

Efficacy and Safety of Mirogabalin as an Add-on to Nonsteroidal Anti-inflammatory Drugs for Neuropathic Pain Caused by Lumbar Disc Herniation: a Randomized Controlled Study (Miro-Hers)

Hidenori Suzuki, Takashi Kaito, Hiroaki Nakashima, Hiroshi Takahashi, Shuhei Yamamoto, Shunsuke Tabata, Hiromitsu Toyoda

H. Suzuki (Corresponding author)

Department of Orthopaedics Surgery, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube City, Yamaguchi 755-8505, Japan

E-mail: hsuzuki@yamaguchi-u.ac.jp

T. Kaito

Department of Orthopedic Surgery, Osaka Rosai Hospital, Sakai, Japan

H. Nakashima

Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

H. Takahashi

Primary Medical Science Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan

19 S. Yamamoto

20 Data Intelligence Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan

21 S. Tabata

22 Medical Affairs Planning Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan

23 H. Toyoda

24 Department of Orthopedic Surgery, Osaka Metropolitan University, Osaka, Japan

25

26

27

28

29

30

31

32

33

34

35

36

Supplementary Materials

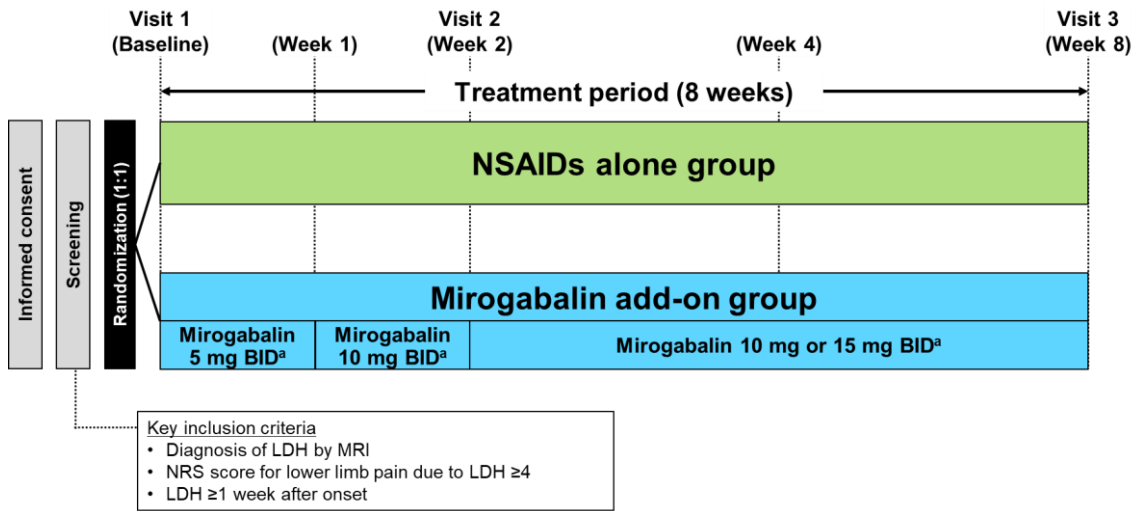


Figure S1. Study design

^a Dose for patients with CrCL of ≥60 mL/min. Patients with CrCL of 30 to <60 mL/min received half the dose of mirogabalin.

BID, twice daily; CrCL, creatinine clearance; LDH, lumbar disc herniation; MRI, magnetic resonance imaging; NRS, numerical rating scale; NSAIDs, non-steroidal anti-inflammatory drugs.

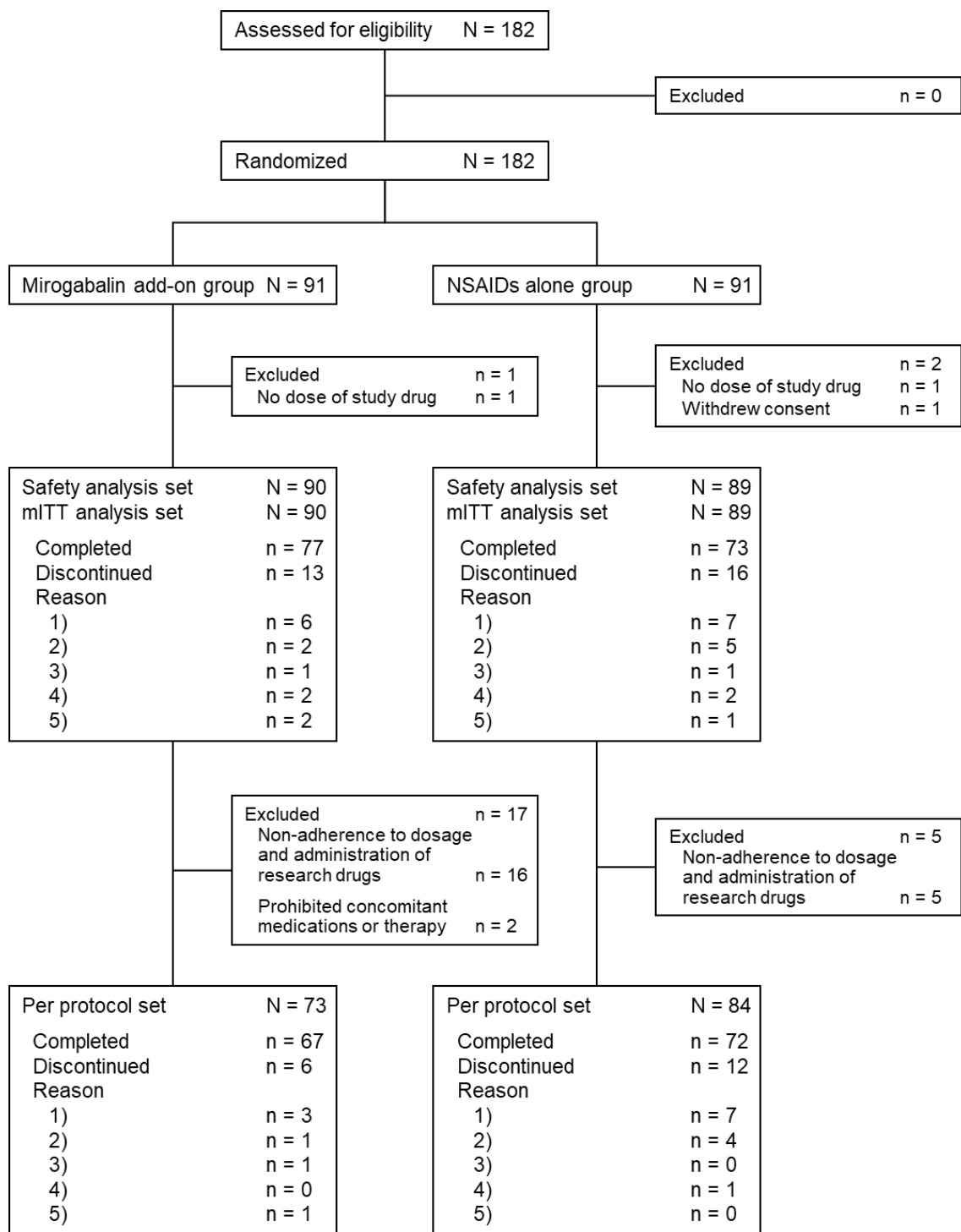


Figure S2. Patient disposition

1) Patient requested study discontinuation

2) Prohibited concomitant medications or therapy deemed necessary by the

51 investigator

52 3) Patient stopped visiting the hospital

53 4) Discontinuation of the study was judged as appropriate due to adverse events

54 5) Other (deemed inappropriate by the principal investigator)

55 mITT, modified intention-to-treat; NSAIDs, non-steroidal anti-inflammatory drugs.

56 **Supplementary Tables**57 **Table S1.** Patient baseline characteristics (PPS population)

Characteristic	Mirogabalin add-on group (N = 73)	NSAIDs alone group (N = 84)
Age, years	48.6 ± 14.9	47.3 ± 16.1
Male	46 (63.0)	55 (65.5)
Body mass index, kg/m ²	24.0 ± 6.4	23.7 ± 4.4
≥25	18 (24.7)	24 (28.6)
Creatinine clearance, mL/min	108.8 ± 46.1	102.5 ± 35.1
30 to <60	4 (5.5)	10 (11.9)
≥60	69 (94.5)	74 (88.1)
VAS score for lower limb pain, mm	62.5 ± 17.6	59.0 ± 17.1
NRS score for lower limb pain	6.3 ± 1.7	6.0 ± 1.5
<6	27 (37.0)	35 (41.7)
≥6	46 (63.0)	49 (58.3)
NRS score for low back pain	4.4 ± 2.4	4.3 ± 2.4
NRS score for sleep disturbance	3.5 ± 2.6	3.1 ± 2.7
Duration of LDH, months	0.9 ± 0.7	1.9 ± 5.8
Median (Q1, Q3)	1.0 (0.0, 1.0)	1.0 (0.0, 2.0)
Min, Max	0, 3	0, 51
<3	72 (98.6)	75 (89.3)
≥3	1 (1.4)	9 (10.7)
Duration of lower limb pain after LDH onset, weeks	4.4 ± 2.9	5.1 ± 3.3

<4	35 (47.9)	31 (36.9)
≥4	38 (52.1)	53 (63.1)
Complication		
Hypertension	19 (26.0)	15 (17.9)
Hyperlipidemia	12 (16.4)	10 (11.9)
Diabetes mellitus	6 (8.2)	7 (8.3)
Cervical spondylosis	2 (2.7)	2 (2.4)
Lumbar spinal stenosis	2 (2.7)	1 (1.2)
Spondylolysis	0	2 (2.4)
Stroke	1 (1.4)	1 (1.2)
Ossification of the posterior longitudinal ligament	1 (1.4)	0
Osteoporotic compression fracture	0	1 (1.2)
Rheumatoid arthritis	0	1 (1.2)
Surgical history		
Cervical vertebrae	1 (1.4)	0
NSAIDs used per the package insert with no change in dosage		
NSAID type		
Loxoprofen sodium hydrate (oral)	50 (68.5)	47 (56.0)
Celecoxib (oral)	17 (23.3)	25 (29.8)
Diclofenac sodium (oral)	5 (6.8)	10 (11.9)
Aspirin (oral)	0	1 (1.2)
Naproxen (oral)	0	1 (1.2)
Lornoxicam (oral)	1 (1.4)	0

- 59 LDH, lumbar disc herniation; NRS, numerical rating scale; NSAIDs, non-steroidal anti-
- 60 inflammatory drugs; PPS, per protocol set; Q, quartile; VAS, visual analog scale.

61 **Table S2.** Daily dose of mirogabalin for 8 weeks by renal function at enrollment

Mirogabalin dose	CrCL ≥60 mL/min					CrCL 30 to <60 mL/min				
	Baseline	Week 1	Week 2	Week 4	Week 8	Baseline	Week 1	Week 2	Week 4	Week 8
mITT population	n = 85	n = 84	n = 81	n = 73	n = 73	n = 5	n = 5	n = 5	n = 5	n = 5
2.5 mg BID	0	0	0	0	0	5 (100.0)	0	1 (20.0)	1 (20.0)	1 (20.0)
5 mg BID	85 (100.0)	3 (3.6)	5 (6.2)	5 (6.8)	5 (6.8)	0	5 (100.0)	1 (20.0)	2 (40.0)	2 (40.0)
7.5 mg BID	0	0	0	0	0	0	0	3 (60.0)	2 (40.0)	2 (40.0)
10 mg BID	0	81 (96.4)	28 (34.6)	23 (31.5)	23 (31.5)	0	0	0	0	0
15 mg BID	0	0	48 (59.3)	45 (61.6)	45 (61.6)	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0	0
PPS population	n = 69	n = 69	n = 69	n = 64	n = 64	n = 4	n = 4	n = 4	n = 4	n = 4
2.5 mg BID	0	0	0	0	0	4 (100.0)	0	0	0	0
5 mg BID	69 (100.0)	1 (1.4)	0	0	0	0	4 (100.0)	1 (25.0)	2 (50.0)	2 (50.0)
7.5 mg BID	0	0	0	0	0	0	0	3 (75.0)	2 (50.0)	2 (50.0)
10 mg BID	0	68 (98.6)	23 (33.3)	20 (31.3)	20 (31.3)	0	0	0	0	0
15 mg BID	0	0	46 (66.7)	44 (68.8)	44 (68.8)	0	0	0	0	0

Other	0	0	0	0	0	0	0	0	0	0
-------	---	---	---	---	---	---	---	---	---	---

62 Data are n (%).

63 BID, twice daily; CrCL, creatinine clearance; mITT, modified intention-to-treat; PPS, per-protocol set.

64 **Table S3.** NRS scores for lower limb pain from baseline to Week 8

		mITT population		PPS population	
		Mirogabalin add-on group	NSAIDs alone group	Mirogabalin add-on group	NSAIDs alone Group
Baseline	n	90	89	73	84
	Mean ± SD	6.2 ± 1.7	6.0 ± 1.5	6.3 ± 1.7	6.0 ± 1.5
Week 1	n	88	86	73	81
	Mean ± SD	4.2 ± 2.3	4.9 ± 2.3	4.2 ± 2.1	4.8 ± 2.3
	Change from baseline	−2.1 ± 2.1	−1.1 ± 2.0	−2.1 ± 2.0	−1.1 ± 2.0
	LS means change from baseline (95% CI) by MMRM	−2.0 (−2.4, −1.6)	−1.2 (−1.6, −0.7)	−2.0 (−2.5, −1.5)	−1.2 (−1.7, −0.8)
	Difference in LS means change (95% CI) by MMRM	−0.8 (−1.4, −0.2) P = 0.007	-	−0.8 (−1.4, −0.1) P = 0.017	-
Week 2	n	87	88	73	83
	Mean ± SD	3.7 ± 2.4	4.7 ± 2.3	3.7 ± 2.3	4.6 ± 2.3
	Change from baseline	−2.5 ± 2.3	−1.3 ± 1.9	−2.6 ± 2.3	−1.3 ± 1.9

	LS means change from baseline (95% CI) by MMRM	-2.5 (-2.9, -2.0)	-1.3 (-1.7, -0.9)	-2.5 (-2.9, -2.0)	-1.4 (-1.8, -0.9)
	Difference in LS means change (95% CI) by MMRM	-1.2 (-1.8, -0.5) P <0.001	-	-1.1 (-1.8, -0.5) P <0.001	-
Week 3	n	78	81	69	77
	Mean ± SD	3.5 ± 2.2	4.6 ± 2.4	3.4 ± 2.2	4.6 ± 2.4
	Change from baseline	-2.8 ± 2.3	-1.3 ± 2.1	-2.8 ± 2.3	-1.4 ± 2.1
	LS means change from baseline (95% CI) by MMRM	-2.7 (-3.2, -2.2)	-1.4 (-1.9, -0.9)	-2.8 (-3.3, -2.3)	-1.4 (-1.9, -1.0)
	Difference in LS means change (95% CI) by MMRM	-1.3 (-2.0, -0.6) P <0.001	-	-1.3 (-2.0, -0.6) P <0.001	-
Week 4	n	76	76	68	74
	Mean ± SD	3.2 ± 2.2	4.3 ± 2.3	3.2 ± 2.1	4.3 ± 2.3
	Change from baseline	-3.0 ± 2.3	-1.6 ± 2.1	-3.0 ± 2.3	-1.6 ± 2.1
	LS means change from baseline (95% CI) by MMRM	-3.0 (-3.5, -2.5)	-1.7 (-2.1, -1.2)	-3.0 (-3.5, -2.5)	-1.7 (-2.2, -1.2)

	Difference in LS means change (95% CI) by MMRM	-1.3 (-2.0, -0.7) P<0.001	-	-1.3 (-2.0, -0.6) P <0.001	-
Week 5	n	76	73	67	71
	Mean ± SD	2.9 ± 2.2	4.1 ± 2.4	2.9 ± 2.1	4.0 ± 2.4
	Change from baseline	-3.3 ± 2.3	-1.8 ± 2.2	-3.3 ± 2.3	-1.8 ± 2.1
	LS means change from baseline (95% CI) by MMRM	-3.3 (-3.8, -2.8)	-1.8 (-2.3, -1.3)	-3.3 (-3.8, -2.8)	-1.8 (-2.3, -1.3)
	Difference in LS means change (95% CI) by MMRM	-1.5 (-2.2, -0.8) P<0.001	-	-1.5 (-2.2, -0.8) P <0.001	-
Week 6	n	75	74	66	72
	Mean ± SD	2.8 ± 2.3	4.0 ± 2.3	2.8 ± 2.2	4.0 ± 2.3
	Change from baseline	-3.4 ± 2.4	-1.8 ± 2.0	-3.4 ± 2.4	-1.8 ± 2.0
	LS means change from baseline (95% CI) by MMRM	-3.4 (-3.9, -2.9)	-1.8 (-2.3, -1.4)	-3.4 (-3.9, -2.9)	-1.9 (-2.4, -1.4)
	Difference in LS means change (95% CI) by MMRM	-1.6 (-2.2, -0.9) P<0.001	-	-1.5 (-2.2, -0.8) P <0.001	-

Week 7	n	73	67	65	66
	Mean ± SD	2.6 ± 2.2	3.5 ± 2.2	2.7 ± 2.2	3.5 ± 2.2
	Change from baseline	−3.6 ± 2.3	−2.2 ± 1.8	−3.6 ± 2.4	−2.2 ± 1.8
	LS means change from baseline (95% CI) by MMRM	−3.6 (−4.1, −3.1)	−2.1 (−2.6, −1.6)	−3.6 (−4.1, −3.1)	−2.2 (−2.7, −1.7)
	Difference in LS means change (95% CI) by MMRM	−1.5 (−2.2, −0.8) P<0.001	-	−1.4 (−2.2, −0.7) P <0.001	-
Week 8	n	54	48	47	47
	Mean ± SD	2.5 ± 2.3	3.3 ± 2.4	2.7 ± 2.4	3.3 ± 2.4
	Change from baseline	−3.6 ± 2.5	−2.3 ± 2.3	−3.6 ± 2.7	−2.3 ± 2.3
	LS means change from baseline (95% CI) by MMRM	−3.8 (−4.4, −3.3)	−2.2 (−2.8, −1.7)	−3.8 (−4.4, −3.2)	−2.3 (−2.9, −1.7)
	Difference in LS means change (95% CI) by MMRM	−1.6 (−2.4, −0.8) P <0.001	–	−1.5 (−2.4, −0.7) P <0.001	-
Week 4	n	90	89	73	84
(LOCF)	Mean ± SD	3.3 ± 2.5	4.3 ± 2.3	3.2 ± 2.3	4.3 ± 2.4

	Change from baseline	-2.9 ± 2.5	-1.7 ± 2.1	-3.1 ± 2.4	-1.7 ± 2.2
	LS means change from baseline (95% CI) by ANCOVA	-2.9 (-3.3, -2.4)	-1.7 (-2.2, -1.2)	-3.0 (-3.5, -2.5)	-1.7 (-2.2, -1.3)
	Difference in LS means change (95% CI) by ANCOVA	-1.2 (-1.8, -0.5) P <0.001	-	-1.3 (-2.0, -0.6) P <0.001	-
Week 8	n	90	89	73	84
(LOCF)	Mean ± SD	2.6 ± 2.6	3.9 ± 2.6	2.5 ± 2.4	3.8 ± 2.6
	Change from baseline	-3.6 ± 2.6	-2.1 ± 2.3	-3.8 ± 2.6	-2.1 ± 2.3
	LS means change from baseline (95% CI) by ANCOVA	-3.5 (-4.0, -3.0)	-2.1 (-2.6, -1.6)	-3.7 (-4.3, -3.2)	-2.2 (-2.7, -1.7)
	Difference in LS means change (95% CI) by ANCOVA	-1.4 (-2.1, -0.7) P <0.001		-1.5 (-2.3, -0.8) P <0.001	-

- 65 The MMRM included treatment group, each treatment duration (Weeks 1–8), and treatment group-week interactions as fixed effects;
- 66 baseline NRS score for lower limb pain as a covariate; and patients as a random effect.
- 67 P value vs the NSAIDs alone group

68 Data are mean $\pm$ SD unless otherwise specified.

69 ANCOVA, analysis of covariance; CI, confidence interval; LOCF, last observation carried forward; LS, least squares; mITT, modified

70 intention-to-treat; MMRM, mixed model for repeated measures; NRS, numerical rating scale; NSAIDs, nonsteroidal anti-inflammatory

71 drugs; PPS, per-protocol set; SD, standard deviation.

Table S4. The responder rate of VAS score for lower limb pain at Week 8 (PPS population)

	Mirogabalin add-on group (N = 66)	NSAIDs alone group (N = 71)
≥30% improvement	53 (80.3)	44 (62.0)
	P = 0.024	
≥50% improvement	49 (74.2)	32 (45.1)
	P <0.001	

Data are n (%).

P value for intergroup difference by Fisher’s exact test.

NSAIDs, non-steroidal anti-inflammatory drugs; PPS, per-protocol set; VAS, visual analog scale.

78 **Table S5.** NRS scores for low back pain

		mITT population		PPS population	
		Mirogabalin add-on group	NSAIDs alone group	Mirogabalin add-on group	NSAIDs alone group
Baseline	n	90	89	73	84
	Mean ± SD	4.6 ± 2.4	4.4 ± 2.4	4.4 ± 2.4	4.3 ± 2.4
Week 1	n	88	86	73	81
	Mean ± SD	3.1 ± 2.2	3.9 ± 2.3	3.1 ± 2.1	3.8 ± 2.3
	Change from baseline	−1.5 ± 2.1	−0.5 ± 2.2	−1.3 ± 2.1	−0.5 ± 2.3
	LS means change from baseline (95% CI) by MMRM	−1.4 (−1.8, −1.0)	−0.5 (−0.9, −0.1)	−1.3 (−1.7, −0.9)	−0.5 (−0.9, −0.1)
	Difference in LS means change (95% CI) by MMRM	−0.9 (−1.4, −0.3) P = 0.002	-	−0.8 (−1.4, −0.2) P = 0.009	-
Week 2	n	87	88	73	83
	Mean ± SD	2.9 ± 2.1	3.9 ± 2.4	2.9 ± 2.2	3.8 ± 2.4
	Change from baseline	−1.6 ± 2.4	−0.5 ± 2.4	−1.5 ± 2.4	−0.5 ± 2.5

	LS means change from baseline (95% CI) by MMRM	-1.5 (-2.0, -1.1)	-0.5 (-0.9, -0.1)	-1.4 (-1.9, -1.0)	-0.5 (-0.9, -0.1)
	Difference in LS means change (95% CI) by MMRM	-1.0 (-1.6, -0.4) P <0.001	-	-0.9 (-1.6, -0.3) P = 0.006	-
Week 3	n	78	81	69	77
	Mean ± SD	2.7 ± 1.9	3.5 ± 2.4	2.7 ± 1.9	3.5 ± 2.4
	Change from baseline	-1.7 ± 2.2	-0.8 ± 2.4	-1.7 ± 2.2	-0.8 ± 2.4
	LS means change from baseline (95% CI) by MMRM	-1.7 (-2.2, -1.3)	-0.9 (-1.3, -0.5)	-1.7 (-2.1, -1.2)	-0.9 (-1.3, -0.5)
	Difference in LS means change (95% CI) by MMRM	-0.9 (-1.4, -0.3) P = 0.004	-	-0.8 (-1.4, -0.2) P = 0.014	-
Week 4	n	76	76	68	74
	Mean ± SD	2.6 ± 2.0	3.2 ± 2.2	2.6 ± 2.0	3.2 ± 2.2
	Change from baseline	-1.8 ± 2.4	-1.0 ± 2.5	-1.7 ± 2.5	-1.0 ± 2.5
	LS means change from baseline (95% CI) by MMRM	-1.8 (-2.3, -1.4)	-1.1 (-1.5, -0.6)	-1.7 (-2.2, -1.3)	-1.1 (-1.5, -0.7)

	Difference in LS means change (95% CI) by MMRM	-0.8 (-1.4, -0.2) P = 0.013	-	-0.6 (-1.3, 0.0) P = 0.048	-
Week 5	n	76	73	67	71
	Mean ± SD	2.4 ± 1.9	3.2 ± 2.4	2.5 ± 1.9	3.1 ± 2.4
	Change from baseline	-2.0 ± 2.4	-1.0 ± 2.5	-1.9 ± 2.4	-1.1 ± 2.5
	LS means change from baseline (95% CI) by MMRM	-2.0 (-2.5, -1.6)	-1.1 (-1.5, -0.6)	-1.9 (-2.4, -1.4)	-1.1 (-1.6, -0.7)
	Difference in LS means change (95% CI) by MMRM	-1.0 (-1.6, -0.3) P = 0.003	-	-0.8 (-1.4, -0.1) P = 0.023	-
Week 6	n	75	73	66	71
	Mean ± SD	2.4 ± 1.9	3.1 ± 2.3	2.4 ± 1.8	3.0 ± 2.3
	Change from baseline	-2.1 ± 2.4	-1.2 ± 2.4	-1.9 ± 2.3	-1.2 ± 2.4
	LS means change from baseline (95% CI) by MMRM	-2.1 (-2.5, -1.7)	-1.3 (-1.7, -0.8)	-1.9 (-2.4, -1.5)	-1.3 (-1.7, -0.9)
	Difference in LS means change (95% CI) by MMRM	-0.8 (-1.4, -0.2) P = 0.007	-	-0.7 (-1.3, 0.0) P = 0.035	-

Week 7	n	73	67	65	66
	Mean ± SD	2.2 ± 1.7	2.8 ± 2.2	2.2 ± 1.6	2.8 ± 2.2
	Change from baseline	-2.2 ± 2.4	-1.5 ± 2.1	-2.1 ± 2.4	-1.5 ± 2.2
	LS means change from baseline (95% CI) by MMRM	-2.3 (-2.7, -1.8)	-1.3 (-1.8, -0.9)	-2.1 (-2.6, -1.7)	-1.4 (-1.8, -0.9)
	Difference in LS means change (95% CI) by MMRM	-0.9 (-1.5, -0.3) P = 0.003	-	-0.7 (-1.4, -0.1) P = 0.021	-
Week 8	n	54	48	47	47
	Mean ± SD	2.3 ± 1.9	2.8 ± 2.4	2.4 ± 1.9	2.8 ± 2.5
	Change from baseline	-2.8 ± 2.6	-1.3 ± 2.5	-2.6 ± 2.7	-1.3 ± 2.5
	LS means change from baseline (95% CI) by MMRM	-2.5 (-3.0, -2.0)	-1.4 (-1.9, -0.9)	-2.4 (-2.9, -1.9)	-1.4 (-1.9, -0.9)
	Difference in LS means change (95% CI) by MMRM	-1.1 (-1.8, -0.4) P = 0.002	-	-1.0 (-1.7, -0.3) P = 0.008	-

79 The MMRM included treatment group, each treatment duration (Weeks 1–8), and treatment group-week interactions as fixed effects;

80 baseline NRS score for low back pain as a covariate; and patients as a random effect.

81 P value vs the NSAIDs alone group

82 Data are mean $\pm$ SD unless otherwise specified.

83 CI, confidence interval; LS, least squares; mITT, modified intention-to-treat; MMRM, mixed model for repeated measures; NRS,

84 numerical rating scale; NSAIDs, nonsteroidal anti-inflammatory drugs; PPS, per-protocol set; SD, standard deviation.

85 **Table S6.** NPSI score (PPS population)

	Mirogabalin add-on group			NSAIDs alone group		
	Baseline	Week 2	Week 8	Baseline	Week 2	Week 8
Total score	n = 73	n = 72	n = 66	n = 84	n = 82	n = 71
Mean ± SD	33.0 ± 19.4	19.6 ± 17.0	11.6 ± 14.4	28.1 ± 16.1	23.0 ± 16.7	16.1 ± 16.9
Change from baseline	-	-13.5 ± 17.4	-22.2 ± 21.1	-	-4.4 ± 12.4	-11.2 ± 17.5
LS means change (95% CI)	-	-12.0	-20.5	-	-5.8	-12.6
from baseline by MMRM		(-15.2, -8.9)	(-24.2, -16.8)		(-8.7, -2.9)	(-16.1, -9.0)
Difference in LS means	-	-6.2 (-10.5, -1.9)	-8.0 (-13.1, -2.8)	-	-	-
change (95% CI) by MMRM		P = 0.005	P = 0.003			
Burning (superficial)	n = 73	n = 72	n = 66	n = 84	n = 82	n = 71
spontaneous pain						
Mean ± SD	3.36 ± 3.05	2.07 ± 2.33	1.09 ± 1.98	2.52 ± 2.74	2.04 ± 2.20	1.15 ± 1.86
Change from baseline	-	-1.26 ± 2.72	-2.30 ± 3.32	-	-0.37 ± 2.43	-1.30 ± 2.50
LS means change (95% CI)	-	-0.94	-1.95	-	-0.69	-1.62
from baseline by MMRM		(-1.40, -0.48)	(-2.41, -1.49)		(-1.12, -0.26)	(-2.05, -1.18)
Difference in LS means	-	-0.25 (-0.88, 0.38)	-0.33 (-0.97, 0.30)	-	-	-
change (95% CI) by MMRM		P = 0.435	P = 0.303			

Pressing (deep)	n = 73	n = 72	n = 66	n = 84	n = 82	n = 71
spontaneous pain						
Mean ± SD	3.81 ± 2.31	2.05 ± 2.01	1.42 ± 1.91	3.51 ± 2.35	2.85 ± 2.24	1.86 ± 2.13
Change from baseline	-	-1.74 ± 2.36	-2.39 ± 2.71	-	-0.57 ± 1.71	-1.54 ± 2.31
LS means change (95% CI)	-	-1.63	-2.33	-	-0.66	-1.66
from baseline by MMRM		(-2.04, -1.22)	(-2.80, -1.85)		(-1.05, -0.28)	(-2.12, -1.21)
Difference in LS means	-	-0.97	-0.67	-	-	-
change (95% CI) by MMRM		(-1.53, -0.41)	(-1.33, -0.01)			
		P < 0.001	P = 0.048			
Paroxysmal pain	n = 73	n = 72	n = 66	n = 84	n = 82	n = 71
Mean ± SD	3.47 ± 2.59	1.97 ± 2.24	1.02 ± 1.56	3.20 ± 2.49	2.20 ± 2.07	1.63 ± 1.99
Change from baseline	-	-1.54 ± 2.32	-2.64 ± 2.56	-	-0.91 ± 1.95	-1.37 ± 2.35
LS means change (95% CI)	-	-1.42	-2.43	-	-1.03	-1.53
from baseline by MMRM		(-1.83, -1.01)	(-2.85, -2.01)		(-1.41, -0.64)	(-1.93, -1.13)
Difference in LS means	-	-0.39	-0.90	-	-	-
change (95% CI) by MMRM		(-0.95, 0.17)	(-1.48, -0.32)			
		P = 0.172	P = 0.003			
Evoked pain	n = 73	n = 72	n = 66	n = 84	n = 82	n = 71
Mean ± SD	2.23 ± 2.33	1.50 ± 2.00	0.84 ± 1.34	1.79 ± 1.69	1.61 ± 1.72	1.32 ± 1.75
Change from baseline	-	-0.75 ± 2.16	-1.48 ± 2.42	-	-0.14 ± 1.76	-0.56 ± 1.99

LS means change (95% CI)		-0.60	-1.28		-0.33	-0.67
from baseline by MMRM		(-0.99, -0.22)	(-1.65, -0.91)		(-0.69, 0.03)	(-1.03, -0.32)
Difference in LS means		-0.27	-0.61			
change (95% CI) by MMRM		(-0.80, 0.25)	(-1.12, -0.10)			
		P = 0.310	P = 0.021			
Paresthesia/dysesthesia	n = 73	n = 72	n = 66	n = 84	n = 82	n = 71
Mean ± SD	4.19 ± 2.63	2.51 ± 1.88	1.56 ± 1.74	3.42 ± 2.30	3.00 ± 2.43	2.00 ± 2.06
Change from baseline		-1.70 ± 2.05	-2.68 ± 2.83		-0.32 ± 2.09	-1.22 ± 2.29
LS means change (95% CI)	-	-1.43	-2.41	-	-0.55	-1.44
from baseline by MMRM		(-1.84, -1.01)	(-2.87, -1.95)		(-0.94, -0.16)	(-1.88, -1.00)
Difference in LS means	-	-0.88	-0.97	-	-	-
change (95% CI) by MMRM		(-1.45, -0.31)	(-1.61, -0.33)			
		P = 0.003	P = 0.004			

- 86 The MMRM included treatment group, each treatment duration (Weeks 1–8), and treatment group–week interactions as fixed effects;
- 87 each NPSI score at baseline as a covariate; and patients as a random effect.
- 88 P value vs the NSAIDs alone group

- 89 CI, confidence interval; LS, least squares; MMRM, mixed model for repeated measures; NPSI, neuropathic pain symptom inventory;
- 90 NSAIDs, non-steroidal anti-inflammatory drugs; PPS, per-protocol set; SD, standard deviation.

91 **Table S7.** JOABPEQ score (PPS population)

	Mirogabalin add-on group			NSAIDs alone group		
	Baseline	Week 2	Week 8	Baseline	Week 2	Week 8
Low back pain	n = 73	n = 72	n = 66	n = 84	n = 82	n = 71
Mean ± SD	44.2 ± 33.6	74.4 ± 30.8	83.1 ± 28.7	40.8 ± 30.8	59.2 ± 30.9	68.6 ± 35.0
Change from baseline	-	30.2 ± 34.6	39.8 ± 37.5	-	17.4 ± 32.4	27.6 ± 38.2
LS means change (95% CI) from baseline by MMRM	-	31.2 (24.7, 37.7)	40.4 (32.9, 47.8)	-	17.0 (10.9, 23.0)	26.2 (19.0, 33.4)
Difference in LS means change (95% CI) by MMRM	-	14.3 (5.4, 23.2) P = 0.002	14.2 (3.8, 24.5) P = 0.008	-	-	-
Lumbar function	n = 73	n = 72	n = 66	n = 84	n = 82	n = 71
Mean ± SD	51.9 ± 27.9	70.9 ± 24.7	79.2 ± 22.2	53.3 ± 25.5	65.1 ± 23.8	74.8 ± 24.3
Change from baseline	-	19.1 ± 25.0	26.9 ± 23.1	-	11.8 ± 17.2	21.5 ± 24.2
LS means change (95% CI) from baseline by MMRM	-	18.7 (14.5, 23.0)	26.4 (21.7, 31.2)	-	12.1 (8.1, 16.1)	21.3 (16.7, 25.9)
Difference in LS means change (95% CI) by MMRM	-	6.6 (0.8, 12.5) P = 0.026	5.1 (-1.5, 11.7) P = 0.125	-	-	-
Walking ability	n = 73	n = 72	n = 66	n = 84	n = 82	n = 71
Mean ± SD	52.8 ± 31.9	69.0 ± 28.3	79.3 ± 26.1	58.8 ± 30.8	66.3 ± 25.4	74.6 ± 28.0

Change from baseline	-	16.4 ± 22.2	28.7 ± 27.1	-	6.9 ± 19.9	14.3 ± 26.2
LS means change (95% CI)	-	15.1 (10.9, 19.2)	26.4 (21.1, 31.8)	-	8.2 (4.3, 12.1)	16.5 (11.4, 21.7)
from baseline by MMRM						
Difference in LS means	-	6.8 (1.1, 12.5)	9.9 (2.5, 17.3)	-	-	-
change (95% CI) by MMRM		P = 0.019	P = 0.010			
Social life function	n = 73	n = 72	n = 66	n = 84	n = 82	n = 71
Mean ± SD	44.9 ± 23.4	63.2 ± 22.9	74.5 ± 20.7	46.8 ± 20.8	55.1 ± 20.0	65.1 ± 21.3
Change from baseline	-	18.4 ± 18.4	30.5 ± 21.3	-	7.8 ± 15.3	17.4 ± 21.6
LS means change (95% CI)	-	17.9 (14.3, 21.5)	29.6 (25.2, 34.1)	-	8.3 (4.9, 11.7)	18.1 (13.8, 22.4)
from baseline by MMRM						
Difference in LS means	-	9.6 (4.7, 14.5)	11.6 (5.4, 17.8)	-	-	-
change (95% CI) by MMRM		P <0.001	P <0.001			
Mental health	n = 73	n = 72	n = 66	n = 84	n = 82	n = 71
Mean ± SD	47.1 ± 18.9	59.0 ± 16.6	64.2 ± 15.7	49.4 ± 13.4	55.2 ± 14.3	59.1 ± 16.1
Change from baseline	-	11.9 ± 14.6	17.7 ± 16.0	-	5.6 ± 11.7	9.9 ± 14.3
LS means change (95% CI)	-	11.4 (8.7, 14.1)	16.9 (13.7, 20.1)	-	6.2 (3.6, 8.7)	10.4 (7.4, 13.5)
from baseline by MMRM						
Difference in LS means	-	5.3 (1.5, 9.0)	6.5 (2.1, 10.9)	-	-	-
change (95% CI) by MMRM		P = 0.006	P = 0.004			

92 The MMRM included treatment group, each treatment duration (Weeks 1–8), and treatment group–week interactions as fixed effects;
93 each JOABPEQ score at baseline as a covariate; and patients as a random effect.
94 P value vs the NSAIDs alone group
95 CI, confidence interval; JOABPEQ, Japanese Orthopedic Association Back Pain Evaluation Questionnaire; LS, least squares; MMRM,
96 mixed model for repeated measures; NSAIDs, non-steroidal anti-inflammatory drugs; PPS, per-protocol set; SD, standard deviation.

97 **Table S8.** NRS scores for sleep disturbance

		mITT population		PPS population	
		Mirogabalin add-on group	NSAIDs alone group	Mirogabalin add-on group	NSAIDs alone group
Baseline	n	90	89	73	84
	Mean ± SD	3.3 ± 2.6	3.1 ± 2.7	3.5 ± 2.6	3.1 ± 2.7
Week 1	n	88	86	73	81
	Mean ± SD	1.9 ± 2.0	2.4 ± 2.4	1.9 ± 2.1	2.3 ± 2.4
	Change from baseline	-1.5 ± 2.4	-0.7 ± 2.1	-1.7 ± 2.4	-0.8 ± 2.1
	LS means change from baseline (95% CI) by MMRM	-1.4 (-1.8, -1.0)	-0.8 (-1.2, -0.4)	-1.5 (-1.9, -1.1)	-0.9 (-1.3, -0.5)
	Difference in LS means change (95% CI) by MMRM	-0.6 (-1.1, 0.0) P = 0.035	-	-0.6 (-1.2, 0.0) P = 0.051	-
Week 2	n	87	88	73	83
	Mean ± SD	1.4 ± 2.0	2.3 ± 2.4	1.4 ± 1.9	2.3 ± 2.5
	Change from baseline	-2.0 ± 2.6	-0.8 ± 2.3	-2.2 ± 2.4	-0.8 ± 2.4

	LS means change from baseline (95% CI) by MMRM	-1.8 (-2.2, -1.4)	-0.9 (-1.3, -0.5)	-2.0 (-2.4, -1.6)	-0.9 (-1.3, -0.5)
	Difference in LS means change (95% CI) by MMRM	-1.0 (-1.5, -0.4) P = 0.001	-	-1.1 (-1.7, -0.5) P <0.001	-
Week 3	n	78	81	69	77
	Mean ± SD	1.2 ± 1.8	2.2 ± 2.2	1.3 ± 1.9	2.2 ± 2.3
	Change from baseline	-2.2 ± 2.6	-0.9 ± 2.2	-2.1 ± 2.7	-0.9 ± 2.2
	LS means change from baseline (95% CI) by MMRM	-1.9 (-2.4, -1.5)	-1.0 (-1.4, -0.6)	-2.0 (-2.5, -1.6)	-1.0 (-1.5, -0.6)
	Difference in LS means change (95% CI) by MMRM	-1.0 (-1.5, -0.4) P = 0.001	-	-1.0 (-1.6, -0.4) P = 0.002	-
Week 4	n	76	76	68	74
	Mean ± SD	1.0 ± 1.3	1.9 ± 2.1	1.1 ± 1.4	1.9 ± 2.2
	Change from baseline	-2.3 ± 2.4	-1.1 ± 2.4	-2.4 ± 2.4	-1.2 ± 2.5
	LS means change from baseline (95% CI) by MMRM	-2.1 (-2.5, -1.8)	-1.3 (-1.6, -0.9)	-2.2 (-2.6, -1.8)	-1.3 (-1.7, -1.0)

	Difference in LS means change (95% CI) by MMRM	-0.9 (-1.4, -0.3) P = 0.001		-0.9 (-1.5, -0.4) P = 0.001	
Week 5	n	76	73	67	71
	Mean ± SD	0.9 ± 1.3	1.8 ± 2.0	1.0 ± 1.4	1.8 ± 2.0
	Change from baseline	-2.4 ± 2.4	-1.2 ± 2.5	-2.4 ± 2.4	-1.3 ± 2.5
	LS means change from baseline (95% CI) by MMRM	-2.2 (-2.6, -1.9)	-1.4 (-1.7, -1.0)	-2.3 (-2.7, -2.0)	-1.4 (-1.8, -1.1)
	Difference in LS means change (95% CI) by MMRM	-0.9 (-1.4, -0.4) P <0.001	-	-0.9 (-1.4, -0.4) P = 0.001	-
Week 6	n	75	73	66	71
	Mean ± SD	0.9 ± 1.3	1.9 ± 2.2	1.0 ± 1.4	1.9 ± 2.2
	Change from baseline	-2.5 ± 2.4	-1.1 ± 2.4	-2.5 ± 2.5	-1.2 ± 2.5
	LS means change from baseline (95% CI) by MMRM	-2.3 (-2.6, -1.9)	-1.3 (-1.6, -0.9)	-2.3 (-2.7, -1.9)	-1.3 (-1.7, -0.9)
	Difference in LS means change (95% CI) by MMRM	-1.0 (-1.5, -0.5) P <0.001	-	-1.0 (-1.6, -0.5) P <0.001	-

Week 7	n	73	67	65	66
	Mean ± SD	0.7 ± 1.2	1.7 ± 2.0	0.8 ± 1.2	1.7 ± 2.0
	Change from baseline	-2.7 ± 2.4	-1.4 ± 2.6	-2.8 ± 2.4	-1.4 ± 2.6
	LS means change from baseline (95% CI) by MMRM	-2.4 (-2.8, -2.1)	-1.3 (-1.7, -1.0)	-2.5 (-2.9, -2.1)	-1.4 (-1.8, -1.0)
	Difference in LS means change (95% CI) by MMRM	-1.1 (-1.6, -0.6) P <0.001	-	-1.1 (-1.7, -0.6) P <0.001	-
Week 8	n	54	48	47	47
	Mean ± SD	0.7 ± 1.1	1.9 ± 2.4	0.7 ± 1.1	1.9 ± 2.4
	Change from baseline	-2.9 ± 2.7	-1.0 ± 2.5	-2.9 ± 2.7	-1.1 ± 2.5
	LS means change from baseline (95% CI) by MMRM	-2.5 (-2.9, -2.1)	-1.2 (-1.6, -0.8)	-2.6 (-3.1, -2.2)	-1.3 (-1.7, -0.9)
	Difference in LS means change (95% CI) by MMRM	-1.3 (-1.9, -0.7) P <0.001	-	-1.3 (-1.9, -0.7) P <0.001	-

98 The MMRM included treatment group, each treatment duration (Weeks 1–8), and treatment group-week interactions as fixed effects,
99 baseline NRS score for sleep disturbance as a covariate, and patients as a random effect.
100 P value vs the NSAIDs alone group

101 CI, confidence interval; LS, least squares; mITT, ,modified intention-to-treat; MMRM, mixed model repeated measures; NRS, numerical
102 rating scale; NSAIDs, nonsteroidal anti-inflammatory drugs; PPS, per-protocol set; SD, standard deviation.

103 **Table S9.** EQ-5D-5L and PGIC (PPS population)

	Mirogabalin add-on group	NSAIDs alone group
EQ-5D-5L		
Baseline	n = 73	n = 84
Mean ± SD	0.6247 ± 0.1949	0.6567 ± 0.1433
Week 2	n = 72	n = 82
Mean ± SD	0.7498 ± 0.1582	0.7081 ± 0.1376
Change from baseline	0.1259 ± 0.1540	0.0491 ± 0.1247
LS means change (95% CI) from baseline by MMRM	0.1163 (0.0891, 0.1434)	0.0574 (0.0320, 0.0828)
Difference in LS means change (95% CI) by MMRM	0.0588 (0.0216, 0.0961) P = 0.002 ^a	-
Week 8	n = 66	n = 71

Mean ± SD	0.8132 ± 0.1366	0.7706 ± 0.1472
Change from baseline	0.1952 ± 0.1827	0.1045 ± 0.1474
LS means change (95% CI) from baseline by MMRM	0.1840 (0.1523, 0.2157)	0.1159 (0.0854, 0.1464)
Difference in LS means change (95% CI) by MMRM	0.0681 (0.0240, 0.1122) P = 0.003 ^a	-
PGIC score at Week 8	n = 66	n = 71
1 ('very much improved')	17 (25.8)	9 (12.7)
2 ('much improved')	28 (42.4)	25 (35.2)
3 ('minimally improved')	14 (21.2)	17 (23.9)
4 ('no change')	4 (6.1)	14 (19.7)
5 ('minimally worse')	3 (4.5)	5 (7.0)
6 ('much worse')	0	1 (1.4)
7 ('very much worse')	0	0

≤3	59 (89.4), P = 0.011 ^b	51 (71.8)
≤2	45 (68.2), P = 0.024 ^b	34 (47.9)

104 Data are mean ± standard deviation or n (%) unless otherwise indicated.

105 The MMRM included treatment group, each treatment duration (Weeks 1–8), and treatment group-week interactions as fixed effects,
106 the EQ-5D-5L score at baseline as a covariate, and patients as a random effect.

107 ^a vs the NSAIDs alone group

108 ^b vs the NSAIDs alone group calculated by Fisher's exact test

109 CI, confidence interval; EQ-5D-5L, EuroQol 5 dimensions 5-level; LS, least squares; MMRM, mixed model for repeated measures;

110 NSAIDs, non-steroidal anti-inflammatory drugs; PGIC, Patient Global Impression of Change; PPS, per-protocol set.