Supplementary materials

Safety and Efficacy of Mirogabalin in Lumbar Spinal Stenosis Patients with Peripheral Neuropathic Pain on NSAIDs: Post Hoc Analysis of the MiroTAS Study

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Supplementary Tables

Table S1. Classification and definitions of effective dose

Classification	Definitions
(A) Dose was increased to at least the lowest effective dose (effective dose group)	1) CrCL at study enrollment is ≥30 to <60 mL/min: The dose of mirogabalin is ≥5 to ≤7.5 mg BID at the end of the study (at discontinuation). 2) CrCL at study enrollment is ≥60 mL/min: The dose of mirogabalin is ≥10 to ≤15 mg BID at the end of the study.
(B) Starting dose was maintained (initial dose-maintained group)	1) CrCL at study enrollment is ≥30 to <60 mL/min: The dose of mirogabalin is <5 mg BID at the end of the study. 2) CrCL at study enrollment is ≥60 mL/min: The dose of mirogabalin is <10 mg BID at the end of the study.

BID twice daily, *CrCL* creatinine clearance

Table S2. EQ-5D-5L scores at baseline and Week 12 in patients with and without mirogabalin-related ADRs in the mirogabalin add-on group (patients who were compliant with the package insert)

	With mirogabalin-related ADRs		**Without mirogabalin-related ADRs**	
	Baseline	**Week 12**	**Baseline**	**Week 12**
	***n* = 33**	***n* = 33**	***n* = 41**	***n* = 41**
EQ-5D-5L score[a]				
Mean ± SD	0.6192 ± 0.1792	0.7144 ± 0.1452	0.6853 ± 0.1380	0.7353 ± 0.1704
Min, Max	0.269,1.000	0.370, 0.895	0.294, 0.895	0.209, 1.000
Median (Q1, Q3)	0.6286 (0.4962, 0.7315)	0.7583 (0.6235, 0.8205)	0.6934 (0.6414, 0.7803)	0.7803 (0.6648, 0.8307)
Change from baseline to Week 12				
Mean ± SD	-	0.0952 ± 0.1594	-	0.0499 ± 0.1594
Min, Max	-	−0.220, 0.367	-	−0.310, 0.402
Median (Q1, Q3)	-	0.1126 (0.0000, 0.2225)	-	0.0145 (−0.0639, 0.1712)
Estimated (95% CI) between-group difference	-	0.0453 (−0.0291, 0.1196) $p = 0.2286$[b]	-	-

[a]Complete case analyses were used; data from patients missing even one visit were excluded.

[b]*t*-test

ADRs adverse drug reactions, *CI* confidence interval, *NSAIDs* non-steroidal anti-inflammatory drugs, *Q* quartile, *SD* standard deviation.

Table S3. PGIC score at Week 12 in patients with and without mirogabalin-related ADRs in the mirogabalin add-on group (patients who were compliant with the package insert)

PGIC score at Week 12	With mirogabalin-related ADRs *n* = 33	Without mirogabalin-related ADRs *n* = 40
1. Very much improved	3 (9.1)	6 (15.0)
2. Much improved	13 (39.4)	12 (30.0)
3. Minimally improved	11 (33.3)	9 (22.5)
4. No change	4 (12.1)	9 (22.5)
5. Minimally worse	1 (3.0)	2 (5.0)
6. Much worse	1 (3.0)	2 (5.0)
7. Very much worse	0 (0.0)	0 (0.0)
PGIC (score ≤3)	27 (81.8)	27 (67.5)
Estimated (95% CI) between-group difference	14.3 (−5.3, 33.9)[a] $p = 0.1653$[b]	-
PGIC (score ≤2)	16 (48.5)	18 (45.0)
Estimated (95% CI) between-group difference	3.5 (−19.5, 26.5)[a] $p = 0.7664$[b]	-

Data are *n* (%) unless specified.

[a]Wald method.

[b]Chi-square test.

ADRs adverse drug reactions, *CI* confidence interval, *NSAIDs* non-steroidal anti-inflammatory drugs; *PGIC* Patient Global Impression of Change.

Table S4. Difference in change in EQ-5D-5L score and VAS score from baseline to Week 12 by baseline SPDQ numbness score (patients who were compliant with the package insert)

	Mirogabalin add-on group	**NSAIDs alone group**
Estimated difference in change in EQ-5D-5L[a] from baseline to Week 12 between patients with baseline SPDQ numbness scores ≤2 and >2	−0.0874 (−0.1596, −0.0152) $p = 0.0184$[c]	−0.0545 (−0.1265, 0.0175) $p = 0.1354$[c]
Estimated difference in change in VAS score[b] from baseline to Week 12 between patients with baseline SPDQ numbness score ≤2 and >2	4.9 (−7.9, 17.7) $p = 0.4464$[b]	6.4 (−5.6, 18.4) $p = 0.2929$[b]

Data are mean (95% confidence interval).

[a]Complete case analyses were used; data from patients missing even one visit were excluded.

[b]Analyzed using the mixed model for repeated measures.

[c]*t*-test.

NSAIDs non-steroidal anti-inflammatory drugs, *SPDQ* spine painDETECT questionnaire, *VAS* visual analogue scale.

Table S5. Estimated difference in change in VAS score and EQ-5D-5L by PGIC score category (patients who were compliant with the package insert)

	Mirogabalin add-on group	**NSAIDs alone group**
Estimated difference in change in EQ-5D-5L[a] scores from baseline to Week 12		
Between patients with PGIC scores ≤3 and >3 at Week 12	0.1359 (0.0560, 0.2159) p = 0.0011[c]	0.1099 (0.0421, 0.1777) p = 0.0019[c]
Between patients with PGIC scores ≤2 and >2 at Week 12	0.0964 (0.0241, 0.1687) p = 0.0097[c]	0.1101 (0.0370, 0.1832) p = 0.0037[c]
Estimated difference in change in VAS scores[b] from baseline to Week 12		
Between patients with PGIC scores ≤3 and >3 at Week 12	−32.9 (−45.6, −20.3) p <0.0001[b]	−24.9 (−35.9, −13.9) p <0.0001[b]
Between patients with PGIC scores ≤2 and >2 at Week 12	−33.3 (−43.8, −22.8) p <0.0001[b]	−33.6 (−44.1, −23.0) p <0.0001[b]

Data are mean (95% confidence interval).

[a]Complete case analyses were used; data from patients missing even one visit were excluded.

[b]The VAS score was analyzed using the mixed model for repeated measures.

[c]*t*-test.

NSAIDs non-steroidal anti-inflammatory drugs, *PGIC* Patient Global Impression of Change, *VAS* visual analogue scale

Table S6. Change in VAS score for leg pain from baseline to Week 12 by lumbar spinal stenosis disease duration (patients who were compliant with the package insert)

	Mirogabalin add-on group		NSAIDs alone group	
Disease duration (months)	**<6**	**≥6**	**<6**	**≥6**
Estimated change in VAS score[a] from baseline to Week 12	−33.8 (−44.3, −23.4) *p* <0.0001	−19.7 (−27.4, −11.9) *p* <0.0001	−22.2 (−32.3, −12.1) *p* <0.0001	−9.2 (−16.2, −2.1) *p* = 0.0116
Difference between <6 months and ≥6 months	-	−14.2 (−27.2, −1.2) *p* = 0.0329[a]	-	−13.0 (−25.3, −0.7) *p* = 0.0386[a]

Data are mean ± standard error (95% confidence interval).

[a]Analyzed using the mixed model for repeated measures.

NSAIDs non-steroidal anti-inflammatory drugs, *VAS* visual analogue scale

Supplementary Figures

Variables		*N*	Population with reduction in VAS for leg pain, ≥20 mm: Improvement rate, *n* (%) [95% CI][1)]	Difference [95% CI][2)]	*p*-value[3)]
All		74	40 (54.1) [42.1, 65.7]		
Sex	Male	35	22 (62.9) [44.9, 78.5]	16.7 [−5.7, 39.1]	0.1500
	Female	39	18 (46.2) [30.1, 62.8]	(Reference)	
Age, years	<65	25	16 (64.0) [42.5, 82.0]	20.5 [−7.1, 48.2]	0.1540
	≥65 to <75	26	14 (53.8) [33.4, 73.4]	10.4 [−17.5, 38.3]	0.4687
	≥75	23	10 (43.5) [23.2, 65.5]	(Reference)	
Baseline VAS score, mm	<60	33	16 (48.5) [30.8, 66.5]	−10.1 [−32.8, 12.7]	0.3884
	≥60	41	24 (58.5) [42.1, 73.7]	(Reference)	
Body mass index	<25	45	25 (55.6) [40.0, 70.4]	3.8 [−19.4, 27.1]	0.7468
	≥25	29	15 (51.7) [32.5, 70.6]	(Reference)	
Site of leg pain	One leg only	58	34 (58.6) [44.9, 71.4]	−21.1 [−5.8, 48.0]	0.1334
	Both legs	16	6 (37.5) [15.2, 64.6]	(Reference)	
Leg numbness	None	15	6 (40.0) [16.3, 67.7]	−17.6 [−45.4, 10.2]	0.2213
	One leg only	59	34 (57.6) [44.1, 70.4]	(Reference)	
Spine painDETECT numbness score	≤2	33	14 (42.4) [25.5, 60.8]	−21.0 [−43.4, 1.4]	0.0717
	≥3	41	26 (63.4) [46.9, 77.9]	(Reference)	
Symptoms of radicular type of LSS	Pain alone	15	6 (40.0) [16.3, 67.7]	−17.6 [−45.4, 10.2]	0.2213
	Both pain and numbness	59	34 (57.6) [44.1, 70.4]	(Reference)	
Duration of radicular type of LSS, months	<6	27	17 (63.0) [42.4, 80.6]	14.0 [−9.1, 37.2]	0.2438
	≥6	47	23 (48.9) [34.1, 63.9]	(Reference)	
Duration of leg pain, months	<6	16	9 (56.3) [29.9, 80.2]	2.8 [−24.7, 30.3]	0.8422
	≥6	58	31 (53.4) [39.9, 66.7]	(Reference)	
CrCL at enrollment, mL/min	≥30 to <60	20	9 (45.0) [23.1, 68.5]	−12.4 [−37.9, 13.1]	0.3415
	≥60	54	31 (57.4) [43.2, 70.8]	(Reference)	
Complications of orthopedic diseases	None	49	24 (49.0) [34.4, 63.7]	−15.0 [−38.5, 8.4]	0.2201
	Yes	25	16 (64.0) [42.5, 82.0]	(Reference)	
Complications	Diabetes	10	8 (80.0) [44.4, 97.5]	30.0 [2.3, 57.7]	0.0767
	Stroke	1	0 (0.0) [0.0, 97.5]	−54.8 [−66.2, −43.4]	0.2748
	Hypertension	40	23 (57.5) [40.9, 73.0]	7.5 [−15.2, 30.2]	0.5188
	Hyperlipidemia	28	14 (50.0) [30.6, 69.4]	−6.5 [−29.9, 16.9]	0.5851
	Cervical spondylosis	2	1 (50.0) [1.3, 98.7]	−4.2 [−74.4, 66.1]	0.9072
	Posterior longitudinal ligament ossification	1	1 (100.0) [2.5, 100.0]	46.6 [35.1, 58.0]	0.3533
	Rheumatoid arthritis	3	1 (33.3) [0.8, 90.6]	−21.6 [−76.2, 33.0]	0.4622
	Herniated intervertebral disc	7	4 (57.1) [18.4, 90.1]	3.4 [−35.1, 42.0]	0.8632
	Spondylolysis/spondylolisthesis	10	9 (90.0) [55.5, 99.7]	41.6 [19.3, 63.8]	0.0142
	Osteoporotic compression fracture	1	0 (0.0) [0.0, 97.5]	−54.8 [−66.2, −43.4]	0.2748
	Scoliosis	5	1 (20.0) [0.5, 71.6]	−36.5 [−73.5, 0.4]	0.1136

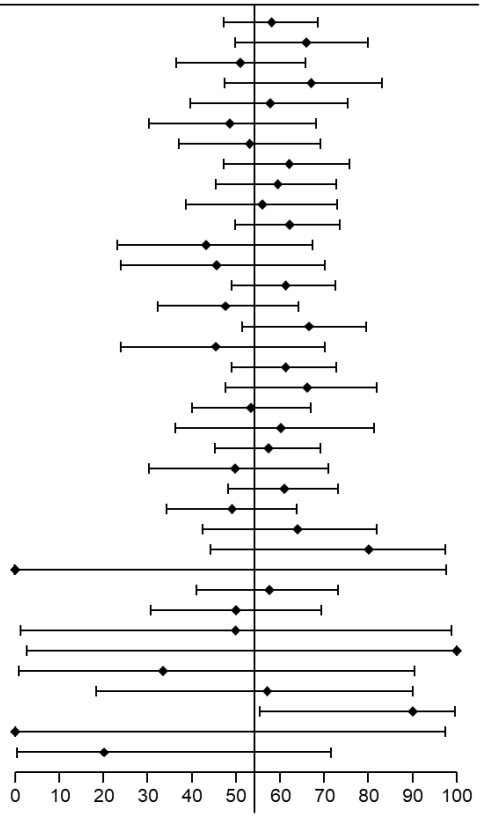

Figure S1. Patient background characteristics and percentage of patients with improvement in VAS score for leg pain of ≥20 mm at Week 12 in the mirogabalin add-on group (patients who were compliant with the package insert)

[1]Clopper–Pearson method

[2]Wald method

[3]Chi-square test

CI confidence interval, *CrCL* creatinine clearance, *LSS* lumbar spinal stenosis, *VAS* visual analogue scale

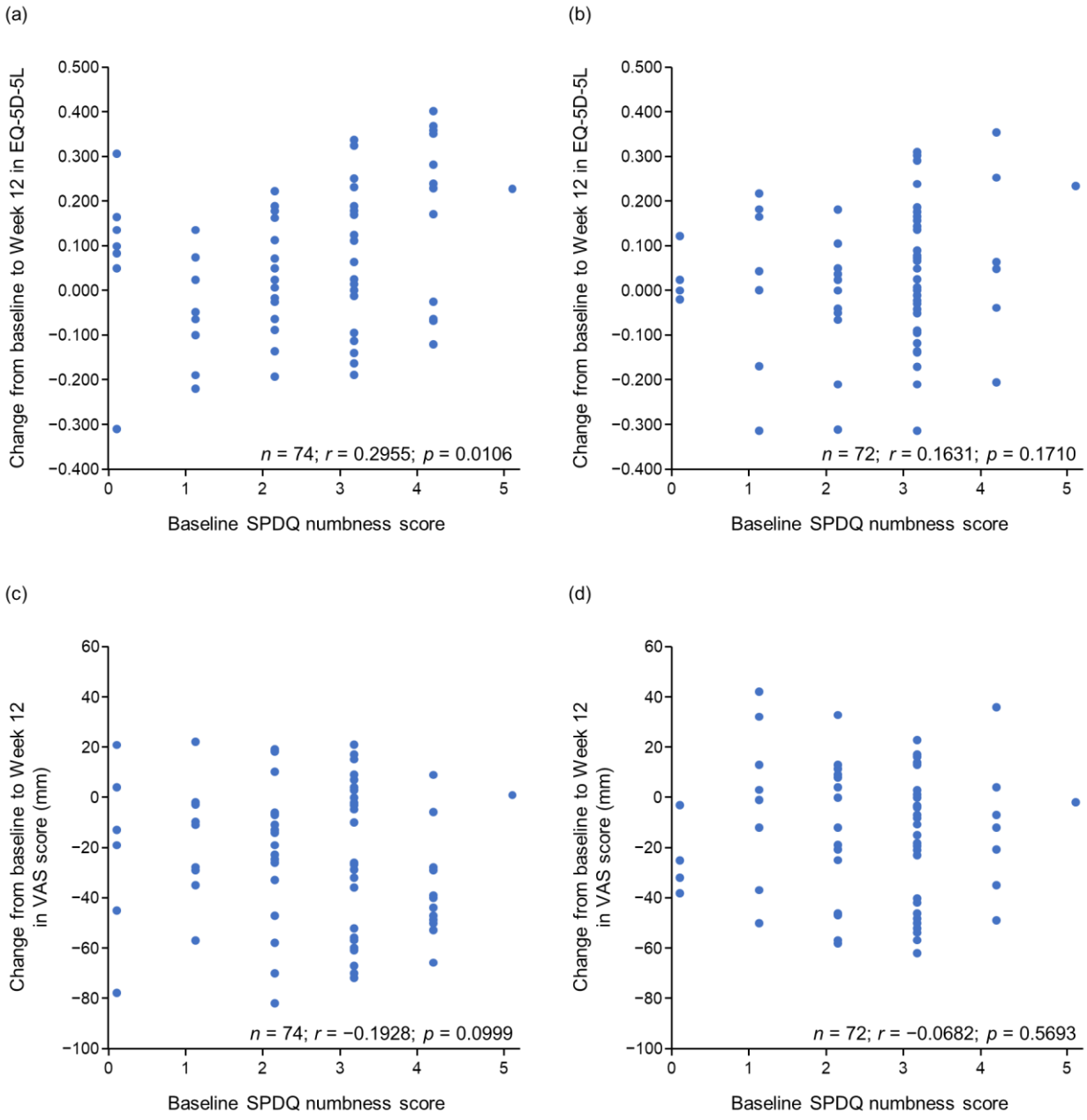

Figure S2. Relationship of SPDQ numbness score at baseline with the change in EQ-5D-5L (**a, b**) and VAS score for leg pain (**c, d**) from baseline to Week 12 in (**a, c**) the mirogabalin add-on group and (**b, d**) the NSAIDs alone group (patients who were compliant with the package insert)

Spearman's rank correlation coefficient

EQ-5D-5L was analyzed using complete case analyses.

VAS score analyzed using the mixed model for repeated measures.

NSAIDs non-steroidal anti-inflammatory drugs, *SPDQ* spine painDETECT questionnaire, *VAS* visual analogue scale

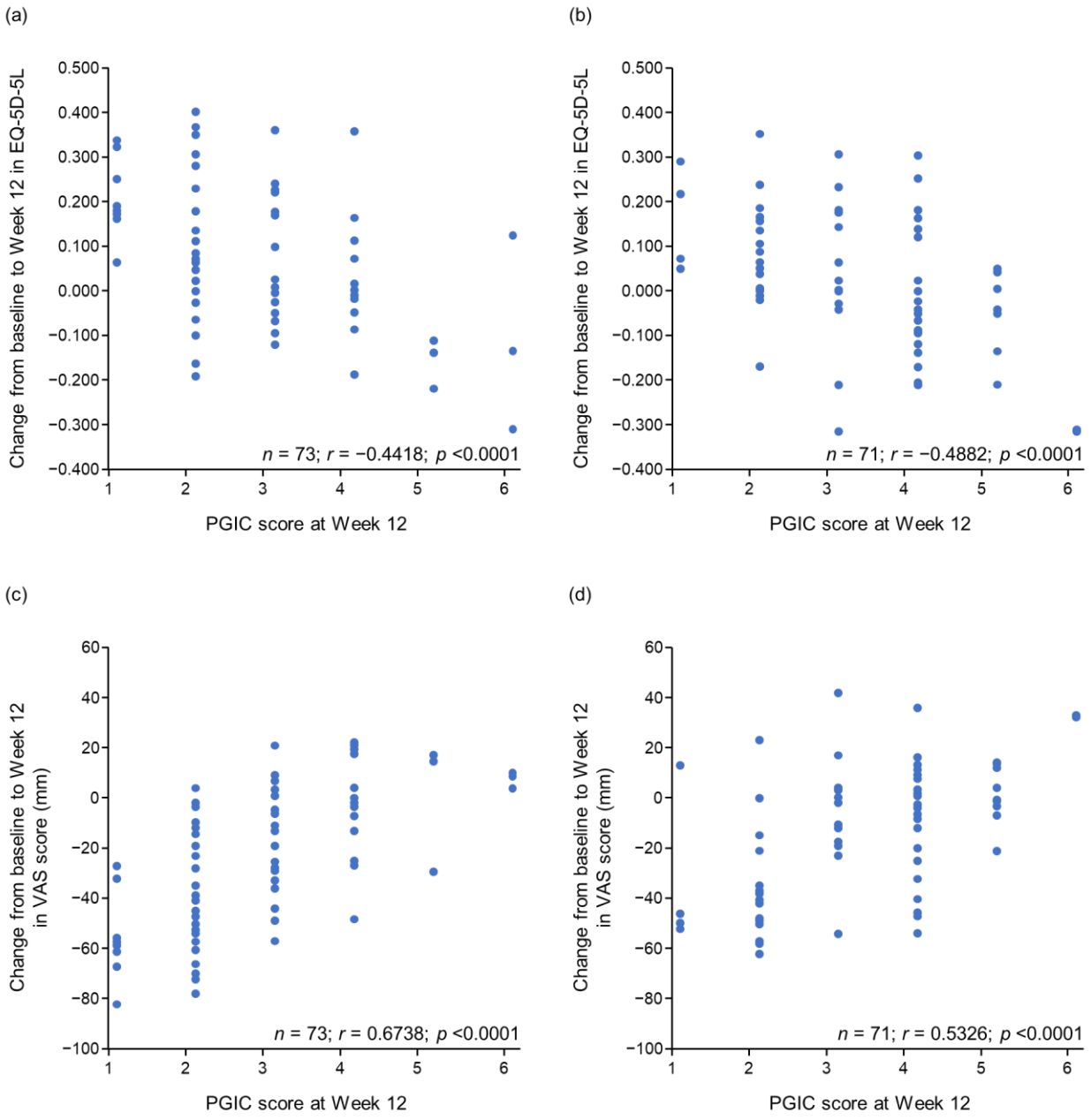

Figure S3. Relationship of PGIC score at Week 12 with the change in EQ-5D-5L (**a, b**) and VAS score for leg pain (**c, d**) from baseline to Week 12 in (**a, c**) the mirogabalin add-on group and (**b, d**) the NSAIDs alone group (patients who were compliant with the package insert)

Spearman's rank correlation coefficient

The VAS score analyzed using the mixed model for repeated measures.

EQ-5D-5L was analyzed using complete case analyses.

NSAIDs non-steroidal anti-inflammatory drugs, *PGIC* Patient Global Impression of Change, *VAS* visual analogue scale