Journal Reading
Mirogabalin for Central Neuropathic Pain after Spinal Cord Injury

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Mirogabalin for Central Neuropathic Pain After Spinal Cord Injury

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study in Asia

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Abstract

Background and Objectives

Patients with spinal cord injury (SCI) commonly experience central neuropathic pain (CNeP), which is challenging to treat. Mirogabalin is effective for peripheral neuropathic pain, but evidence for CNeP is lacking.

Methods

This randomized, double-blind, placebo-controlled, phase 3 study investigated mirogabalin efficacy and safety for the treatment of CNeP in patients with traumatic SCI. Adult patients from 120 sites throughout Japan, Korea, and Taiwan were randomized (1:1) to receive placebo or mirogabalin (5 mg twice daily [BID] for 1 week, 10 mg BID for 1 week, and 10 or 15 mg BID for 12 weeks). Patients with moderate renal impairment received half the dosage. The primary efficacy endpoint was change from baseline in the weekly average daily pain score (ADPS) at week 14. The secondary endpoints included ADPS responder rates, the Short-Form McGill Pain Questionnaire (SF-MPQ), average daily sleep interference score (ADSIS), and Neuropathic Pain Symptom Inventory (NPSI). Adverse events were monitored for safety.

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Criteria for rating therapeutic and diagnostic studies
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Abstrak

Abstract

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This randomized, double-blind, placebo-controlled, phase 3 study investigated mirogabalin efficacy and safety for the treatment of CNeP in patients with traumatic SCI. Adult patients from 120 sites throughout Japan, Korea, and Taiwan were randomized (1:1) to receive placebo or mirogabalin (5 mg twice daily [BID] for 1 week, 10 mg BID for 1 week, and 10 or 15 mg BID for 12 weeks). Patients with moderate renal impairment received half the dosage. The primary efficacy endpoint was change from baseline in the weekly average daily pain score (ADPS) at week 14. The secondary endpoints included ADPS responder rates, the Short-Form McGill Pain Questionnaire (SF-MPQ), average daily sleep interference score (ADSIS), and Neuropathic Pain Symptom Inventory (NPSI). Adverse events were monitored for safety.

Results

Each treatment group comprised 150 patients. Mirogabalin elicited a statistical and clinically relevant improvement in change from baseline in the weekly ADPS at week 14 (least-squares mean difference [95% CI] vs placebo −0.71 [−1.08 to −0.34], $p = 0.0001$). Responder rates at week 14 were higher for mirogabalin than those for placebo (odds ratio [95% CI] 1.91 [1.11–3.27] for the ≥30% responder rate; 2.52 [1.11–5.71] for the ≥50% responder rate). Statistical improvements (i.e., least-squares mean difference [95% CI] vs placebo) were also observed in the SF-MPQ (−2.4 [−3.8 to −1.1]), ADSIS −0.71 (−1.04 to −0.38), and NPSI −7.7 (−11.1 to −4.4) scores. Most treatment-emergent adverse events were mild; no serious adverse drug reactions were reported.

Discussion

Mirogabalin elicited clinically relevant decreases in pain and was well tolerated, suggesting that mirogabalin is a promising treatment for patients with CNeP due to SCI.

Pendahuluan

Neuropathic pain diklasifikasikan menjadi sentral dan perifer, berdasarkan elemen sistem saraf yang terlibat.

↓

Nyeri neuropatik perifer (PNeP): neuropati diabetik, *postherpetic neuralgia*, dan radikulopati.
Nyeri neuropatik sentral (CNeP): cedera tulang belakang (SCI), nyeri *post stroke,* dan *multiple sclerosis.*

↓

Gejala klinis nyeri neuropatik: nyeri spontan, hyperalgesia, allodynia.

↓

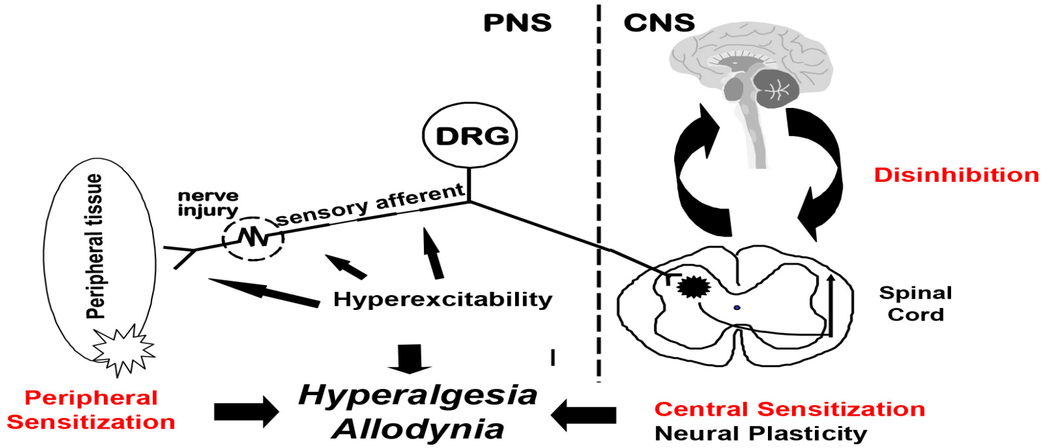
Diagnosis CNeP membutuhkan riwayat penyakit dan cedera, serta distribusi nyeri secara neuroanatomi (ex. Pasien SCI → diagnosis CNeP jika nyeri terjadi pada dermatome di bawah atau tepat pada tingkat SCI)

Pendahuluan

Farmakoterapi untuk nyeri neuropatik saat ini:

- tidak meredakan nyeri yang memadai
- berkaitan dengan ADR sistemik maupun terkait SSP (pusing, somnolen, edema, mual, dan konstipasi)
- secara signifikan menurunkan kepatuhan dan penghentian obat sebelum efek terapeutik dicapai → dibutuhkan pilihan terapi yang lebih baik.

Fig. 1 PATHOGENESIS OF NEUROPATHIC PAIN



PNS –Peripheral Nervous System, CNS- Central Nervous System, DRG- Dorsal Root Ganglion

Mirogabalin

- Ligan α2δ oral selektif, kelas gabapentinoid, disetujui di Jepang th 2019 untuk pengobatan PNeP.
- Studi preklinik di model tikus dengan SCI → efek analgesik bertahan lama dengan dosis tunggal → manfaat potensial untuk pasien CNeP.
- Studi klinis selanjutnya:
  - Efektif dan dapat ditoleransi dengan baik
  - Aman dan efektif meredakan nyeri
  - Mengurangi VAS pada pasien stenosis tulang belakang dan HNP
- Jumlah pasien yang direkrut kecil → dipertimbangkan sebagai data awal.

Tujuan Penelitian

Belum ada penelitian uji klinis sebelumnya yang menguji efektifitas dan keamanan penggunaan mirogabalin pada pasien CNeP. → studi fase 3, double blind, terkontrol placebo dilakukan untuk menilai efektifitas dan keamanan mirogabalin pada pasien Asia dengan CNeP pasca SCI. → membandingkan perubahan skor nyeri *average daily pain score* (ADPS) secara mingguan pada minggu ke 14 pada pasien dengan CNeP ec SCI penerima mirogabalin vs placebo.

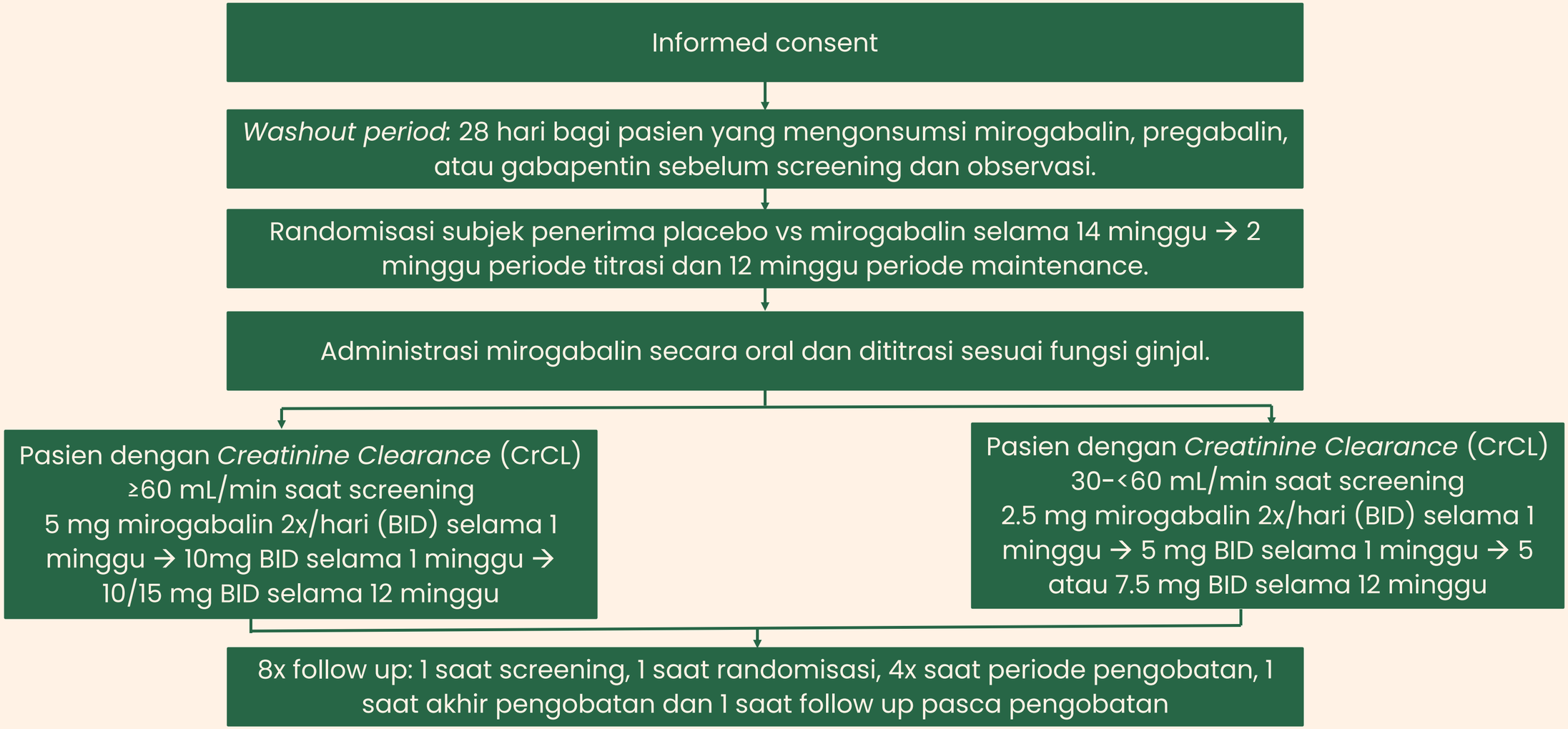
Metode Penelitian

- Uji klinis fase 3, *multinational, randomized, double blind, placebo controlled trial* dari mirogabalin untuk pengobatan CNeP pada SCI.
- Dilakukan di 120 tempat meliputi Jepang, Korea dan Taiwan.
- Pasien merupakan pasien rawat inap maupun rawat jalan.
- Obat yang dilarang digunakan bersamaan saat uji klinis → mirogabalin, pregabalin, gabapentin, opioid.
- Obat yang dapat digunakan bersamaan → antiepilepsi (kecuali gabapentin dan pregabalin), antidepresan, hipnotik, anxiolytics, tramadol. Hanya diizinkan jika dosisnya tidak diubah selama 28 hari sebelum skrining. Perubahan dosis tidak diizinkan. Acetaminophen diizinkan sebagai rescue drug.
- Terapi yang diizinkan jika frekuensi penggunaan tidak berubah: nerve block, terapi laser, akupuntur, dan spinal cord stimulataion.

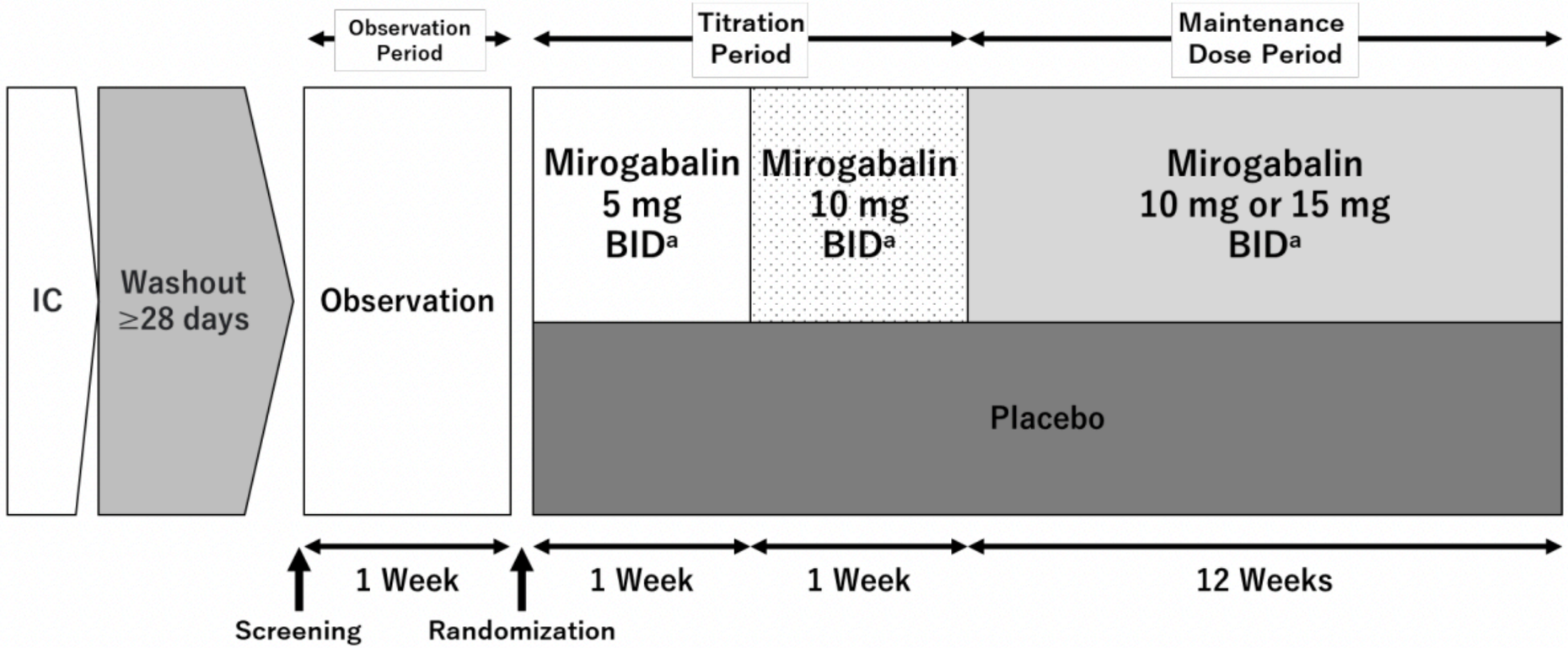
Analisis Statistik

- Data diasumsikan berdistribusi normal dengan SD 1,75 untuk perubahan ADPS pada minggu ke 14
- **Student's T Test** digunakan dengan signifikansi 1 sisi 0.025 dengan minimal 80% statistical power
- SD diasumsikan berdasarkan penelitian sebelumnya pada DPNP dan PHN
- Variabel efikasii primer dianalisis menggunakan modified intention to treat (miTT) set,
- Semua analisis dilakukan di software SAS version 9.4 atau diatasnya

Alur Penelitian



Alur Penelitian



[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.

Kriteria Restriksi

01

Kriteria Inklusi

- **Usia ≥20 tahun** saat informed consent
- Memberikan informed consent
- Memahami prosedur uji klinis
- Menyelesaikan kuisioner
- Dengan **diagnosis SCI C4-T12** yang dikonfirmasi dengan MRI; American Spinal Injury Association impairment scale A, B, C, atau D
- area nyeri neuropatik di bawah/pada level SCI;
- **SCI ≥ 6** bulan saat skrining, **nyeri stabil CNeP** selama paling sedikit 3 bulan sebelum skrining
- **Skor nyeri ≥40mm** dengan Short form McGill Pain Questionnaire (SF-MPQ),
- VAS pada skrining dan randomisasi; dan penyelesaian paling sedikit 4 hari dari daily pain diary saat randomisasi dengan ADPS ≥4 dari 11 poin numeral rating scale.

02

Kriteria Eksklusi

- Skor nyeri harian 10 paling tidak 1x selama observasi
- Penyakit nyeri/neurologis lainnya yang tidak terkait CNeP dan SNI yang akan mempengaruhi evaluasi obat
- SCI dikarenakan percobaan bunuh diri
- CrCL <30mL/menit

Kriteria Eksklusi

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 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 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.

Randomisasi & Blinding

- Responden dirandomisasi dengan rasio 1:1 untuk menerima mirogabalin vs placebo, dengan faktor stratifikasi ADPS mingguan dasar (<6.0 atau ≥6.0) dan wilayah (Jepang atau diluar jepang).
- Randomisasi dihasilkan oleh ahli biostatistik independen menggunakan sistem Interactive Response Technology.
- Blinding diterapkan kepada semua personel terkait kecuali ahli biostatistik independent.
- Obat penelitian dan placebo tidak dapat dibedakan dalam penelitian (identical dalam bentuk dan ukuran).

Efficacy Outcome

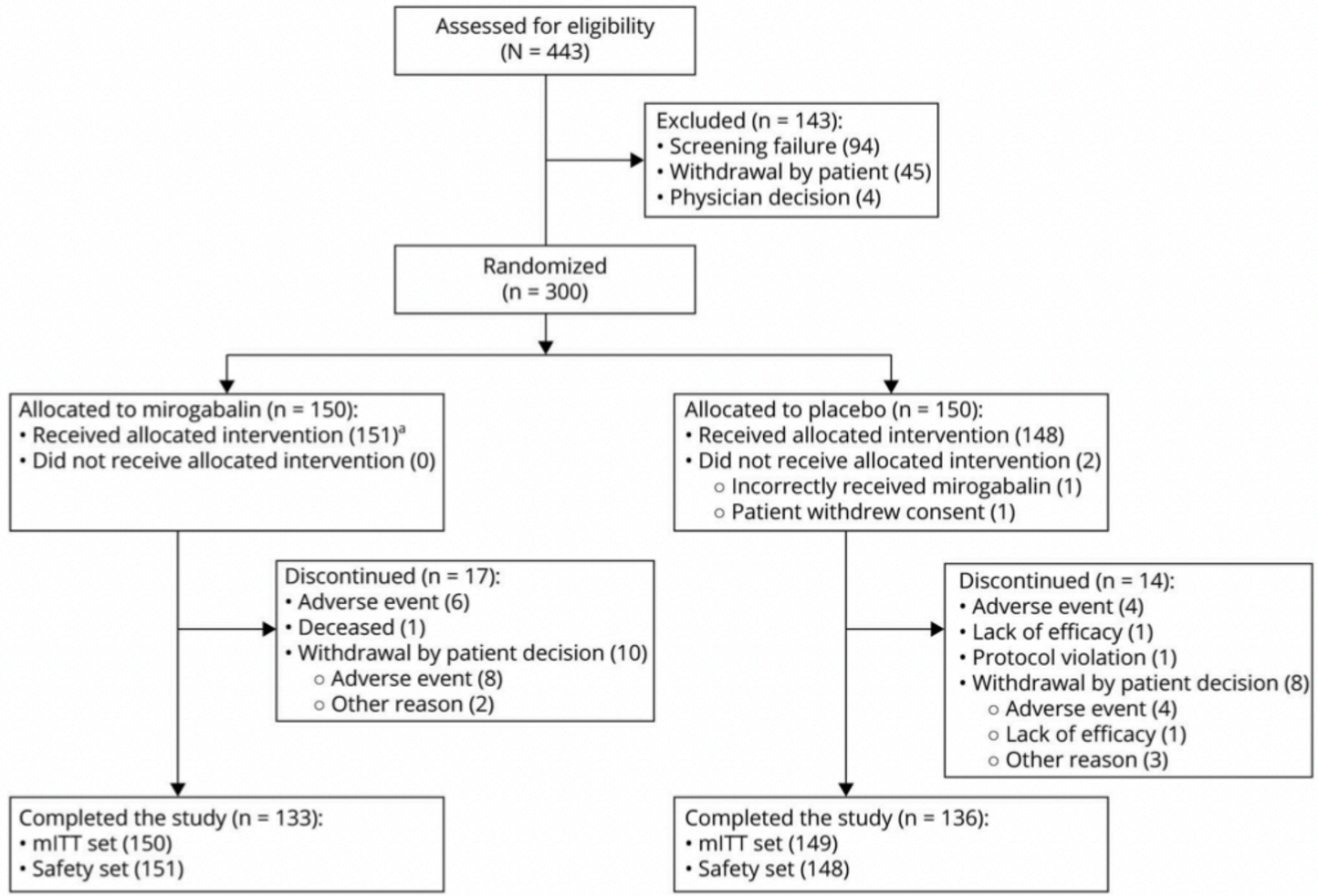
Primary endpoint: perubahan dari ADPS mingguan pada minggu ke-14

Secondary endpoints:

1. ADPS responder rate (penurunan ≥30% atau ≥50% pada ADPS mingguan di minggu 14)
2. Perubahan SF-MPQ
3. Patient Global Impression of Change (PGIC), yang dievaluasi pada kunjungan ke-7, di mana pasien diminta untuk menilai sendiri kondisi mereka dibandingkan dengan saat skrining, pada skala 7 poin (1 = sangat membaik; 7 = sangat jauh lebih buruk).
4. Perubahan ADSIS (daily sleep interference score) dari 0-10
5. Perubahan NPSI (Neuropathic pain symptom inventory): pasien ditanya saat randomisasi visit ke 2, dan diulang pada visit 7.
6. Perubahan pada EuQoL 5 dimensions 5 Levels.

Hasil & Diskusi

Distribusi Responden



[a]One patient from the placebo group received mirogabalin by mistake and was therefore included in the mirogabalin group for safety analysis. mITT = modified intention-to-treat.

Pendaftaran subjek → 14 Maret 2019. Selesai follow up → 9 September 2020

Karakteristik Responden

The overall mean ± SD treatment compliance, calculated as 100 × (number of tablets actually taken/number of tablets planned to be taken), was 98.16% ± 7.226% and was similar between both arms (data not shown)

Table 1 Baseline Characteristics (Modified Intention-to-Treat Analysis Set)

	Mirogabalin (n = 150)	Placebo (n = 149)	Total (N = 299)
Age at informed consent, y, mean ± SD	57.3 ± 14.31	59.6 ± 13.96	58.5 ± 14.16
Sex, male	131 (87.3)	125 (83.9)	256 (85.6)
Country			
Japan	121 (80.7)	121 (81.2)	242 (80.9)
Korea	19 (12.7)	16 (10.7)	35 (11.7)
Taiwan	10 (6.7)	12 (8.1)	22 (7.4)
Body mass index, kg/m^2, mean ± SD	23.78 ± 3.773	23.71 ± 3.685	23.74 ± 3.723
Baseline CrCL, mL/min			
30–<60	10 (6.7)	24 (16.1)	34 (11.4)
60–<90	43 (28.7)	36 (24.2)	79 (26.4)
≥90	97 (64.7)	89 (59.7)	186 (62.2)
Baseline weekly average daily pain score			
<6.0	76 (50.7)	73 (49.0)	149 (49.8)
≥6.0	74 (49.3)	76 (51.0)	150 (50.2)
ASIA impairment scale			
Complete (A)	39 (26.0)	37 (24.8)	76 (25.4)
Incomplete (B, C, or D)	111 (74.0)	112 (75.2)	223 (74.6)
Cause of SCI			
Fall	82 (54.7)	84 (56.4)	166 (55.5)
Traffic accident	49 (32.7)	49 (32.9)	98 (32.8)
Sports accident	9 (6.0)	6 (4.0)	15 (5.0)
Other	10 (6.7)	10 (6.7)	20 (6.7)
Type of paralysis			
Tetraplegia	105 (70.0)	101 (67.8)	206 (68.9)
Paraplegia	45 (30.0)	48 (32.2)	93 (31.1)
Duration of SCI, mo, mean ± SD	103.0 ± 113.00	94.7 ± 115.45	98.9 ± 114.11
Duration of CNeP after SCI, mo, mean ± SD	94.5 ± 98.29	88.1 ± 106.17	91.3 ± 102.18

Abbreviations: ASIA = American Spinal Injury Association; CNeP = central neuropathic pain; CrCL = creatinine clearance; SCI = spinal cord injury.
Data are n (%) unless otherwise specified.

ASIA: American Spinal Injury Association

Analisis Efikasi

Both responder rates at week 14 were statistically significantly higher in the mirogabalin group than in the placebo group.

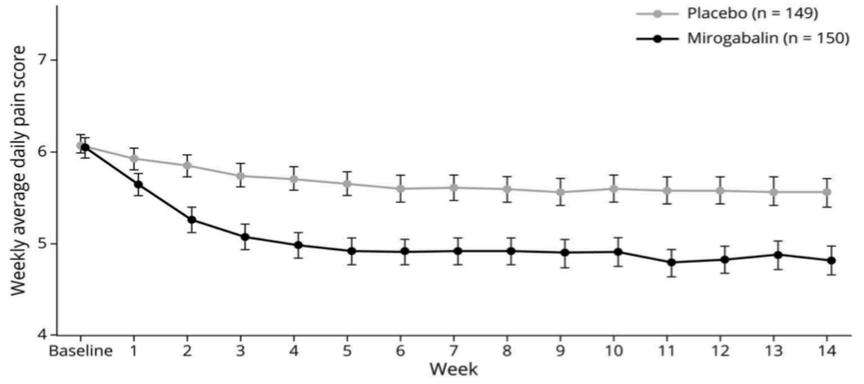
Kelompok mirogabalin menunjukkan penurunan nyeri vs plasebo dari tahap awal, dengan peningkatan yang signifikan secara statistik diamati dari hari ke 6 pemberian.

Table 2 Change From Baseline in the Weekly ADPS at Week 14 and Mirogabalin Responder Rates (Modified Intention-to-Treat Analysis Set)

	Mirogabalin (n = 150)	Placebo (n = 149)
Baseline ADPS		
Mean ± SD	6.04 ± 1.309	6.09 ± 1.270
Median (range)	5.86 (4.0–9.0)	6.00 (4.0–9.0)
Week 14 ADPS (imputed)[a]		
LS mean ± SE	4.83 ± 0.132	5.54 ± 0.132
Change from baseline in ADPS at week 14 (imputed)[a]		
LS mean ± SE	−1.23 ± 0.132	−0.52 ± 0.132
Difference of LS mean vs placebo ± SE	−0.71 ± 0.187	—
95% CI; *p* value	−1.08 to −0.34; 0.0001	—
Patients with ≥30% reduction in ADPS from baseline at week 14, n (%)	46 (30.7)	28 (18.8)
OR (95% CI); *p* value	1.91 (1.11–3.27); 0.0192	—
Patients with ≥50% reduction in ADPS from baseline at week 14, n (%)	21 (14.0)	9 (6.0)
OR (95% CI); *p* value	2.52 (1.11–5.71); 0.0269	—

Abbreviations: ADPS = average daily pain score; LS = least-squares; OR = odds ratio.
[a] Based on a nonfuture dependence model using the pattern mixture model approach with shifting parameters under the missing not at random mechanism for the missing weekly ADPS.

Figure 2 Time Course of Least-Squares Mean Weekly Average Daily Pain Score



Data were imputed using a multiple imputation method based on a "non-future dependence" model using a pattern mixture approach under the missing not at random mechanism. Error bars represent SE.

Secondary Efficacy Endpoints

Table 3 Change From Baseline in Short-Form McGill Pain Questionnaire Scores at Week 14 (Modified Intention-to-Treat Analysis Set) *(continued)*

Parameter	Statistic	Mirogabalin (n = 150)	Placebo (n = 149)
Present pain intensity			
Baseline	n	150	149
	Mean ± SD	2.4 ± 0.93	2.4 ± 0.85
Week 14[a]	n	150	149
	Mean ± SD	1.8 ± 0.88	2.2 ± 1.09
Change from baseline at week 14[a]	n	149	149
	Mean ± SD	−0.6 ± 0.92	−0.3 ± 0.95
	Difference of LS mean vs placebo ± SE	−0.3 ± 0.10	—
	95% CI; *p* value	−0.5 to −0.1; 0.0016	—

Abbreviations: LOCF = last observation carried forward; LS = least-squares.
[a] Missing values were imputed using the LOCF approach, and the data were analyzed based on the analysis of covariance model with treatment as a fixed effect and baseline value as a covariate.

Table 3 Change From Baseline in Short-Form McGill Pain Questionnaire Scores at Week 14 (Modified Intention-to-Treat Analysis Set)

Parameter	Statistic	Mirogabalin (n = 150)	Placebo (n = 149)
Visual analog scale			
Baseline	n	149	149
	Mean ± SD	63.3 ± 12.36	63.8 ± 13.08
Week 14[a]	n	150	149
	Mean ± SD	48.9 ± 20.39	56.4 ± 20.97
Change from baseline at week 14[a]	n	148	149
	Mean ± SD	−14.2 ± 19.09	−7.4 ± 18.22
	Difference of LS mean vs placebo ± SE	−6.9 ± 2.13	—
	95% CI; *p* value	−11.1 to −2.7; 0.0013	—
Sensory score			
Baseline	n	150	149
	Mean ± SD	10.3 ± 6.26	10.6 ± 6.51
Week 14[a]	n	150	149
	Mean ± SD	6.9 ± 5.63	8.7 ± 6.73
Change from baseline at week 14[a]	n	149	149
	Mean ± SD	−3.4 ± 5.63	−1.8 ± 4.47
	Difference of LS mean vs placebo ± SE	−1.7 ± 0.53	—
	95% CI; *p* value	−2.7 to −0.6; 0.0017	—
Affective score			
Baseline	n	150	149
	Mean ± SD	3.0 ± 2.77	2.7 ± 2.54
Week 14[a]	n	150	149
	Mean ± SD	1.6 ± 2.22	2.2 ± 2.51
Change from baseline at week 14[a]	n	149	149
	Mean ± SD	−1.4 ± 2.30	−0.6 ± 1.92
	Difference of LS mean vs placebo ± SE	−0.7 ± 0.21	—
	95% CI; *p* value	−1.1 to −0.3; 0.0005	—
Total score			
Baseline	n	150	149
	Mean ± SD	13.3 ± 8.62	13.3 ± 8.58
Week 14[a]	n	150	149
	Mean ± SD	8.5 ± 7.49	10.9 ± 8.88
Change from baseline at week 14[a]	n	149	149
	Mean ± SD	−4.8 ± 7.40	−2.4 ± 5.88
	Difference of LS mean vs placebo ± SE	−2.4 ± 0.69	—
	95% CI; *p* value	−3.8 to −1.1; 0.0005	—

Continued

Secondary Efficacy Endpoints

- The mirogabalin group showed statistically significant improvement over the placebo group in **NPSI** total score after 14 weeks of treatment: mean ± SD change from baseline was −12.0 ± 15.47 vs −4.5 ± 15.90 in the mirogabalin vs placebo groups
- **PGIC** assessment: patients in the mirogabalin group showed a statistically sig- nificant improvement over the placebo group after 14 weeks of treatment
- **ADSIS:** patients treated with mirogabalin showed statistically significant improvement in the ADSIS at week 14: the difference of LS mean vs placebo (95% CI) was −0.71 (−1.04 to −0.38), p < 0.0001

NPSI: Neuropathic Pain Symptom Inventory
PGIC: Patients' Global Impression of Change
ADSIS: average daily sleep interference score

Table 4 Changes From Baseline at Week 14 in Total Score and Subscores of the NPSI, ADSIS, PGIC, and EQ-5D-5L (Modified Intention-to-Treat Analysis Set)

Parameter	Statistic	Mirogabalin (n = 150)	Placebo (n = 149)
NPSI[a]			
Total score	Mean ± SD	−12.0 ± 15.47	−4.5 ± 15.90
	Difference of LS mean vs placebo ± SE (95% CI); *p* value	−7.7 ± 1.70 (−11.1 to −4.4); <0.0001	—
Superficial spontaneous pain	Mean ± SD	−1.5 ± 2.55	−0.3 ± 2.57
	Difference of LS mean vs placebo ± SE (95% CI); *p* value	−1.2 ± 0.26 (−1.7 to −0.6); <0.0001	—
Deep spontaneous pain	Mean ± SD	−2.7 ± 4.22	−1.2 ± 4.52
	Difference of LS mean vs placebo ± SE (95% CI); *p* value	−1.7 ± 0.45 (−2.5 to −0.8); 0.0003	—
Paroxysmal pain	Mean ± SD	−2.5 ± 4.40	−0.9 ± 4.78
	Difference of LS mean vs placebo ± SE (95% CI); *p* value	−1.6 ± 0.46 (−2.5 to −0.7); 0.0006	—
Evoked pain	Mean ± SD	−2.6 ± 5.80	−1.0 ± 6.52
	Difference of LS mean vs placebo ± SE (95% CI); *p* value	−1.8 ± 0.65 (−3.1 to −0.5); 0.0059	—
Paresthesia/dysesthesia	Mean ± SD	−2.7 ± 4.29	−1.2 ± 3.67
	Difference of LS mean vs placebo ± SE (95% CI); *p* value	−1.5 ± 0.43 (−2.4 to −0.7); 0.0004	—
ADSIS[b]			
Baseline	Mean ± SD	4.03 ± 2.262	3.66 ± 2.306
Week 14	Mean ± SD	2.88 ± 2.157	3.31 ± 2.402
Change from baseline at week 14	Mean ± SD	−1.14 ± 1.705	−0.35 ± 1.306
	Difference of LS mean vs placebo ± SE (95% CI); *p* value	−0.71 ± 0.166 (−1.04 to −0.38); <0.0001	—
PGIC[c]			
Scores at week 14			
1 (very much improved)	n (%)	4 (2.7)	2 (1.3)
2 (much improved)	n (%)	22 (14.7)	9 (6.0)
3 (minimally improved)	n (%)	54 (36.0)	42 (28.2)
4 (no change)	n (%)	39 (26.0)	54 (36.2)
5 (minimally worse)	n (%)	11 (7.3)	18 (12.1)
6 (much worse)	n (%)	2 (1.3)	6 (4.0)
7 (very much worse)	n (%)	1 (0.7)	1 (0.7)
Missing	n (%)	17 (11.3)	17 (11.4)
Much improved or better (≤2)	n (%)	26 (17.3)	11 (7.4)
	OR (95% CI); *p* value	2.63 (1.25 to 5.54); 0.0110	—
Minimally improved or better (≤3)	n (%)	80 (53.3)	53 (35.6)
	OR (95% CI); *p* value	2.07 (1.30 to 3.29); 0.0021	—

Continued

Secondary Efficacy Endpoints

- TEAE yang muncul pada mirogabalin → sebagian besar ringan.
- TEAE yang menyebabkan penghentian pengobatan dilaporkan pada kelompok penerima mirogabalin (14 pasien ; 9.3%) dan kelompok penerima placebo (6 pasien ; 4.1%)

Classification of Evidence

- Studi ini memberikan bukti Kelas I bahwa pada pasien dewasa dengan CNeP karena SCI traumatis, mirogabalin, 10 atau 15 mg BID, secara efektif meningkatkan ADPS mingguan pada minggu ke 14.

Table 4 Changes From Baseline at Week 14 in Total Score and Subscores of the NPSI, ADSIS, PGIC, and EQ-5D-5L (Modified Intention-to-Treat Analysis Set) *(continued)*

Parameter	Statistic	Mirogabalin (n = 150)	Placebo (n = 149)
EQ-5D-5L[d]			
Index value			
Baseline	Mean ± SD	0.5401 ± 0.24694	0.5122 ± 0.22922
Week 14	Mean ± SD	0.5796 ± 0.23768	0.5275 ± 0.23894
Change from baseline at week 14	Mean ± SD	0.0395 ± 0.13627	0.0153 ± 0.13397
	Difference of LS mean vs placebo ± SE (95% CI); *p* value	0.0287 ± 0.01504 (−0.0009 to 0.0583); 0.0572	—
Visual analog scale			
Baseline	Mean ± SD	59.3 ± 19.53	60.1 ± 19.48
Week 14	Mean ± SD	64.2 ± 19.69	58.3 ± 20.20
Change from baseline at week 14	Mean ± SD	4.9 ± 21.76	−1.8 ± 21.28
	Difference of LS mean vs placebo ± SE (95% CI); *p* value	6.2 ± 2.11 (2.0 to 10.4); 0.0037	—

Abbreviations: ADSIS = average daily sleep interference score; ANCOVA = analysis of covariance; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels; LOCF = last observation carried forward; LS = least-squares; NPSI = Neuropathic Pain Symptom Inventory; PGIC = Patient Global Impression of Change; OR = odds ratio.
[a] Missing values at week 14 were imputed using the LOCF approach, and the imputed value was analyzed based on an ANCOVA model including treatment as fixed effect and baseline values as covariates.
[b] Missing weekly ADSIS data at week 14 were imputed using the LOCF approach, and the imputed weekly ADSIS data were analyzed based on an ANCOVA model including treatment as fixed effects and baseline ADSIS as the covariate.
[c] Patients with missing data at week 14 were classified as nonresponders, and logistic regression analysis with treatment as a factor was applied for comparisons vs placebo.
[d] Analyzed based on an ANCOVA model including treatment as fixed effect and baseline values as covariates. Missing data were imputed using the LOCF approach.

Table 5 TEAEs With an Incidence of ≥5% in Either Treatment Group

	Mirogabalin (n = 151)[a]				Placebo (n = 148)				Total (N = 299)			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Number of patients with ≥1 TEAE (%)	84 (55.6)	28 (18.5)	6 (4.0)	118 (78.1)	61 (41.2)	20 (13.5)	1 (0.7)	82 (55.4)	145 (48.5)	48 (16.1)	7 (2.3)	200 (66.9)
TEAEs by PT (%)												
Somnolence	34 (22.5)	11 (7.3)	0 (0.0)	45 (29.8)	6 (4.1)	2 (1.4)	0 (0.0)	8 (5.4)	40 (13.4)	13 (4.3)	0 (0.0)	53 (17.7)
Dizziness	11 (7.3)	2 (1.3)	0 (0.0)	13 (8.6)	4 (2.7)	1 (0.7)	0 (0.0)	5 (3.4)	15 (5.0)	3 (1.0)	0 (0.0)	18 (6.0)
Nasopharyngitis	12 (7.9)	0 (0.0)	0 (0.0)	12 (7.9)	8 (5.4)	0 (0.0)	0 (0.0)	8 (5.4)	20 (6.7)	0 (0.0)	0 (0.0)	20 (6.7)
Weight increased	8 (5.3)	3 (2.0)	0 (0.0)	11 (7.3)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	9 (3.0)	3 (1.0)	0 (0.0)	12 (4.0)
Constipation	7 (4.6)	2 (1.3)	0 (0.0)	9 (6.0)	1 (0.7)	1 (0.7)	0 (0.0)	2 (1.4)	8 (2.7)	3 (1.0)	0 (0.0)	11 (3.7)
Edema peripheral	8 (5.3)	1 (0.7)	0 (0.0)	9 (6.0)	2 (1.4)	0 (0.0)	0 (0.0)	2 (1.4)	10 (3.3)	1 (0.3)	0 (0.0)	11 (3.7)

Abbreviations: PT = preferred term; TEAE = treatment-emergent adverse event.
Coded by the Medical Dictionary for Regulatory Activities, version 23.0.
[a] One patient from the placebo group who mistakenly received mirogabalin was included in the mirogabalin group for the safety analysis.

Diskusi

- Efikasi dari mirogabalin untuk pengobatan CNeP ditunjukkan dengan perbaikan signifikan secara klinis pada ADPS di minggu ke-14, dan perbaikan nyeri diobservasi dari hari ke-6, yang didemonstrasikan oleh perbaikan total dan subskor NPSI pada minggu ke-14.
- Hasil PGIC, ADSIS, dan EQ-5D-5L menyatakan bahwa terdapat perbaikan pada QoL.
- Mirogabalin ditoleransi dengan baik, dengan beberapa penghentian dikarenakan TEAEs.
- Pasien dapat meningkatkan dosis ke dosis harian maksimum, dan keamanannya selaras dengan profil keamanan mirogabalin yang diketahui.
- Studi fase 3 sebelumnya untuk pengobatan pasien asia dengan DPNP dan PHN → hasil serupa (perbaikan klinis setelah 14 minggu).
- LS mean difference pada ADPS vs placebo → -0,71 (melebihi perbedaan klinis minimum pada pasien dengan DPNP) → perbedaan bermakna secara klinis
- Mirogabalin efektif dalam mengobati CNeP dan PNeP.

Diskusi

- Studi sebelumnya :
  - Pasien dengan **DPNP**, tingkat responden lebih tingg iuntuk pasien yang mencapai perbaikan ≥50% dilaporkan setelah 14 minggu pengobatan, tetapi hanya pada pasien yang menerima dosis mirogabalin tertinggi (15 mg BID).
  - Pada pasien dengan **PHN**, tingkat responden yang lebih tinggi vs plasebo untuk semua dosis mirogabalin dilaporkan setelah 14 minggu pengobatan, tetapi hanya pada kelompok perbaikan ≥30%.
  - Uji coba acak 17 minggu pasien dengan SCI, terdapat perbaikan ≥ 30% untuk pasien yang menerima pregabalin vs plasebo, dan studi acak 12 minggu lainnya dari pasien dengan SCI melaporkan nilai yang lebih tinggi ≥30% dan ≥50% dengan pregabalin vs plasebo.

Diskusi

- Insiden somnolen pada kelompok mirogabalin agak lebih tinggi dalam penelitian ini dibandingkan yang dilaporkan dalam uji coba fase 3 mirogabalin untuk DPNP dan PHN (masing-masing 29,8% vs 14,5% dan 23,9%). Alasan untuk hal ini tidak diketahui, tetapi kejadian somnolen juga lebih tinggi pada kelompok plasebo dalam penelitian ini vs pasien yang menerima plasebo dalam percobaan fase 3 yang disebutkan di atas (5,4% vs 3,9% dan 3,6%), menunjukkan bahwa pasien dengan SCI mungkin lebih rentan terhadap kantuk secara umum.
- Beberapa pasien menghentikan mirogabalin karena TEAE yang terjadi pada penelitian ini (9,3%); → konsisten dengan studi fase 3 sebelumnya, yang keduanya memiliki tingkat penghentian terkait TEAE sebesar 9,7% untuk pasien yang menerima 15 mg mirogabalin BID.

Diskusi

- Tingkat edema, edema perifer, somnolen, dan pusing secara numerik **lebih tinggi untuk pasien yang menerima pregabalin** daripada yang dilaporkan dalam penelitian kami tentang mirogabalin.
- Mirogabalin dapat ditoleransi dengan baik, dengan keseimbangan efikasi dan keamanan yang sangat baik. Tingkat penghentian yang rendah karena TEAE yang diamati dalam penelitian kami menjanjikan karena sebagian besar pasien cenderung dapat melanjutkan pengobatan untuk mencapai penghilang rasa sakit yang cukup.
- Peningkatan dosis mirogabalin dapat diimplementasikan dengan aman di awal pengobatan dan efek penghilang rasa sakit dari mirogabalin dapat diamati bahkan sebelum dosis maksimum tercapai.
- Peningkatan ADPS pada tahap awal (setelah <1 minggu pemberian) dapat meningkatkan kemungkinan pemberian lanjutan dan berkontribusi pada kemanjuran pengobatan secara keseluruhan.

Keterbatasan Penelitian

- Studi ini dilakukan secara eksklusif di Asia, membatasi generalisasi untuk populasi ras/etnis lainnya.
- Durasi studi yang singkat menghalangi kesimpulan tentang kemanjuran dan keamanan jangka panjang,
- Penggunaan plasebo daripada pembanding aktif membatasi perbandingan langsung antara keamanan/kemanjuran dengan terapi yang ada.
- Karena sumber daya yang terbatas untuk diagnosis dan evaluasi CNeP, ada kemungkinan bahwa kemanjuran mirogabalin sebagian disebabkan oleh efek pada jenis nyeri lainnya.
- Tidak mengumpulkan informasi rinci tentang obat yang diberikan sebelum masuk studi atau rincian tentang nyeri neuropatik keras, sehingga kemungkinan pengaruh faktor ini masih harus ditentukan.
- Sifat psikometrik dari ADPS menggunakan skala peringkat numerik pada pasien dengan SCI belum dilaporkan, meskipun penelitian pada sukarelawan sehat menunjukkan bahwa sifat psikometrik mungkin bergantung pada area tubuh yang terpengaruh.
- tidak memeriksa perbedaan respons terhadap mirogabalin berdasarkan tingkat SCI atau perbedaan pada pasien dengan SCI serviks/toraks tinggi vs SCI dada rendah. Akhirnya, kami mengecualikan pasien dengan CrCL <30 mL/menit; oleh karena itu, efikasi dan keamanan mirogabalin pada pasien dengan gangguan ginjal berat masih belum diketahui.
- Meskipun hasil saat ini diperoleh hanya pada pasien dengan CNeP karena SCI, mirogabalin menunjukkan harapan untuk CNeP dengan etiologi lain; studi di masa depan harus menyelidiki indikasi potensial ini.

Kesimpulan

Mirogabalin memiliki profil efikasi dan keamanan yang baik dalam tatalaksana CNeP ec SNI, menunjukkan bahwa mirogabalin dapat menjadi tatalaksana alternatif bagi pasien dengan efek samping atau efikasi yang kurang memadai dengan terapi lainnya. Meskipun hasil ini diperoleh hanya pada pasien CNeP dengan SNI, mirogabalin menunjukkan harapan pada etiologi lainnya; sehingga penelitian selanjutnya harus menyelidiki indikasi potensial ini.

PICO analysis

Populasi

443 subjek yang memenuhi kriteria pada 120 tempat penelitian meliputi Jepang, Korea, dan Taiwan yang selanjutnya dirandomisasi menjadi 300 subjek dan dibagi menjadi 150 subjek pada kelompok mirogabalin dan 150 pada kelompok placebo.

Intervensi

Pada kelompok intervensi diberikan mirogabalin secara oral dan dititrasi berdasarkan CrCL subjek selama 14 minggu, dan diwajibkan mendatangi klinik sebanyak 8 kali kunjungan.

Comparison

150 orang masuk kedalam kelompok eksperimental dan 150 orang masuk kedalam kelompok kontrol (placebo). Pemilihan dilakukan secara acak.

Outcome

Terdapat perbaikan signifikan pada skor ADPS minggu ke 14, SF-MPQ dan NPSI pada kelompok mirogabalin. TEAE yang timbul merupakan gejala ringan, dan 9.3% menyebabkan penghentian terapi.

JBI CRITICAL APPRAISAL

JBI Critical Appraisal Checklist for Randomized Controlled Trials

Reviewer_____Date_____

Author _____Year_____Record Number_____

		Yes	No	Unclear	NA
1.	Was true randomization used for assignment of participants to treatment groups?	●	☐	☐	☐
2.	Was allocation to treatment groups concealed?	●	☐	☐	☐
3.	Were treatment groups similar at the baseline?	☐	●	☐	☐
4.	Were participants blind to treatment assignment?	●	☐	☐	☐
5.	Were those delivering treatment blind to treatment assignment?	●	☐	☐	☐
6.	Were outcomes assessors blind to treatment assignment?	●	☐	☐	☐
7.	Were treatment groups treated identically other than the intervention of interest?	●	☐	☐	☐
8.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	●	☐	☐	☐
9.	Were participants analyzed in the groups to which they were randomized?	●	☐	☐	☐
10.	Were outcomes measured in the same way for treatment groups?	●	☐	☐	☐
11.	Were outcomes measured in a reliable way?	●	☐	☐	☐
12.	Was appropriate statistical analysis used?	●	☐	☐	☐
13.	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	●	☐	☐	☐

Overall appraisal: Include ● Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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Daftar Pustaka

1. Finnerup NB, Kuner R, Jensen TS. Neuropathic pain: from mechanisms to treatment. Physiol Rev. 2021;101(1):259-301. doi:10.1152/physrev.00045.2019.
2. Murphy D, Lester D, Clay Smither F, Balakhanlou E. Peripheral neuropathic pain. Neurorehabilitation. 2020;47(3):265-283. doi:10.3233/nre-208002.
3. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 2010;9(8):807-819. doi:10.1016/s1474-4422(10)70143-5.
4. Lee S, Zhao X, Hatch M, Chun S, Chang EY. Central neuropathic pain in spinal cord injury. Crit Rev Phys Rehabil Med. 2013;25(3-4):159-172. doi:10.1615/critrevphysrehabilmed.2013007944. 5. Scholz J, Finnerup NB, Attal N, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain. 2019;160(1):53-59. doi:10.1097/j.pain.0000000000001365. 6. Selvy M, Cume´nal M, Kerckhove N, Courteix C, Busserolles J, Balayssac D. The safety of medications used to treat peripheral neuropathic pain, part 1 (antidepressants and antiepileptics): review of double-blind, placebo-controlled, randomized clinical trials.
Expert Opin Drug Saf. 2020;19(6):707-733. doi:10.1080/14740338.2020.1764934. 7. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007;132(3):237-251.
doi:10.1016/j.pain.2007.08.033.
8. Deeks ED. Mirogabalin: first global approval. Drugs. 2019;79(4):463-468. doi: 10.1007/s40265-019-01070-8.
9. Zaja¸czkowska R, Mika J, Leppert W, Kocot-Ke¸pska M, Malec-Milewska M, Wor- dliczek J. Mirogabalin - a novel selective ligand for the α2δ calcium channel subunit. Pharmaceuticals (Basel). 2021;14(2):112. doi:10.3390/ph14020112.
10. Domon Y, Kitano Y, Makino M. Analgesic effects of the novel α2δ ligand mirogabalin in a rat model of spinal cord injury. Pharmazie. 2018;73(11):659-661.
doi:10.1691/ ph.2018.8550.
11. Kato J, Matsui N, Kakehi Y, Murayama E, Ohwada S, Sugihara M. Mirogabalin for the management of postherpetic neuralgia: a randomized, double-blind, placebo-controlled phase 3 study in Asian patients. Pain. 2019;160(5):1175-1185. doi: 10.1097/j.pain.0000000000001501.
12. Baba M, Matsui N, Kuroha M, Wasaki Y, Ohwada S. Mirogabalin for the treatment of diabetic peripheral neuropathic pain: a randomized, double-blind, placebo-controlled phase III study in Asian patients. J Diabetes Investig. 2019;10(5):1299-1306. doi: 10.1111/jdi.13013.

Daftar Pustaka

13. Kimura Y, Yamaguchi S, Suzuki T, et al. Switching from pregabalin to mirogabalin in patients with peripheral neuropathic pain: a multi-center, prospective, single-arm, open-label study (MIROP study). Pain Ther. 2021;10(1):711-727. doi:10.1007/s40122-021-00255-y.
14. Melzack R. The short-form McGill Pain Questionnaire. Pain. 1987;30(2):191-197. doi:10.1016/0304-3959(87)91074-8.
15. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. Pain. 2012; 153(6):1148-1158. doi:10.1016/j.pain.2012.03.003.
16. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole MR. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94(2):149-158. doi:10.1016/s0304-3959(01)00349-9.
17. EuroQol Research Foundation. EQ-5D user guides, version 3.0. 2019. Accessed November 25, 2021. euroqol.org/publications/user-guides/.
18. Kirby S, Chuang-Stein C, Morris M. Determining a minimum clinically important difference between treatments for a patient-reported outcome. J Biopharm Stat. 2010; 20(5):1043-1054. doi:10.1080/10543400903315757.
19. US Food & Drug Administration, Center for Drug Evaluation and Research/ Center for Biologics Evaluation and Research. E9(R1) Statistical principles for clinical trials: addendum: estimands and sensitivity analysis in clinical trials; 2021.
Accessed November 25, 2021. fda.gov/regulatory-information/search-fda-guid- ance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands- and-sensitivity-analysis-clinical.
20.Jansen M, Warrington S, Dishy V, et al. A randomized, placebo-controlled, double- blind study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and repeated doses of mirogabalin in healthy Asian volunteers. Clin Pharmacol Drug Dev. 2018;7(6):661-669. doi:10.1002/cpdd.448.
21.Cardenas DD, Nieshoff EC, Suda K, et al. A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. Neurology. 2013;80(6):533-539. doi: 10.1212/wnl.0b013e318281546b.
22.Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. Neurology. 2006;67(10):1792-1800. doi:10.1212/01.wnl.0000244422.45278.ff.
23.Wessberg P, Frennered K. Central lumbar spinal stenosis: natural history of non- surgical patients. Eur Spine J. 2017;26(10):2536-2542. doi:10.1007/s00586-017-5075-x.

Daftar Pustaka

20.Copay AG, Glassman SD, Subach BR, Berven S, Schuler TC, Carreon LY. Minimum clinically important difference in lumbar spine surgery patients: a choice of methods using the Oswestry Disability Index, Medical Outcomes Study questionnaire Short Form 36, and pain scales. Spine J. 2008;8(6):968-974. doi:10.1016/j.spinee.2007.11.006.

21.Ogura Y, Ogura K, Kobayashi Y, et al. Minimum clinically important difference of major patient-reported outcome measures in patients undergoing decompression surgery for lumbar spinal stenosis. Clin Neurol Neurosurg. 2020;196:105966. doi: 10.1016/j.clineuro.2020.105966.

26. Kato H, Miyazaki M, Takeuchi M, et al. A retrospective study to identify risk factors for somnolence and dizziness in patients treated with pregabalin. J Pharm Health Care Sci. 2015;1:22. doi:10.1186/s40780-015-0022-7.

27. Mendell J, Levy-Cooperman n, Sellers E, et al. Abuse potential of mirogabalin in recreational polydrug users. Ther Adv Drug Saf. 2019;10:2042098619836032. doi: 10.1177/2042098619836032.

28. Onakpoya IJ, Thomas ET, Lee JJ, Goldacre B, Heneghan CJ. Benefits and harms of pregabalin in the management of neuropathic pain: a rapid review and meta-analysis of randomised clinical trials. BMJ Open. 2019;9(1):e023600. doi:10.1136/bmjopen- 2018-023600.

29. Yu X, Liu T, Zhao D, et al. Efficacy and safety of pregabalin in neuropathic pain followed spinal cord injury: a review and meta-analysis of randomized controlled trials. Clin J Pain. 2019;35(3):272-278. doi:10.1097/ajp.0000000000000675.

30. Aquarone RL, Faro ACMe, Nogueira PC. Central neuropathic pain: implications on quality of life of spinal cord injury patients. Rev Dor (São Paulo). 2015;16(4):280-284. doi:10.5935/1806-0013.20150057.

31. Saltychev M, Vastam¨aki H, Mattie R, McCormick Z, Vastam¨aki M, Laimi K. Psy- chometric properties of the pain numeric rating scale when applied to multiple body regions among professional musicians. PLoS One. 2016;11(9):e0161874. doi: 10.1371/journal.pone.0161874.

Thank You!