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Mirogabalin for Central Neuropathic Pain After Spinal Cord Injury: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study in Asia

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Abstract

Background and Objectives: Patients with spinal cord injury (SCI) commonly experience central neuropathic pain (CNeP), which is challenging to treat. Mirogabalin is effective for peripheral neuropathic pain, but evidence for CNeP is lacking.

Methods: This randomized, double-blind, placebo-controlled, phase 3 study investigated mirogabalin efficacy and safety for treatment of CNeP in patients with traumatic SCI. Adult patients from 120 sites throughout Japan, Korea, and Taiwan, were randomized (1:1) to receive placebo or mirogabalin (5 mg twice daily [BID] for 1 week, 10 mg BID for 1 week, and 10 or 15 mg BID for 12 weeks). Patients with moderate renal impairment received half the dosage. The primary efficacy endpoint was change from baseline in the weekly average daily pain score (ADPS) at Week 14. Secondary endpoints included ADPS responder rates, Short-Form McGill Pain Questionnaire (SF-MPQ), average daily sleep interference score (ADSIS), and Neuropathic Pain Symptom Inventory (NPSI). Adverse events were monitored for safety.

Results: Each treatment group comprised 150 patients. Mirogabalin elicited a statistical and clinically relevant improvement in change from baseline in the weekly ADPS at Week 14 (least-squares mean difference [95% confidence interval [CI]] vs placebo −0.71 [−1.08, −0.34], *p*=0.0001). Responder rates at Week 14 were higher for mirogabalin vs placebo (odds ratio [95% CI] 1.91 [1.11, 3.27] for the ≥30% responder rate; 2.52 [1.11, 5.71] for the ≥50% responder rate). Statistical improvements (i.e., least-squares mean difference [95% CI] vs placebo) were also observed in SF-MPQ (−2.4 [−3.8, −1.1]), ADSIS −0.71 (−1.04, −0.38), and NPSI −7.7 (−11.1, −4.4) scores. Most treatment-emergent adverse events were mild; no serious adverse drug reactions were reported.

Discussion: Mirogabalin elicited clinically relevant decreases in pain and was well-tolerated, suggesting that mirogabalin is a promising treatment for patients with CNeP due to SCI.

Trial Registration: ClinicalTrials.gov (NCT03901352); first submitted 3 April 2019; first patient enrolled 14 March 2019; available at https://clinicaltrials.gov/ct2/show/NCT03901352.

Classification of Evidence: This study provides Class I evidence that in adult patients with CNeP due to traumatic SCI, mirogabalin, 10 or 15 mg BID, effectively improves weekly ADPS at Week 14.

Introduction

Neuropathic pain is classified as either peripheral or central, depending on the involvement of nervous system elements. Features commonly observed in patients with neuropathic pain include spontaneous pain, hyperalgesia, and allodynia, although the severity and duration of symptoms vary greatly depending on the etiology.[1] Peripheral neuropathic pain (PNeP) is commonly associated with diabetes mellitus (i.e., diabetic peripheral neuropathic pain [DPNP]), post-herpetic neuralgia (PHN), and radiculopathy.[2,3] Conversely, central neuropathic pain (CNeP) is characteristic of patients with spinal cord injury (SCI), post-stroke pain, and multiple sclerosis.[4,5] Diagnosis of CNeP requires both a history of relevant disease or injury, and a neuroanatomically plausible distribution of the pain itself.[5] For example, in patients with SCI, a CNeP diagnosis is appropriate only if the pain occurs in dermatomes at or below the level of the SCI.

The currently available pharmacotherapies for neuropathic pain do not provide adequate pain relief in many cases and are associated with both systemic and CNS-related adverse drug reactions (ADRs), including dizziness, somnolence, edema, nausea, and constipation.[6] These ADRs can significantly lower compliance, sometimes leading to discontinuation before a therapeutic effect can be achieved.[7] Therefore, there is an unmet need for better treatment options.

Mirogabalin is a selective oral $\alpha_2\delta$ ligand belonging to the gabapentinoid class of neurological drugs and was first approved in Japan in 2019 for the treatment of PNeP.[8,9] A preclinical study of mirogabalin in a rat model of SCI demonstrated a lasting analgesic effect after a single dose, suggesting potential utility for patients with CNeP.[10] Subsequent clinical studies have shown favorable efficacy and safety profiles for various types of neuropathic pain. In a phase 3 study involving patients with PHN, mirogabalin was effective and well tolerated.[11] Another phase 3 study demonstrated that mirogabalin safely and effectively relieved pain in a dose-dependent manner in patients with DPNP, as shown by improvements in the average

daily pain scores after 14 weeks of treatment.[12] A subgroup analysis of the MIROP study revealed that mirogabalin significantly reduced visual analogue scale (VAS) pain scores in patients with lumbar spinal stenosis or lumbar disc herniation; however, because of the small number of patients recruited, these data should be considered preliminary.[13]

Based on the research to date, mirogabalin may be useful in the treatment of CNeP. However, the primary research questions, namely, whether mirogabalin is effective and safe for the treatment of CNeP, have not yet been investigated in clinical trials. Therefore, this double-blind, placebo-controlled, phase 3 study was conducted to assess the efficacy and safety of mirogabalin in Asian patients with CNeP after SCI. The primary objective was to compare change from baseline in the weekly average daily pain score (ADPS) at Week 14 in patients with CNeP and SCI receiving mirogabalin versus placebo.

Methods

Study Design and Participants

This was a phase 3, multinational, randomized, double-blind, placebo-controlled trial of mirogabalin for the treatment of CNeP in patients with SCI. The study was conducted at 120 study sites in Japan, Korea, and Taiwan, and patients were recruited as either inpatients or outpatients. The study design is shown in **eFigure 1** in the Supplement. After providing informed consent, patients who had been taking mirogabalin, pregabalin, or gabapentin underwent a 28-day washout period before proceeding to screening and a 1-week observation period. Patients were then randomized to receive placebo or mirogabalin for 14 weeks, which included a 2-week titration period and 12-week maintenance dose period.

Mirogabalin was self-administered orally and titrated according to renal function. Patients with creatinine clearance (CrCL) ≥60 mL/min at screening received mirogabalin 5 mg twice daily (BID) for 1 week, followed by 10 mg BID for 1 week, and finally 10 or 15 mg BID for 12 weeks. Patients with CrCL 30–<60 mL/min received mirogabalin 2.5 mg BID for 1 week,

5 mg BID for 1 week, and 5 or 7.5 mg BID for 12 weeks. Patients were planned to attend the clinic for a total of eight visits: once each at screening and at randomization, four times during the treatment period, and once each at the end of treatment and at post-treatment follow-up.

Prohibited concomitant medications included mirogabalin, pregabalin, gabapentin, strong opioids, or any other investigational medications. Permitted medications for concomitant use included antiepileptics (except for gabapentin and pregabalin), antidepressants, hypnotics, anxiolytics, and tramadol, among others (a full list is provided in the **eMethods** in the Supplement). These medications were permitted only if their dosage had not changed for 28 days prior to screening; changes in dosage were not permitted during the study. Acetaminophen was permitted as rescue medication. The following therapies were permitted for concomitant use if the frequency of use had not changed for 28 days prior to screening and remained unchanged throughout the study period: nerve blocks, laser therapy, acupuncture, and spinal cord stimulation. A full list of restricted concomitant therapies is provided in the **eMethods**.

The inclusion criteria were as follows: age ≥20 years at informed consent; able to provide informed consent for study participation, to understand the study procedures, and to complete the patient-reported questionnaires; traumatic SCI; C4 to T12 SCI identified by magnetic resonance imaging; American Spinal Injury Association impairment scale A, B, C, or D; area of neuropathic pain at or below the level of the SCI; ≥6 months after SCI at screening; stable CNeP after SCI for at least 3 months prior to screening; a pain score of ≥40 mm on the Short-form McGill Pain Questionnaire (SF-MPQ)[14] VAS at both screening and randomization; and completion of at least 4 days of a daily pain diary at the time of randomization with an ADPS ≥4 on an 11-point numerical rating scale. Key exclusion criteria were a daily pain score of 10 at least once during the observation period,[15] any other severe pain/neurological disease not related to the SCI-caused CNeP that would affect the evaluation of the study drug, SCI due to

suicide attempt, and CrCL<30 mL/min. A full description of all exclusion criteria is provided in the **eMethods in the Supplement**.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol, protocol amendments, informed consent forms, and information sheets were approved by the relevant Independent Ethics Committees or Institutional Review Boards at each study center. This study was conducted in compliance with the protocol and ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and the Japanese Ministry of Health, Labour and Welfare. All patients provided written informed consent prior to participating in the study. This trial was registered in ClinicalTrials.gov under the identifier NCT03901352.

Randomization and Blinding

Eligible patients were randomized in a 1:1 ratio to receive mirogabalin or placebo, with stratification factors of baseline weekly ADPS (<6.0 or ≥6.0) and region (Japan or not Japan). The randomization schedule was generated by an independent biostatistician using an Interactive Response Technology system. Blinding was applied to all personnel related to the study except the independent biostatistician, and the randomization schedule was kept strictly confidential until after database lock. The study drug and placebo were indistinguishable in appearance, as white, film-coated tablets identical in shape and size.

Efficacy Outcomes

The primary efficacy endpoint was change from baseline in the weekly ADPS at Week 14. Patients recorded pain scores in diaries, once daily from the day after the screening visit (Visit 1) until Visit 7. Patients were instructed to rate their pain over the previous 24 hours each

morning (prior to taking the study medication) on a scale of 0 (no pain) to 10 (worst possible pain).[16]

The secondary efficacy endpoints included the following. (1) ADPS responder rate (defined as the percentage of patients with a ≥30% or ≥50% reduction in the weekly ADPS at Week 14). (2) Change from baseline in parameters assessed using the SF-MPQ, including self-assessment of pain intensity (VAS, on a scale of 0 mm [no pain] to 100 mm [worst possible pain]), sensory/affective subscales and total scores of 15 pain descriptors rated on a scale of 0 (none) to 3 (severe), and present pain intensity on a scale of 0 (no pain) to 5 (worst pain). (3) Patient Global Impression of Change (PGIC), which was evaluated at Visit 7, where patients were asked to self-assess their condition compared with that at screening, on a 7-point scale (1="very much improved"; 7="very much worse"). (4) Change from baseline in the weekly average daily sleep interference score (ADSIS): assessed in a similar manner to the ADPS; patients were asked to rate their sleep quality on a daily basis from the day after screening until Visit 7, on a scale of 0 (pain did not interfere with sleep) to 10 (pain completely interfered with sleep). (5) Change from baseline in the Neuropathic Pain Symptom Inventory (NPSI): patients were asked at the randomization visit (Visit 2) and at Visit 7 to complete a self-assessment using the NPSI, which uses an 11-point scale to assess five distinct dimensions of pain (superficial spontaneous, deep spontaneous, paroxysmal, evoked, and paresthesia/dysesthesia). (6) Change from baseline in EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L): this questionnaire yields a profile of the patient's self-assessed quality of life (QoL) across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each measured on a 5-point scale. Patients also subjectively rated their overall health using a VAS, with a score of 0 indicating worst imaginable health, and 100 indicating best imaginable health.[17]

The numbers of patients who received effective doses based on renal function at screening were also recorded. Normal renal function was defined as CrCL ≥90 mL/min, mild renal impairment as CrCL 60–<90 mL/min, and moderate renal impairment as CrCL 30–<60 mL/min.

Evaluation of the change in daily pain score after 21 days was conducted post hoc.

Safety

Safety endpoints included treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, and 12-lead electrocardiography. TEAEs were coded by System Organ Class and Preferred Term according to the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0.

Statistical Analysis

The primary endpoint was analyzed by analysis of covariance with treatment as a fixed effect and baseline weekly ADPS as a covariate to compare the change from baseline in the weekly ADPS at Week 14 for mirogabalin vs placebo. We assumed normal distributions with a common SD of 1.75 for the change from baseline in the weekly ADPS at Week 14 in both groups. Applying Student's t-test with a one-sided significance level of 0.025, a total of 270 patients (135 per group) were required to provide 80% statistical power, under the assumption of a treatment difference of 0.6 (vs placebo). The treatment difference and common SD were assumed based on the results of two Asian Phase 3 studies, one in patients with DPNP[12] and one in patients with pain associated with PHN.[11] The minimum clinically significant treatment difference was defined according to a previous report for patient-reported outcomes.[18] To account for dropouts between randomization and the first administration of the study drug, we planned for 274 patients to be randomized.

The primary efficacy variable was analyzed in the modified intention-to-treat (mITT) set, which was defined as all randomized patients who received at least one dose of the study drug. The safety analysis set included all patients who provided informed consent and received at least one dose of the study drug.

The pain score was not collected after treatment discontinuation, which was considered an intercurrent event for the primary estimand of this study.[19] The estimand in this study was the mean difference (mirogabalin vs placebo) of the change from baseline in weekly ADPS at Week 14. Missing data owing to study discontinuation were imputed for the weekly ADPS using a multiple imputation method. Imputation was based on a "nonfuture dependence" model using a pattern mixture approach under the missing not at random mechanism. The reason for treatment discontinuation and time of discontinuation were used to construct the missing data patterns in the pattern mixture model. The pattern mixture model with different shifting parameters, depending on the reason for discontinuation (AE, lack of efficacy, or other), was used in the multiple imputation to impose a penalty (i.e., a bad score) on the imputed weekly ADPS. For secondary endpoints, a last observation carried forward (LOCF) approach was used.

Futhermore, we performed a sensitivity analysis based on the degree to which the pain worsened after study discontinuation as the primary analysis in the same estimand, and divided into three levels based on the reason for discontinuation: AE, lack of efficacy, and any other reason, with the shift parameters (1.0, 1.0, 0.5), (3, 3, 1.5), (5, 5, 2.5), and (0, 0, 0). Supplementary analyses were performed with three different missing completion methods and one change in the population to be analyzed when the estimand was different from the primary analysis.

All analyses were performed with SAS Version 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request at https://vivli.org/ourmember/daiichi-sankyo/. The full trial protocol and statistical analysis plan are available in eSAP 1 and eSAP 2, respectively.

Results

Patients

Patients were enrolled from 14 March 2019, and follow-up was completed on 9 September 2020. The patient disposition is shown in **Figure 1**. Of 443 patients assessed for eligibility, 300 were randomly assigned to treatment: 150 each to the mirogabalin and placebo groups. The mITT set included all 150 patients in the mirogabalin group and 149 in the placebo group. In the mirogabalin and placebo groups, 133 and 136 patients, respectively, completed the study; the most common reasons for study withdrawal were patient decision and AEs **(Figure 1)**.

The patient demographics and baseline characteristics are shown in **Table 1**. The mean ± SD age was 58.5 ± 14.16 years, most patients were male (85.6%), and most were from Japan (80.9%). The majority of patients (62.2%) had normal renal function (CrCL ≥90 mL/min) and the mean ± SD durations of SCI and CNeP due to SCI were 98.9 ± 114.11 and 91.3 ± 102.18 months, respectively. There were no notable differences between treatment groups. The overall mean ± SD treatment compliance, calculated as 100 × (number of tablets actually taken / number of tablets planned to be taken), was 98.16% ± 7.226% and was similar between both arms (data not shown).

Efficacy Analysis

Weekly ADPS

Regarding the primary endpoint, there was a statistically significant improvement in change from baseline in the weekly ADPS at Week 14 for patients treated with mirogabalin: the least-squares (LS) mean difference (95% confidence interval [CI]) vs placebo was −0.71 (−1.08, −0.34); $p = 0.0001$ **(Table 2)**. The time-course of the weekly ADPS data is shown in **Figure 2**. The LS mean weekly ADPS decreased from Week 1 in the mirogabalin group and subsequently remained at a lower level than that seen with placebo throughout the treatment period.

Time-course of ADPS

The mirogabalin group showed improvements in pain vs placebo from an early stage, with statistically significant improvement observed from Day 6 of administration. The time-course of the ADPS data for 21 days from baseline is shown in **eTable 1** in the Supplement.

Responder Rates

The ≥30% and ≥50% responder rates for the weekly ADPS are shown in **Table 2**. Both responder rates at Week 14 were statistically significantly higher in the mirogabalin group than in the placebo group. Odds ratios (ORs) (95% CI) were 1.91 (1.11, 3.27), and 2.52 (1.11, 5.71) for the ≥30% and ≥50% responder rates, respectively.

Other Secondary Efficacy Endpoints

The results of the SF-MPQ showed that the mirogabalin group had statistically significant improvement across all metrics, including the VAS, sensory, affective, and total scores, as well as present pain intensity **(Table 3)**. The difference of the LS mean (95% CI) total score change from baseline at Week 14 vs placebo was −2.4 (−3.8, −1.1).

Results of the NPSI and other secondary efficacy endpoints are shown in **Table 4**. The mirogabalin group showed statistically significant improvement over the placebo group in NPSI total score after 14 weeks of treatment: mean ± SD change from baseline was −12.0 ± 15.47 vs −4.5 ± 15.90 in the mirogabalin vs placebo groups, respectively; the difference of LS mean vs placebo (95% CI) was −7.7 (−11.1, −4.4), $p < 0.0001$. Statistically significant improvements with mirogabalin vs placebo were also observed in all five subscores (superficial spontaneous pain, deep spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia). Regarding the ADSIS, patients treated with mirogabalin showed statistically significant improvement in the ADSIS at Week 14: the difference of LS mean vs placebo (95% CI) was −0.71 (−1.04, −0.38), $p < 0.0001$. For the PGIC assessment, patients in the mirogabalin group showed a statistically significant improvement over the placebo group after 14 weeks of treatment; for status of "much improved" or better (score ≤2): OR (95% CI) 2.63 (1.25, 5.54); and "minimally improved" or better (score ≤3): 2.07 (1.30, 3.29). For the LS mean (95% CI) changes from baseline in index values (0.0287 [−0.0009, 0.0583]) and VAS scores (6.2 [2.0, 10.4]) of the EQ-5D-5L, the mirogabalin group showed a trend towards improvement over the placebo group.

Safety

In the safety analysis set (N = 299), 66.9% of patients experienced at least one TEAE (78.1% in the mirogabalin group and 55.4% in the placebo group). TEAEs occurring in ≥5% of patients in either group are listed in **Table 5**. Somnolence, dizziness, peripheral edema, nasopharyngitis, constipation, and weight gain were more common in the mirogabalin group than in the placebo group.

The majority of TEAEs occurring in the mirogabalin group were not severe, and most were mild. Fewer patients in the placebo group than the mirogabalin group discontinued treatment because of a TEAE. TEAEs leading to treatment discontinuation were reported in 14 patients

(9.3%) in the mirogabalin group and six patients (4.1%) in the placebo group. These included somnolence (n = 6, 4.0%), suicidal ideation (n = 2, 1.3%), pneumonia, syncope, dry throat, oropharyngeal discomfort, pollakiuria, cardiac death, and cervical SCI (n = 1, 0.7% each) in the mirogabalin group, and suicidal ideation (n = 3, 2.0%) and pneumonia, hypoesthesia, and hypertension (n = 1, 0.7% each) in the placebo group. Serious TEAEs occurred in nine (6.0%) and seven (4.7%) patients in the mirogabalin and placebo groups, respectively (**eTable 2 in the Supplement**).

ADRs were reported in 62 (41.1%) and 19 patients (12.8%) in the mirogabalin and placebo groups, respectively; the most common ADRs included somnolence, dizziness, weight gain, constipation, peripheral edema, nausea, and dry mouth. No serious ADRs occurred. No notable differences or clinically relevant changes were observed between treatment groups in laboratory tests, vital signs, or 12-lead electrocardiography results during the study.

Classification of Evidence

This study provides Class I evidence that in adult patients with CNeP due to traumatic SCI, mirogabalin, 10 or 15 mg BID, effectively improves weekly ADPS at Week 14.

Discussion

This randomized, double-blind, placebo-controlled, phase 3 study assessed the efficacy and safety of mirogabalin for the treatment of CNeP in Asian patients with SCI. The efficacy of mirogabalin for CNeP was shown by the clinically meaningful improvements in ADPS at Week 14 and by the responder rates vs placebo, and improvements in pain were observed from Day 6. Improvements were observed for various types of pain, as demonstrated by the universal improvements in NPSI total and subscores after 14 weeks of treatment. Furthermore, the results from the PGIC, ADSIS, and EQ-5D-5L suggested that improvements

were achieved in QoL. Mirogabalin was generally well tolerated, with few discontinuations owing to TEAEs. Many patients were able to increase their dose to the maximum daily dose, and the safety results were aligned with the known safety profile of mirogabalin.[20]

Previous phase 3 studies of mirogabalin for treatment of Asian patients with DPNP[12] and PHN[11] yielded results similar to ours with respect to efficacy, with both studies reporting clinically meaningful improvements in ADPS for patients who received mirogabalin vs placebo after 14 weeks of treatment. The LS mean difference in weekly ADPS vs placebo was −0.71 in our study, which exceeds the minimum clinically important difference defined for patients with DPNP (−0.6) and PHN (−0.5);[18] thus, we interpret our results to represent a clinically meaningful difference. Taken together, these data confirm the efficacy of mirogabalin in ameliorating both PNeP and CNeP. Furthermore, studies of pregabalin (a gabapentinoid drug with a similar mechanism of action to mirogabalin) showed that pregabalin could effectively relieve CNeP in patients with SCI, as shown by improvements in pain scores after 17 and 12 weeks of treatment.[21,22]

Prior studies of gabapentinoids in neuropathic pain indications have reported mixed results in terms of responder rates. In patients with DPNP, a higher responder rate vs placebo for patients achieving ≥50% improvement was reported after 14 weeks of treatment, but only in patients who received the highest dose of mirogabalin (15 mg BID).[12] Conversely, in patients with PHN, higher responder rates vs placebo for all doses of mirogabalin were reported after 14 weeks of treatment, but only in the ≥30% improvement group.[11] In a 17-week randomized trial of patients with SCI, there was a higher ≥30% pain responder rate for patients receiving pregabalin vs placebo,[21] and another 12-week randomized study of patients with SCI reported higher ≥30% and ≥50% pain responder rates with pregabalin vs placebo.[22] In our study, patients treated with mirogabalin had statistically significant improvements in both the ≥30% and ≥50% responder rates compared with placebo, which suggests that mirogabalin may be an effective option for treatment of CNeP after SCI.

We also observed statistically significant improvements in the SF-MPQ VAS scores for patients who received mirogabalin vs placebo. This is aligned with other studies in which patients received 15 mg BID mirogabalin for PNeP,[11,12] or flexible-dose pregabalin for CNeP caused by SCI.[22] The change in SF-MPQ VAS score at Week 14 in our study was −14.2 ± 19.09, which was the minimum clinically important difference (VAS 16-20 mm). [23-25] Furthermore, improvements in sleep quality, as measured by the ADSIS, were consistent among our study and the abovementioned studies.

Regarding safety, the incidence of key AEs associated with mirogabalin in our study was largely consistent with that of previous studies of mirogabalin in neuropathic pain indications.[11,12] TEAEs such as somnolence, dizziness, peripheral edema, nasopharyngitis, constipation, and weight gain were more common in patients treated with mirogabalin than in patients who received placebo. The incidence of somnolence in the mirogabalin arm was somewhat higher in the present study than that reported in the phase 3 trials of mirogabalin for DPNP and PHN (29.8% vs 14.5% and 23.9%, respectively). The reason for this is not known, but the incidence of somnolence was also higher in the placebo group in our study vs patients who received placebo in the abovementioned phase 3 trials (5.4% vs 3.9% and 3.6%), suggesting that patients with SCI may be more prone to somnolence in general. A retrospective study of pregabalin for neuropathic pain identified that age ≥65 years and use of strong opioids were associated with an increased risk of somnolence or dizziness.[26] However, the mean age in our study was lower than that of both prior phase 3 trials for mirogabalin and none of the studies permitted opioid use, so these factors seem unlikely to have contributed to the increased incidence of somnolence in our study. Few patients discontinued mirogabalin due to TEAEs in the present study (9.3%); this is consistent with the previous phase 3 studies, which both had TEAE-related discontinuation rates of 9.7% for patients receiving 15-mg BID mirogabalin.[11,12]

There were some notable differences in the safety profile of mirogabalin compared with previous studies of pregabalin. The rates of edema, peripheral edema, somnolence, and dizziness were numerically higher for patients receiving pregabalin than those reported in our study of mirogabalin (20.0%, 10.0%, 41.4%, and 24.3%, respectively, for pregabalin,[22] vs 3.3%, 6.0%, 29.8%, and 8.6% for mirogabalin). In the 12-week trial in patients with CNeP caused by SCI, 21% of patients receiving pregabalin discontinued the study because of a TEAE,[22] whereas the rate reported in the 17-week trial was 7.1%.[21] Nevertheless, the overall incidences of TEAEs were generally similar among the abovementioned studies and are considered to be manageable in the clinical setting.

Concern regarding the possibility of abuse or misuse of gabapentinoid drugs has prompted research into the abuse potential of this drug class. Although the present clinical study did not address this, it is worth noting that therapeutic doses of mirogabalin were shown to have similar drug-liking effects as placebo, which were significantly less than those for comparators such as diazepam and pregabalin.[27]

Pregabalin is used by many patients as a first-line drug in clinical practice.[28,29] Our results demonstrate that mirogabalin is similarly well tolerated, with an excellent balance of efficacy and safety. The low rate of discontinuation due to TEAEs observed in our study is promising in that most patients are likely to be able to continue treatment to achieve sufficient pain relief. Furthermore, our study demonstrated that increasing the dose of mirogabalin can be safely implemented early in treatment, and that pain-relieving effects of mirogabalin can be observed even before the maximum dose is reached. Importantly, improvement in the ADPS at an early stage (after <1 week of administration) may increase the likelihood of continued administration and contribute to the overall efficacy of treatment. In addition to the pain-relieving effect of mirogabalin, improvements in QoL metrics were suggested by the ADSIS and EQ-5D-5L data. This is important because QoL may be severely impaired in patients with CNeP.[4,30] To date, QoL metrics have not yet been reported in studies of pregabalin for CNeP.

Limitations

The present study was conducted exclusively in Asia, limiting the generalizability to other racial/ethnic populations. The short study duration precludes conclusions about long-term efficacy and safety, and the use of placebo rather than an active comparator limits any direct comparison of safety/efficacy with existing therapies. Because there are limited resources for diagnosis and evaluation of CNeP, it is possible that the efficacy of mirogabalin may have been partly due to effects on other types of pain. Furthermore, we did not collect detailed information on drugs administered prior to study entry or details about intractable neuropathic pain, so the possible influence of these factors remains to be determined. Psychometric properties of the ADPS using a numeric rating scale in patients with SCI have not been reported, although research in healthy volunteers suggests that psychometric properties may depend on the body area affected.[31] We did not examine differences in response to mirogabalin based on the level of SCI, or differences in patients with cervical/high thoracic SCI vs low thoracic SCI. Finally, we excluded patients with a CrCL of <30 mL/min; therefore, the efficacy and safety of mirogabalin in patients with severe renal impairment remain unknown.

Conclusions

Mirogabalin has well-balanced efficacy and safety profiles in the treatment of CNeP due to SCI, suggesting that it may be a promising alternative treatment in patients who experience side effects or insufficient efficacy with other pharmacotherapies. Although the present results were obtained only in patients with CNeP due to SCI, mirogabalin shows promise for CNeP with other etiologies; future studies should investigate this potential indication.

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Table 1. Baseline Characteristics (Modified Intention-to-treat Analysis Set)

	Mirogabalin (n = 150)	**Placebo (n = 149)**	**Total (N = 299)**
Age at informed consent, years (mean ± SD)	57.3 ± 14.31	59.6 ± 13.96	58.5 ± 14.16
Sex, male	131 (87.3)	125 (83.9)	256 (85.6)
Country			
Japan	121 (80.7)	121 (81.2)	242 (80.9)
Korea	19 (12.7)	16 (10.7)	35 (11.7)
Taiwan	10 (6.7)	12 (8.1)	22 (7.4)
Body mass index, kg/m^2 (mean ± SD)	23.78 ± 3.773	23.71 ± 3.685	23.74 ± 3.723
Baseline CrCL, mL/min			
30 to <60	10 (6.7)	24 (16.1)	34 (11.4)
60 to <90	43 (28.7)	36 (24.2)	79 (26.4)
≥90	97 (64.7)	89 (59.7)	186 (62.2)
Baseline weekly average daily pain score			
<6.0	76 (50.7)	73 (49.0)	149 (49.8)
≥6.0	74 (49.3)	76 (51.0)	150 (50.2)
ASIA impairment scale			
Complete (A)	39 (26.0)	37 (24.8)	76 (25.4)
Incomplete (B, C, or D)	111 (74.0)	112 (75.2)	223 (74.6)
Cause of SCI			
Fall	82 (54.7)	84 (56.4)	166 (55.5)
Traffic accident	49 (32.7)	49 (32.9)	98 (32.8)
Sports accident	9 (6.0)	6 (4.0)	15 (5.0)
Other	10 (6.7)	10 (6.7)	20 (6.7)
Type of paralysis			
Tetraplegia	105 (70.0)	101 (67.8)	206 (68.9)
Paraplegia	45 (30.0)	48 (32.2)	93 (31.1)
Duration of SCI, months (mean ± SD)	103.0 ± 113.00	94.7 ± 115.45	98.9 ± 114.11
Duration of CNeP after SCI, months (mean ± SD)	94.5 ± 98.29	88.1 ± 106.17	91.3 ± 102.18

Data are n (%) unless otherwise specified.

Abbreviations: ASIA = American Spinal Injury Association; CNeP = central neuropathic pain; CrCL = creatinine clearance; SCI = spinal cord injury; SD = standard deviation.

Table 2. Change from Baseline in the Weekly ADPS at Week 14 and mirogabalin responder rates (Modified Intention-to-treat Analysis Set)

	Mirogabalin (n = 150)	**Placebo (n = 149)**
Baseline ADPS		
Mean ± SD	6.04 ± 1.309	6.09 ± 1.270
Median (range)	5.86 (4.0–9.0)	6.00 (4.0–9.0)
Week 14 ADPS (imputed)[a]		
LS mean ± SE	4.83 ± 0.132	5.54 ± 0.132
Change from baseline in ADPS at Week 14 (imputed)[a]		
LS mean ± SE	−1.23 ± 0.132	−0.52 ± 0.132
Difference of LS mean *vs* placebo ± SE	−0.71 ± 0.187	—
(95% CI); *p* value	(−1.08, −0.34); 0.0001	—
Patients with ≥30% reduction in ADPS from baseline at Week 14, n (%)	46 (30.7)	28 (18.8)
OR (95% CI); *p* value	1.91 (1.11, 3.27); 0.0192	—
Patients with ≥50% reduction in ADPS from baseline at Week 14, n (%)	21 (14.0)	9 (6.0)
OR (95% CI); *p* value	2.52 (1.11, 5.71); 0.0269	—

[a]Based on a "nonfuture dependence" model using the pattern mixture model approach with shifting parameters under the missing not at random mechanism for the missing weekly ADPS.

Abbreviations: ADPS = average daily pain score; CI = confidence interval; LS = least-squares; OR = odds ratio; SD = standard deviation; SE = standard error.

Table 3. Change from Baseline in Short-form McGill Pain Questionnaire Scores at Week 14 (Modified Intention-to-treat Analysis Set)

Parameter	Statistic	Mirogabalin (n = 150)	Placebo (n = 149)
Visual analogue scale			
Baseline	n	149	149
	Mean ± SD	63.3 ± 12.36	63.8 ± 13.08
Week 14[a]	n	150	149
	Mean ± SD	48.9 ± 20.39	56.4 ± 20.97
Change from baseline at Week 14[a]	n	148	149
	Mean ± SD	−14.2 ± 19.09	−7.4 ± 18.22
	Difference of LS mean *vs* placebo ± SE	−6.9 ± 2.13	—
	(95% CI); *p* value	(−11.1, −2.7); 0.0013	—
Sensory score			
Baseline	n	150	149
	Mean ± SD	10.3 ± 6.26	10.6 ± 6.51
Week 14[a]	n	150	149
	Mean ± SD	6.9 ± 5.63	8.7 ± 6.73
Change from baseline at Week 14[a]	n	149	149
	Mean ± SD	−3.4 ± 5.63	−1.8 ± 4.47
	Difference of LS mean *vs* placebo ± SE	−1.7 ± 0.53	—
	(95% CI); *p* value	(−2.7, −0.6); 0.0017	—
Affective score			
Baseline	n	150	149
	Mean ± SD	3.0 ± 2.77	2.7 ± 2.54
Week 14[a]	n	150	149
	Mean ± SD	1.6 ± 2.22	2.2 ± 2.51
Change from baseline at Week 14[a]	n	149	149
	Mean ± SD	−1.4 ± 2.30	−0.6 ± 1.92
	Difference of LS mean *vs* placebo ± SE	−0.7 ± 0.21	—
	(95% CI); *p* value	(−1.1, −0.3); 0.0005	—
Total score			
Baseline	n	150	149
	Mean ± SD	13.3 ± 8.62	13.3 ± 8.58

Week 14[a]	n	150	149
	Mean ± SD	8.5 ± 7.49	10.9 ± 8.88
Change from baseline at Week 14[a]	n	149	149
	Mean ± SD	−4.8 ± 7.40	−2.4 ± 5.88
	Difference of LS mean *vs* placebo ± SE	−2.4 ± 0.69	—
	(95% CI); *p* value	(−3.8, −1.1); 0.0005	—
Present pain intensity			
Baseline	n	150	149
	Mean ± SD	2.4 ± 0.93	2.4 ± 0.85
Week 14[a]	n	150	149
	Mean ± SD	1.8 ± 0.88	2.2 ± 1.09
Change from baseline at Week 14[a]	n	149	149
	Mean ± SD	−0.6 ± 0.92	−0.3 ± 0.95
	Difference of LS mean *vs* placebo ± SE	−0.3 ± 0.10	—
	(95% CI); *p* value	(−0.5, −0.1); 0.0016	—

Abbreviations: CI = confidence interval; LOCF = last observation carried forward; LS = least-squares; SD = standard deviation; SE = standard error.

[a]Missing values were imputed using the LOCF approach, and the data were analyzed based on the analysis of covariance model with treatment as a fixed effect and baseline value as a covariate.

Table 4. Changes from Baseline at Week 14 in Total Score and Subscores of the NPSI, ADSIS, PGIC, and EQ-5D-5L (Modified Intention-to-treat Analysis Set)

		Mirogabalin (n = 150)	Placebo (n = 149)
NPSI[a]			
Total score	Mean ± SD	−12.0 ± 15.47	−4.5 ± 15.90
	Difference of LS mean *vs* placebo ± SE (95% CI); *p* value	−7.7 ± 1.70 (−11.1, −4.4); <0.0001	—
Superficial spontaneous pain	Mean ± SD	−1.5 ± 2.55	−0.3 ± 2.57
	Difference of LS mean *vs* placebo ± SE (95% CI); *p* value	−1.2 ± 0.26 (−1.7, −0.6); <0.0001	—
Deep spontaneous pain	Mean ± SD	−2.7 ± 4.22	−1.2 ± 4.52
	Difference of LS mean *vs* placebo ± SE (95% CI); *p* value	−1.7 ± 0.45 (−2.5, −0.8); 0.0003	—
Paroxysmal pain	Mean ± SD	−2.5 ± 4.40	−0.9 ± 4.78
	Difference of LS mean *vs* placebo ± SE (95% CI); *p* value	−1.6 ± 0.46 (−2.5, −0.7); 0.0006	—
Evoked pain	Mean ± SD	−2.6 ± 5.80	−1.0 ± 6.52
	Difference of LS mean *vs* placebo ± SE (95% CI); *p* value	−1.8 ± 0.65 (−3.1, −0.5); 0.0059	—
Paresthesia/dysesthesia	Mean ± SD	−2.7 ± 4.29	−1.2 ± 3.67
	Difference of LS mean *vs* placebo ± SE (95% CI); *p* value	−1.5 ± 0.43 (−2.4, −0.7); 0.0004	—
ADSIS[b]			
Baseline	Mean ± SD	4.03 ± 2.262	3.66 ± 2.306
Week 14	Mean ± SD	2.88 ± 2.157	3.31 ± 2.402
Change from baseline at Week 14	Mean ± SD	−1.14 ± 1.705	−0.35 ± 1.306
	Difference of LS mean *vs* placebo ± SE (95% CI); *p* value	−0.71 ± 0.166 (−1.04, −0.38); <0.0001	—
PGIC[c]			
Scores at Week 14			
1 (very much improved)	n (%)	4 (2.7)	2 (1.3)
2 (much improved)	n (%)	22 (14.7)	9 (6.0)
3 (minimally improved)	n (%)	54 (36.0)	42 (28.2)
4 (no change)	n (%)	39 (26.0)	54 (36.2)
5 (minimally worse)	n (%)	11 (7.3)	18 (12.1)
6 (much worse)	n (%)	2 (1.3)	6 (4.0)

7 (very much worse)	n (%)	1 (0.7)	1 (0.7)
Missing	n (%)	17 (11.3)	17 (11.4)
Much improved or better (≤2)	n (%)	26 (17.3)	11 (7.4)
	OR (95% CI); *p* value	2.63 (1.25, 5.54); 0.0110	—
Minimally improved or better (≤3)	n (%)	80 (53.3)	53 (35.6)
	OR (95% CI); *p* value	2.07 (1.30, 3.29); 0.0021	—
EQ-5D-5L[d]			
Index Value			
Baseline	Mean ± SD	0.5401 ± 0.24694	0.5122 ± 0.22922
Week 14	Mean ± SD	0.5796 ± 0.23768	0.5275 ± 0.23894
Change from baseline at Week 14	Mean ± SD	0.0395 ± 0.13627	0.0153 ± 0.13397
	Difference of LS mean *vs* placebo ± SE (95% CI); *p* value	0.0287 ± 0.01504 (−0.0009, 0.0583); 0.0572	—
Visual Analogue Scale			
Baseline	Mean ± SD	59.3 ± 19.53	60.1 ± 19.48
Week 14	Mean ± SD	64.2 ± 19.69	58.3 ± 20.20
Change from baseline at Week 14	Mean ± SD	4.9 ± 21.76	−1.8 ± 21.28
	Difference of LS mean *vs* placebo ± SE (95% CI); *p* value	6.2 ± 2.11 (2.0, 10.4); 0.0037	—

[a] Missing values at Week 14 were imputed using the LOCF approach and the imputed value was analyzed based on an ANCOVA model including treatment as fixed effect and baseline values as covariates.

[b] Missing weekly ADSIS data at Week 14 were imputed using the LOCF approach and the imputed weekly ADSIS data were analyzed based on an ANCOVA model including treatment as fixed effects and baseline ADSIS as the covariate.

[c] Patients with missing data at Week 14 were classified as non-responders and logistic regression analysis with treatment as a factor was applied for comparisons *vs* placebo.

[d] Analyzed based on ANCOVA model including treatment as fixed effect and baseline values as covariates. Missing data were imputed using the LOCF approach.

Abbreviations: ADSIS = average daily sleep interference score; ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels; LOCF = last observation carried forward; LS = least-squares; NPSI = Neuropathic Pain Symptom Inventory; PGIC = Patient Global Impression of Change; OR = odds ratio; SD = standard deviation; SE = standard error.

Table 5. TEAEs with an Incidence of ≥5% in Either Treatment Group

	Mirogabalin (n = 151)[a]				Placebo (n = 148)				Total (N = 299)			
	Mild	**Moderate**	**Severe**	**Total**	**Mild**	**Moderate**	**Severe**	**Total**	**Mild**	**Moderate**	**Severe**	**Total**
Number of patients with ≥1 TEAE (%)	84 (55.6)	28 (18.5)	6 (4.0)	118 (78.1)	61 (41.2)	20 (13.5)	1 (0.7)	82 (55.4)	145 (48.5)	48 (16.1)	7 (2.3)	200 (66.9)
TEAEs by PT (%)												
Somnolence	34 (22.5)	11 (7.3)	0 (0.0)	45 (29.8)	6 (4.1)	2 (1.4)	0 (0.0)	8 (5.4)	40 (13.4)	13 (4.3)	0 (0.0)	53 (17.7)
Dizziness	11 (7.3)	2 (1.3)	0 (0.0)	13 (8.6)	4 (2.7)	1 (0.7)	0 (0.0)	5 (3.4)	15 (5.0)	3 (1.0)	0 (0.0)	18 (6.0)
Nasopharyngitis	12 (7.9)	0 (0.0)	0 (0.0)	12 (7.9)	8 (5.4)	0 (0.0)	0 (0.0)	8 (5.4)	20 (6.7)	0 (0.0)	0 (0.0)	20 (6.7)
Weight increased	8 (5.3)	3 (2.0)	0 (0.0)	11 (7.3)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	9 (3.0)	3 (1.0)	0 (0.0)	12 (4.0)
Constipation	7 (4.6)	2 (1.3)	0 (0.0)	9 (6.0)	1 (0.7)	1 (0.7)	0 (0.0)	2 (1.4)	8 (2.7)	3 (1.0)	0 (0.0)	11 (3.7)
Edema peripheral	8 (5.3)	1 (0.7)	0 (0.0)	9 (6.0)	2 (1.4)	0 (0.0)	0 (0.0)	2 (1.4)	10 (3.3)	1 (0.3)	0 (0.0)	11 (3.7)

[a] One patient from the placebo group who mistakenly received mirogabalin was included in the mirogabalin arm of the safety analysis.

Coded by the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0

Abbreviations: PT = Preferred Term; TEAE = treatment-emergent adverse event.

Figure Legends

Figure 1. Patient Disposition

[a]One patient from the placebo group received mirogabalin by mistake and was therefore included in the mirogabalin arm for the safety analysis.

Abbreviation: mITT = modified intention-to-treat.

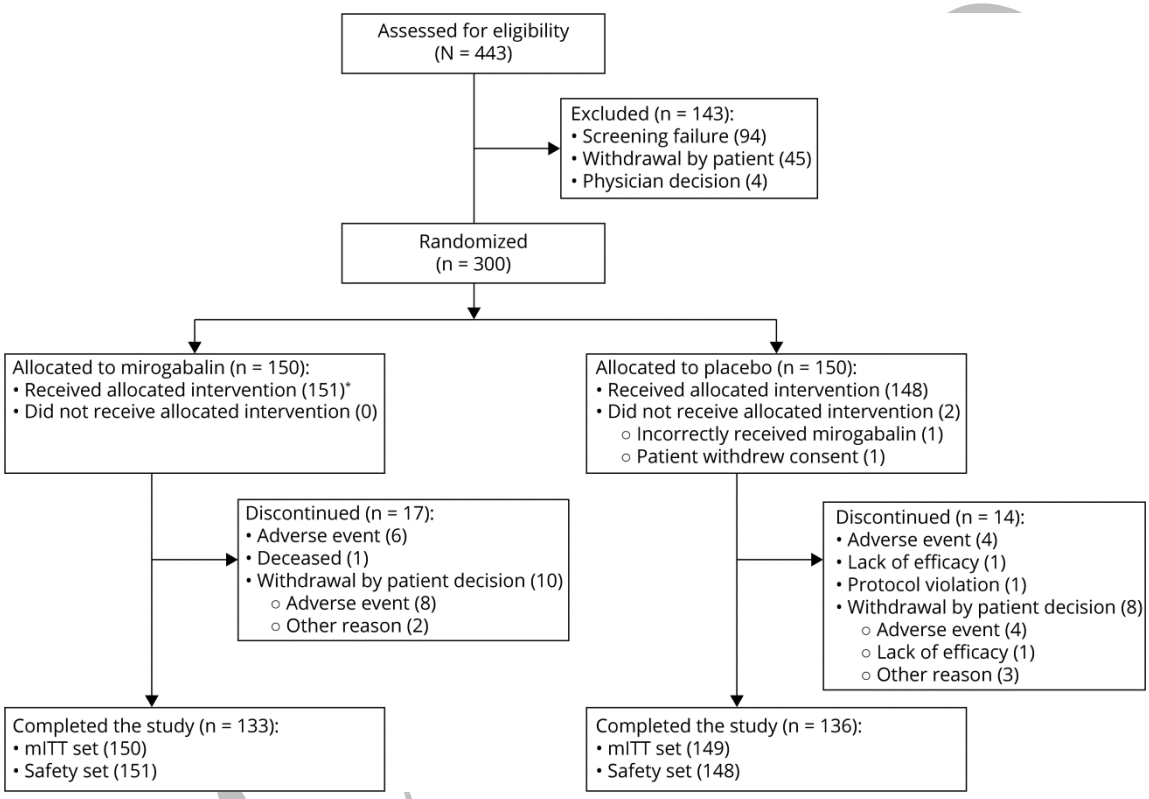
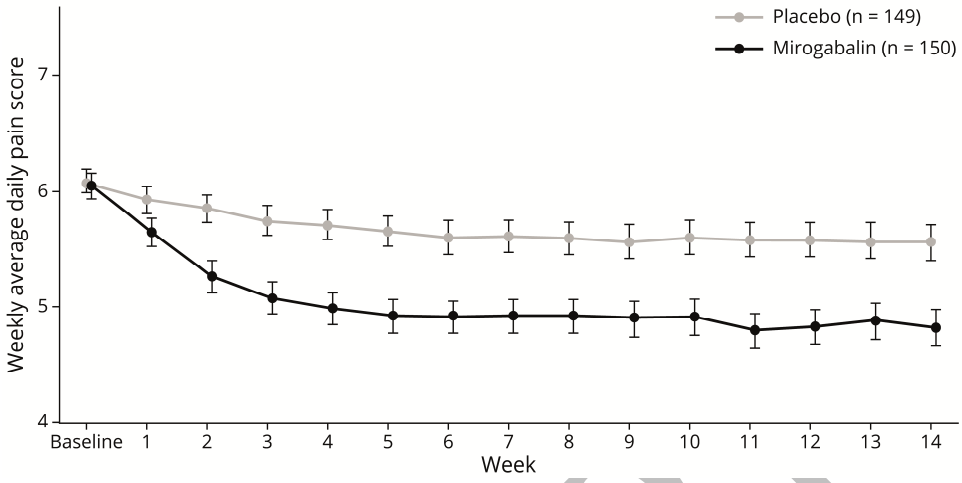


Figure 2. Time-course of Least-squares Mean Weekly Average Daily Pain Score

Data were imputed using a multiple imputation method based on a "nonfuture dependence" model using a pattern mixture approach under the missing not at random mechanism. Error bars represent SE.

Abbreviation: SE = standard error.



Mirogabalin for Central Neuropathic Pain After Spinal Cord Injury: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study in Asia

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