Supplement

eMethods

1. Permitted Concomitant Medications and Therapies.

The following drugs were permitted for concomitant use if their dosage had not changed for 28 days prior to the screening visit, and their dosage remained unchanged throughout the study:

- Antiepileptics, except for gabapentin and pregabalin
- Antidepressants
- Hypnotics, anxiolytics
- Tramadol
- Neurotropin®
- N-methyl-D-aspartate receptor antagonists (e.g., dextromethorphan, ketamine, memantine)
- Non-steroidal anti-inflammatory drugs (except for external use and for purposes other than CNeP caused by SCI)
- Muscle relaxants
- Topical capsaicin for CNeP caused by SCI
- Local anaesthetics for CNeP caused by SCI (e.g., lidocaine)
- Sodium channel blockers (e.g., mexiletine)
- Centrally acting sympatholytic agents (e.g., clonidine)
- Steroids for CNeP caused by SCI
- Cilostazol, prostaglandin (except for external use and for purposes other than CNeP caused by SCI)
- Baclofen.

The following therapies were permitted for concomitant use if the frequency of use had not changed for 28 days prior to screening, and remained unchanged throughout the study:

- Nerve blocks
- Laser therapy
- Acupuncture
- Spinal cord stimulation
- Surgery that could confound the assessments of CNeP caused by SCI
- Psychological therapies (e.g., psychoeducation, behavioral therapy, cognitive behavioral therapy)
- Rehabilitation (e.g., physical therapy, occupational therapy)
- Other forms of analgesic therapy that could confound the assessments of CNeP caused by SCI.

2. Exclusion criteria.

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

- A pain score of 10 on a scale of 0 (no pain) to 10 (worst possible pain) at any time during the observation period

- Other severe pain at screening or randomization, unrelated to CNeP caused by SCI, that could confound the assessment of the study drug
- Neurologic disorder at screening or randomization, unrelated to CNeP caused by SCI, that could confound the assessment of the study drug
- Major psychiatric disorder within 1 year prior to screening
- Secondary gain from SCI-related CNeP (e.g., legal dispute or settlement negotiations) at screening or randomization
- SCI due to suicidal behavior
- Patient who blames a third party of having caused the SCI (i.e., psychiatric influence on CNeP)
- Prior treatment for ≥4 weeks with pregabalin ≥300 mg/day for patients with CrCL (calculated using the Cockcroft–Gault equation) ≥60 mL/min or pregabalin ≥150 mg/day for patients with CrCL 30–<60 mL/min, with a declared lack of effect
- Prior treatment for ≥4 weeks with gabapentin ≥1,200 mg/day for subjects with CrCL≥60 mL/min or gabapentin ≥600 mg/day for subjects with CrCL 30–<60 mL/min, with a declared lack of effect
- Use of mirogabalin, pregabalin, or gabapentin within 28 days prior to screening
- Use of strong opioids for SCI-caused CNeP relief within 3 months prior to screening
- CrCL (calculated using the Cockcroft–Gault equation) <30 mL/min at screening
- Malignancy other than basal cell carcinoma within 2 years prior to screening
- Clinically significant unstable endocrine (e.g., diabetes mellitus), neurologic, ophthalmologic, hepatobiliary, respiratory, or hematologic illness; or cardiovascular disease (e.g., uncontrolled cardiac arrhythmia or myocardial infarction) at screening or randomization
- Clinically significant findings on electrocardiogram at screening
- History of pernicious anemia, untreated hypothyroidism, or HIV infection
- Pregnancy, potential pregnancy, breast feeding, or unwillingness to practice reliable contraceptive measures during the study and for 4 weeks after study completion
- Known hypersensitivity to mirogabalin, pregabalin, or gabapentin
- Participation in another clinical study, either currently or within 30 days prior to providing informed consent
- Past participation in a clinical study of mirogabalin in which the patient received the study drug
- History of illicit drug or alcohol abuse
- Response of “yes” to any of the questions on the Colombia Suicide Rating Scale at screening or randomization in relation to events occurring within the past 12 months
- At screening, laboratory values exceeding the following limits:
- Platelets <100,000/mm^3
- Aspartate aminotransferase >2.0 × ULN
    - Alanine aminotransferase > 2.0 × ULN
    - Alkaline phosphatase >1.5 × ULN
    - Total bilirubin >1.5 × ULN (except patients with documented Gilbert’s syndrome)

- Otherwise considered an inappropriate subject for the study by the investigator or subinvestigator.

Abbreviations: CNeP = central neuropathic pain; SCI = spinal cord injury; ULN = upper limit of normal.

eTable 1. Time-course of Average Daily Pain Scores from Baseline to Day 21.

	Placebo			Mirogabalin				
Day	**n**	**Mean ± SD**	**Change from baseline**	**n**	**Mean ± SD**	**Change from baseline**	**Difference vs placebo (95% CI)**	***p* value**
0	148	6.18 ± 1.40	—	148	6.14 ± 1.34	—	—	—
1	149	6.11 ± 1.52	−0.06 ± 1.01	149	5.92 ± 1.56	−0.26 ± 1.22	−0.20 (−0.45, 0.05)	0.1126
2	149	5.93 ± 1.57	−0.25 ± 1.03	149	5.65 ± 1.55	−0.51 ± 1.29	−0.26 (−0.52, −0.01)	0.0443
3	148	5.86 ± 1.60	−0.32 ± 1.10	149	5.66 ± 1.59	−0.54 ± 1.50	−0.21 (−0.50, 0.07)	0.1433
4	149	5.94 ± 1.48	−0.23 ± 1.04	147	5.56 ± 1.66	−0.61 ± 1.51	−0.38 (−0.66, −0.10)	0.0089
5	149	5.88 ± 1.65	−0.30 ± 1.23	147	5.59 ± 1.58	−0.56 ± 1.36	−0.27 (−0.55, 0.02)	0.0652
6	149	5.93 ± 1.57	−0.24 ± 1.12	148	5.58 ± 1.60	−0.59 ± 1.32	−0.35 (−0.62, −0.08)	0.0108
7	149	5.85 ± 1.66	−0.33 ± 1.24	148	5.47 ± 1.66	−0.68 ± 1.40	−0.36 (−0.65, −0.06)	0.0169
8	148	5.89 ± 1.60	−0.26 ± 1.23	147	5.48 ± 1.65	−0.70 ± 1.56	−0.43 (−0.74, −0.12)	0.0060
9	147	5.80 ± 1.62	−0.35 ± 1.20	145	5.28 ± 1.68	−0.88 ± 1.53	−0.53 (−0.83, −0.22)	0.0008
10	146	5.95 ± 1.48	−0.20 ± 1.16	147	5.33 ± 1.70	−0.84 ± 1.51	−0.63 (−0.93, −0.34)	<0.0001
11	147	5.69 ± 1.61	−0.46 ± 1.23	147	5.27 ± 1.79	−0.91 ± 1.71	−0.45 (−0.77, −0.12)	0.0076
12	146	5.86 ± 1.58	−0.30 ± 1.18	145	5.21 ± 1.78	−0.96 ± 1.65	−0.65 (−0.97, −0.34)	<0.0001
13	147	5.81 ± 1.64	−0.34 ± 1.39	147	5.16 ± 1.73	−1.01 ± 1.63	−0.66 (−0.99, −0.33)	<0.0001
14	145	5.84 ± 1.67	−0.31 ± 1.36	147	5.07 ± 1.74	−1.11 ± 1.59	−0.79 (−1.12, −0.46)	<0.0001
15	142	5.72 ± 1.65	−0.45 ± 1.22	143	5.08 ± 1.73	−1.10 ± 1.67	−0.65 (−0.97, −0.32)	0.0001
16	140	5.81 ± 1.65	−0.34 ± 1.29	142	5.01 ± 1.77	−1.13 ± 1.71	−0.80 (−1.14, −0.46)	<0.0001
17	140	5.74 ± 1.71	−0.42 ± 1.34	144	5.04 ± 1.82	−1.12 ± 1.66	−0.70 (−1.04, −0.35)	<0.0001
18	140	5.78 ± 1.59	−0.39 ± 1.23	144	5.10 ± 1.80	−1.06 ± 1.66	−0.67 (−1.00, −0.34)	<0.0001
19	141	5.65 ± 1.74	−0.50 ± 1.23	143	4.95 ± 1.81	−1.22 ± 1.69	−0.71 (−1.05, −0.37)	<0.0001
20	142	5.68 ± 1.70	−0.50 ± 1.13	144	5.09 ± 1.85	−1.07 ± 1.64	−0.57 (−0.90, −0.25)	0.0006
21	142	5.65 ± 1.74	−0.52 ± 1.36	144	4.95 ± 1.78	−1.21 ± 1.75	−0.69 (−1.04, −0.34)	0.0001

Abbreviation: CI = confidence interval, SD = standard deviation.

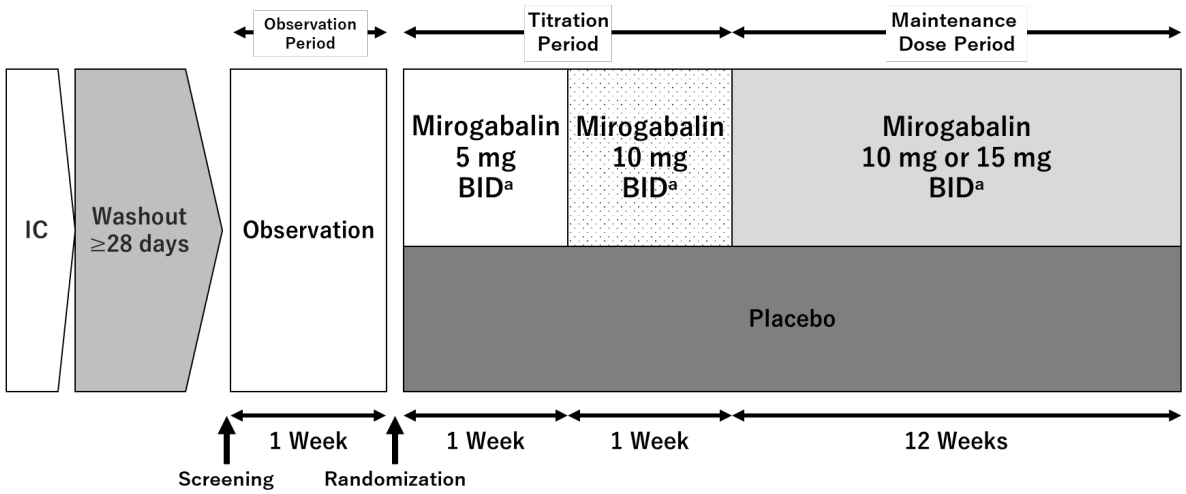
eTable 2. All Serious TEAEs.

SOC PT	Mirogabalin (n = 151)	Placebo (n = 148)	Total (N = 299)
Patients with at ≥1 serious TEAE	9 (6.0)	7 (4.7)	16 (5.4)
Cellulitis	2 (1.3)	0 (0.0)	2 (0.7)
Pneumonia	1 (0.7)	1 (0.7)	2 (0.7)
Appendicitis	1 (0.7)	0 (0.0)	1 (0.3)
Wound infection	0 (0.0)	1 (0.7)	1 (0.3)
Dehydration	1 (0.7)	1 (0.7)	2 (0.7)
Altered state of consciousness	1 (0.7)	0 (0.0)	1 (0.3)
Syncope	1 (0.7)	0 (0.0)	1 (0.3)
Nausea	0 (0.0)	1 (0.7)	1 (0.3)
Ranula	0 (0.0)	1 (0.7)	1 (0.3)
Decubitus ulcer	0 (0.0)	1 (0.7)	1 (0.3)
Cardiac death	1 (0.7)	0 (0.0)	1 (0.3)
Fibula fracture	0 (0.0)	1 (0.7)	1 (0.3)
Inflammation of wound	0 (0.0)	1 (0.7)	1 (0.3)
Spinal cord injury cervical	1 (0.7)	0 (0.0)	1 (0.3)
Tibia fracture	0 (0.0)	1 (0.7)	1 (0.3)

Data are n (%).

Coded by the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0.

Abbreviations: PT = Preferred Term, SOC = System Organ Class, TEAE = treatment-emergent adverse event.



[a]Patients with CrCL of 30–<60 mL/min at screening received mirogabalin at 50% of the normal dose.
Abbreviations: BID = twice daily; CrCL = creatinine clearance; IC = informed consent.

eFigure 1. Study Design

[a]Patients with CrCL of 30–<60 mL/min at screening received mirogabalin at 50% of the normal dose.

Abbreviations: BID = twice daily; CrCL = creatinine clearance; IC = informed consent.

Additional Supplemental Files

- Study Protocol
- Statistical Analysis Plan
- CONSORT Checklist