)	0 (0)	2 (5.7)
Dizziness	2 (6.7)	0 (0)	2 (5.7)
Diarrhea	2 (6.7)	0 (0)	2 (5.7)
Nausea	2 (6.7)	0 (0)	2 (5.7)
Sensory disturbance	2 (6.7)	0 (0)	2 (5.7)

Notes: Data are shown as n (%). The percentage was calculated using the number of patients in the column heading as the denominator. An ADR was defined as a TEAE which was considered related to the study drug (ie, a causal relationship could not be ruled out).

Abbreviations: ADR, adverse drug reaction; AE, adverse event; CLCR, creatinine clearance; TEAE, treatment-emergent AE.

impairment and −0.5 (0.7) in patients with severe impairment (Table 3).

Discussion

Despite the fact that PNP (including DPNP and PHN) is highly prevalent in the general population, treatment for these conditions is often suboptimal,^{6,7} and patient dissatisfaction remains high.^{35,36} The orally administered gabapentinoid mirogabalin was recently approved for the treatment of PNP in Japan, and the results of Phase III RCTs demonstrated that mirogabalin was able to provide significant pain relief and was generally well tolerated.^{17,18}

This study aimed to characterize mirogabalin in patients with renal impairment, a characteristic common in the elderly patients who will likely make up a large proportion of mirogabalin users. The results indicate that mirogabalin was safe and well tolerated in patients with

DPNP or PHN and renal impairment when used at a fixed dose of 7.5 mg BID (moderate renal impairment) or 7.5 mg QD (severe renal impairment).

The key finding from our study in patients with renal impairment was that the safety outcomes in this population were comparable with those from non-impaired patients in the Phase III studies, with no new safety signals. In the Phase III studies in DPNP¹⁷ and PHN,¹⁸ the most frequently reported TEAEs with mirogabalin 15 mg BID were nasopharyngitis (16.4% and 12.9%, respectively), somnolence (14.5% and 23.9%), and dizziness (10.9% and 15.5%). While the frequency of nasopharyngitis was slightly increased in our study (22.9%), rates of somnolence (11.4%) and dizziness (5.7%) were slightly lower. Treatment compliance in our study was high, and most TEAEs were mild or moderate in severity. Discontinuations due to TEAEs were low (11.4%), and consistent with discontinuation rates due to TEAEs

Table 3 Efficacy Outcomes (Efficacy Analysis Set)

	Moderate Renal Impairment (CL _{CR} 30–59 mL/min) n=30	Severe Renal Impairment (CL _{CR} 15–29 mL/min) n=5	Total N=35
ADPS, baseline, mean (SD) Week 14 change from baseline (imputed), LS mean [95% CI]	5.7 (1.0) –1.8 [–2.5, –1.1]	6.0 (1.3) –2.1 [–3.8, –0.4]	5.7 (1.1) –1.9 [–2.8, –1.0]
ADPS responder rate ^a ≥30% reduction in ADPS at Week 14, n (%) [95% CI] ≥50% reduction in ADPS at Week 14, n (%) [95% CI]	13 (43.3) [27.4, 60.8] 8 (26.7) [14.2, 44.4]	2 (40.0) [11.8, 76.9] 2 (40.0) [11.8, 76.9]	15 (42.9) [28.0, 59.1] 10 (28.6) [16.3, 45.1]
SF-MPQ, baseline, mean (SD) Sensory score Week 14/LOCF change from baseline Affective score Week 14/LOCF change from baseline Total score Week 14/LOCF change from baseline VAS (mm) Week 14/LOCF change from baseline Present pain intensity Week 14/LOCF change from baseline	7.7 (4.3) –5.1 (4.4) 1.3 (1.5) –1.0 (1.6) 9 (5.3) –6.1 (5.4) 59.1 (9.1) –20.8 (17.7) 1.9 (1.0) –0.8 (0.8)	8.6 (8.8) –1.8 (2.5) 2.6 (2.7) –0.8 (0.5) 11.2 (11.4) –2.6 (2.7) 62.8 (13.4) –26.0 (22.8) 2 (0.7) –0.2 (0.8)	7.8 (5.0) –4.6 (4.3) 1.5 (1.7) –1.0 (1.5) 9.3 (6.3) –5.6 (5.2) 59.6 (9.6) –21.5 (18.2) 1.9 (0.9) –0.7 (0.8)
PGIC ^{a,b} Much improved or better (≤2) at Week 14, n (%) [95% CI] Minimally improved or better (≤3) at Week 14, n (%) [95% CI]	11 (36.7) [21.9, 54.5] 23 (76.7) [59.1, 88.2]	1 (20.0) [3.6, 62.4] 4 (80.0) [37.6, 96.4]	12 (34.3) [20.8, 50.8] 27 (77.1) [61.0, 87.9]
ADSiS, baseline ^c , mean (SD) Week 14/LOCF change from baseline	3.5 (1.8) –1.4 (1.6)	3.8 (3.4) –0.5 (0.7)	3.5 (2.1) –1.3 (1.5)

Notes: ^aThe 95% CI was calculated using the Wilson score method without continuity correction. ^bFor patients who were missing PGIC data at Week 14 but who had data prior to Week 14, the LOCF approach was used. Patients who had no PGIC data throughout the study were regarded as non-responders. ^cBaseline ADSiS was defined as the average of up to 7 available sleep interference scores in the previous 7 days at or before first study treatment.

Abbreviations: ADPS, average daily pain score; ADSiS, average daily sleep interference score; CI, confidence interval; CL_{CR}, creatinine clearance; LOCF, last observation carried forward; LS, least squares; PGIC, patient global impression of change; SD, standard deviation; SF-MPQ, short-form McGill Pain Questionnaire; VAS, visual analog scale.

observed with mirogabalin 15 mg BID in the Phase III studies (9.7%¹⁷ and 7.7%¹⁸).

In addition, despite the reduced dosages, mirogabalin significantly decreased ADPS, reduced ADSiS, and improved PGIC scores over 14 weeks of treatment. The least squares mean reduction in ADPS of –1.9 at Week 14 in this study was consistent with the improvements reported in the recent Phase III studies,^{17,18} although differences in study design and population size mean that comparisons should be made with caution. For patients without moderate or severe renal impairment receiving mirogabalin 15, 20, and 30 mg/day, the least squares mean changes in ADPS at Week 14 were –1.6, –1.7, and

–2.0, respectively, in the DPNP study¹⁷ and –1.3, –1.5 and –1.8, respectively, in the PHN study.¹⁸

Dosage adjustment for renally impaired individuals is often necessary for therapeutic agents which are renally excreted, and regulatory authorities recommend pharmacokinetic evaluation during clinical development.³⁷ The doses used in this study were selected to produce exposures equivalent to those observed in patients with normal renal function receiving mirogabalin 15 mg BID, based on previously published data.^{17,18,23,28} The requirement for a reduced dosage of mirogabalin in patients with renal impairment was not unexpected, given that reduced dosages are also recommended for the gabapentinoids

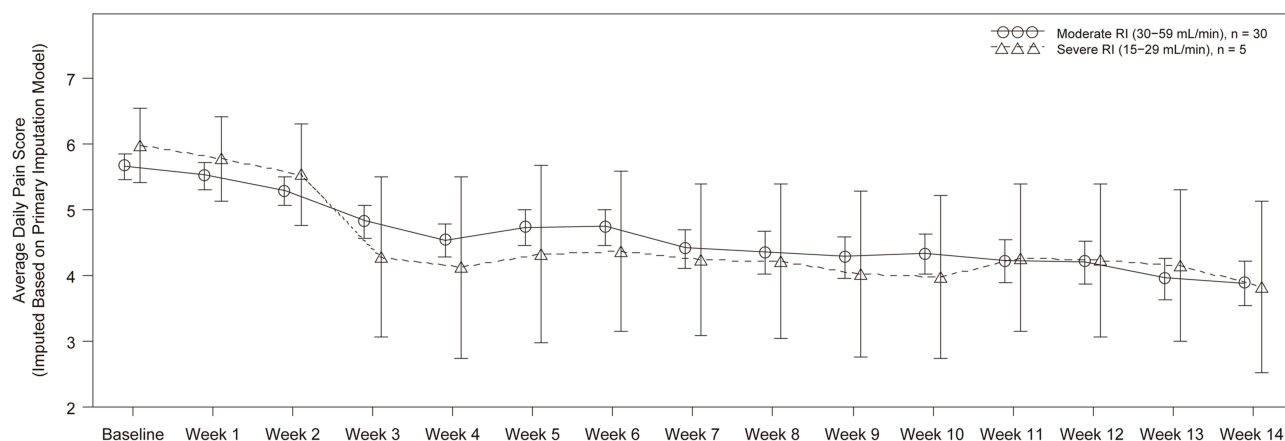


Figure 3 Time course of average daily pain scores^a (efficacy analysis set).

Notes: ^aData are shown as least squares mean \pm SE. The MI method using pattern mixture model with different shifting parameters according to the reason for treatment discontinuation was applied. The MMRM with CL_{CR} group, week and CL_{CR} group-by-week as fixed effects and baseline ADPS as a covariate was performed to estimate the least squares means and the corresponding SE for each week.

Abbreviations: ADPS, average daily pain score; CL_{CR}, creatinine clearance; MI, multiple imputation; MMRM, mixed-effects model with repeated measures; RI, renal impairment; SE, standard error.

pregabalin³⁸ (indicated for DPNP and PHN in the US³⁸ and for neuropathic pain in Japan³⁹) and gabapentin (approved for PHN in the US)⁴⁰ in this context. It is worth noting, however, that duloxetine (indicated in the US for DPNP) is contraindicated for use in patients with severe renal impairment.⁴¹

Since this was an uncontrolled study in patients with renal impairment, it was deemed necessary to be able to compare safety outcomes with a control group of patients with relatively normal renal function. The prior Phase III RCTs of mirogabalin in patients with DPNP and PHN, which enrolled patients without moderate or severe renal impairment,^{17,18} provided a suitable historical control population. Background factors of the patients in our study, such as ADPS at baseline (5.7), mean age (73.4 years), and duration of DPNP (51.0 months) or PHN (14.5 months) were broadly consistent with those of patients in the Phase III DPNP study (5.6, 61.4 years, and 35.0 months, respectively)¹⁷ and the Phase III PHN study (5.7, 66.5 years, and 18.0 months, respectively).¹⁸ However, to facilitate inter-study comparisons, study designs must be similar. Since the Phase III studies utilized a 12-week fixed-dose period, in accordance with the recommendation from the European Medicines Agency,⁴² the current study was also designed with a 12-week fixed-dose period. In addition, taking subject safety into consideration, the current study incorporated a 2-week titration period prior to the fixed-dose period.

We recognize that our study has several limitations; namely, that it was an open-label study in which all

patients were aware of their treatment regimen, and no directly comparable control cohort was enrolled. However, the use of a similar study design to the Phase III mirogabalin RCTs was intended to partially mitigate against this potential weakness, by allowing comparison of our study data with results from two larger, methodologically robust studies, thus placing our results into the wider context of therapeutic evidence for mirogabalin use. The small study size also potentially limits extrapolation of the data to the wider population of patients with DPNP or PHN, although the demographic data indicate that the patients enrolled in this analysis were representative of individuals seen in general practice. In particular, the small number of patients enrolled with severe renal impairment means that the study lacks statistical power to definitively demonstrate efficacy and safety in this population; although we consider that mirogabalin 7.5 mg QD can be safely administered and will provide benefit to patients with severe renal impairment, additional data are needed to confirm this. Despite these caveats, we believe that the data accruing from our study extend the evidence base for optimal mirogabalin use in special populations with PNP, and elucidate key therapeutic aspects for clinicians treating patients with neuropathic pain and renal impairment.

Conclusion

Mirogabalin was safe and well tolerated in patients with DPNP or PHN and renal impairment when used at a fixed dose of 7.5 mg QD (severe impairment) or 7.5 mg BID (moderate impairment). Furthermore, these reduced doses

of mirogabalin were able to reduce pain from baseline to Week 14 in renally impaired patients with DPNP or PHN.

Abbreviations

ADPS, average daily pain score; ADSIS, average daily sleep interference score; AE, adverse event; AUC_{last}, area under the plasma concentration–time curve up to the last quantifiable time; BID, twice daily; CL_{CR}, creatinine clearance; C-SSRS, Columbia-Suicide Severity Rating Scale; DPNP, diabetic peripheral neuropathic pain; HADS, Hospital Anxiety and Depression Scale; HbA1c, glycated hemoglobin; LOCF, last observation carried forward; MI, multiple imputation; MINI, Mini-international Neuropsychiatric Interview; MMRM, mixed-effects model with repeated measures; PGIC, patient global impression of change; PHN, post-herpetic neuralgia; QD, once daily; RCT, randomized, controlled trial; REGPMM, regression with predictive mean matching; SD, standard deviation; SF-MPQ, short-form McGill Pain Questionnaire; TEAE, treatment-emergent adverse event; VAS, visual analog scale.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

This study was conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation consolidated Guideline E6 for Good Clinical Practice (CPMP/ICH/135/95), and all applicable national and international regulatory requirements. The protocol, amendments, the informed consent forms, and information sheets were approved by the Institutional Review Boards at each participating study center. All patients provided written informed consent prior to initiation of any study procedures.

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Disclosure

All authors have received personal fees from Daiichi Sankyo Co., Ltd. HT, NM, and SO are employees of Daiichi Sankyo Co., Ltd. The authors report no other conflicts of interest in this work.

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