Once-Daily Gastroretentive Gabapentin for Postherpetic Neuralgia: Integrated Efficacy, Time to Onset of Pain Relief and Safety Analyses of Data From Two Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Studies

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Abstract

Context. Treatment options for postherpetic neuralgia (PHN), a complication of herpes zoster, are commonly unsatisfactory and associated with adverse events.

Objectives. To evaluate the efficacy, onset of pain relief, and safety of gastroretentive gabapentin (G-GR) in patients with PHN.

Methods. In two placebo-controlled studies, 357 patients with PHN were randomized to 1800 mg G-GR and 364 patients were randomized to placebo taken with the evening meal. Patients underwent a two week titration, eight weeks of stable dosing, and one week of tapering. Efficacy assessments included change in average daily pain (ADP) score from baseline to Week 10, time to onset of pain relief, the proportion of patients feeling improved using the Patient Global Impression of Change, and the proportion of responders (≥30% pain reduction).

Results. At Week 10, patients randomized to G-GR reported greater reductions in ADP score compared with placebo (−37.0% vs. −29.1; P = 0.0025). More G-GR patients felt improved compared with placebo (44% vs. 33%; P = 0.003) and responded to treatment (54% vs. 41%; P = 0.001). As early as Day 2, greater pain reductions were observed for the G-GR group compared with the placebo group (−6.6% vs. −1.6%; P = 0.0017). The median time to a one point or greater reduction in ADP score was four days for G-GR and six days for placebo (P < 0.0001). The most frequently reported adverse events were dizziness (G-GR, 11%; placebo, 2%) and somnolence (G-GR, 5%; placebo, 3%).

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Conclusion. PHN pain reduction after G-GR treatment can be observed as early as the second day of dosing and continues for at least 10 weeks. J Pain Symptom Manage 2013;46:219–228. © 2013 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Postherpetic neuralgia, gastroretentive gabapentin, onset of pain relief

Introduction
Postherpetic neuralgia (PHN) is a chronic pain syndrome characterized by persistence of pain after healing of acute herpes zoster (shingles). The pain can last for weeks or months and may persist for many years. Among individuals experiencing herpes zoster, the primary risk factor for the development of PHN is age, with approximately 85% of PHN occurring in patients aged 50 years or older. The pain and discomfort of PHN can affect patients’ quality of life, disrupting sleep and other activities of daily living. Antiviral therapy may reduce the severity and duration of herpes zoster but does not prevent PHN.

Originally developed and approved as an antiepileptic drug, gabapentin’s therapeutic applications expanded in 2002 to include PHN. Although there may have been concerns about the efficacy of gabapentin in various off-label uses, its efficacy for the treatment of PHN has been established in large, well-controlled studies. Gabapentin is a first-line treatment for PHN, with the immediate-release formulation administered three times daily (TID). Use of the immediate-release formulation is associated with a high incidence of adverse events (AEs), specifically, dizziness and somnolence. A gastroretentive formulation of gabapentin was approved for the management of PHN by the U.S. Food and Drug Administration in 2011. This gastroretentive formulation of gabapentin (gastroretentive gabapentin [G-GR]) uses a patented polymer-based technology designed to optimize drug delivery. The dosage of G-GR is titrated to 1800 mg/day over 14 days and administered once daily with the evening meal. After oral administration, the polymer swells to a size that promotes gastric retention of the tablet in the fed state while gradually releasing the drug over approximately eight hours to the upper small intestine where gabapentin is best absorbed.

This controlled and slow release of drug reduces the saturation of the transport mechanism of gabapentin and enables the drug to be administered once daily while providing equivalent bioavailability compared with immediate-release gabapentin administered three or more times daily. Several randomized, placebo-controlled studies have demonstrated the efficacy and safety of G-GR in patients with PHN. To better understand the onset of pain relief, we integrated and analyzed the data from two Phase 3, 10-week, randomized, double-blind, placebo-controlled studies of G-GR in patients with PHN.

Methods
Patients
Patient data for these integrated efficacy analyses were drawn from two similarly designed multicenter, randomized, placebo-controlled, Phase 3 PHN studies (Study 81-0045, clinicaltrial.gov identifier: NCT00335933 and Study 81-0062, clinicaltrial.gov identifier: NTC00636636). Details of these two studies have been previously described. Among the 859 patients randomized in these two studies, 357 patients were randomized to receive 1800 mg G-GR (Gralise; Depomed, Inc., Menlo Park, CA) and 364 patients were randomized to receive matching placebo with the evening meal. The remaining 138 patients were randomized to receive G-GR as an asymmetrically divided dose of 1200 mg with the evening meal and 600 mg with breakfast; this group is not included in the analyses presented here. The protocols were approved by a central institutional review board; the studies were conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice. Patients at least 18 years old with a diagnosis of PHN and an average numeric rating scale (NRS) score of ≥4 were
eligible if three or more months (Study 81-0045) or six or more months (Study 81-0062) had elapsed since the healing of the herpes zoster rash. Patients were excluded if they had failed to respond to treatment with gabapentin TID (≥1200 mg/day) or pregabaline (≥300 mg/day), had experienced dose-limiting AEs with gabapentin TID, or had hypersensitivity to gabapentin. Patients also were excluded for the concomitant use of benzodiazepines, skeletal muscle relaxants, orally administered steroids, capsaicin, mexiletine, centrally acting analgesics (dextromethorphan and tramadol), opioids, topical lidocaine, anticonvulsants, and serotonin-norepinephrine reuptake inhibitors; gastric-reduction surgery; severe chronic diarrhea; uncontrolled irritable bowel syndrome; unexplained weight loss; or an estimated creatinine clearance <50 mL/minute (as calculated by the Cockroft-Gault method). During the study, patients were permitted to continue tricyclic or selective serotonin reuptake inhibitors, acetaminophen (up to 4 g/day), nonsteroidal anti-inflammatory drugs (including cyclooxygenase 2 inhibitors), and aspirin (up to 325 mg/day). All patients or their authorized representatives signed written informed consent before study participation.

Procedures
Both studies included a one-week baseline period followed by a two-week titration period, an eight-week stable dose treatment period, and a one-week dose-tapering period. During the two-week titration period, doses were increased to a daily dose of 1800 mg, using a predetermined dosing schedule: Day 1, 300 mg; Day 2, 600 mg; Days 3–6, 900 mg; Days 7–10, 1200 mg; Days 11–14, 1500 mg; Day 15, 1800 mg. Patients continued on a stable dose of 1800 mg/day for an additional eight weeks, followed by a one-week dose-tapering period. Patients used an electronic diary (DiaryPRO; invivodata, Inc., Pittsburgh, PA) each morning from the beginning of baseline to the end of the efficacy treatment period (Treatment Week 10) to record their pain intensity during the previous 24 hours and sleep interference caused by pain. Pain intensity scoring used an 11-point NRS (where 0 = no pain and 10 = worst possible pain); sleep interference scoring used the same 11-point NRS (where 0 = no interference and 10 = worst possible interference). Investigator-rated Clinical Global Impressions of Change (CGIC) and Patient Global Impression of Change (PGIC) and a neurologic examination were completed at Week 10 or on early termination.

Efficacy Measures
Efficacy outcomes included the change and percent change in average daily pain (ADP) score from baseline to Week 10; proportion of responders defined as those patients achieving 30% or more reduction from baseline to Week 10; proportion of patients achieving a 50% or more reduction from baseline to Week 10; proportion of patients categorized as “very much” or “much” improved on PGIC; proportion of patients categorized as very much or much improved on CGIC; and mean change and percent change in average daily sleep interference score from baseline to Week 10. The integrated analysis is based on the intent-to-treat (ITT) population that comprised all patients who received any study treatment and had valid baseline efficacy measures. Mean percentage changes and mean numeric changes in ADP scores and in average daily sleep interference scores from baseline to Week 10 were analyzed using an analysis of covariance model that included treatment and center factors and baseline score as a covariate. Missing post-treatment scores were imputed using a last observation carried forward (LOCF) approach. The percentage of responders achieving ≥30% and ≥50% reduction in ADP score were compared between treatment groups using a z-test. The percentage of patients reporting PGIC or CGIC improvement (very much or much improved) was compared between treatment groups using Fisher’s exact test.

Time to onset of pain relief was defined as the first of two consecutive days with significantly (P < 0.05) greater percent reduction in ADP score from baseline in the G-GR group compared with the placebo group. In addition, to describe the speed of onset in individual patients, the time (in days) to the first occurrence of a one point or greater reduction in pain score from baseline was analyzed using the Kaplan-Meier method, and the log-rank test was used to compare the median times to onset of pain relief between the
G-GR and placebo groups. For those not achieving a one point or greater reduction in pain score from baseline, the length of follow-up was censored at Day 70, and for those who did not complete the 10-week treatment period, the length of follow-up was censored at the last dosing day.

Safety
Integrated safety analyses were performed on the safety population, comprising all patients who received at least one dose of study drug. Safety data included the incidence of treatment-emergent AEs, serious AEs (SAEs), clinical laboratory assessments, and vital signs. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, v. 9.0). The number and percentage of patients reporting one or more AEs were categorized by AE preferred term and AE system organ class and summarized by treatment group. Patients were analyzed as randomized for the efficacy analyses and as treated for the safety analyses.

Results

Patients
As shown in Fig. 1a, in the first study (81-0045), a total of 407 patients were randomized (136 to the once-daily G-GR treatment group, 137 to the G-GR asymmetric dose treatment group, and 134 to the placebo group), but only 405 randomized patients received study medication. Of those, 11 patients received nonrandomized treatment, resulting in 138 patients receiving once-daily G-GR, 134 patients receiving G-GR as a divided dose, and 133 patients receiving placebo. In the second study, a total of 452 patients were
randomized (221 to the G-GR group and 231 to the placebo group), but only 451 completed the baseline period. One patient, randomized to the G-GR group, was excluded from the ITT population but was included in the safety population. In addition, one patient entered the study twice at two different sites, with two different ID numbers. This patient was first randomized to the G-GR group and later randomized to the placebo group; the patient was included in the ITT population for the G-GR group but excluded from the placebo group and included in both the G-GR and placebo groups for the safety population. In total, in both studies, 357 patients were randomized to receive 1800 mg G-GR and 364 patients were randomized to receive matching placebo with the evening meal; in reality, 359 patients received G-GR and 364 patients received matching placebo (Fig. 1b). Almost all (95%) patients in the G-GR group completed the titration period and 83.6% completed the study. For the placebo group, only 80.5% of patients completed the study. Withdrawals as a result of lack of efficacy occurred for nine (2.5%) patients in the G-GR group compared with 22 (6.0%) patients in the placebo group. Withdrawals resulting from AEs occurred for 35 (9.7%) patients in the G-GR group compared with 25 (6.9%) patients in the placebo group. The most commonly reported AE for treatment discontinuation in the G-GR patients was dizziness \( n = 8 \) [2.2%] compared with \( n = 2 \) [0.5%] in the placebo group. There were two deaths among patients in the placebo group. Both patients experienced myocardial infarction after randomization. Neither death was considered by the investigator to be related to study drug.

The demographics and baseline characteristics of the ITT population are shown in Table 1. The mean age was 66 years. Most patients were female. The mean ADP scores at baseline were 6.5 and 6.6 for the G-GR and placebo groups, respectively, and the mean duration of PHN pain was comparable between the G-GR and placebo groups (27.1 and 28.7 months, respectively). The mean average daily sleep interference scores at baseline were 5.2 and 5.0 for the G-GR and placebo groups, respectively. No statistically significant differences were observed between treatment groups.

### Efficacy

At Week 10, G-GR significantly reduced pain from baseline compared with placebo (Fig. 2). Day 2 was the first of two consecutive days with

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>G-GR (1800 mg) (n = 356)</th>
<th>Placebo (n = 365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>66.4 (12.8)</td>
<td>66.0 (11.7)</td>
</tr>
<tr>
<td>&lt;65 years, n (%)</td>
<td>131 (36.8)</td>
<td>144 (39.7)</td>
</tr>
<tr>
<td>≥65 years, n (%)</td>
<td>225 (63.2)</td>
<td>219 (60.3)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>210 (59.0)</td>
<td>201 (55.4)</td>
</tr>
<tr>
<td>Male</td>
<td>146 (41.0)</td>
<td>162 (44.6)</td>
</tr>
<tr>
<td>Race, n (%)</td>
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<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>311 (87.4)</td>
<td>326 (89.8)</td>
</tr>
<tr>
<td>Black</td>
<td>16 (4.5)</td>
<td>10 (2.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (1.1)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>81.9 (18.6)</td>
<td>80.6 (17.2)</td>
</tr>
<tr>
<td>Time after shingles resolution before study entry (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 months, n (%)</td>
<td>33 (9.3)</td>
<td>35 (9.6)</td>
</tr>
<tr>
<td>6–12 months, n (%)</td>
<td>95 (26.7)</td>
<td>102 (28.1)</td>
</tr>
<tr>
<td>&gt;12 months, n (%)</td>
<td>227 (63.8)</td>
<td>222 (61.2)</td>
</tr>
<tr>
<td>Mean no. of months (SD)</td>
<td>27.1 (34.86)</td>
<td>28.7 (37.3)</td>
</tr>
<tr>
<td>Baseline ADP score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.5 (1.4)</td>
<td>6.6 (1.4)</td>
</tr>
<tr>
<td>Baseline sleep interference score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.2 (2.18)</td>
<td>5.0 (2.27)</td>
</tr>
</tbody>
</table>

G-GR = gastroretentive gabapentin; ADP = average daily pain.
a significantly \((P < 0.05)\) greater percent reduction in ADP score from baseline in the G-GR group compared with the placebo group \((-6.6\% \text{ vs. } -1.6\%; P = 0.0017; \text{Fig. 3})\). At Day 10, the mean percent decrease in ADP score was 20.2\%, further decreasing to 30.0\% at Day 22. Pain reductions continued to increase, reaching a maximum at approximately Day 40 \((-36.0\% \text{ vs. } -26.5\%; P = 0.0005)\) and remained statistically greater in the G-GR group compared with placebo group throughout the 10-week treatment period (with the exception of Day 65). At Week 10, the mean percent LOCF change in ADP score was significantly greater with G-GR than with placebo \((-37.0\% \text{ vs. } -29.1\%; P = 0.0025)\). In individual patients, the median time to a one point or greater reduction in mean ADP score from baseline occurred earlier for G-GR patients than for placebo patients: four days for G-GR and six days for placebo \((P < 0.0001; \text{Fig. 4})\).

At Week 10, a \(\geq 30\%\) reduction in ADP score from baseline was achieved in 54\% of G-GR patients compared with 41\% of placebo patients \((P = 0.001)\). A \(\geq 50\%\) reduction in ADP score from baseline was achieved in 36\% of G-GR patients compared with 26\% of placebo patients \((P = 0.005; \text{Fig. 5})\). Analyses of PGIC and CGIC demonstrated that significantly more G-GR patients felt or were considered very much or much improved compared with placebo patients (Fig. 6). G-GR also was superior

![Fig. 2. Absolute and percent change in ADP score from baseline to Week 10. ADP = average daily pain; G-GR = gastroretentive gabapentin.](image)

![Fig. 3. Mean percent change in ADP score by day. G-GR showed greater improvement in mean pain scores than placebo \((P < 0.05)\) for all days except Days 1 and 65. Values shown are LS mean (SEM), estimated from the analysis of covariance model that includes treatment and center factors and baseline as a covariate. LS = least square; ADP = average daily pain; G-GR = gastroretentive gabapentin.](image)

![Fig. 4. Time to onset of pain relief. G-GR = gastroretentive gabapentin.](image)

![Fig. 5. Percentage of patients responding with \(\geq 30\%\) and \(\geq 50\%\) reduction in last observation carried forward ADP score from baseline. The \(P\) value is based on the \(z\)-test for the difference in proportions between two groups. ADP = average daily pain; G-GR = gastroretentive gabapentin.](image)
to placebo in reducing the least square mean percent change from baseline to Week 10 of the average daily sleep interference score (−51% vs. −33%; \(P < 0.0001\)).

Safety

AEs were reported by 54% of patients in the G-GR group compared with 42% of patients in the placebo group. The most common treatment-emergent AEs in the G-GR group were dizziness, somnolence, and headache (Table 2). AEs of dizziness, somnolence, and peripheral edema were reported more frequently in the G-GR group than in the placebo group. Weight increase was reported by seven patients (1.9%) in the G-GR group compared with two patients (0.5%) in the placebo group.

SAEs were experienced by seven (1.9%) patients in the G-GR group (pneumonia, left arm fracture, Pancoast tumor, osteochondrosis, and chronic pancreatitis) compared with 10 (2.7%) patients in the placebo group (congestive cardiac failure, myocardial infarction, cellulitis, hematuria, thrombophlebitis, inguinal hernia, and atrial fibrillation). One SAE (chronic pancreatitis, experienced by one G-GR patient) was considered by the investigator to be related to study drug. The relationship of the chronic pancreatitis to study drug was challenged when the patient was seen by a gastroenterologist.

No clinically important differences in vital sign or laboratory changes from baseline were observed between treatment groups. The mean ± SD increase in weight from baseline was 0.72 ± 0.31 kg for G-GR compared with 0.18 ± 0.13 kg for placebo. Concomitant medications included selective serotonin reuptake inhibitors (5.9% for patients in the G-GR group compared with 6.9% in the placebo group), other antidepressants (2.5% for patients in the G-GR group compared with 0.8% for patients in the placebo group), and cyclooxygenase-2 inhibitors (2.0% for patients in the G-GR group compared with 1.9% for patients in the placebo group).

Discussion

A rapid time to onset of pain relief is a meaningful objective in the treatment of PHN. Analyses of the integrated results indicate that the early onset of pain relief associated with G-GR is sustained, with statistically significant differences compared with placebo noted as early as Day 2 of treatment, when patients were taking a daily dose of 600 mg. On Day 10 when patients in the G-GR group were still being titrated up and were taking 1200 mg/day, a mean percent decrease in pain score of 20% was observed, and at Day 22, by which time patients had reached the approved dose of 1800 mg/day, a mean percent decrease in pain score of 30% was observed. Pain reductions reached a maximum at approximately Day 40 and were statistically superior in the G-GR group compared with the placebo group over the 10-week treatment period. Using the definition of a reduction in ADP score from baseline of one point or more, the median time to onset of pain relief was significantly

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Table 2

<table>
<thead>
<tr>
<th>AEs</th>
<th>G-GR (1800 mg) ((n = 359)) (%)</th>
<th>Placebo ((n = 364)) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>10.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Headache</td>
<td>4.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>3.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2.5</td>
<td>2.2</td>
</tr>
</tbody>
</table>

AE = adverse event; G-GR = gastroretentive gabapentin.

Includes events reported for at least 2% of patients in either treatment group and more frequent in the G-GR group than in the placebo group.
faster with G-GR than with placebo (four vs. six days) and occurred at a dose of 900 mg. These onset results are comparable with the time to onset of pain relief reported in a retrospective analysis of four placebo-controlled studies in patients with PHN treated with pregabalin that showed significantly reduced pain with pregabalin as early as Day 1 or 2 and that the median time to a one point or greater reduction in mean pain score was Day 5. The median time to pain relief also was similar to that observed in a four-week randomized study in patients with PHN comparing flexibly dosed pregabalin (150–600 mg/day), fixed-dose pregabalin (600 mg/day), and placebo in which the median time to onset of pain relief was 3.5 days, 1.5 days, and more than four weeks, respectively. Early onset of pain relief was also reported in an eight-week placebo-controlled study in which pregabalin significantly reduced pain in PHN after the first full day of treatment and throughout the study and in a 12-week study in patients with PHN or diabetic peripheral neuropathy in which a decrease of one point on the 11-point NRS was reached on Day 1 with fixed-dose pregabalin (600 mg/day). G-GR administered as a once-daily 1800 mg dose was well tolerated and achieved significant, clinically meaningful reduction in pain compared with placebo. The proportion of patients with ≥30% and ≥50% reduction in pain was greater in the G-GR group than in the placebo group, with more than half the G-GR patients reporting clinically significant pain reduction (≥30%). These outcomes are consistent with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations for substantial and moderate benefit in chronic pain studies. Thirty-six percent of patients treated with G-GR reported a ≥50% reduction in ADP score, and this value is similar to the 33% reporting at least 50% pain relief with gabapentin in the Cochrane review. The LOCF methodology was used in these analyses, a commonly used and standard method to impute missing data. Although there is concern that LOCF is not a sufficiently conservative method, LOCF is the method that was used in all the previously published efficacy studies of gabapentin (and pregabalin) for the treatment of PHN. Thus, the presentation of these data using LOCF methodology enables direct comparison of these results with those in the literature.

Global impressions of change at Week 10 (CGIC and PGIC) were both higher for G-GR compared with placebo for clinician and patient ratings in the category of very much and much improved. G-GR also was efficacious in reducing sleep interference scores associated with PHN, indicating that G-GR improved pain-related sleep interference.

Integrated safety data from the two trials demonstrate a favorable safety profile for G-GR that is consistent with the observations from previous G-GR studies. Although no comparative studies with gabapentin TID have been performed, the incidence of AEs with G-GR appears lower than that observed in clinical trials of gabapentin TID. The incidences of dizziness and somnolence for G-GR were 10.9% and 4.5%, respectively (Table 2). In studies with immediate-release gabapentin, dizziness was reported in 23.9% of patients (n=113) who received 2400 or 3600 mg/day in divided doses compared with 5.2% (n=116) taking placebo and in 31% of patients who received 1800 or 2400 mg/day in divided doses (n=115) compared with 9.9% (n=111) in the placebo group. Also, the incidence of somnolence was high: 27.4% in patients receiving 2400 or 3600 mg/day in divided doses (n=113) compared with placebo (5.2%; n=116) and 17.4% in patients receiving 1800 or 2400 mg/day in divided doses (n=115) compared with placebo (6.3%; n=111). Limitations of the analyses include the eight weeks of stable dosing, which provide short-term rather than long-term assessments of safety and efficacy, and the possible enrichment by exclusion of patients with PHN from the clinical study if they had previously not responded to treatment with gabapentin (doses ≥1200 mg/day) or pregabalin (doses ≥300 mg/day) or had experienced dose-limiting AEs. Although these exclusion criteria may have enriched the study population with patients likely to be tolerant to gabapentin, it was considered unethical to require a study patient to participate in an 11-week study receiving daily administration of a drug he/she was unable to tolerate or was known to be ineffective for the treatment of his/her pain. This approach was used previously for studying
gabapentin TID in patients with PHN, and as such, the patient population of the G-GR studies presented here and in the gabapentin TID clinical trial by Rice and Maton are comparable.

**Conclusion**

In patients with PHN, G-GR (1800 mg, administered once daily) was well tolerated, provided a rapid onset of pain reduction, and produced clinically meaningful pain relief compared with placebo, with a low incidence of AEs.

**Disclosures and Acknowledgments**

This study was supported by Depomed, Inc., Menlo Park, CA. Dr. Sweeney is a Depomed employee, owns Depomed stock, and holds Depomed stock options. Dr. Vanhove is a former Depomed employee. Drs. Rauck and Wallace were investigators in the Depomed studies and also serve as consultants to Depomed. Dr. Rauck is a speaker for Depomed. Dr. Irving received compensation for serving on the advisory board and the speakers bureau for Depomed. He also served on the advisory board for Eli Lilly, Endo, Neurogesx, and Zogenix.

All authors are responsible for the work described in this article, and they contributed to the conception, data interpretation, and drafting of the manuscript and/or revising the manuscript for important intellectual content. All authors provided final approval of the version to be published.

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