

Supplementary Materials

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled 14-Week study of Mirogabalin in Chinese Patients with Diabetic Peripheral Neuropathic Pain

Xiaohui Guo,^{1*} Yang Yu,¹ Yongbo Zhang,² Li Sun,³ Yufeng Li,⁴ Bing Song,⁵ Li Hang,⁶ Masayuki Baba,⁷ Yosuke Wasaki,⁸ Kunika Kikumori,⁹ Emiko Murayama¹⁰

¹Department of Endocrinology, Peking University First Hospital, No. 8 Xishiku Street, Xicheng District, Beijing 100034, China

²Department of Neurology, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong'an Road, Beijing 100050, China.

³Siping Central People's Hospital, No. 89 South Yingbin Street, Tiexie District, Siping, Jilin Province 136000, China

⁴Beijing Pinggu Hospital, No. 59 Xingping North Road, Pinggu District, Beijing 101200, China

⁵The First Affiliated Hospital of Jinzhou Medical University, No. 2, 5h Part, Renmin Street, Guta District, Jinzhou city, Liaoning province 121001, China

⁶Daiichi Sankyo (China) Holdings Co., Ltd., Floor 51, Wheelock Square, 1717 Nanjing West Road, Shanghai 200040, China

⁷Neurology Center, Aomori Prefectural Central Hospital, 2-1-1 Higashitsukurimichi, Aomori 030-8553, Japan

⁸Asset Portfolio Management Department, Daiichi Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa, Tokyo 140-8710, Japan

⁹Data Intelligence Department, Daiichi Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa,
Tokyo 140-8710, Japan

¹⁰Specialty Medicine Clinical Development Department, Daiichi Sankyo Co., Ltd., 1-2-58
Hiromachi, Shinagawa, Tokyo 140-8710, Japan

*Corresponding author

Xiaohui Guo

Email: bdyguoxiaohui@sina.com

Supplementary Text

Text S1. Prohibited and Restricted Concomitant Medications

Acetaminophen was permitted as rescue medication. Dose interruption occurred if investigators decided it was necessary for safety reasons, but dose reduction was not permitted. To assess compliance, patients were instructed to return any remaining investigational product at each study visit.

Prohibited concomitant medications included pregabalin, anti-epileptics, antidepressants other than selective serotonin reuptake inhibitors, hypnotics (except ultrashort-acting drugs), anxiolytics, non-steroidal anti-inflammatory drugs, and opioids. Patients using any of the above medications were required to undergo a 1-week washout period prior to beginning the study. The following restricted concomitant medications were permitted for use during the study, provided that the dosage did not change: antidiabetic drugs other than insulin, selective serotonin reuptake inhibitors (for the treatment of depression or anxiety only), ultrashort-acting hypnotics, vasodilators (except for cilostazol and prostaglandin), and aspirin (as prophylaxis for cardiovascular disease).

Text S2. Eligibility Criteria

Patients had to meet all of the following criteria to be included in the study:

1. Age $\geq$ 18 years at informed consent
2. Able to give written informed consent for study participation, understand procedures of this study, and complete patient-reported questionnaires adequately
3. Type 1 or type 2 diabetes mellitus at screening
4. Painful distal symmetric polyneuropathy, diagnosed at least 6 months prior to screening

5. Pain score of ≥ 40 mm on the visual analog scale (VAS) of the Short-form McGill Pain Questionnaire (SF-MPQ) at screening
6. Pain score of ≥ 40 mm on the VAS of the SF-MPQ, and completion of at least 4 days of daily pain diaries with an average daily pain score (ADPS) of ≥ 4 over the past 7 days on the 11-point numerical rating scale at randomization.

Patients who met any of the following criteria were excluded from the study:

1. Pain score of ≥ 90 mm on the VAS of the SF-MPQ at screening
2. Pain score of ≥ 90 mm on the VAS of the SF-MPQ, or a daily pain score of 10 during the observation period at randomization
3. Glycated hemoglobin (HbA1c, National Glycohemoglobin Standardization Program) $> 10.0\%$ at screening
4. Uncontrolled blood glucose within 1 month prior to screening, at screening, or at randomization
5. Other severe pain at screening or randomization, unrelated to diabetic peripheral neuropathy (DPN), that may confound the assessment of diabetic peripheral neuropathic pain (DPNP)
6. Neurologic disorders at screening or randomization, unrelated to DPN, that may confound the assessment of DPNP
7. Major psychiatric disorders at screening or randomization
8. Amputation of lower limb parts, other than toes, prior to screening or randomization
9. Use of prohibited concomitant drugs within 7 days or change of restricted concomitant drugs within 28 days prior to screening
10. Skin conditions that could confound the assessment of DPNP

11. Previous administration of pregabalin ≥ 300 mg/day or gabapentin ≥ 1200 mg/day, with a declared lack of effect
12. Creatinine clearance (using the Cockcroft–Gault equation) < 60 mL/min at screening
13. Malignancy other than basal cell carcinoma within the past 2 years prior to screening
14. Clinically significant unstable neurologic, ophthalmologic, hepatobiliary, respiratory, or hematologic illness or cardiovascular disease (e.g., severe hypotension, uncontrolled cardiac arrhythmia, or myocardial infarction, based on electrocardiography) at screening
15. History of pernicious anemia, untreated hypothyroidism, or human immunodeficiency virus infection
16. Pregnancy, potential pregnancy, breast feeding, or unwillingness to take reliable contraceptive measures during the study and for 4 weeks after study completion
17. Known hypersensitivity to pregabalin or gabapentin
18. Participation in another clinical study, either currently or within 28 days prior to providing informed consent
19. Prior participation in a mirogabalin clinical study in which the investigational product was administered
20. Abuse of illicit drugs or alcohol within 1 year prior to screening
21. Response of “yes” to any of the questions on the Colombia-Suicide Severity Rating Scale at screening or randomization in relation to events occurring within the past 12 months
22. Clinical laboratory values exceeding limits listed below (at screening):

Hematology/blood chemistry limits

AST (GOT)	$> 2.0 \times \text{ULN}$
ALT (GPT)	$> 2.0 \times \text{ULN}$
ALP	$> 1.5 \times \text{ULN}$

T-Bil	$> 1.2^a \times \text{ULN}$
BU	$> 1.5 \times \text{ULN}$
Creatinine kinase	$> 3.0 \times \text{ULN}$

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BU* blood urea, *GOT* glutamic oxaloacetic transaminase, *GPT* glutamic pyruvic transaminase, *T-Bil* total bilirubin, *ULN* upper limit of normal

^aPatients with total bilirubin $> 1.2 \times \text{ULN}$: unconjugated and conjugated bilirubin fractions should be analyzed and only patients documented to have Gilbert's syndrome may be enrolled.

23. Considered inappropriate for the study at the discretion of the investigator or sub-investigator.

Text S3. Definition of Severity/Seriousness of Adverse Events (AEs)

Severity of AEs was defined as follows:

- Mild: Awareness of sign or symptom, but easily tolerated, *i.e.*, does not interfere with subject's usual function.
- Moderate: Discomfort enough to cause interference with usual activity.
- Severe: Incapacitating with inability to work or do usual activity, *i.e.*, interferes significantly with subject's usual function.

Serious AEs were defined according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidelines (ICH Harmonised Tripartite Guideline) for Clinical Safety Data Management [1]. Specifically, serious AEs included any untoward medical occurrence that: results in death or is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect; or is an important medical event that is not immediately life-threatening but may jeopardize the patient or require intervention to prevent one of the above outcomes.

Reference

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite Guideline). Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A. 1994. Available from: https://database.ich.org/sites/default/files/E2A_Guideline.pdf. Accessed 20 June 2023.

Text S4. Randomization and Blinding

Patients were randomly allocated in a 1:1 ratio to receive mirogabalin or placebo, with stratification by baseline ADPS (< 6.0 or ≥ 6.0). The randomization schedule was generated by an independent biostatistician and incorporated into an interactive response technology system to maintain blinding, assigning patients a unique identification number. Both patients and study investigators were blinded to the treatment, and the study drug and placebo were indistinguishable in appearance, as white, film-coated tablets identical in shape and size.

Text S5. Statistical Analysis

The primary efficacy endpoint, the mean change from baseline in the weekly ADPS at Week 14, was compared between the mirogabalin and placebo groups based on the mITT analysis set as a primary analysis using a multiple imputation method and mixed effects model for repeated measurements [1, 2]. The primary imputation was based on the “nonfuture dependence” model using the pattern mixture approach with shifting parameters of (AE, lack of efficacy, any other reason) = (1.0, 1.0, 0.5) for the reason of

discontinuations under the missing not at random mechanism for the missing weekly ADPS data [3, 4, 5]. For the primary efficacy endpoint, the additional analysis adjusted by baseline CrCL as a covariate.

References

1. Mallinckrodt CH, Lin Q, Lipkovich I. A structured approach to choosing estimands and estimators in longitudinal clinical trials. *Pharm Stat.* 2012;11:456–61.
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5. Kenward MG, Molenberghs G, Thijs H. Pattern mixture models with proper time dependence. *Biometrika.* 2003;90:53–71.

Supplementary Tables

Table S1 Participating investigators and institutions (with ethics committees that approved the study)

Hospital Name	Investigator Name	Responsibility
Peking University First Hospital	Xiaohui Guo	Principal Investigator
	Yang Yu	Investigator
	Ying Gao	Investigator
West China Hospital, Sichuan University	Li He	Principal Investigator
	Yang Zhang	Investigator
	Yanan Zhang	Investigator
	Jie Zhou	Investigator
The First Affiliated Hospital of Henan University of Science and Technology	Ganqin Du	Principal Investigator
	Chunyan Cao	Investigator
	Xiaona Zhang	Investigator
	Jian Shi	Investigator
	Zhen Zhang	Investigator
	Baoru Liu	Investigator
	Xiaoshuai Cao	Investigator
	Xiaowei Du	Investigator
	Canfei Zhang	Investigator
Wuxi People's Hospital	Lan Xu	Principal Investigator
	Yanmin Jiang	Investigator

Yangpu District Central Hospital, Shanghai (Yangpu Hospital, Tongji University)	Zunhai Zhou	Principal Investigator
	Bo Wang	Investigator
	Xuelian Zhang	Investigator
	Xiaoyan Zhang	Investigator
	Shimin Zhang	Investigator
	Shouchao Du	Investigator
	Xuane Zhang	Investigator
Beijing Friendship Hospital, Capital Medical University	Yongbo Zhang	Principal Investigator
	Chunling Xu	Investigator
	Yanfei Han	Investigator
The First Affiliated Hospital of Anhui Medical University	Qiu Zhang	Principal Investigator
	Yong He	Investigator
	Yiqing Chen	Investigator
	Yan Wang	Investigator
	Nan Zhang	Investigator
	Liping Xue	Investigator
	Li Xia	Investigator
Renmin Hospital of Wuhan University (Hubei General Hospital)	Shanlei Zhou	Investigator
	Zuneng Lu	Principal Investigator
	Yin Liu	Investigator
	Chao Weng	Investigator
	Jing Yang	Principal Investigator
The First Hospital of Shanxi Medical University	Yunfeng Liu	Investigator

	Xiaoqin Wu	Investigator
Siping Central People's Hospital	Li Sun	Principal Investigator
	Shuangyan	Investigator
	Chu	
	Li Liu	Investigator
	Zhiliang Zhu	Investigator
	Genzhuo Chen	Investigator
	Zhuo Chen	Investigator
	Liping Fan	Investigator
	Hui Jiang	Investigator
	Xue Han	Investigator
Luoyang Central Hospital	Hui Liu	Principal Investigator
	Yanfang Zhang	Investigator
	Jie Su	Investigator
	Ke Huang	Investigator
	Lina Ma	Investigator
	Haiyan Chen	Investigator
	Yiping Yang	Investigator
	Kun Zhang	Investigator
The First Hospital of Changsha	Yinzhen Pi	Principal Investigator
	Luokun Liu	Investigator
	Tengshun Yang	Investigator
	Jinjin Zhao	Investigator

	Li Hu	Investigator
	Juan Chen	Investigator
	Xiang Ou	Investigator
	Haiyan Gong	Investigator
	Huanjun Wang	Investigator
	Haihua Gao	Investigator
Central Hospital of Minhang District Shanghai	Jialin Yang	Principal Investigator
	Yujuan Fan	Investigator
	Xuesong Li	Investigator
The Second Xiangya Hospital of Central South University	Xiangqi Tang	Principal Investigator
	Xiaomei Wu	Investigator
	Yang Chen	Investigator
	Haiping Zheng	Investigator
	Chunli Chen	Investigator
	Jie Zhang	Investigator
	Hainan Zhang	Investigator
	Weifan Yin	Investigator
	Jian Lin	Investigator
	Jia Fang	Investigator
Huashan Hospital, Fudan University	Zhen Hong	Principal Investigator
	Peimin Yu	Investigator
The Second Affiliated Hospital of Nanchang University	Lijun Xu	Principal Investigator
	Ruiqing Luo	Investigator

	Min Li	Investigator
The Second Affiliated Hospital Wenzhou Medical University (Yuying Children's Hospital)	Beilei Hu	Principal Investigator
	Keyang Chen	Investigator
	Songfang Chen	Investigator
	Rongpei Liu	Investigator
	Jianyong Wang	Investigator
	Ming Zou	Investigator
	Longlong Xu	Investigator
Affiliated Hospital of Jiangnan University	Wenjin Hua	Principal Investigator
	Jun Xue	Investigator
	Wenjun Xue	Investigator
	Yanping Wang	Investigator
	Min Cao	Investigator
	Qiaojing Dong	Investigator
	Dan Yu	Investigator
	Hui Chen	Investigator
	Anxing Zhang	Investigator
The Affiliated Hospital of Qingdao University	Yangang Wang	Principal Investigator
	Lili Xu	Investigator
	Fangchao Liu	Investigator
The First Affiliated Hospital of Xiamen University	Qilin Ma	Principal Investigator
	Kunmu Zheng	Investigator
	Xingkai An	Investigator

	Qingsong He	Investigator
	Cen Yue	Investigator
	Jie Zhou	Investigator
	Yidan Zhang	Investigator
	Jianpeng Li	Investigator
	Danni Wang	Investigator
	Quan Lan	Investigator
	Qi Liu	Investigator
	Yihong Zhan	Investigator
	Qing Lin	Investigator
	Hongli Qu	Investigator
	Hanshui Chen	Investigator
	Min Bi	Investigator
	QiuHong Zhang	Investigator
Shanghai Tenth People's Hospital (Tenth Hospital of Tongji University)	Shen Qu	Principal Investigator
	Manna Zhang	Investigator
	Ran Cui	Investigator
The First People's Hospital of Yunnan Province	Jiang Liu	Principal Investigator
	Hao Fu	Investigator
	Lan Lin	Investigator
	Ruihan Yang	Investigator
	Lei Zhang	Investigator
	Xiaoyan Wang	Investigator

	Ning Tang Huimin Zhu Shu Zhang Shan Li Fengli Zhang Xueye Mao Ying Yang	Investigator Investigator Investigator Investigator Investigator Investigator Investigator
The First Affiliated Hospital of Xi'an Jiaotong University	Bingyin Shi Hongjun Lv Yi Wang Yuan Wu Hui Guo	Principal Investigator Investigator Investigator Investigator Investigator
Beijing Pinggu hospital	Yufeng Li Jingjing Wang Lianying Wang Lijuan Wang Nan Jia	Principal Investigator Investigator Investigator Investigator Investigator
Nanfang Hospital of Southern Medical University	Yaoming Xue Xinzhao Fan Huijie Zhang	Principal Investigator Investigator Investigator
Cangzhou Central Hospital	Xinsheng Li Ailing Chang Jincheng Zhang	Principal Investigator Investigator Investigator

	Hongxia Qian	Investigator
	Jing Wei	Investigator
Shanghai Pudong Hospital (Fudan University Pudong Medical Center)	Ligang Zhou	Principal Investigator
	Min Gong	Investigator
	Xinlu Yuan	Investigator
	Xiucan Li	Investigator
	Yanju He	Investigator
	Congcong Wang	Investigator
	Chenglin Xu	Investigator
	Zhaoxun Wang	Investigator
	Fang Yu	Investigator
	Dongxiang Xu	Investigator
PLA Rocket Force Characteristic Medical Center	Ruiqin Du	Principal Investigator
	FengXia Xu	Investigator
Heping Hospital Affiliated to Changzhi Medical College	Huwei Shen	Principal Investigator
	Haoyu Dong	Investigator
	Hong Fan	Investigator
	Qianyu Shen	Investigator
	Li Xing	Investigator
	Yajie Zhang	Investigator
Jilin Central General Hospital	Fenghua You	Principal Investigator
	Jiaping Li	Principal Investigator

	Yongpo Song Lifang Wang Shali Liuiu Xiusong Yao	Investigator Investigator Investigator Investigator
The First People's Hospital of Foshan	Jingsong Chen Xiaozhou Wang Xuejuan Xu Si Feng	Principal Investigator Investigator Investigator Investigator
Huazhong University of Science and Technology Union Shenzhen Hospital (Nanshan Hospital)	Liayan Zheng Jianqing Pan Jianying Li Zhigang Yang Lingling Zhang	Principal Investigator Investigator Investigator Investigator Investigator
The First Affiliated Hospital of Jinzhou Medical University	Bing Song Zhuo Ren Yanwei Li Xinyu Liu Shuo Wang Xiaoyan Zhang Ling Chen	Principal Investigator Investigator Investigator Investigator Investigator Investigator Investigator
Guizhou Provincial People's Hospital	Richeng Yu Jianhua Luo Qian Liu	Principal Investigator Investigator Investigator

	Yuke Li	Investigator
	Lisa Li	Investigator
The Fifth Affiliated Hospital Sun Yat-sen University	Li Cong	Principal Investigator
	Fang Hu	Investigator
Chongqing Emergency Medical Center (The Fourth People's Hospital of Chongqing, Chongqing University Central Hospital)	Wuquan Deng	Principal Investigator
	Wang Min	Investigator
Xuanwu Hospital Capital Medical University	Hai Chen	Principal Investigator
	Min Xu	Investigator
	Li Di	Investigator
	Wenjia Zhu	Investigator
	Yan Lu	Investigator
	Min Wang	Investigator
Jiaxing Second Hospital	Pengfei Du	Principal Investigator
	Junli Wu	Investigator
	Yufen Shen	Investigator
	Qiong Yu	Investigator
Beijing Chaoyang Hospital, Capital Medical University	Guang Wang	Principal Investigator
	Jia Liu	Investigator
	Kun Zhao	Investigator
	Jing Fu	Investigator

	Jing Li	Investigator
	Yan Duan	Investigator
	Qiongrong Pan	Investigator
	Yanjin Hu	Investigator
	Heng Zhang	Investigator
	Xiaomeng Feng	Investigator
Zigong Fourth People's Hospital	Chunying Deng	Principal Investigator
	Liwei Tong	Investigator
	Jingya Ding	Investigator
	Xiaojiao Li	Investigator
	Wenqu Liu	Investigator

Table S2 Change from baseline and difference vs placebo in the weekly ADPS at Week 14 adjusted by baseline CrCL as a covariate

	Mirogabalin	Placebo
	(n = 197)	(n = 196)
Change from baseline at Week 14 (imputed) ^a		
LS mean ± SE	-2.20 ± 0.13	-1.81 ± 0.13
LS mean difference vs placebo ± SE	-0.39 ± 0.18	—
(95% CI), <i>p</i> value	(-0.74, -0.04), 0.028	—

^aBased on a nonfuture dependence model using the pattern mixture model with shifting parameters under the missing not at random mechanism for the missing weekly ADPS data. The shifting parameter values (1.0, 1.0, 0.5) are used for dropout reasons of adverse event, lack of efficacy, and any other reason, respectively. The multiple imputation model included age and sex as covariates using the data from the placebo group. The imputation continued using the Regression with Predictive Mean Matching method. The mixed-effects model for repeated measures includes treatment, week, and treatment-by-week as fixed effects; week as a repeated measure; and baseline ADPS and baseline CrCL as a covariate. In the mixed-effects model for repeated measures, an unstructured covariance structure was used and the Satterthwaite method was applied for adjustment of degrees of freedom. A total of 1000 multiple imputed datasets were combined using Rubin's rule. ADPS average daily pain score, CI confidence interval, CrCL creatinine clearance, LS least-squares, SE standard error.

Table S3 Patient global impression of change scores at Week 14 (modified intention-to-treat analysis set)

Parameter	Mirogabalin (<i>n</i> = 196)	Placebo (<i>n</i> = 197)
1 (very much improved)	28 (14.3)	32 (16.2)
2 (much improved)	92 (46.9)	49 (24.9)
3 (minimally improved)	41 (20.9)	68 (34.5)
4 (no change)	9 (4.6)	20 (10.2)
5 (minimally worse)	2 (1.0)	4 (2.0)
6 (much worse)	1 (0.5)	0 (0.0)
7 (very much worse)	0 (0.0)	0 (0.0)
Missing	23 (11.7)	24 (12.2)

Data are *n* (%).

Table S4 Change from baseline in MOS-Sleep scores at Week 14 (modified intention-to-treat analysis set)

Parameter	Statistic	Mirogabalin (<i>n</i> = 196)	Placebo (<i>n</i> = 197)
MOS-Sleep score			
Sleep disturbance			
Baseline	Mean ± SD	44.319 ± 9.9743	45.056 ± 9.5858
Week 14 (LOCF) ^a	Mean ± SD	50.614 ± 8.7497	48.162 ± 9.6738
Change from baseline at Week 14 (LOCF) ^{a, b}	Mean ± SD	6.295 ± 9.1031	3.106 ± 9.2770
	LS mean difference vs placebo ± SE	2.823 ± 0.7886	—
	(95% CI), <i>p</i> value	(1.272–4.373), 0.0004	—
Snoring			
Baseline	Mean ± SD	47.554 ± 10.3693	46.576 ± 10.8125
Week 14 (LOCF) ^a	Mean ± SD	46.236 ± 10.4318	47.579 ± 10.6019
Change from baseline at Week 14 (LOCF) ^{a, b}	Mean ± SD	−1.318 ± 8.2916	1.003 ± 7.6110
	LS mean difference vs placebo ± SE	−2.038 ± 0.7426	—

	(95% CI), <i>p</i> value	(-3.498--0.578), 0.0063	—
Awakening due to shortness of breath or headache			
Baseline	Mean ± SD	48.819 ± 10.2846	46.818 ± 11.6029
Week 14 (LOCF) ^a	Mean ± SD	50.502 ± 8.9749	49.449 ± 9.0336
Change from baseline at Week 14 (LOCF) ^{a, b}	Mean ± SD	1.683 ± 8.6864	2.632 ± 11.7872
	LS mean difference vs placebo ± SE	0.270 ± 0.8032	—
	(95% CI), <i>p</i> value	(-1.309-1.849), 0.7371	—
Sleep adequacy			
Baseline	Mean ± SD	50.639 ± 10.4298	51.191 ± 9.8519
Week 14 (LOCF) ^a	Mean ± SD	55.186 ± 9.8048	52.887 ± 10.5046
Change from baseline at Week 14 (LOCF) ^{a, c}	Mean ± SD	4.547 ± 11.3741	1.696 ± 9.3407
	LS mean difference vs placebo ± SE	2.562 ± 0.9037	—
	(95% CI), <i>p</i> value	(0.785-4.339), 0.0048	—

Sleep somnolence				
Baseline	Mean ± SD	43.528 ± 10.3664	43.357 ± 10.1576	
Week 14 (LOCF) ^a	Mean ± SD	44.846 ± 10.6548	45.020 ± 9.9741	
Change from baseline at Week 14 (LOCF) ^{a, b}	Mean ± SD	1.318 ± 9.3472	1.664 ± 10.4018	
	LS mean difference vs placebo ± SE	-0.266 ± 0.8786	—	
	(95% CI), <i>p</i> value	(-1.994–1.461), 0.7618	—	
9-Item sleep problems index				
Baseline	Mean ± SD	46.305 ± 9.8946	46.598 ± 9.0230	
Week 14 (LOCF) ^a	Mean ± SD	51.905 ± 9.0700	49.753 ± 9.4567	
Change from baseline at Week 14 (LOCF) ^{a, b}	Mean ± SD	5.600 ± 8.8292	3.155 ± 8.3734	
	LS mean difference vs placebo ± SE	2.318 ± 0.7637	—	
	(95% CI), <i>p</i> value	(0.816–3.819), 0.0026	—	
Sleep quantity				
Baseline	Mean ± SD	6.0 ± 1.38	6.1 ± 1.39	

Week 14 (LOCF) ^a	Mean ± SD	6.5 ± 1.29	6.4 ± 1.45
Change from baseline at Week 14 (LOCF) ^{a, c}	Mean ± SD	0.5 ± 1.23	0.3 ± 1.26
	LS mean difference vs placebo ± SE	0.2 ± 0.11	—
	(95% CI), <i>p</i> value	(0.0–0.4), 0.1022	—
Optimal sleep			
Baseline	Yes, n (%)	67 (34.2)	65 (33.0)
Week 14 (LOCF) ^d	Yes, n (%)	86 (43.9)	81 (41.1)
	Odds ratio (95% CI), <i>p</i> value	1.12 (0.75–1.67), 0.5799	—

^aMissing values at Week 14 were imputed using the LOCF approach, and the imputed values were analyzed based on the analysis of covariance model, with the treatment group as a fixed effect and baseline value as a covariate.

^bNegative change indicates improvement.

^cPositive change indicates improvement.

^dA logistic regression analysis with the treatment group as a factor was applied to the data at Week 14 using the LOCF approach for treatment comparisons versus placebo. Baseline value was defined as the last non-missing available value at or before the randomization visit (Visit 3).

CI confidence interval, *LOCF* last observation carried forward, *LS* least-squares, *MOS-Sleep* Medical Outcomes Study Sleep Scale, *SD* standard deviation, *SE* standard error

Table S5 All serious TEAEs occurring during the study and their outcomes

	Age (years)/sex	TEAE (PT)	Duration of TEAE (study day)	Severity	Study drug action taken	Other action	Causality	Outcome
Mirogabalin	67/Female	Angina unstable	89/92	Mild	NC	M, H, O	Unrelated	R
	69/Male	Rib fracture	92/-	Moderate	NC	M, H	Unrelated	RI
		Scapula fracture	92/-	Moderate	NC	M, H	Unrelated	RI
	52/Female	Cataract	46/58	Severe	NC	M, H, O	Unrelated	R
	70/Female	Diabetes mellitus	79/-	Severe	NC	H	Unrelated	RI
	50/Female	Pulmonary mass	21/-	Moderate	NC	M, H, O	Unrelated	NR
	38/Male	Pneumonia	10/22	Moderate	NC	M, H	Unrelated	R
	26/Male	Ligament sprain	75/104	Moderate	NC	H, O	Unrelated	R
	73/Female	Blood glucose fluctuation	21/31	Severe	W	M, H	Related	R
		Parkinson's disease	23/31	Severe	NA	M, H	Unrelated	R
Placebo	59/Male	Appendicitis	52/56	Severe	INT	M, H, O	Unrelated	R
	60/Male	Myocardial infarction	104/-	Moderate	NA	M, H, O	Unrelated	RI
	73/Male	Coronary artery disease	56/68	Moderate	NC	M, H, O	Unrelated	R
	29/Male	Diabetic ketosis	21/29	Severe	NC	M, H	Unrelated	R

52/Female	Diabetic retinopathy	52/71	Moderate	W	M, H, O	Unrelated	R
55/Male	Arteriosclerosis coronary artery	65/129	Moderate	NA	M, H, O	Unrelated	R
64/Female	Ophthalmoplegia	43/-	Moderate	NC	M, O	Unrelated	RI
58/Female	Neoplasm skin	105/106	Mild	NA	M, H, O	Unrelated	R
49/Male	Craniocerebral injury	58/64	Moderate	NC	M, H	Unrelated	R

All TEAEs were coded according to the Medical Dictionary for Regulatory Activities, version 24.1.

H hospitalization or prolongation of hospitalization required, *INT* drug interrupted, *M* medication required, *NA* not applicable, *NC* no change, *NR* not recovered/not resolved, *O* other, *PT* Preferred Term, *R* recovered/resolved, *RI* recovering/resolving, *TEAE* treatment-emergent adverse event, *W* withdrawn