Supplementary Materials

Efficacy and Safety of Add-on Mirogabalin to NSAIDs in Lumbar Spinal Stenosis with Peripheral Neuropathic Pain: A Randomized, Open-label Study

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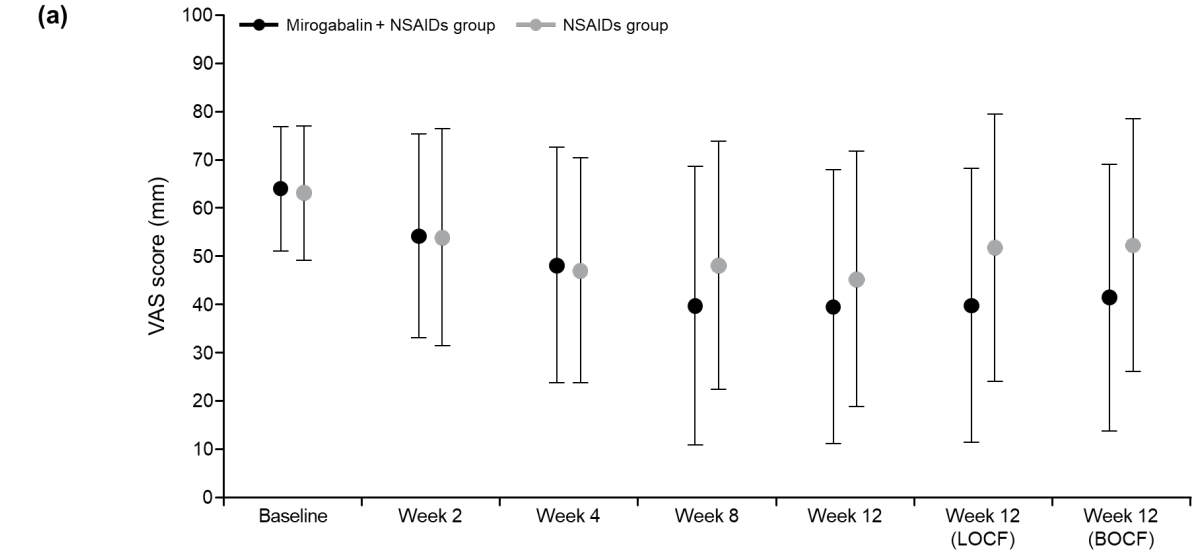
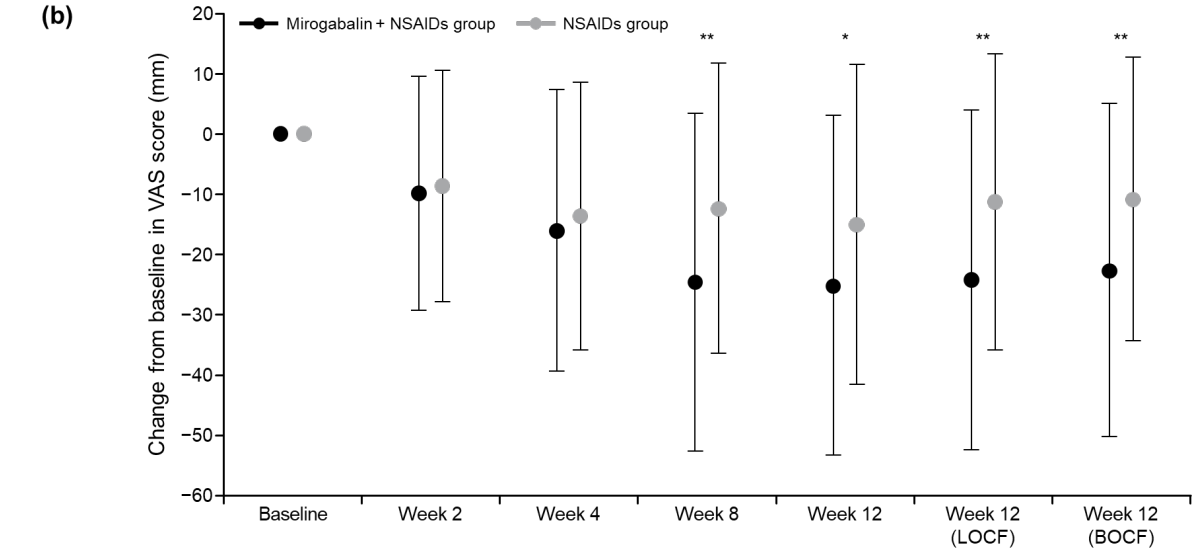
Supplementary Materials



		Baseline	Week 2	Week 4	Week 8	Week 12	Week 12 (LOCF)	Week 12 (BOCF)
Mirogabalin + NSAIDs group	n	82	82	82	78	74	82	82
	Mean ± SD	63.9 ± 12.9	54.1 ± 21.1	48.0 ± 24.4	39.5 ± 28.9	39.4 ± 28.4	39.7 ± 28.5	41.3 ± 27.6
NSAIDs group	n	100	94	80	76	72	100	100
	Mean ± SD	63.0 ± 14.0	53.8 ± 22.5	46.9 ± 23.3	48.0 ± 25.7	45.2 ± 26.5	51.7 ± 27.7	52.2 ± 26.2



		Week 2	Week 4	Week 8	Week 12	Week 12 (LOCF)	Week 12 (BOCF)
Mirogabalin + NSAIDs group	n	82	82	78	74	82	82
	Mean ± SD	−9.8 ± 19.4	−16.0 ± 23.4	−24.6 ± 28.0	−25.1 ± 28.1	−24.2 ± 28.2	−22.6 ± 27.7
NSAIDs group	n	94	80	76	72	100	100
	Mean ± SD	−8.6 ± 19.2	−13.6 ± 22.2	−12.3 ± 24.1	−15.0 ± 26.5	−11.3 ± 24.6	−10.8 ± 23.5
Difference between groups Estimated value (95% CI)		−1.3 (−7.0, 4.5)	−2.4 (−9.5, 4.7)	−12.3 (−20.6, −4.0)	−10.1 (−19.0, −1.1)	−13.0 (−20.7, −5.3)	−11.8 (−19.3, −4.3)

Figure S1. (a) VAS score for leg pain and (b) its change from baseline in compliant subgroups (mITT population)

Data are mean ± SD.

No statistical tests were conducted for the results shown in Figure S1a.

*P < 0.05 for between-group differences by t-test

**$P < 0.01$ for between-group differences by *t*-test

BOCF baseline observation carried forward, *CI* confidence interval, *LOCF* last observation carried forward, *mITT* modified intention-to-treat, *NSAIDs* non-steroidal anti-inflammatory drugs, *SD* standard deviation, *VAS* visual analog scale

Table S1. Baseline patient demographic and clinical characteristics in patients who were compliant with the package insert (modified intention-to-treat population)

Characteristics	Compliant	
	Mirogabalin and NSAIDs (*n* = 82)	**NSAIDs (*n* = 100)**
Age, years	68.3 ± 11.2	71.0 ± 9.2
≥ 65	55 (67.1)	75 (75.0)
Sex		
Male	38 (46.3)	53 (53.0)
Female	44 (53.7)	47 (47.0)
Body weight, kg	63.5 ± 14.5	62.2 ± 13.0
< 60	33 (40.2)	39 (39.0)
VAS score at enrollment, mm	63.9 ± 12.9	63.0 ± 14.0
< 60	38 (46.3)	47 (47.0)
≥ 60	44 (53.7)	53 (53.0)
CrCL at enrollment, mL/min	80.9 ± 36.1	70.4 ± 23.0
≥ 60	58 (70.7)	66 (66.0)
30 to < 60	24 (29.3)	34 (34.0)
Duration of radicular type of LSS, months	24.6 ± 33.3	25.7 ± 36.3
Median (Q1, Q3)	9.0 (4.0, 30.0)	11.0 (5.0, 29.5)
≥ 6	54 (65.9)	67 (67.0)
Duration of limb pain, months	30.2 ± 35.9	26.5 ± 37.2
Median (Q1, Q3)	12.5 (6.0, 46.0)	12.5 (5.0, 30.5)
Symptoms of radicular type of LSS		
Pain	16 (19.5)	21 (21.0)
Numbness	0 (0.0)	0 (0.0)
Pain and numbness	66 (80.5)	79 (79.0)

Data are mean ± SD or *n* (%).

CrCL creatinine clearance, *LSS* lumbar spinal stenosis, *NSAIDs* non-steroidal anti-inflammatory drugs, *VAS* visual analog scale

Table S2. Daily dose of mirogabalin for 12 weeks by renal function at enrollment (mITT population, *N* = 110)

Mirogabalin dose	CrCL ≥ 60 mL/min					CrCL 30 to < 60 mL/min				
	Baseline (*n* = 80)	**Week 2 (*n* = 78)**	**Week 4 (*n* = 75)**	**Week 8 (*n* = 66)**	**Week 12 (*n* = 62)**	**Baseline (*n* = 30)**	**Week 2 (*n* = 30)**	**Week 4 (*n* = 28)**	**Week 8 (*n* = 26)**	**Week 12 (*n* = 23)**
2.5 mg BID	0 (0.0)	1 (1.3)	1 (1.3)	2 (3.0)	2 (3.2)	30 (100.0)	1 (3.3)	2 (7.1)	2 (7.7)	2 (8.7)
5 mg BID	80 (100.0)	7 (9.0)	9 (12.0)	6 (9.1)	5 (8.1)	0 (0.0)	29 (96.7)	7 (25.0)	6 (23.1)	5 (21.7)
7.5 mg BID	0 (0.0)	0 (0.0)	1 (1.3)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	18 (64.3)	17 (65.4)	15 (65.2)
10 mg BID	0 (0.0)	69 (88.5)	12 (16.0)	10 (15.2)	9 (14.5)	0 (0.0)	0 (0.0)	1 (3.6)	1 (3.8)	1 (4.3)
15 mg BID	0 (0.0)	0 (0.0)	50 (66.7)	45 (68.2)	44 (71.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (1.3)	2 (2.7)	2 (3.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are *n* (%).

BID twice daily, *CrCL* creatinine clearance, *mITT* modified intention-to-treat

Table S3. Change in VAS score from baseline to Week 12 among patients who were compliant with the package insert, baseline VAS, renal function, type of LSS symptoms, SPDQ score, and SF-SPDQ score by MMRM analysis (mITT population)

		Mirogabalin and NSAIDs	NSAIDs	Difference between groups
Compliance with the package insert				
Compliant	*n*	74	72	
	LS mean ± SE	−24.2 ± 3.1	−14.0 ± 3.1	−10.2 ± 4.4
	95% CI	−30.3, −18.1	−20.2, −7.9	−18.8, −1.5
	P-value	< 0.0001[a]	< 0.0001[a]	0.0212[b]
VAS at baseline				
VAS score < 60 mm	*n*	40	39	
	LS mean ± SE	−20.3 ± 3.5	−9.5 ± 3.6	−10.7 ± 5.0
	95% CI	−27.2, −13.3	−16.7, −2.4	−20.7, −0.7
	P-value	< 0.0001[a]	0.0096[a]	0.0355[b]
VAS score ≥ 60 mm	*n*	45	36	
	LS mean ± SE	−27.3 ± 4.3	−19.2 ± 4.9	−8.1 ± 6.5
	95% CI	−35.8, −18.7	−29.0, −9.5	−21.0, 4.9
	P-value	< 0.0001[a]	0.0002[a]	0.2205[b]
Renal function				
CrCL ≥ 60 mL/min	*n*	62	53	

	LS mean ± SE	−27.1 ± 3.2	−16.4 ± 3.5	−10.7 ± 4.7
	95% CI	−33.3, −20.8	−23.2, −9.5	−20.0, −1.4
	P-value	< 0.0001[a]	< 0.0001[a]	0.0241[b]
CrCL 30 to < 60 mL/min	*n*	23	22	
	LS mean ± SE	−16.1 ± 5.7	−9.8 ± 5.9	−6.3 ± 8.2
	95% CI	−27.5, −4.6	−21.7, 2.2	−22.9, 10.3
	P-value	0.0071[a]	0.1065[a]	0.4470[b]
Type of LSS symptoms				
Pain	*n*	18	21	
	LS mean ± SE	−24.7 ± 6.0	−16.1 ± 5.6	−8.6 ± 8.2
	95% CI	−36.9, −12.5	−27.5, −4.8	−25.2, 8.1
	P-value	0.0002[a]	0.0067[a]	0.3024[b]
Pain and numbness	*n*	67	54	
	LS mean ± SE	−23.9 ± 3.2	−13.3 ± 3.6	−10.6 ± 4.8
	95% CI	−30.2, −17.6	−20.5, −6.2	−20.1, −1.1
	P-value	< 0.0001[a]	0.0003[a]	0.0296[b]
SPDQ				
Total score < 0	*n*	16	13	
	LS mean ± SE	−20.2 ± 7.0	−9.0 ± 7.7	−11.2 ± 10.4

	95% CI	−34.4, −6.0	−24.8, 6.8	−32.4, 10.1
	P-value	0.0069[a]	0.2520[a]	0.2924[b]
Total score ≥ 0	*n*	68	62	
	LS mean ± SE	−25.3 ± 3.1	−15.3 ± 3.3	−9.9 ± 4.6
	95% CI	−31.4, −19.1	−21.9, −8.8	−19.0, −0.9
	P-value	< 0.0001[a]	< 0.0001[a]	0.0309[b]
SF-SPDQ				
Score < 0	*n*	10	10	
	LS mean ± SE	−15.5 ± 9.2	−15.3 ± 9.4	−0.1 ± 13.2
	95% CI	−34.7, 3.7	−35.0, 4.3	−27.7, 27.4
	P-value	0.1086[a]	0.1186[a]	0.9927[b]
Score ≥ 0	*n*	74	65	
	LS mean ± SE	−25.3 ± 3.0	−14.1 ± 3.2	−11.2 ± 4.4
	95% CI	−31.2, −19.4	−20.4, −7.7	−19.9, −2.6
	P-value	< 0.0001[a]	< 0.0001[a]	0.0112[b]

[a]*P*-value for Week 12 vs baseline.

[b]*P*-value for mirogabalin and NSAIDs group vs NSAIDs group.

CI confidence interval, *CrCL* creatinine clearance, *LS* least squares, *LSS* lumbar spinal stenosis, *mITT* modified intention-to-treat, *MMRM* mixed model for repeated measure model, *NSAIDs* non-steroidal anti-inflammatory drugs, *SE* standard error, *SPDQ* spine pain DETECT questionnaire, *SF-SPDQ* short form SPDQ, *VAS* visual analog scale

Table S4. Each item of EQ-5D-5L five-dimensional descriptive system at baseline and Week 12 (mITT population)

		Mirogabalin and NSAIDs (*n* = 85)		NSAIDs (*n* = 75)	
		Baseline	**Week 12**	**Baseline**	**Week 12**
Mobility	No problems	11 (12.9)	21 (24.7)	20 (26.7)	25 (33.3)
	Slight problems	25 (29.4)	36 (42.4)	20 (26.7)	29 (38.7)
	Moderate problems	26 (30.6)	20 (23.5)	23 (30.7)	14 (18.7)
	Severe problems	22 (25.9)	7 (8.2)	12 (16.0)	7 (9.3)
	Extreme problems	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)
	Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Self-care	No problems	60 (70.6)	71 (83.5)	54 (72.0)	58 (77.3)
	Slight problems	17 (20.0)	11 (12.9)	16 (21.3)	13 (17.3)
	Moderate problems	5 (5.9)	2 (2.4)	4 (5.3)	3 (4.0)
	Severe problems	3 (3.5)	1 (1.2)	1 (1.3)	1 (1.3)
	Extreme problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Usual activities	No problems	22 (25.9)	33 (38.8)	26 (34.7)	35 (46.7)

	Slight problems	32 (37.6)	31 (36.5)	29 (38.7)	24 (32.0)
	Moderate problems	19 (22.4)	14 (16.5)	15 (20.0)	14 (18.7)
	Severe problems	10 (11.8)	7 (8.2)	5 (6.7)	2 (2.7)
	Extreme problems	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
	Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain/discomfort	No problems	3 (3.5)	8 (9.4)	2 (2.7)	5 (6.7)
	Slight problems	27 (31.8)	41 (48.2)	30 (40.0)	33 (44.0)
	Moderate problems	34 (40.0)	26 (30.6)	34 (45.3)	22 (29.3)
	Severe problems	20 (23.5)	8 (9.4)	8 (10.7)	14 (18.7)
	Extreme problems	1 (1.2)	2 (2.4)	1 (1.3)	1 (1.3)
	Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety/depression	No problems	53 (62.4)	60 (70.6)	47 (62.7)	46 (61.3)
	Slight problems	23 (27.1)	19 (22.4)	23 (30.7)	19 (25.3)
	Moderate problems	8 (9.4)	3 (3.5)	3 (4.0)	7 (9.3)
	Severe problems	1 (1.2)	3 (3.5)	2 (2.7)	0 (0.0)
	Extreme problems	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.0)

	Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are *n* (%).

EQ-5D-5L EuroQol five-dimensional descriptive system, *mITT* modified intention-to-treat, *NSAIDs* non-steroidal anti-inflammatory drugs

Table S5. Change in EQ-5D-5L score from baseline to Week 12 among patients who were compliant with the package insert (mITT population)

	Compliant			
	Mirogabalin and NSAIDs (*n* = 74)		**NSAIDs (*n* = 72)**	
	Baseline	**Week 12**	**Baseline**	**Week 12**
EQ-5D-5L score[a]				
Mean ± SD	0.6558 ± 0.1600	0.7260 ± 0.1589	0.7034 ± 0.1557	0.7268 ± 0.1674
Median (Q1, Q3)	0.6848 (0.5571, 0.7600)	0.7596 (0.6361, 0.8307)	0.7341 (0.5929, 0.8228)	0.7575 (0.6455, 0.8460)
Min, Max	0.269, 1.000	0.209, 1.000	0.245, 1.000	0.208, 1.000
Change from baseline[a]				
Mean ± SD	-	0.0701 ± 0.1599	-	0.0235 ± 0.1515
Mean difference (95% CI) vs NSAIDs	-	0.0467 (−0.0043, 0.0977)	-	-
P-value vs NSAIDs[b]	-	0.0725	-	-

[a]Complete Case Analyses were used; even data from patients missing the first visit were excluded.

[b]*t*-test

CI confidence interval, *EQ-5D-5L* EuroQol five-dimensional descriptive system, *mITT* modified intention-to-treat, *NSAIDs* non-steroidal anti-inflammatory drugs, *Q* quartile, *SD* standard deviation

Table S6. PGIC at Week 12 among patients who were compliant with the package insert (mITT population)

	Compliant	
	Mirogabalin and NSAIDs (*n* = 73)	**NSAIDs (*n* = 71)**
1. Very much improved	9 (12.3)	4 (5.6)
2. Much improved	25 (34.2)	19 (26.8)
3. Minimally improved	20 (27.4)	13 (18.3)
4. No change	13 (17.8)	25 (35.2)
5. Minimally worse	3 (4.1)	8 (11.3)
6. Much worse	3 (4.1)	2 (2.8)
7. Very much worse	0 (0.0)	0 (0.0)
PGIC (score ≤ 3)	54 (74.0)	36 (50.7)
Difference	23.3	-
95% CI	7.9, 38.6	-
P-value vs NSAIDs[a]	0.0039	-
PGIC (score ≤ 2)	34 (46.6)	23 (32.4)
Difference	14.2	
95% CI	−1.6, 30.0	
P-value vs NSAIDs[a]	0.0819	

Data are *n* (%) unless otherwise indicated.

[a]Chi-square test.

CI confidence interval, *mITT* modified intention-to-treat, *NSAIDs* non-steroidal anti-inflammatory drugs, *PGIC* Patient Global Impression of Change

Table S7. TEAEs and ADRs occurring in ≥ 2% patients in subgroups according to compliance with the package insert (safety analysis set)

	Compliant	
	Mirogabalin and NSAIDs (*n* = 82)	**NSAIDs (*n* = 102)**
Overall TEAEs	46 (56.1)	12 (11.8)
Somnolence	22 (26.8)	0 (0.0)
Dizziness	18 (22.0)	0 (0.0)
Edema peripheral	6 (7.3)	0 (0.0)
Constipation	2 (2.4)	0 (0.0)
Unpleasant sensation in the abdomen	2 (2.4)	3 (2.9)
Nasopharyngitis	2 (2.4)	1 (1.0)
Fall	2 (2.4)	1 (1.0)
Serious TEAEs	0 (0.0)	1 (1.0)[a]
Discontinuations due to TEAEs	2 (2.4)[b]	0 (0.0)
Overall ADRs	42 (51.2)	2 (2.0)
Somnolence	22 (26.8)	0 (0.0)
Dizziness	18 (22.0)	0 (0.0)
Edema peripheral	6 (7.3)	0 (0.0)
Constipation	2 (2.4)	0 (0.0)
Fall	2 (2.4)	0 (0.0)
Serious ADRs	0 (0.0)	0 (0.0)
Discontinuations due to ADRs	2 (2.4)[b]	0 (0.0)

Data are *n* (%).

Coded using the MedDRA/J, version 24.1.

[a]This was an event of breast cancer.

[b]One patient discontinued due to the occurrence of more than one AE or ADR.

ADR adverse drug reaction, *MedDRA/J* Japanese Medical Dictionary for Regulatory Activities, *NSAIDs* non-steroidal anti-inflammatory drugs, *TEAE* treatment-emergent adverse event

Table S8. List of participating institutions and principal investigators

Name of institution	Name of the principal investigator at the study site
Fukushima Medical University Hospital	Takuya Nikaido[a]
Kato Seikei Zaitaku Clinic	Yasuji Kato
Chiba University Hospital	Seiji Ohtori
Tokyo Medical University Hospital	Kazuma Murata
Tokyo Medical and Dental University Hospital	Atsushi Okawa
Sobajima Clinic	Satoshi Sobajima
Miyake Orthopedic Clinic	Nobumasa Miyake
Hamamatsu University Hospital	Yukihiro Matsuyama
Kurume University Hospital	Kimiaki Sato
Jin Orthopaedic Clinic	Yasutomo Matsubayashi
Kasaharaiin	Takashi Kasahara
Keio University Hospital	Osahiko Tsuji
Kudanzaka Hospital	Shigeo Shindo
Yokohama City University Hospital	Yohei Ito
Funabashi Central Hospital	Masaomi Yamashita
Tohoku Rosai Hospital	Takashi Kusakabe
Sendai Orthopaedic Hospital	Tetsuro Sato
Tottori University Hospital	Shinji Tanishima
Wakayama Medical University Hospital	Hiroshi Hashizume
Osaka City University Hospital	Shinji Takahashi
Saga University Hospital	Tadatsugu Morimoto
Aichi Medical University Hospital	Shinsuke Inoue
Kyoto University Hospital	Shunsuke Fujibayashi
Tohoku Medical and Pharmaceutical University Hospital	Hiroshi Ozawa
AR-Ex Spine Clinic	Kiyoshi Yoshihara
Osaka University Hospital	Takashi Kaito
Saiseikai Kawaguchi General Hospital	Masaki Tomori

Tohoku University Hospital	Toshimi Aizawa
Yamaguchi Rosai Hospital	Tsukasa Kanchiku
Fukuoka-Mirai Hospital	Masayoshi Oga
Jichi Medical University Hospital	Hirokazu Inoue
Toyama University Hospital	Taketoshi Yasuda

[a]Study principal investigator.