

Efficacy and Safety of a New Sustained-release Pregabalin Formulation Compared With Immediate-release Pregabalin in Patients With Peripheral Neuropathic Pain

A Randomized Noninferiority Phase 3 Trial

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Objective: This study investigated whether a new sustained-release (SR) pregabalin formulation is noninferior to immediate-release (IR) pregabalin in alleviating peripheral neuropathic pain in Korean patients.

Materials and Methods: This was a randomized, double-blind, active-controlled phase 3 study of patients with diabetic peripheral neuropathy or postherpetic neuralgia from 41 sites in South Korea in 2017-2018. Eligible patients were randomized (1:1) to receive once-daily SR pregabalin or twice-daily IR pregabalin (150 to

600 mg/d) in a double-dummy manner for 12 weeks according to a stratified permuted block randomization scheme. The primary endpoint was the Daily Pain Rating Scale score at the end of treatment, averaged from the last 7 available scores.

Results: A total of 319 of 371 (86.0%) randomized patients completed the 12-week treatment (SR pregabalin: n=154; IR pregabalin: n=165; per-protocol set: n=296). The least square mean difference between both groups for the primary endpoint was 0.06 (SE 0.19); (95% confidence interval -0.31 to 0.42), with the lower limit of the confidence interval above the pre-specified margin (-0.78; $P_{\text{noninferiority}} < 0.0001$). Drug-related treatment-emergent adverse events (TEAEs) were comparable between both groups. The incidence of drug-related TEAEs leading to treatment discontinuation was low (SR pregabalin: 2.7%; IR pregabalin: 1.1%). No serious drug-related TEAEs or deaths occurred.

Discussion: The results demonstrate that the new once-daily SR pregabalin formulation is noninferior to twice-daily IR pregabalin in reducing peripheral neuropathic pain and is well tolerated in Korean patients with diabetic peripheral neuropathy or postherpetic neuralgia after 12 weeks of treatment.

Key Words: pregabalin, sustained-release formulation, neuropathic pain, diabetic peripheral neuropathy, postherpetic neuralgia

(*Clin J Pain* 2022;38:343-350)

Received for publication December 8, 2020; revised December 1, 2021; accepted December 6, 2021.

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Supported by Yuhan Corporation (Seoul, Republic of Korea), which was involved in all aspects of study design, data collection, data analysis, data interpretation, assisted in writing the report, and approved the final version of the manuscript for publication in conjunction with the authors. S.K. and T.A. are employees of Yuhan Corporation, Seoul, Republic of Korea. The remaining authors declare no conflict of interest.

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Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.clinicalpain.com.

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DOI: 10.1097/AJP.0000000000001028

Neuropathic pain is a chronic pain condition that can interfere with general activity, sleep, mobility, mood, and work.¹ Peripheral neuropathic pain, defined by the International Association for the Study of Pain (IASP) as "pain caused by a lesion or disease of the peripheral somatosensory nervous system," is a common chronic pain syndrome with a broad range of underlying aetiologies.² Diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) are common types of peripheral neuropathic pain.³ DPN is reported to occur in 10% to 20% of patients with diabetes and in 40% to 50% of those with diabetic neuropathy.⁴ PHN is reported to occur in approximately 30% of patients with herpes zoster, increasing in frequency with age.^{5,6} Given the adverse impact of neuropathic pain on patients, it is important that patients receive appropriate pain treatment.

Pregabalin is a calcium channel blocker with high affinity for the α -2- δ subunits of voltage-gated calcium channels within the nervous system.⁷ Binding of pregabalin inhibits calcium influx into nerve cells, reducing neuronal hyperexcitability, and this is hypothesized to contribute to its analgesic effects.⁷ Pregabalin is currently available as an immediate-release (IR) formulation (LYRICA capsules; Pfizer Inc.) and as an extended-release (ER) formulation (LYRICA CR extended-release tablets; Pfizer Inc.) for the management of neuropathic pain.^{8,9} The Food and Drug Administration (FDA) has approved IR pregabalin as a twice-daily or thrice-daily treatment for the management of neuropathic pain associated with DPN, PHN, and spinal cord injury.⁸ ER pregabalin is approved as a once-daily treatment for the management of neuropathic pain associated with DPN and PHN.⁹ Although, in principle, the ER formulation offers the convenience of once-daily dosing, variable absorption of pregabalin is a potential issue because the gastric retention time of pregabalin is affected by calorie intake.^{8,9} This variability is attributed to the narrow absorption window of pregabalin.¹⁰

A new once-daily sustained-release (SR) pregabalin formulation (YHD1119 tablets; Yuhan Corporation, Seoul, Republic of Korea), designed using a proprietary floating and swelling gastroretentive drug delivery system, has been developed to overcome the issue of narrow absorption window while providing convenient dosing.¹¹ The tablets containing pregabalin swell to a size larger than that of the pylorus, which allows them to remain floating for >12 hours in the gastric region. Controlled release of pregabalin is achieved by using a matrix system that releases the active ingredient at a specified rate.¹¹ A phase 1 trial showed that once-daily SR pregabalin is bioequivalent to twice-daily IR pregabalin at 300 mg daily dose in healthy volunteers, with a comparable safety profile.^{12,13} However, there is a lack of data comparing these 2 formulations for the treatment of neuropathic pain. Hence, this randomized, multicenter, double-blind phase 3 trial sought to evaluate the efficacy and safety of SR pregabalin compared with IR pregabalin after 12 weeks of treatment in patients with peripheral neuropathic pain in South Korea. The primary objective was to demonstrate the noninferiority of once-daily SR pregabalin compared with twice-daily IR pregabalin in alleviating neuropathic pain.

MATERIALS AND METHODS

Study Design

This was a randomized, double-blind, active-controlled, multicenter, phase 3 study conducted at 41 sites in South Korea between February 2017 and May 2018. The institutional review board at each site reviewed and approved the study protocol and other relevant documents before study initiation. The study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice of the International Conference for Harmonisation, and the applicable local laws and regulations. All patients provided written informed consent before any study-related procedures were performed. This study was registered at ClinicalTrials.gov (identifier NCT02985216).

Study Population

Patients were assessed for study eligibility at the screening visit. Key inclusion criteria included: aged 19 to 79 years old; patients with DPN who had glycated hemoglobin $\leq 9.5\%$ and experienced pain for at least 6 months or patients with PHN who experienced pain for at least

3 months after the diagnosis of skin rash due to herpes zoster; and Daily Pain Rating Scale (DPRS) score ≥ 4 at least 3 times per week from 1 month before the screening visit. A full list of inclusion and exclusion criteria is available in the Supplementary Material (Text, Supplemental Digital Content 1, <http://links.lww.com/CJP/A861>).

Randomization and Allocation Concealment

Eligible patients who had DPRS score ≥ 4 for at least 4 days during the placebo run-in period and were assessed as not having any suicidal attempts or impulses via the Columbia-Suicide Severity Rating Scale were randomized. Patients were randomly assigned to SR pregabalin or IR pregabalin groups at a ratio of 1:1 via an Interactive Web Response System. The study medications were administered in a double-blind, double-dummy manner. The SR pregabalin group received SR pregabalin tablets once daily and IR placebo capsules twice daily, whereas the IR pregabalin group received IR pregabalin capsules twice daily and SR placebo tablets once daily. Randomization was stratified by chronic pain disorder (DPN vs. PHN) using a block randomization method. The randomization list was generated by an independent statistician. Assignment to study medications was blinded to patients, physicians, clinical staffs, and study sponsor.

Study Treatments

Eligible patients entered a 1-week placebo run-in period, during which a single-blind placebo was given twice daily (Fig. 1). This was followed by a 12-week double-blind treatment period (consisting of an initial dose period [days 1 to 7], dose titration period [days 8 to 28], and a fixed-dose period [days 29 to 84]) where patients who met the randomization criteria were randomized to receive once-daily SR pregabalin (150 mg/d) or twice-daily IR pregabalin (150 mg/d) along with dummy treatments from days 1 to 7. At the end of the initial dose period, the dose of study medication was increased to 300 mg/d, starting from day 8. At days 15 and 22, the dose of the study medication was increased in increments of 150 mg/d, with a 1-week interval in between, up to a maximum dose of 600 mg/d for patients whose weekly mean DPRS score did not decrease by 30% or more from baseline. For patients who reported intolerable adverse events, the dose of study medication was reduced in increments of 150 mg/d, with a 1-week interval in between, to a minimum dose of 150 mg/d based on the physician's judgment. At the end of the dose titration period, the optimal dose of the study medication was administered from days 29 to 84 for 8 weeks. All patients were followed for a further 1 week until day 92.

Patients were allowed to use rescue medication when intolerable pain occurred during the study period but were prohibited from using it within 8 hours before recording the DPRS score in the patient diary. A maximum dose of acetaminophen 4000 mg/d was allowed. Apart from the use of prescribed study medications and rescue medication, use of any treatment that could influence the results of the study was prohibited during the study period (Text, Supplemental Digital Content 1, <http://links.lww.com/CJP/A861>).

Study Endpoints and Assessments

During the treatment period, patients had 4 visits with 1-week intervals and 2 visits with 4-week intervals for efficacy and safety assessments. The visits were scheduled on days 8 (week 1), 15 (week 2), 22 (week 3), 29 (week 4), 57 (week 8), and 85 (week 12). The primary efficacy endpoint was the mean DPRS score at the end of treatment, averaged from the last 7

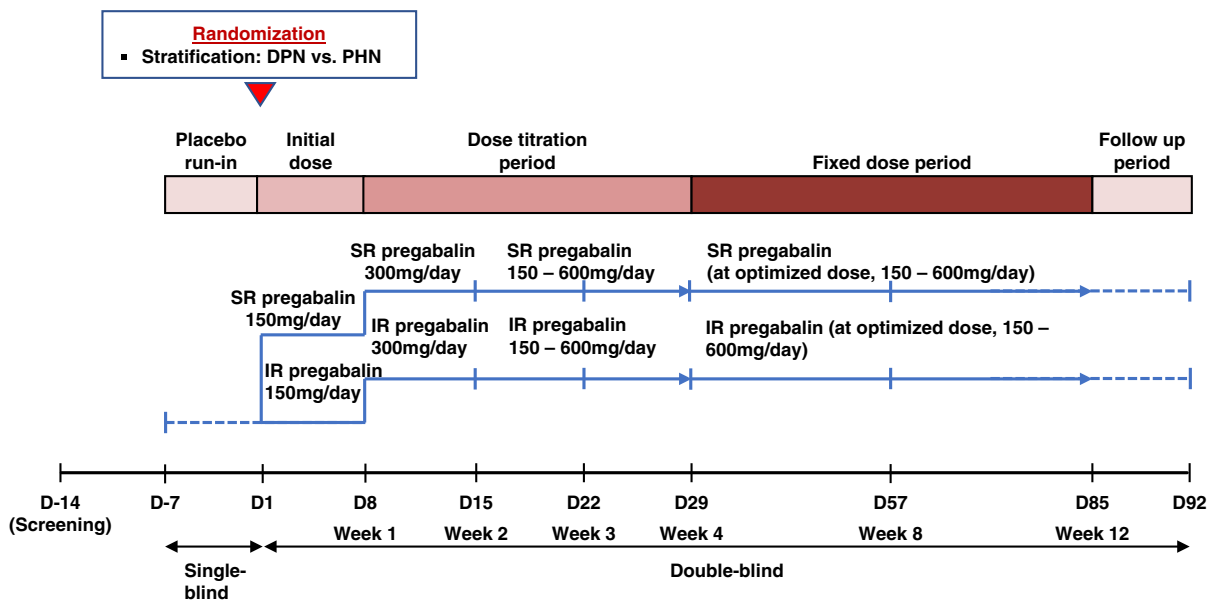


FIGURE 1. Study design. D indicates day; DPN, diabetic peripheral neuropathy; IR, immediate-release; PHN, postherpetic neuralgia; SR, sustained-release.

available DPRS scores of the 12-week treatment period. Secondary efficacy endpoints included the mean DPRS score at each visit (averaged from the last 7 available DPRS scores at each visit), change in mean DPRS score from baseline at each visit, proportion of responders (patients with $\geq 30\%$ reduction in mean DPRS score from baseline) at each visit, and frequency, dose, and duration of rescue medication use. Key safety endpoints included the incidence of treatment-emergent adverse events (TEAEs), TEAEs leading to treatment discontinuation, changes in physical examination, neurological examination, clinical laboratory tests, vital signs, electrocardiogram, and Columbia-Suicide Severity Rating Scale¹⁴ from the baseline at each evaluation point. TEAEs were defined as adverse events that were observed after the first administration of study medication to the end of the study. Exploratory endpoints including Patient Global Impression of Change, Clinician Global Impression of Change, Short Form-12 (composing the Physical Component Summary and Mental Component Summary measures), and the Daily Sleep Interference Scale were also assessed in the study, but these were not reported in this manuscript because they are not the focus of this manuscript. Patients rated their pain intensity during the preceding 24 hours every morning using the DPRS and recorded in the patient diary. The DPRS consists of an 11-point numeric rating scale ranging from 0 (no pain) to 10 (worst possible pain).^{15,16} When patients took a rescue medication, they were asked to record the date and dose in the patient diary.

Statistical Analyses

The primary objective of this study was to demonstrate SR pregabalin is noninferior to IR pregabalin, as assessed by the mean DPRS score at the end of treatment. The sample size was calculated based on previous studies on IR pregabalin in patients with DPN or PHN.¹⁷⁻²¹ Assuming no difference in mean DPRS score between both groups and a SD of 2.1, ~153 patients per treatment group would be required to demonstrate noninferiority of SR pregabalin to IR pregabalin, with a noninferiority margin of -0.78, 90% power, and a significance

level of 2.5% for a 1-sided test. Assuming a 15% dropout rate, ~180 patients per group would be required for this study.

The full analysis set (FAS) consisted of randomized patients who received at least 1 dose of the study medication and had baseline efficacy data and at least 1 postbaseline efficacy data. The per-protocol set (PPS) was a subset of the FAS and consisted of patients who satisfied the major inclusion and exclusion criteria and did not have any major protocol deviation that directly affected efficacy assessment. The safety set (SAF) included all randomized patients who received at least 1 dose of the study medication during the treatment period.

The PPS was the main analysis set used for efficacy analyses, while the FAS was used to assess the robustness of efficacy analyses. Safety analyses were performed on the SAF. The mean DPRS score at the end of treatment was analyzed using the mixed-effects model for repeated measures, including visit, baseline DPRS score (averaged from the last 7 available DPRS scores during the placebo run-in period), stratification factor (DPN and PHN), and treatment group as fixed effects, as well as visit-by-baseline score interaction and visit-by-treatment group interaction. If the lower limit of the 95% confidence interval (CI) for the least square (LS) mean difference between the treatment groups was above the pre-specified noninferiority margin of -0.78, SR pregabalin was deemed as noninferior to IR pregabalin.

The mean DPRS score at each visit and change in mean DPRS score from baseline at each visit were analyzed using the same statistical method that was used for the primary efficacy endpoint. Other secondary efficacy endpoints, including the proportion of responders at each visit and rescue medication used during the treatment period, were summarized using descriptive statistics. Demographics, baseline characteristics, treatment compliance, and safety endpoints were also summarized using descriptive statistics. Treatment compliance was calculated by dividing the number of tablets taken by the number of tablets required to be taken and then multiplying by 100. Subgroup analyses were conducted based on the stratification factor (DPN and PHN) for the primary and secondary efficacy endpoints.

Among the efficacy endpoints, missing values were handled by using the mixed-effects model for repeated measures for continuous variables, and the last observation carried forward method for categorical variables. At each scheduled visit, if the patient's diary was at least 50% completed, the average of the recorded DPRS score was used for analysis. Otherwise, it was considered as missing, and the missing data were replaced as specified above. For the safety endpoints, adjustment for missing data was not carried out, and the data were analyzed as they were. SAS, Version 9.4 (SAS Institute Inc., Cary, NC) was used for all statistical analyses, and a *P*-value <0.05 was considered statistically significant.

RESULTS

Patient Demographics and Baseline Characteristics

The flow of patients through the study is presented in Figure 2. A total of 501 patients from 41 institutions were

screened for their eligibility to enter the study. Of these, 371 patients were randomized to receive SR pregabalin (n = 185) or IR pregabalin (n = 186). After randomization, 1 patient in the SR pregabalin group discontinued from the study before receiving the study medication, and 30 patients in the SR pregabalin group and 21 in the IR pregabalin group discontinued during treatment, leaving 319 patients (86.0%) (SR pregabalin: 154; IR pregabalin: 165) who completed the 12-week treatment. The reasons for discontinuation are summarized in Figure 2. There were 296 patients (SR pregabalin: 146; IR pregabalin: 150) in the PPS, 363 patients (SR pregabalin: 180; IR pregabalin: 183) in the FAS, and 370 patients (SR pregabalin: 184; IR pregabalin: 186) in the SAF.

Patient demographics and baseline characteristics were generally comparable between treatment groups (Table 1). Patients in both SR pregabalin and IR pregabalin groups had median age below 70 years, higher proportion of males (67.1% and 52.0%, respectively) than females, and a mean baseline DPRS score around 6. Close to three quarter in both groups had DPN. Treatment compliance was similar in

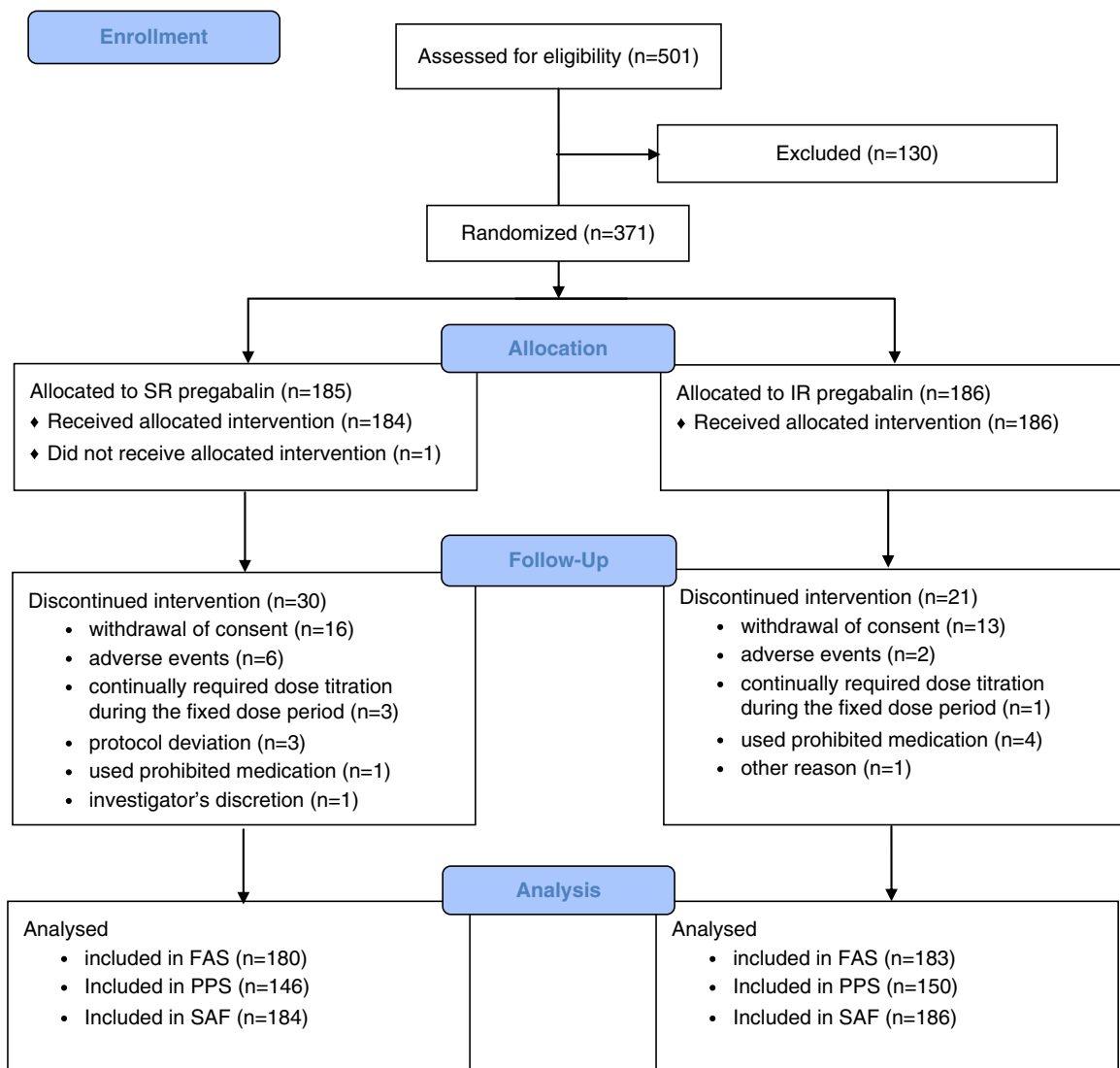


FIGURE 2. Patient disposition during the study period. FAS indicates full analysis set; IR, immediate-release; PPS, per-protocol set; SAF, safety analysis set; SR, sustained-release.

TABLE 1. Patient Demographics and Baseline Characteristics (Per-protocol Set)

	SR Pregabalin (N = 146)	IR Pregabalin (N = 150)
Age, median (minimum-maximum) (y)	65.0 (29.0-79.0)	67.0 (28.0-79.0)
Sex, n (%)		
Male	98 (67.1)	78 (52.0)
Female	48 (32.9)	72 (48.0)
Diagnosis, n (%)		
DPN	106 (72.6)	110 (73.3)
PHN	40 (27.4)	40 (26.7)
Duration of condition, median (minimum-maximum) (mo)		
DPN	37.5 (4.0-233.4)	36.7 (5.1-261.1)
PHN	23.8 (3.8-170.6)	25.2 (3.0-131.7)
Used rescue medication before randomization, n (%)	12 (8.2)	16 (10.7)
Baseline DPRS score	5.8 (1.4)	5.7 (1.3)
Baseline PCS score*	43.3 (8.4)	42.7 (8.7)
Baseline MCS score*	47.9 (9.4)	50.0 (10.0)

Values are presented as mean (SD) unless otherwise stated.

*Assessed using Short Form-12 version 2 (Korean version).

DPN indicates diabetic peripheral neuropathy; DPRS, Daily Pain Rating Scale; MCS, Mental Component Summary; PCS, Physical Component Summary; PHN, postherpetic neuralgia.

both groups. The mean (SD) overall compliance rates with the medications were 93.42% (14.73%) and 96.17% (8.17%) in the SR pregabalin and IR pregabalin groups, respectively.

Efficacy

Only results for the main analysis set, that is, PPS, are presented here. The results of all efficacy analyses conducted in the FAS (data not shown) were consistent with those of the PPS analyses.

The primary efficacy assessment was to compare the mean DPRS score at the end of treatment between patients receiving SR pregabalin and those receiving IR pregabalin.

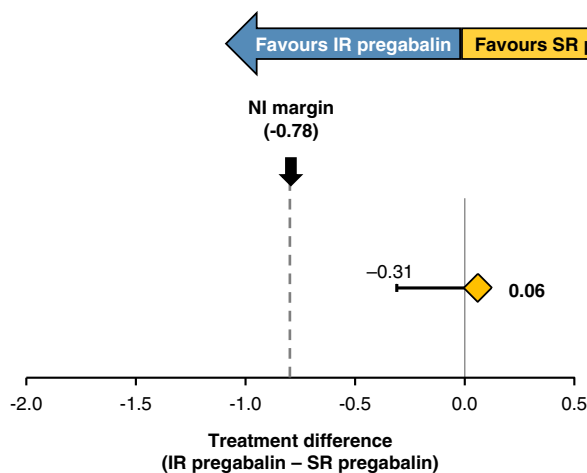
The LS mean (SE) DPRS score at the end of treatment was 3.01 (0.13) in the SR pregabalin group and 3.06 (0.13) in the IR pregabalin group. The between-group difference LS mean (SE) DPRS score at the end of treatment was 0.06 (0.19) (95% CI, -0.31 to 0.42) (Fig. 3). Given that the lower limit of the confidence interval for the difference between groups was above the pre-specified margin, SR pregabalin was not inferior to IR pregabalin in reducing pain intensity ($P_{\text{noninferiority}} < 0.0001$).

The mean DPRS score at each visit and change in mean DPRS score from baseline at each visit are presented in Figure 4A. The between-group difference in mean DPRS score was not statistically significant at any of the visits ($P > 0.05$ for all). The mean DPRS scores in both treatment groups decreased significantly from baseline at all visits ($P < 0.0001$ for all), with the greatest improvement observed at week 12 (LS mean [SE]: -2.75 [0.13] for SR pregabalin, and -2.69 [0.13] for IR pregabalin).

The proportion of responders at each visit are shown in Figure 4B. The proportion of responders at each visit were comparable between the treatment groups. From weeks 1 to 12, proportion of responders increased from 15.1% to 78.8% in the SR pregabalin group and from 20.0% to 76.7% in IR pregabalin group.

Only 9.6% (n = 14) of patients in the SR pregabalin group and 12.7% (n = 19) of patients in the IR pregabalin group required rescue medications during the treatment period. The median (range) duration of rescue medication use was longer in the SR pregabalin group (16 d [1 to 66 d]) than in the IR pregabalin group (8 d [1 to 85 d]). The median (range) dose of rescue medication was 11,700 mg (1000 to 84,500 mg) in the SR pregabalin group and 9000 mg (1000 to 323,700 mg) in the IR pregabalin group.

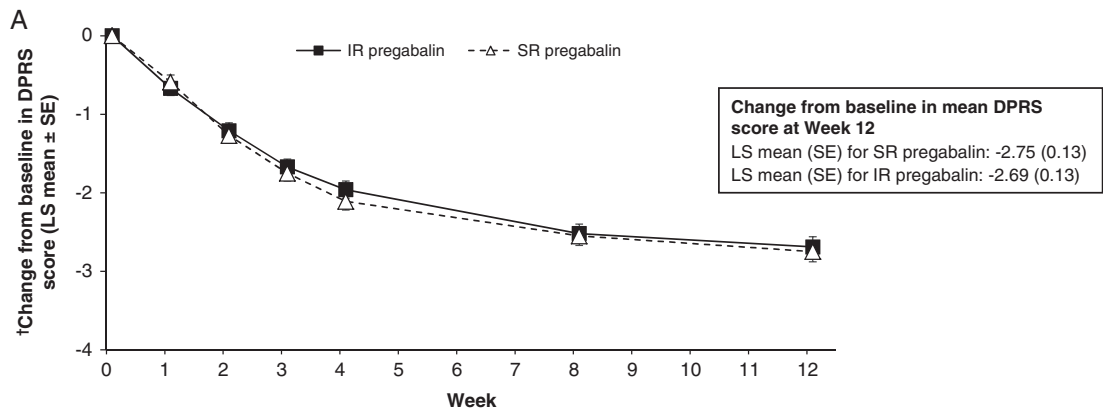
The results of the analyses in the DPN subgroup and PHN subgroup were similar to those for the overall study population (Figures, Supplemental Digital Content 2a, <http://links.lww.com/CJP/A862>, 2b, <http://links.lww.com/CJP/A863>). The SR pregabalin group was not inferior to the IR pregabalin group in both subgroups. Moreover, subgroup analysis results for the secondary efficacy



†Between-group difference in mean DPRS score at the end of treatment:

LS mean (SE) difference: 0.06 (0.19) (95% CI -0.31 to 0.42); p-value for non-inferiority <0.0001

FIGURE 3. Difference in mean DPRS score at the end of treatment between SR pregabalin and IR pregabalin groups (per-protocol set). †Mixed-effects model for repeated measures included visit, baseline DPRS score (averaged from the last 7 available DPRS scores during the placebo run-in period), stratification factor (diabetic peripheral neuropathy and postherpetic neuralgia), and treatment group as fixed effects, as well as visit-by-baseline score interaction and visit-by-treatment group interaction. CI indicates confidence interval; DPRS, Daily Pain Rating Scale; IR, immediate-release; LS, least square; NI, noninferiority; SR, sustained-release.



Change from baseline in mean DPRS score at Week 12
 LS mean (SE) for SR pregabalin: -2.75 (0.13)
 LS mean (SE) for IR pregabalin: -2.69 (0.13)

	Baseline	1	2	3	4	8	12
<u>Number of patients</u>							
SR pregabalin	146	146	146	145	146	145	146
IR pregabalin	150	148	149	148	147	147	150
<u>Change from baseline in mean DPRS score, LS mean (SE):</u>							
SR pregabalin	-	-0.59 (0.09)	-1.27 (0.10)	-1.75 (0.10)	-2.11 (0.11)	-2.55 (0.12)	-2.75 (0.13)
IR pregabalin	-	-0.67 (0.09)	-1.21 (0.10)	-1.67 (0.10)	-1.96 (0.11)	-2.52 (0.12)	-2.69 (0.13)
<u>Mean DPRS score, LS mean (SE):</u>							
SR pregabalin	-	5.17 (0.09)	4.48 (0.10)	4.01 (0.10)	3.65 (0.11)	3.21 (0.12)	3.01 (0.13)
IR pregabalin	-	5.09 (0.09)	4.55 (0.10)	4.09 (0.10)	3.79 (0.11)	3.24 (0.12)	3.06 (0.13)
<u>Between-group difference in mean DPRS score, LS mean (SE) difference:</u>							
Difference	-	-0.08 (0.12)	0.06 (0.14)	0.08 (0.14)	0.15 (0.15)	0.03 (0.12)	0.06 (0.19)
p-value	-	0.4898	0.6494	0.5597	0.3407	0.8480	0.7655

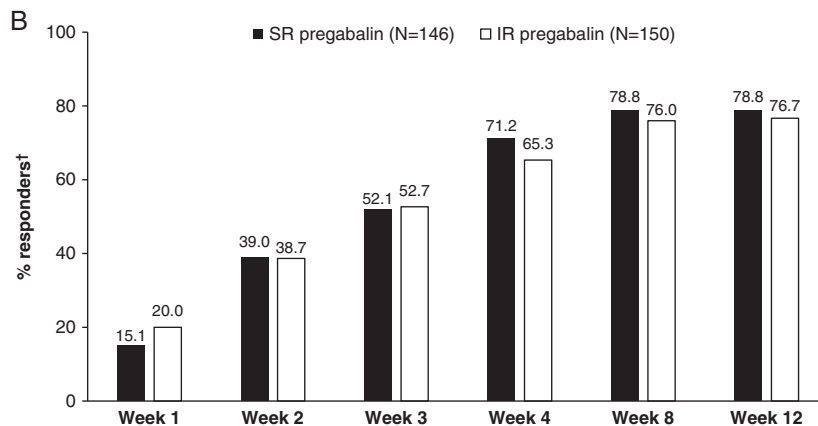


FIGURE 4. A, Change from baseline in mean DPRS score at each visit (per-protocol set). Points represent LS mean values; error bars represent SE. †Mixed-effects model for repeated measures included visit, baseline DPRS score (averaged from the last 7 available DPRS scores during the placebo run-in period), stratification factor (diabetic peripheral neuropathy and postherpetic neuralgia), and treatment group as fixed effects, as well as visit-by-baseline score interaction and visit-by-treatment group interaction. B, Proportion of responders† at each visit (per-protocol set). †Defined as having ≥ 30% reduction in mean DPRS score from baseline. DPRS indicates Daily Pain Rating Scale; IR, immediate-release; LS, least square; SR, sustained-release.

endpoints did not show differences between the SR pregabalin group and IR pregabalin group, similar to the results for the overall study population.

Safety Outcomes

An overall summary of TEAEs is presented in Table 2. The incidence of drug-related TEAEs in the SR pregabalin group were not markedly different from that of the IR pregabalin group. The incidence of drug-related TEAEs leading to treatment discontinuation was low in both groups (SR pregabalin:

2.7%; IR pregabalin: 1.1%). No serious drug-related TEAEs or deaths occurred in this study. The most common TEAEs in both groups were dizziness (SR pregabalin: 28.8%; IR pregabalin: 17.7%) and somnolence (SR pregabalin: 8.7%; IR pregabalin: 5.9%), which were mostly mild or moderate in severity.

DISCUSSION

A new, once-daily SR pregabalin formulation has been developed using a floating and swelling gastroretentive drug

TABLE 2. Overall Summary of TEAEs (Safety Analysis Set)

	SR Pregabalin (N = 184)	IR Pregabalin (N = 186)
TEAEs	97 (52.7)	93 (50.0)
Drug-related TEAEs	83 (45.1)	68 (36.6)
Serious TEAEs	0 (0.0)	5 (2.7)
Serious drug-related TEAEs	0 (0.0)	0 (0.0)
TEAEs leading to discontinuation of IP	6 (3.3)	2 (1.1)
Drug-related TEAEs leading to discontinuation of IP	5 (2.7)	2 (1.1)
TEAEs leading to death	0 (0.0)	0 (0.0)
Drug-related TEAEs leading to death	0 (0.0)	0 (0.0)
Most common TEAEs (≥ 5% of patients)		
Dizziness	53 (28.8)	33 (17.7)
Mild	44 (23.9)	24 (12.9)
Moderate	9 (4.9)	9 (4.8)
Severe	0 (0.0)	0 (0.0)
Somnolence	16 (8.7)	11 (5.9)
Mild	10 (5.4)	9 (4.8)
Moderate	6 (3.3)	2 (1.1)
Severe	0 (0.0)	0 (0.0)

Values are presented as n (%).

IP indicates investigational product; TEAE, treatment-emergent adverse event.

delivery system to prolong gastric retention of pregabalin.¹¹ Other SR tablets of pregabalin that used a conventional SR formulation technology has been reported.²² This was the first randomized, double-blind study to evaluate the efficacy and safety of the new SR pregabalin formulation compared with IR pregabalin in South Korean patients with peripheral neuropathic pain. The primary efficacy assessment was to compare the mean DPRS score at the end of treatment between patients receiving SR pregabalin and those receiving IR pregabalin. The results demonstrate that once-daily SR pregabalin was noninferior to twice-daily IR pregabalin in reducing neuropathic pain when administered 150 to 600 mg/d for 12 weeks in patients diagnosed with DPN or PHN. SR pregabalin was well tolerated after 12 weeks of treatment, with a safety profile similar to IR pregabalin.

A previous trial in healthy volunteers has shown that once-daily SR pregabalin is bioequivalent to twice-daily IR pregabalin, suggesting that SR pregabalin may show a similar effect with pregabalin IR.^{12,15} The geometric mean ratios of SR pregabalin to IR pregabalin were 1.1642 (90% CI, 1.1043-1.2272) for C_{max,ss} and 0.9704 (90% CI, 0.9372-1.0047) for AUC_{0-τ}.¹³ The present study extends the findings to demonstrate the efficacy of SR pregabalin in reducing peripheral neuropathic pain in patients with DPN or PHN. In this study, once-daily SR pregabalin was noninferior to twice-daily IR pregabalin in reducing neuropathic pain, as assessed by the mean DPRS score at the end of treatment. The efficacy was consistently observed across all secondary efficacy measures, including the mean DPRS score at each visit, change in mean DPRS score from baseline, proportion of responders, and frequency of rescue medication use, with SR pregabalin demonstrating a similar efficacy to IR pregabalin. Similar DPRS scores were noted in both groups at each visit. Significant improvements in pain intensity from baseline were noted from week 1

onwards, with the greatest improvements observed at the end of the 12-week treatment in both groups. The proportion of responders increased over the treatment period, with close to 80% of patients having at least 30% reduction in pain intensity from baseline at the end of treatment. Notably, only around 10% of patients used rescue medication during the treatment period, with comparable doses used in both groups. Although the duration of rescue medication use appears to be longer in the SR pregabalin group than IR pregabalin, this needs to be interpreted with caution, taking into account the small number of patients requiring rescue medication. Considering the small proportion of patients who took rescue medications and that patients were prohibited from using rescue medications within 8 hours before recording the DPRS score, it is unlikely that rescue medications would confound the results. In addition, the present study examined the efficacy of SR pregabalin compared with IR pregabalin in subgroups of patients who were diagnosed with DPN only, as well as in those with PHN only. Consistent with the results for the overall study population, SR pregabalin was noninferior to IR pregabalin in both DPN and PHN subgroups. Moreover, SR pregabalin demonstrates a similar efficacy to IR pregabalin across all secondary efficacy measures in each of these chronic pain disorders. Taken together, these findings demonstrate that once-daily SR pregabalin (150 to 600 mg/d) is noninferior to twice-daily IR pregabalin in alleviating neuropathic pain in patients with DPN or PHN.

Overall, the safety and tolerability profile of SR pregabalin was generally consistent with that of IR pregabalin in this study. The incidence of drug-related TEAEs and treatment discontinuation due to drug-related TEAEs in the SR pregabalin group were comparable with those observed in the IR pregabalin group. These findings corroborated those from an earlier trial where once-daily SR pregabalin demonstrated a safety profile similar to twice-daily IR pregabalin in healthy volunteers.¹² In the present study, the TEAEs observed in each treatment group are consistent with those expected for IR pregabalin.⁸ The most common TEAEs in each treatment group were dizziness and somnolence, which are consistent with the well-established TEAE profile for IR pregabalin.⁸ No serious drug-related TEAEs or deaths occurred in this study. Taken together, these findings demonstrate that once-daily SR pregabalin administered in daily doses of 150 to 600 mg over 12 weeks is well tolerated in patients with DPN or PHN, with a safety profile consistent with that expected for IR pregabalin.

Patients with chronic conditions often face the challenge of having to take a high number of medications on a daily basis over a long period of time due to their underlying condition and other comorbidities.^{23,24} Such a high pill burden is associated with the problem of poor medication adherence, which in turn lead to increased morbidity despite patients having access to effective treatments.^{25,26} Studies in patients with chronic diseases have shown that medications with less frequent dosing schedule are associated with improved adherence and clinical outcomes.²⁷⁻²⁹ In the present study, we are unable to assess patients' actual medication adherence towards SR pregabalin versus IR pregabalin due to the nature of the study. Future research examining patients' adherence to both pregabalin formulations in the real-world setting and evaluating its impact on clinical outcomes will be helpful to guide physicians and patients in treatment selection.

A limitation of the present study is the relatively short treatment duration that precluded longer term assessment of the efficacy and safety of SR pregabalin in this population. Studies with longer duration are necessary to define the long-term efficacy and safety of SR pregabalin for relieving neuropathic pain. Next, the study's inclusion and exclusion criteria limit the ability to extrapolate beyond the selected population. Future studies on SR pregabalin in more heterogeneous patient populations in the real-world setting are necessary to inform the use of SR pregabalin in real-world practice. Although the study has assessed functional outcomes as exploratory endpoints, the corresponding results were not reported in this manuscript because the results of the primary endpoint, secondary endpoints, and safety endpoints have taken precedence over those of the exploratory endpoints. Future work reporting the results of the functional outcomes will provide insights on the effects of SR pregabalin on patients' quality of life.

In summary, the results of this study demonstrate that the new once-daily SR pregabalin formulation, in daily doses of 150 to 600 mg/d, is noninferior to twice-daily IR pregabalin in alleviating peripheral neuropathic pain and is well tolerated in South Korean patients with DPN or PHN after 12 weeks of treatment. SR pregabalin represents a promising treatment for peripheral neuropathic pain, providing patients and healthcare providers with the option of reduced dosing frequency.

ACKNOWLEDGMENTS

Medical writing and editorial assistance were provided by Tech Observer Asia Pacific Pte Ltd, Singapore.

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