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ORIGINAL RESEARCH

Efficacy and Safety of Mirogabalin in Patients with Neuropathic Pain Due to Cervical Spondylotic Radiculopathy: Miro-Cens, A Randomized, Controlled, Interventional Study

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ABSTRACT

Introduction: There are few studies of pharmacotherapy of neuropathic pain in cervical spondylotic radiculopathy (CSR). Miro-Cens aimed to examine the efficacy and safety of mirogabalin for treating pain in patients with CSR on non-steroidal anti-inflammatory drugs (NSAIDs), compared with NSAIDs alone.

Methods: Miro-Cens was a 12-week, multicenter, randomized, controlled, open-label, interventional study in Japan. Eligible patients with CSR having upper limb pain (visual analog scale score ≥ 40 mm) were randomly assigned in a 1:1 ratio to the mirogabalin add-on to NSAIDs group and the NSAIDs alone group. The primary endpoint was the change in the weekly average numerical rating scale (NRS) score for upper limb pain from baseline at Week 12.

Results: The mirogabalin add-on group and NSAIDs alone group included 72 and 70 patients, respectively. The mirogabalin add-on group had a significantly greater reduction in the NRS score for upper limb pain than the NSAIDs alone group: estimated changes from baseline at Week 12, – 2.63 [95% confidence interval (CI) – 3.14, – 2.11] in the mirogabalin add-on group; – 1.07 (– 1.62, – 0.53) in the NSAIDs alone group; intergroup difference, – 1.55 (– 2.31, – 0.80; $p < 0.001$). The responder rate on the NRS score at Week 12 was significantly higher in the mirogabalin add-on group than in the NSAIDs alone group: ≥ 30% improvement, 71.7% vs. 39.6%; ≥ 50% improvement, 58.3% vs. 22.6% (both $p < 0.001$). The frequent treatment-emergent adverse drug reactions in the mirogabalin add-on group were the known ones (somnolence and dizziness), with most being mild or moderate in severity.

Conclusion: In patients with CSR, combination therapy with mirogabalin and NSAIDs

Prior Publication: The rationale and design of this study were previously presented at the 53rd Annual Meeting of the Japanese Society for Spine Surgery and Related Research (April 18–20, 2024, Kanagawa, Japan).

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significantly improved neuropathic pain compared with NSAID monotherapy. No new safety concerns were identified, although caution should be exercised regarding somnolence and dizziness. These findings suggest that concomitant use of mirogabalin with NSAIDs could be tolerable and a novel treatment option for CSR patients with insufficient analgesic effects on NSAIDs.
***Trial Registration Number*:** jRCTs031210629.

Keywords: $\alpha_2\delta$ ligand; Cervical spondylotic radiculopathy; Gabapentinoid; Mirogabalin; Neuropathic pain; NSAID; Randomized, controlled, interventional study

Key Summary Points

Why carry out this study?

Although conservative therapy is considered the preferred initial intervention, there is little evidence regarding pharmacotherapy options in the treatment of pain in cervical spondylotic radiculopathy (CSR).

We conducted Miro-Cens to examine the efficacy and safety of mirogabalin for treating neuropathic pain in patients with CSR on non-steroidal anti-inflammatory drugs (NSAIDs), compared with NSAIDs alone.

What was learned from the study?

In patients with CSR, combination therapy with mirogabalin and NSAIDs significantly improved neuropathic pain compared with NSAID monotherapy.

Although known treatment-emergent adverse drug reactions (TEADRs) were frequently observed in patients treated with mirogabalin combination therapy, most TEADRs were mild or moderate in severity, indicating that combination therapy of mirogabalin and NSAIDs is tolerable without any novel safety concerns.

INTRODUCTION

Cervical spondylotic radiculopathy (CSR), caused by spinal foraminal stenosis due to degenerative change and/or intervertebral herniation, is a common type of cervical spondylosis [1]. Patients with CSR experience neck pain and unilateral radicular pain, and their neck movements are restricted, which can decrease their quality of life (QoL) and interfere with their activities of daily living (ADL). Treatment of CSR can range from conservative therapy to surgery, and the recent systematic review reported that surgical treatment can provide a faster pain relief, but did not have a significant advantage in range of motion or the Neck Disability Index compared with conservative treatment [2]. If patients need rapid pain relief, such as those with signs of refractory painful neuropathy or significant motor weakness, surgical treatments are effective and necessary. However, in the clinical setting, the preferred approach for treating CSR is basically conservative treatment as the first intervention because it avoids the complications of surgical treatment.

The manifestations of CSR occur as a result of underlying nerve root compression, and the pain and numbness, therefore, include both nociceptive and neuropathic components [3–5]. In clinical practice in Japan, the first-line treatment of nociceptive pain is often non-steroidal anti-inflammatory drugs (NSAIDs), but residual pain continues in some patients, which is thought to be derived from the neuropathic component. In such cases, various neuropathic pain (NeP) medications, such as mecobalamin and pregabalin, are used as monotherapy or combination therapy with NSAIDs. However, very few studies have examined the pharmacotherapy options in the treatment of NeP in patients with CSR.

A randomized, controlled trial reported that an $\alpha_2\delta$ ligand, pregabalin, in combination with NSAIDs, was an effective treatment option for patients with CSR with NeP [6]. However, the study did not compare the pregabalin combination therapy with NSAID monotherapy. In another prospective, observational study, pregabalin alone or in combination with pregabalin

and conventional therapy improved the pain of patients with cervical radiculopathy [7], but this study included a mixed study population having cervical radiculopathy with neck pain radiating to the arms and lumbosacral radiculopathy with calf or foot pain. Thus, at present, in patients having only CSR, the therapeutic efficacy and safety of pregabalin, and even $\alpha_2\delta$ ligands, are not fully understood.

Mirogabalin besylate (mirogabalin) is another oral gabapentinoid that is a selective $\alpha_2\delta$ ligand. In Japan, based on the results of several phase 3 studies [8–11], it has been approved for the treatment of NeP [12]. In randomized, controlled, clinical studies, mirogabalin was shown to significantly improve leg pain from lumbar spinal canal stenosis in combination with NSAIDs compared with NSAIDs alone [13], and it was also shown to significantly reduce pain after traumatic spinal cord injury compared with placebo [10]. However, no studies to date have examined the efficacy and safety of mirogabalin for NeP in CSR patients.

The present study, Miro-Cens, examined the efficacy and safety of the combination therapy of mirogabalin with NSAIDs for treating NeP caused by cervical spondylosis, compared with that of NSAIDs alone.

METHODS

Study Design

Miro-Cens was a multicenter, randomized, open-label, parallel group, interventional study in 35 centers in Japan between March 2022 and April 2024 (Fig. 1). A complete list of investigators and institutions is shown in the Acknowledgements section. Eligible patients were randomly assigned in a 1:1 ratio to each treatment group by a registration system using the permuted block method based on the numerical rating scale (NRS) score (< 6 or ≥ 6) for pain at study enrollment (baseline) as an allocation factor.

The study was approved by Tokyo Medical and Dental University (current name, Institution of Science Tokyo) Certified Review Board (CRB No. 3240003). The study was conducted

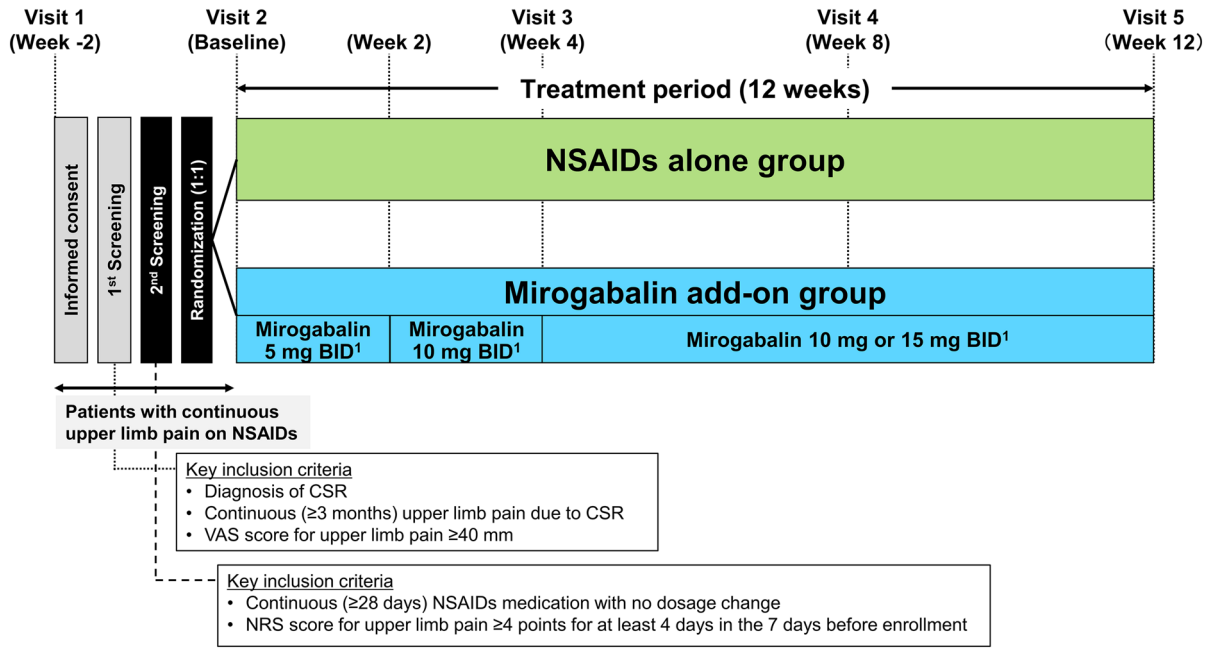

Fig. 1 Study design. [1]Dose for patients with CrCL of ≥ 60 mL/min. Patients with CrCL of 30 to < 60 mL/min receive half the dose of mirogabalin. *BID* twice daily, *CrCL* creatinine clearance, *CSR* cervical spondylotic radiculopathy, *NRS* numerical rating scale, *NSAIDs* non-steroidal anti-inflammatory drugs, *VAS* visual analog scale

in accordance with the Clinical Trials Act in Japan, as well as the ethical principles and relevant notifications stipulated in the Declaration of Helsinki (as revised in 2013). This study was registered in the Japan Registry of Clinical Trials under the identifier, jRCTs031210629. All patients provided informed consent to participate in the study.

Intervention

NSAIDs were given according to their Japanese package inserts, and no dose changes were permitted during the study period in either treatment group. Mirogabalin was administered based on patient's baseline renal function according to its Japanese package insert [12]: for patients with creatinine clearance (CrCL) ≥ 60 mL/min, mirogabalin was administered at 5 mg twice daily (BID) for the first 2 weeks, 10 mg BID for the next 2 weeks, and 15 mg BID or 10 mg BID after Week 5; and for patients with CrCL 30 to < 60 mL/min, the dose of mirogabalin was half that for those with CrCL ≥ 60 mL/min.

The use of concomitant medications, such as gabapentin, pregabalin, duloxetine, opioids, probenecid, cimetidine, and lorazepam, nerve blocks and any surgical analgesic treatments that might affect the efficacy assessment of upper extremity pain caused by CSR were prohibited during study participation.

Patients

After informed consent was obtained, patients were screened for study eligibility in steps. Inclusion criteria were: at the first screening, age ≥ 20 years at the time of consent; a diagnosis of CSR with continuous upper limb pain for ≥ 3 months before enrollment and upper limb pain [visual analog scale (VAS) rating ≥ 40 mm] at enrollment; at the second screening, continuously received NSAIDs with no dosage change (≥ 28 days before enrollment); and with mean NRS score for upper limb pain ≥ 4 points in the 7 days before enrollment. A diagnosis of CSR was based on the following criteria: (1) patients with pain/numbness of a unilateral arm or hand; (2) positive on the Spurling test [14] or the Jackson test; (3) cervical spondylotic changes on X-ray, CT, or MRI; and (4) a clear diagnosis of radiculopathy pain based on other neurological findings even if the Spurling test or the Jackson test was negative.

Key exclusion criteria were: patients with severe pain caused by other than CSR for whom pain assessment was difficult; cervical spondylotic myelopathy; history of cervical spine surgery; CrCL < 30 mL/min; history of mirogabalin use within 28 days prior to obtaining consent; Brief Scale for Psychiatric Problems in Orthopaedic Patients score ≥ 11 for physicians or both ≥ 10 for physicians and ≥ 15 for patients at enrollment [15]; received prohibited concomitant drugs and therapies in the 14 days before enrollment; and having serious underlying disease and complications.

Endpoints

The primary endpoint was the change in the weekly average NRS score for upper limb pain from baseline at Week 12 [16]. Patients were asked to rate the pain they had experienced over the previous 7 days on an 11-point NRS ranging from 0 ("no pain") to 10 ("worst pain possible").

Secondary endpoints included: responder rate ≥ 30% or ≥ 50% reduction in the NRS score of the primary endpoint; change from baseline in the VAS score for upper limb pain (range 0–100 mm, with 0 mm meaning no pain and 100 mm meaning the worst pain imaginable); change from baseline in the EQ-5D-5L score [17]; Patient Global Impression of Change (PGIC) score at Week 12 (1 = "very much improved" to 7 = "very much worse"); and change from baseline in the weekly average NRS score for sleep disturbance (0 = "no sleep disturbance" to 10 = "sleep completely disturbed by pain").

The safety endpoints included the incidences of treatment-emergent adverse events (TEAEs) and of treatment-emergent adverse drug reactions (TEADRs).

Sample Size

Based on the results of previous phase 3 clinical trials of mirogabalin [8, 9], the difference

between two groups in the mean weekly change in the NRS score from baseline at Week 12 was estimated to be 1.2, with a standard deviation (SD) of 2.4. Under this assumption, the number of patients needed to ensure 80% power at a two-sided significance level of 5% was 128 (64 for each group). Given possible dropouts, the target sample size was set at 140 (70 for each group) patients.

Statistical Analysis

The primary efficacy analyses used the modified intention-to-treat (mITT) population, which was defined as all randomized patients who received at least one dose of the study drug. A linear mixed model for repeated measures (MMRM) was used to calculate the estimated differences in adjusted means between the mirogabalin add-on group and the NSAIDs alone group, 95% confidence intervals (CIs), and *P* values for the primary endpoint data. The MMRM included treatment group, treatment duration (week), and treatment group–week interactions as fixed effects, the weekly mean NRS score for upper limb pain at baseline as a covariate, and patients as a random effect. A similar MMRM was used for the secondary efficacy endpoints. As a sensitivity analysis, the last observation carried forward (LOCF) and baseline observation carried forward (BOCF) methods were used to impute the weekly mean NRS scores at Week 12 in the mITT population. Then, analysis of covariance (ANCOVA) was used to compare estimated differences in adjusted means between treatment groups, 95% CIs, and *P* values. The same analysis was also carried out in the per-protocol set (PPS), which was defined as all patients in the mITT population who adhered to the study protocol and the package inserts.

For the safety analyses, the safety analysis set was used, which was defined as all patients enrolled in the study who received at least one dose of the study drug. TEAEs were coded using the Japanese Medical Dictionary for Regulatory Activities version 27.0. A TEADR was defined as a TEAE judged by the attending physician to have a causal relationship with the study drug.

The significance level for hypothesis testing was set at 5% (two-sided). Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patients

Of the 168 patients screened, 143 met the eligibility criteria and were randomly assigned to the mirogabalin add-on and NSAIDs alone groups (Fig. 2). Both the mITT population and safety analysis set included 72 patients in the mirogabalin add-on group and 70 patients in the NSAIDs alone group. After exclusion of patients who were non-compliant with the study protocol and package insert of study drugs, 60 and 66 patients, respectively, constituted the PPS. The proportions of patients who completed the study in the mITT population were 84.7% (61/72) and 78.6% (55/70) in the mirogabalin add-on group and NSAIDs alone group, respectively. The most common reason for study withdrawal in the mirogabalin add-on group was the occurrence of TEAEs.

The patients' baseline characteristics are shown in Table 1 for the mITT population and Table S1 for the PPS. Baseline characteristics were similar between the mirogabalin add-on and NSAIDs alone groups, including the respective mean ages (59.1 and 57.6 years), proportions of male patients (56.9% and 60.0%), mean body mass index (24.9 and 24.2 kg/m^2), mean CrCL values (91.5 and 88.6 mL/min), patients with CrCL ≥ 60 mL/min (81.9% and 87.1%), mean VAS score for upper limb pain (64.4 and 61.2 mm), weekly mean average NRS score for upper limb pain (5.99 and 5.93), and the mean duration of CSR (22.3 and 22.8 months). The common NSAIDs prescribed were celecoxib and loxoprofen.

The daily dose of mirogabalin according to renal function is shown in Table S2. Most patients with CrCL ≥ 60 mL/min received 10 or 15 mg BID (*n* = 47/51, 92.2%), and those with CrCL 30 to < 60 mL/min received 5 or 7.5 mg

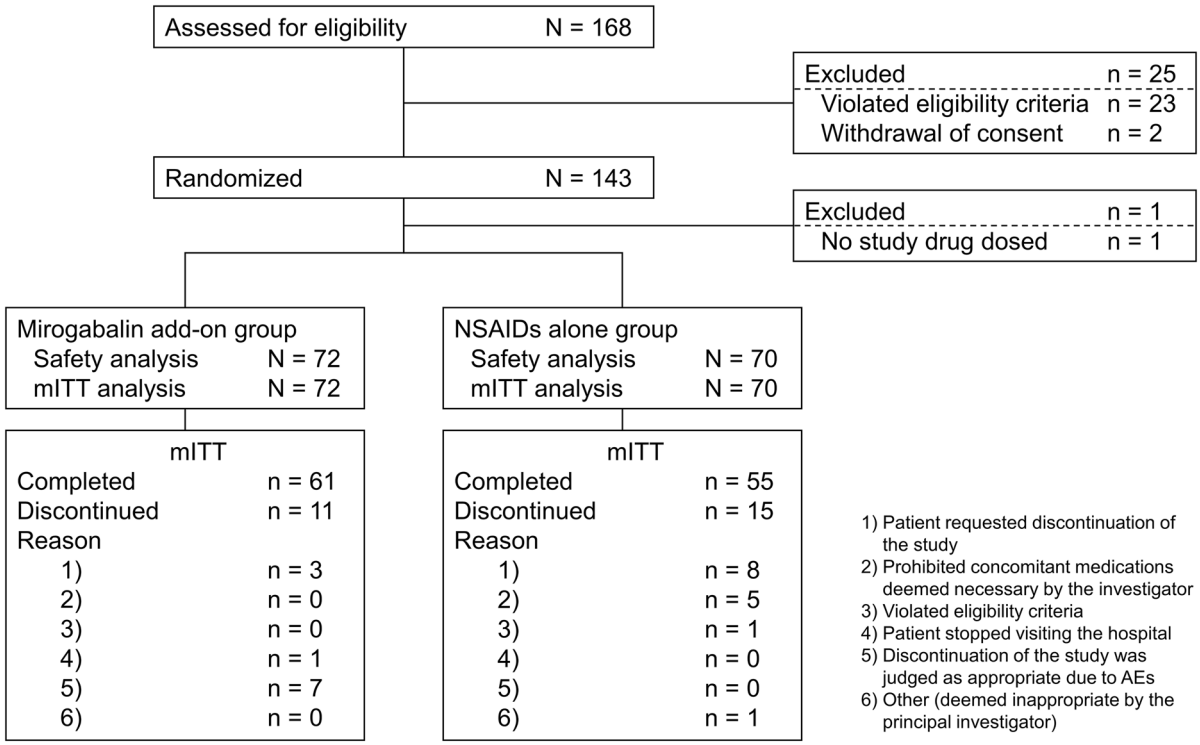

Fig. 2 Patient disposition. *AEs* adverse events, *mITT* modified intention-to-treat, *NSAIDs* non-steroidal anti-inflammatory drugs

BID (n = 8/8, 100%) at Week 12 in the mirogabalin add-on group.

Efficacy for Upper Limb Pain

Estimated changes in the MMRM from baseline at Week 12 in the NRS score for upper limb pain (the primary endpoint) were – 2.63 (95% CI – 3.14, – 2.11; $p < 0.001$ vs. baseline) and – 1.07 (– 1.62, – 0.53; $p < 0.001$ vs. baseline) in the mirogabalin add-on and NSAIDs alone groups, respectively (Fig. 3a, Table 2). The mirogabalin add-on group had a significantly greater reduction in the NRS score, with an intergroup difference of – 1.55 (– 2.31, – 0.80; $p < 0.001$), compared with the NSAIDs alone group. Sensitivity analysis also showed significant improvement in the mirogabalin add-on group (Table S3), and similar results were observed in the PPS (Fig. S1a, Table S3). The NRS score decreased gradually from baseline and decreased significantly from Week 4 to Week 12 in both treatment groups, and significant intergroup differences were also observed between the groups at Weeks 4 and 8 (Table S3). The decrease in NRS scores in the NSAIDs alone group plateaued from Week 8 to Week 12, but a downward trend after Week 12 was observed in the mirogabalin add-on group both in the mITT population and PPS (Fig. 3a, Fig. S1a).

The responder rate on the NRS score for upper limb pain at Week 12 was significantly higher in the mirogabalin add-on group than in the NSAIDs alone group: ≥ 30% improvement, 71.7% vs. 39.6%; ≥ 50% improvement, 58.3% vs. 22.6% (both $p < 0.001$ by Fisher's exact test) (Fig. 3b). Similar results were obtained in the PPS (Fig. S1b).

As with the NRS score, the VAS score for upper limb pain also showed significantly greater improvement from baseline at Week 12 in the mirogabalin add-on group than in the NSAID alone group: estimated changes in the MMRM from baseline, – 30.6 mm (95% CI – 37.0 mm, – 24.2 mm; $p < 0.001$ vs.

Table 1 Patients' characteristics (mITT population)

Characteristic	Mirogabalin add-on group (*n* = 72)	NSAIDs alone group (*n* = 70)
Age, years	59.1 ± 14.0	57.6 ± 12.0
≥ 65	28 (38.9)	21 (30.0)
Male/female	41 (56.9)/31 (43.1)	42 (60.0)/28 (40.0)
BMI, kg/m^2	24.9 ± 4.2	24.2 ± 2.9
≥ 25	36 (50.0)	24 (34.3)
CrCL, mL/min	91.5 ± 29.0	88.6 ± 26.0
30 to < 60	13 (18.1)	9 (12.9)
≥ 60	59 (81.9)	61 (87.1)
VAS score for upper limb pain, mm	64.4 ± 14.8	61.2 ± 15.3
Weekly average NRS score for upper limb pain	5.99 ± 1.45	5.93 ± 1.36
< 6	36 (50.0)	35 (50.0)
≥ 6	36 (50.0)	35 (50.0)
Weekly average NRS score for sleep disturbance	2.95 ± 2.59	2.73 ± 2.28
Duration of CSR, months	22.3 ± 36.6	22.8 ± 37.6
Median (Q1, Q3)	8.5 (4.0, 19.5)	7.0 (4.0, 21.0)
< 6	27 (37.5)	28 (40.0)
≥ 6	45 (62.5)	42 (60.0)
Duration of upper limb pain after CSR onset, months	26.8 ± 44.4	21.2 ± 35.9
Complication	26 (36.1)	32 (45.7)
Diabetes mellitus	7 (9.7)	8 (11.4)
Peripheral arterial disease	0	0
Stroke	1 (1.4)	1 (1.4)
Hypertension	17 (23.6)	21 (30.0)
Hyperlipidemia	13 (18.1)	13 (18.6)
Surgical history other than on the cervical spine	7 (9.7)	8 (11.4)
Thoracic spine	0	1 (1.4)
Lumbar spine	7 (9.7)	8 (11.4)
Sacral vertebrae	0	0
Coccygeal vertebrae	0	0
NSAIDs used per the package insert with no change in dosage	71 (98.6)	70 (100.0)

Table 1 continued

Characteristic	Mirogabalin add-on group (n = 72)	NSAIDs alone group (n = 70)
NSAID type		
Celecoxib (p.o.)	32 (44.4)	26 (37.1)
Loxoprofen sodium hydrate (p.o.)	23 (31.9)	23 (32.9)
Loxoprofen sodium hydrate (us.ext.)	9 (12.5)	13 (18.6)
Etodolac (p.o.)	3 (4.2)	7 (10.0)
Lornoxicam (p.o.)	4 (5.6)	2 (2.9)
Ketoprofen (us.ext.)	4 (5.6)	2 (2.9)
Diclofenac sodium (us.ext.)	3 (4.2)	2 (2.9)
Felbinac (us.ext.)	3 (4.2)	1 (1.4)
Diclofenac sodium (p.o.)	2 (2.8)	2 (2.9)
Zaltoprofen (p.o.)	0	1 (1.4)
Meloxicam (p.o.)	1 (1.4)	0
Compliant with package inserts of both mirogabalin and NSAIDs	67 (93.1)	70 (100.0)

Data are mean ± SD or n (%) values unless otherwise indicated

BMI body mass index, *CrCL* creatinine clearance, *CSR* cervical spondylotic radiculopathy, *mITT* modified intention-to-treat, *NRS* numerical rating scale, *NSAIDs* non-steroidal anti-inflammatory drugs, *SD* standard deviation, *VAS* visual analog scale, *p.o.* oral administration, *us.ext.* topical medicine

baseline) vs. – 13.3 mm (– 20.0 mm, – 6.6 mm; $p < 0.001$ vs. baseline) with an intergroup difference of – 17.3 mm (– 26.5 mm, – 8.0 mm; $p < 0.001$) (Table S4). Similar results were obtained in the PPS (Table S4).

Efficacy for QoL Score

EQ-5D-5L scores increased gradually from baseline to Week 12 in both treatment groups and improved significantly from baseline at Weeks 4, 8, and 12 (Fig. 4; Table S5). The estimated change in the MMRM from baseline at Week 12 was numerically higher in the mirogabalin add-on group than in the NSAIDs alone group (0.0640 vs. 0.0411; $p = 0.278$), but this difference was not significant. The same tendency was observed in the PPS (Table S5). Results for the EQ-5D-5L VAS score are shown in Table S5.

Other Efficacy

Almost all patients (n = 54/60, 90.0%) in the mirogabalin add-on group, and more than half of patients (n = 30/54, 55.6%) reported improvement of PGIC at Week 12 in the NSAIDs alone group (Table S6). The proportions of patients with PGIC scores ≤ 2 (more than much improved) and ≤ 3 (more than minimally improved) were significantly higher in the mirogabalin add-on group than in the NSAIDs alone group: ≤ 2, 65.0% vs. 33.3% ($p = 0.001$ by Fisher's exact test); ≤ 3, 90.0% vs. 55.6%, respectively ($p < 0.001$ by Fisher's exact test) (Fig. 5). The same trends were observed in the PPS (Table S6).

The NRS score for sleep disturbance decreased from baseline at Week 12 in both treatment

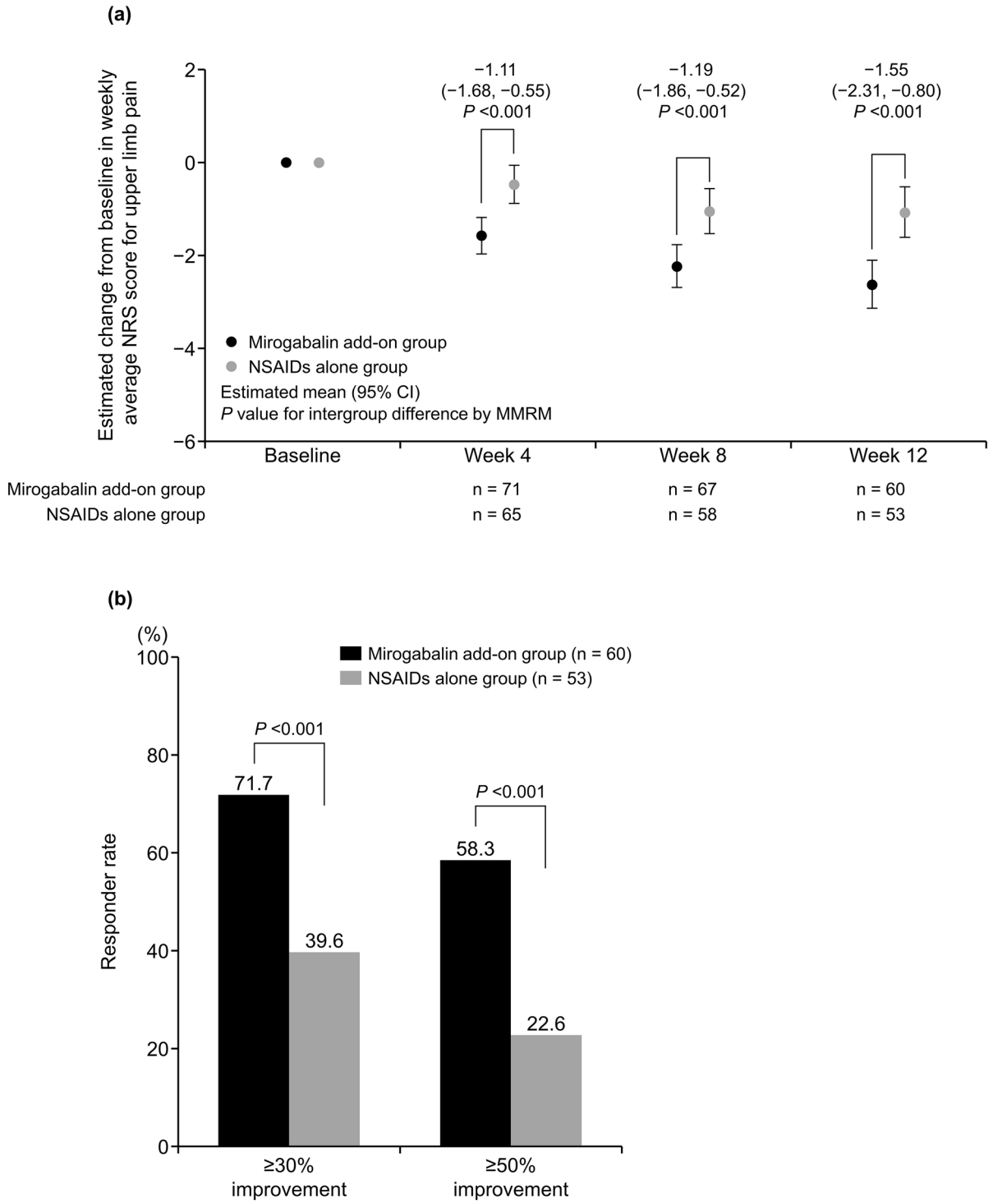

Fig. 3 (**a**) Estimated change from baseline in the weekly average NRS score for upper limb pain over 12 weeks and (**b**) responder rate on the NRS score for upper limb pain at Week 12 (mITT population). For panel (**a**), data for NRS scores are estimated mean (95% CI) values. *p* value for intergroup difference by MMRM analysis. *Error bars* indicate 95% CIs. For (**b**), *p* value by Fisher's exact test. *CI* confidence interval, *MMRM* mixed model for repeated measures, *mITT* modified intention-to-treat, *NRS* numerical rating scale, *NSAIDs* non-steroidal anti-inflammatory drugs

Table 2 Estimated changes in NRS scores for upper limb pain from baseline at Week 12 (mITT population)

	Mirogabalin add-on group	NSAIDs alone group
Primary analysis (MMRM)	$n = 60$	$n = 53$
Estimated change (95% CI) from baseline	− 2.63 (− 3.14, − 2.11) $P < 0.001$[a]	− 1.07 (− 1.62, − 0.53) $P < 0.001$[a]
Difference in estimated mean change (95% CI)	− 1.55 (− 2.31, − 0.80) $P < 0.001$[b]	–

CI confidence interval, *mITT* modified intention-to-treat, *MMRM* mixed model for repeated measures, *NRS* numerical rating scale, *NSAIDs* non-steroidal anti-inflammatory drugs

[a]Versus baseline

[b]Versus the NSAIDs alone group

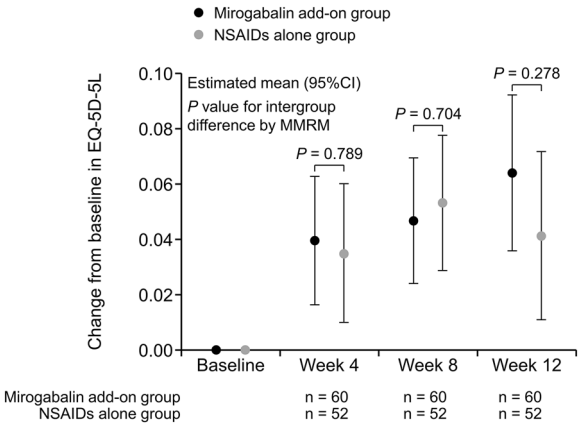

Fig. 4 Estimated change from baseline in EQ-5D-5L score over 12 weeks (mITT population). Data for EQ-5D-5L scores are estimated mean (95% CI) values. *p* value for intergroup difference by MMRM analysis. *Error bars* indicate 95% CIs. A linear mixed MMRM including treatment group, treatment duration (week), and treatment group–week interactions as fixed effects, the EQ-5D-5L score at baseline as a covariate, and patients as a random effect. *CI* confidence interval, *MMRM* mixed model for repeated measures, *mITT* modified intention-to-treat, *NSAIDs* non-steroidal anti-inflammatory drugs

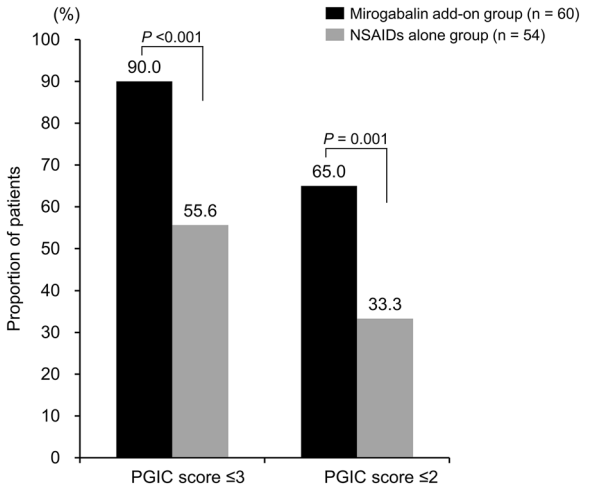

Fig. 5 Proportions of patients with PGIC score ≤ 2 and ≤ 3 at Week 12 (mITT population). Data are % of patients. *p* value by Fisher's exact test. *mITT* modified intention-to-treat, *NSAIDs* non-steroidal anti-inflammatory drugs, *PGIC* Patient Global Impression of Change

groups and was significantly improved in the mirogabalin add-on group compared with the NSAIDs alone group: estimated changes in the MMRM from baseline, − 1.12 (95% CI − 1.54, − 0.69) vs. − 0.49 (− 0.94, − 0.04) with an intergroup difference of − 0.63 (− 1.25, − 0.01; $p = 0.046$) (Fig. S2; Table S7). The same tendency was observed in the PPS (Table S7).

Safety

The incidences of TEAEs were 48.6% and 8.6% in the mirogabalin add-on and NSAIDs alone groups, respectively (Table 3). In the mirogabalin add-on group, frequent TEAEs were somnolence (23.6%) and dizziness (13.9%); most TEAEs were mild or moderate in severity. TEADRs occurred in 38.9% of patients in the mirogabalin add-on group, with somnolence (23.6%) and dizziness

Table 3 TEAEs and TEADRs (safety analysis set)

	Mirogabalin add-on group (*n* = 72)	**NSAIDs alone group (*n* = 70)**
Any TEAEs	35 (48.6)	6 (8.6)
TEAEs occurring in ≥ 2% of patients in either treatment group[a]		
Somnolence	17 (23.6)	0
Dizziness	10 (13.9)	0
COVID-19	3 (4.2)	0
Abdominal discomfort	2 (2.8)	0
Edema	2 (2.8)	0
Conjunctivitis	1 (1.4)	1 (1.4)
Herpes zoster	1 (1.4)	1 (1.4)
Oropharyngeal pain	0	1 (1.4)
Gastrooesophageal reflux disease	0	1 (1.4)
Urticaria	0	1 (1.4)
Skin mass	0	1 (1.4)
Serious TEAEs	1 (1.4)[b]	0
TEAEs leading to study discontinuation	4 (5.6)	0
Any TEADRs	28 (38.9)	0
Somnolence	17 (23.6)	0
Dizziness	10 (13.9)	0
Edema	2 (2.8)	0
Anemia	1 (1.4)	0
Dizziness postural	1 (1.4)	0
Vertigo	1 (1.4)	0
Abdominal discomfort	1 (1.4)	0
Constipation	1 (1.4)	0
Nausea	1 (1.4)	0
Renal impairment	1 (1.4)	0
Erectile dysfunction	1 (1.4)	0
Fatigue	1 (1.4)	0
Edema peripheral	1 (1.4)	0
Thirst	1 (1.4)	0
Weight increased	1 (1.4)	0

Table 3 continued

	Mirogabalin add-on group (n = 72)	NSAIDs alone group (n = 70)
Falling	1 (1.4)	0
Serious TEADRs	0	0
TEADRs leading to study discontinuation	4 (5.6)	0

Data are n (%) values. Coded using MedDRA/J, version 27.0

MedDRA/J Japanese Medical Dictionary for Regulatory Activities, *NSAIDs* non-steroidal anti-inflammatory drugs, *TEADRs* treatment-emergent adverse drug reactions, *TEAEs* treatment-emergent adverse events

[a]For the NSAIDs alone group, all TEAEs are shown in the column

[b]Subarachnoid hemorrhage

(13.9%) being frequent. In the mirogabalin add-on group, a serious TEAE (subarachnoid hemorrhage) occurred in one patient, and it was not considered a TEADR (a TEAE related to mirogabalin treatment). In the mirogabalin add-on group, TEAEs leading to study discontinuation occurred in four patients (due to dizziness, somnolence, renal impairment, malaise, thirst, and fall), and all were considered TEADRs.

DISCUSSION

Miro-Cens was the first multicenter, randomized, controlled study to compare the efficacy and safety of mirogabalin in combination with NSAIDs and of NSAIDs alone in patients with CSR. A total of 143 patients were enrolled in this study, and baseline patient demographic and clinical characteristics were generally well balanced between the two treatment groups.

To exclude the possibility of pain of types other than neuropathic pain due to CSR, the present study included patients with CSR with pain who had upper limb pain VAS ≥ 40 mm for ≥ 3 months and mean NRS score for upper limb pain ≥ 4 points, even on continuous (≥ 28 days) NSAIDs. Furthermore, the definitive diagnosis of CSR was made referring to the guideline published by the North American Spine Society [18], and this study included patients with pain/numbness of a unilateral arm or hand; positive on the Spurling test [14] or the Jackson test; and cervical spondylotic changes on X-ray, CT, or MRI imaging tests. Therefore, the patients enrolled in this study were considered to be patients with uncontrolled pain due to CSR on NSAIDs.

The NRS score for upper limb pain showed significantly greater improvement at Week 12 in the mirogabalin add-on to NSAIDs group compared with the NSAIDs alone group [intergroup differences of – 1.55 (95% CI – 2.31, – 0.80)], and a similar significantly greater improvement in pain was observed based on the VAS score [intergroup differences of – 17.3 (– 26.5, – 8.0) mm]. Although patients had different characteristics, these improvements of pain scores in the mirogabalin add-on to NSAIDs group were consistent with the previous mirogabalin studies: NRS score change at Week 12, – 1.5 in patients with cancer [19]; VAS score change at Week 14, – 22.5 mm and – 21.4 mm in phase 3 clinical trials of Asian patients with diabetic peripheral neuropathic pain and postherpetic neuralgia who received 15 mg BID, respectively [8, 9]; and mean VAS score change at Week 12, – 24.1 mm with the combination of mirogabalin and NSAIDs in patients with lumbar spinal stenosis [13]. In the present study, mirogabalin added on to NSAID treatment significantly improved NRS scores for pain from the early stage (Week 4) of administration compared with NSAIDs alone treatment, consistent with previous mirogabalin studies [8–10, 13, 20]. Furthermore, the present results were generally consistent with the previous pregabalin studies showing that: the combination of pregabalin with NSAIDs improved VAS scores for refractory radicular leg pain due

to lumbar spinal stenosis at Week 6 (95% CI – 2.3, – 0.9) [21]; the combination of pregabalin with limaprost alfadex decreased VAS scores for lumbar spinal stenosis (baseline, 6.7 cm; Week 8, 4.2 cm) [22]; and pregabalin improved the VAS score of 5.7 cm at baseline to 3.0 cm at Week 8 in patients with cervical spondylosis [23]. In clinical practice, VAS improvement of > 16 or 20 mm is considered a clinically meaningful difference [24–26], although these reports were not based on neuropathic pain in patients with CSR. In addition, the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) state that analgesia can be considered clinically meaningful if it results in a decrease in pain severity by ≥ 30% (moderately important improvement) [27]. In the present study, the pain improvement effects based on the NRS and VAS scores of mirogabalin add-on therapy substantially achieved the above clinically meaningful cut-off. Furthermore, the responder rate of the NRS score for upper limb pain was significantly higher in the mirogabalin add-on group than in the NSAIDs alone group: ≥ 30% improvement, 71.7% vs. 39.6%; ≥ 50% improvement, 58.3% vs. 22.6%. Given these findings, the addition of mirogabalin to NSAIDs provides clinically meaningful improvement of upper limb pain due to CSR compared with NSAIDs alone.

It is generally agreed that the goal of neuropathic pain treatment is to improve patients' ADL and QoL, as well as to reduce the pain as much as possible [28]. In the present study, the EQ-5D-5L score improved to 0.0640 at Week 12, which was similar to the reported minimal clinically important difference of 0.061 [29]. Furthermore, the mirogabalin add-on group had a significantly higher proportion of patients with PGIC scores ≤ 2 (65.0% vs. 33.3%) and ≤ 3 (90.0% vs. 55.6%) than the NSAIDs alone group. This improvement was numerically higher than in the previous mirogabalin study (MiroTAS study) that included patients with lumbar spinal canal stenosis [13]. One possible reason for this difference is that the patients were younger in the present study than those in the MiroTAS study (mean ages of mirogabalin add-on/NSAIDs alone groups, 59.1/57.6 years vs. 67.8/70.9 years) [13]. A systematic review reported that older age is a predictor for persistence of neuropathic pain [30]. Furthermore, the present study had lower rates of complication (such as diabetes mellitus, stroke, hypertension, and hyperlipidemia) than the MiroTAS study (complication rates of mirogabalin add-on/NSAIDs alone groups, 36.1%/45.7% vs. 74.5%/76.0%) [13]. Therefore, it was suggested that, due to the younger age and lower complication rates, patients with CSR in the present study may be more likely to show improvement in PGIC scores than those with lumbar spinal canal stenosis in the MiroTAS study. Notably, the present results showed that the addition of mirogabalin to NSAIDs not only effectively reduced pain but also improved QoL in patients with CSR as well as in those with lumbar spinal canal stenosis.

Regarding sleep disturbance, the improvement in sleep disturbance based on NRS at Week 12 was significantly greater in the mirogabalin add-on group than in the NSAIDs alone group. However, the intergroup difference was small, which may be due to the low baseline NRS (means of 2.95 and 2.73, respectively). Patients had a mild or moderate sleep disturbance in this study; thus, the impact of sleep disturbance on QoL may also have been small.

There was no notable difference in the proportion of patients who dropped out between the two groups. Although the mirogabalin add-on group had a numerically higher incidence of TEAEs than the NSAIDs alone group, the incidence of TEAEs with mirogabalin add-on was comparable to previous studies of mirogabalin [8, 9, 13], pregabalin [21, 22, 31], and gabapentin [32]. The major types of AEs, such as dizziness and somnolence, were not novel and, in fact, were similar to those observed in previous studies [8, 9, 13, 21, 32]. Furthermore, most TEAEs were mild or moderate in severity in the mirogabalin add-on group. Although careful attention should be paid to the possibility of patients developing somnolence and dizziness, these results indicate that the combination of mirogabalin and NSAIDs is a well-tolerated option in the treatment of patients with CSR.

LIMITATIONS

The present study has limitations and biases based on its study design, such as open-label, and the relatively short study period. In addition, the present study excluded patients with severe renal impairment, those with mild pain (NRS < 4), and those with only numbness and no pain. Since this study was conducted in Japan, caution is needed in generalizing the results to other populations.

CONCLUSIONS

Miro-Cens, the first multicenter, randomized, controlled study comparing NSAIDs alone with mirogabalin added on to NSAIDs for the treatment of CSR patients demonstrated that the addition of mirogabalin significantly improved neuropathic pain in patients with CSR. No new safety concerns were identified, although caution should be exercised with regard to the development of somnolence and dizziness. The results of the present study suggest that concomitant use of mirogabalin with NSAIDs could be tolerable and a novel treatment option for patients with CSR for whom NSAIDs provided insufficient analgesic effects.

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Declarations

Conflict of Interest. Takashi Hirai had no conflict of interest to be declared. Atsushi Okawa and Toshitaka Yoshii received lecture fees from Daiichi Sankyo Co., Ltd. Hiroshi Takahashi and Kazuhito Shiosakai are employees of Daiichi Sankyo Co., Ltd.

Ethical Approval. The study was approved by Tokyo Medical and Dental University Certified Review Board (current name, Institution of Science Tokyo) (CRB No. 3240003). The study was conducted in accordance with the Clinical Research Act in Japan, and the ethical principles, clinical research laws, and relevant notifications stipulated in the Declaration of Helsinki (as revised in 2013). This study was registered in the Japan Registry of Clinical Trials under the identifier jRCTs031210629. All patients provided informed consent to participate in the study.

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