EXPERT OPINION

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Clinical development of a once-daily gastroretentive formulation of gabapentin for treatment of postherpetic neuralgia: an overview

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Introduction: Gabapentin immediate-release formulations (G-IR) administered three times a day is an efficacious treatment for postherpetic neuralgia (PHN), but its potential benefits may not be fully realized due to tolerability issues as well as its pharmacokinetic (PK) properties such as its short half-life, and regional and saturable absorption in the proximal small intestine. The gastroretentive once-daily formulation of gabapentin (G-GR) allows for less frequent dosing while maintaining efficacy and may also reduce adverse events (AEs) associated with high plasma concentration of gabapentin occurring during the waking hours. G-GR slowly releases the drug from the tablet to the upper small intestine, where gabapentin is best absorbed, over approximately 10 h.

Area covered: This report reviews the development of the gastroretentive technology used in the once-daily formulation of gabapentin (G-GR), and describes the clinical development of G-GR from PK studies through the Phase III efficacy and safety studies, with comparisons made with G-IR.

Expert opinion: The technology takes advantage of the normal physiology of the stomach in the fed state to provide gastroretention, which in turn allows for gradual release of the active ingredient over several hours to the small intestine where gabapentin is best absorbed. The GR technology used in G-GR resulted in a decreased dosing frequency from three times per day for the IR product to once daily in the treatment of PHN, while maintaining the same efficacy with an apparent reduced incidence of AEs common to G-IR therapy.

Keywords: efficacy, gabapentin, gastroretention, oral drug delivery, pharmacokinetics, postherpetic neuralgia, tolerability

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1. Introduction

Gabapentin, an analog of γ-aminobutyric acid (GABA), was introduced in the USA as an anticonvulsant drug during the 1990s [1]. Subsequent preclinical testing demonstrated that gabapentin does not bind to GABA receptors but instead acts via the α2δ subunit of voltage-dependent calcium channels in neuronal tissue [2,3]. The indications for which gabapentin is now used have expanded considerably, and the efficacy, safety and low propensity for drug–drug interactions, make gabapentin a first-line treatment for postherpetic neuralgia (PHN), a disease predominantly present in the elderly, who often take one or more other medications for concomitant conditions [4,5]. However, since gabapentin is absorbed by a saturable

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Article highlights.

- The constraints of the normal gastrointestinal physiology must be taken into account when developing a gastroretentive dosage form.
- The gastroretentive gabapentin tablets swell to a size that promoted retention in the stomach when in contact with gastric fluid and then gradually release the active over a prolonged period of time.
- The pharmacokinetic (PK) profiles of once-daily gastroretentive gabapentin (G-GR) tablets were characterized under various conditions and compared with immediate-release (IR) gabapentin.
- The efficacy and tolerability of G-GR 1800 mg/day was investigated in placebo-controlled studies.
- The efficacy and tolerability results were compared with IR gabapentin.

This box summarizes key points contained in the article.

low-capacity transporter expressed primarily in the upper small intestine, and because it has a short elimination half-life (5 – 7 h), three times per day (TID) dosing of the immediate-release (IR) product is required. While IR gabapentin administered TID has demonstrated benefit in treating PHN, a major impediment to its more effective use is the high incidence of dizziness and somnolence. In a controlled clinical study in PHN patients administered the recommended dose of 600 mg TID (1800 mg/day) 31 and 17% of the subjects experienced dizziness and somnolence, respectively [6]. Additionally, medication compliance varies inversely with the frequency of daily dosing [7,8] and so it follows that a TID daily regimen of gabapentin could potentially jeopardize optimal treatment outcomes. These factors may limit the patient from actually being treated with an effective dose, reduce adherence and result in discontinuation and addition of other therapies in clinical practice. Indeed, results from a retrospective administrative claims database analysis demonstrated that the mean daily dosage for G-IR for PHN was only 826 mg and that only 14% of patients treated with gabapentin reached the target dose of 1800 mg/day and that on average, it took patients 10 weeks to reach that dose [9]. In addition, the results demonstrated that approximately one-third of patients had medication added to gabapentin for their treatment of PHN and more than half switched to a different medication. Of those who added medication, more than half added opioids and of those who switched, approximately one-third switched to opioids.

Gabapentin is incompletely absorbed from the gastrointestinal (GI) tract [10,11] with decreasing bioavailability as the dose increases. Single oral dose studies of G-IR formulations indicate that there is a lack of dose proportionality with increasing doses with the highest dose (1600 mg) being only 55% bioavailable relative to a 600 mg dose [10,12]. This reduction in bioavailability is likely due to decreased absorption due to saturation of the L-amino acid transporter [12] rather than an alteration in elimination, as the elimination kinetic was not changed with dose [10]. Additionally, the expression of the L-amino acid transporter responsible for the absorption of gabapentin decreases along the small intestine and is not present in the colon [13]. This is consistent with a significantly higher systemic exposure following administration of gabapentin solution into human duodenum or ileum compared with delivery in the colon, where absorption is passive [10]. Therefore, a gastroretentive formulation of gabapentin that gradually releases the drug over 10 h may ameliorate the absorption problem by slowly delivering gabapentin to the sites of the saturable L-amino acid transporter in the small intestine. However, to understand the mechanism of this gastroretentive technology, an understanding of GI physiology is essential.

2. Gastrointestinal physiology

In the fasted state the stomach and duodenum exhibit a cyclic pattern of contractile activity known as the migrating motor complex (MMC) cycle. The MMC cycle is divided into four phases. Phase I is a quiescent state, whereas Phase II activity consists of intermittent contractions that are smaller in force when compared with maximal Phase III contractions. Phase III activity is a period of maximal contractile activity lasting 10 – 15 min in the stomach and duodenum [14]. Under normal physiological conditions, Phase III contractions are the strongest ones to occur in the stomach and duodenum [15,16]. Phase III activity in the antrum is characterized by groups of three to six contractions that gradually increase in force until two contractions of maximal force occur [16]. When these contractions occur, the pylorus is completely relaxed and contractile activity of the duodenum is inhibited [15,16]. This relaxation allows the pylorus to be stretched to its maximal aperture during gastric emptying of large indigestible particles. With the termination of each group of antral contractions, contractile activity returns to the pylorus and duodenum along with an increase in tone of the pylorus [15]. This sequence is repeated several times during Phase III activity. Phase IV activity is a brief period of intermittent contractile activity that may follow Phase III. The MMC cycle has a duration of 90 – 120 min.

When food is ingested the MMC cycle is replaced with a different pattern of contractile activity. In the antrum the powerful contractions of Phase III activity are replaced by lower force aboard propagating contractions occurring three times per min. The force of these contractions is only about 15 – 25% of Phase III contractile activity until about 50% of the meal is emptied [17]. After approximately 50% of the meal has been emptied, the antral contractions gradually increase in force until the meal is completely emptied. Throughout the fed state contractions of the pylorus are coordinated with the propagating antral contractions such that the pylorus is closed 3 – 4 s before the propagating contraction reaches the distal antrum [18]. Additionally, there is an increase in isolated pyloric contractions and tone following a meal [19].

Thus, the reduced force of the antral contractions, along with the coordinated closure of the pylorus, are likely responsible for retaining non-digestible solids of a critical size in the stomach until the digestive state is complete and fasting contractile activity returns.

Following a mixed liquid/solid meal gastric emptying of the liquid portion begins within 5 min, while the solid portion has a lag time of 15 – 60 min. The lag time for solid emptying is due to the time necessary for the stomach to triturate the food into small enough particles (1 – 5 mm in diameter) to pass through the pylorus, which acts as a sieve.

The pylorus has a fasting resting diameter of approximately 12 – 13 mm [20] and non-disintegrating dosage forms with a diameter up to 12 mm may be emptied during the postprandial state [21]. However, as the diameter of the tablet increases the probability of the tablet emptying during the fed state decreases [22]. A study by Timmermans and Moes [22] demonstrated that swelling tablets with an initial diameter of 4.8, 7.5 and 9.9 mm emptied from the stomach during the fed state in 50, 40 and 11% of the subjects, respectively. In concurrence with this study, the authors found that 23, 15 and 8% of GR tablets with initial tablet dimensions of 7 × 18, 10 × 18 and 13 × 18 mm, respectively, emptied from the stomach during the postprandial state in healthy subjects [23]. Additionally, following administration with a low-fat meal there was a bimodal distribution of gastric emptying times with the 13 mm GR tablets, of approximately 19 and 5 h, with about 50% of the subjects in each range. The distribution was also bimodal for the smaller diameter tablets, but the proportion of subjects in the lower range increased substantially with a low fat meal. With very large non-disintegrating capsules (3.5 cm) the same bimodal distribution was observed with somewhat fewer subjects in the fast emptying population. Thus, even for extremely large non-disintegrating capsules it was observed that there was still a substantial proportion of subjects (36%) who emptied them in < 5 h from the stomach after a low fat meal.

These constraints of the normal physiology of the GI tract must be taken into account when developing a GR dosage form. The gastroretentive technology discussed below is optimized to take advantage of the normal physiology of the GI tract in the fed state to attain gastric retention and a gradual release of gabapentin over approximately 10 h to the upper small intestine where it is best absorbed [10].

3. Gastroretentive technology

Over the past two to three decades many approaches to gastroretentive drug delivery systems have been developed and tested. Among these are systems that depend on size (large single units), low (floating) and high (sinking) density, bio-adhesion (single and multi-unit) and swelling. Several reviews have discussed the various types of GR dosage forms in more detail [24-27]. This article discusses the clinical development of a polymeric swellable GR formulation of gabapentin (G-GR, GRALISE®).

G-GR delivery technology is a unique, patented, polymer-based technology designed to optimize drug delivery to the upper GI tract, the preferential site of absorption for many oral drugs, including gabapentin. Unlike IR formulations that rapidly dissolve allowing gabapentin to be emptied from the stomach within approximately 60 min, this technology utilizes swelling polymers that cause the tablets to be retained in the stomach for approximately 8 – 10 h following a meal [23]. During this time gabapentin is released by diffusion linearly with the square root of time. The linear release with the square root of time provides an additional early contribution to the bioavailability for subject who may be rapid gastric emptiers.

Although GI transit studies were not conducted with G-GR tablets, they were conducted on placebo tablets and on a very similar metformin formulation. When the placebo tablets or the metformin formulation was administered with a high calorie high fat meal (HC HF; 1000 calories, 50% from fat), excellent gastric retention for 12 – 14 h was demonstrated (**Figure 1**). After administration with a high calorie low fat meal (HC LF; 1000 calories 30% from fat) the placebo tablet and metformin formulation were retained in the stomach for approximately 8 h, whereas with a low calorie low fat meal (LC LF; 500 calories, 30% from fat) the placebo tablets were retained in the stomach for approximately 5 h (**Figure 1**) [23,28]. Transit time through the small intestine was approximately 3 h independent of the type of meal (**Figure 1**). Thus, for a compound such as gabapentin that is absorbed throughout the small intestine, transit through the small bowel provides for an additional 3 h of absorption time. The mean transit time to the colon of the GR tablets is approximately 11 h, which is greater than the 10 h *in vitro* delivery time for the G-GR tablets, suggesting that complete release of gabapentin from the tablet occurs before the tablet passes the absorption window.

Thus, because of improved intestinal absorption at the therapeutically effective dosage afforded by this technology, G-GR dosing frequency can be reduced to once daily for PHN compared with the IR formulation, as demonstrated in the pharmacokinetic (PK) studies.

4. Pharmacokinetic studies

Several PK studies were conducted to evaluate the *in vivo* performance of G-GR tablets. These studies elucidated the biopharmaceutical and clinical PK characteristics of the drug product. The studies were open-label, randomized crossover investigations in healthy volunteers to evaluate the effect of food, steady-state PK and dose proportionality. All subjects were between the ages of 18 and 65 years. Female subjects of childbearing potential had a negative pregnancy test and consented to using contraceptive methods. Subjects were excluded if they were hypersensitivity to gabapentin; had a clinically significant medical problems; had acute GI symptoms such as diarrhea, dyspepsia or gastric or duodenal

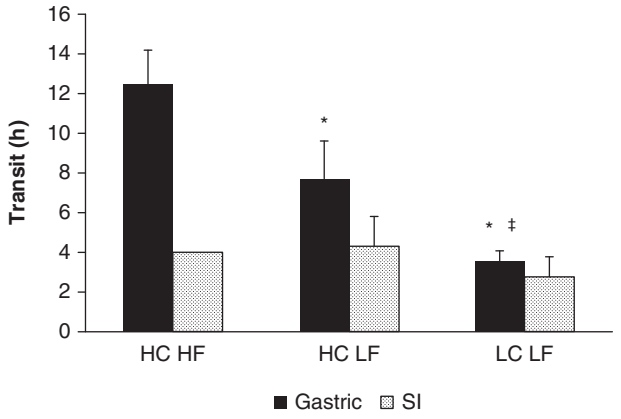

Figure 1. Gastrointestinal transit of gastroretentive tables administered after a high calorie high fat meal (HC HF) (1000 calories 50% from fat), a high calorie low fat meal (HC LF) (1000 calories 30% from fat) and low calorie low fat meal (LC LF) (500 calories 30% from fat).

*p < 0.05 compared with HC HF.

‡p < 0.05 compared with HC LF.

SI: Small intestine.

ulcers; a history of gastric reduction surgery; a history or evidence of psychiatric or psychological diseases; a history of alcohol abuse; or a history of or positive screen results for drugs of abuse. The influence of food on bioavailability of gabapentin was characterized with a high fat meal, low fat meal and under fasting conditions. The bioavailability and plasma gabapentin concentration–time profiles were characterized and compared with the IR product after a single dose and at steady state. Dose proportionality was assessed within the range of 600 – 2400 mg in increments of 600 mg. In each study, serial plasma and urine (GR vs. IR single-dose study only) samples were collected at timed intervals and gabapentin concentrations were determined using validated liquid chromatograph tandem mass spectrometry assays. Non-compartmental PK analysis was used to calculate area under the concentration–time profile (AUC). Maximum concentration (C_{max}), time to maximum concentration (t_{max}) and minimum concentration (C_{min}, for steady state only) were determined by inspection of the data. Overall in all the PK studies, G-GR was well tolerated and no safety issues were raised.

4.1 Gastroretentive gabapentin tablets versus IR tablets following a single oral administration

The objective of this study was to compare the PK of three formulations of G-GR with IR gabapentin in the fed state. Fifteen healthy subjects were administered a single dose of each of the following formulations: i) 600 mg G-IR (2 Neurontin® 300 mg capsules, Parke-Davis); ii) 600 mg G-GR6 (2 × 300 mg tablets); iii) 600 mg G-GR8 (2 × 300 mg tablets) or iv) 600 mg G-GR8 (1 × 600 mg tablet). G-GR6 and G-GR8 were defined as having ~ 90% cumulative release of gabapentin in an *in vitro* dissolution test at 6 and 8 h, respectively. The subjects were administered each formulation 5 min after a 1000 calorie high fat (~ 50% of calories from fat) meal [29].

The PK parameters from plasma and urine data are listed in **Table 1**. The G-GR tablets exhibited two major features that differed from those of the G-IR formulation including a trend for a longer t_{max} and a lower C_{max}. The median t_{max} for the G-GR tablets was 5.0 h (ranged from 2.5 to 12 h) versus 4.0 h (ranged from 2.5 to 5 h) for the G-IR tablets. Mean C_{max} ranged from 2970 to 3130 ng/ml for the G-GR formulations versus 4720 ng/ml for the G-IR formulation. Similar AUC and half-life values were observed between the G-IR and G-GR formulations (**Table 1**). Among the three G-GR formulations tested, similar plasma concentration–time profiles were observed as reflected from the comparable PK parameters (**Table 1**). The G-GR tablets had a urinary recovery of about 300 mg and renal clearance of about 110 ml/min, which was also similar to that of the G-IR capsules (**Table 1**). As might be expected for a gastroretentive formulations that gradually releases gabapentin over 6 – 8 h, the t_{max} was extended and the C_{max} was reduced compared with the immediate release formulation. Additionally, the elimination-related parameters such as renal clearance and terminal half-life were similar to the IR product indicating that gastroretention and gradual release of gabapentin were responsible for the extended concentration–time profile of G-GR. Although the three formulations demonstrated similar PK parameters, the G-GR8 formulation was chosen for optimization as it demonstrated a better stability profile with regards to the major degradant of gabapentin, gabapentin lactam (USP Related Compound A).

4.2 Dose proportionality [29]

As stated above, G-IR has previously been demonstrated to have non-linear PK such that the bioavailability decreases as the dose increases [10,11]. To determine whether G-GR could improve the dose proportionality of gabapentin, a dose-escalating study was conducted in 24 healthy male subjects. A single dose of 1, 2, 3 or 4 G-GR 600 mg tablets were administered following a standardized 500 – 600 calories, moderate fat meal (approximately 40% of the calories from fat). Linear regression was used to determine the relationship between AUC or C_{max}, and gabapentin dose.

The PK parameters are listed in **Table 2**. The results suggest a somewhat less than proportional increase in exposure, as accessed by AUC and C_{max} of gabapentin with increasing dose, while t_{max} was relatively constant. However, in comparison with G-IR where the relative bioavailability of the highest dose (1600 mg) was only 55% compared with the 600 mg dose [10], the relative bioavailability of the G-GR at the approved dose for PHN (1800 mg) was 87% compared with the 600 mg dose. Linear regression analysis demonstrated a nearly linear increase in AUC and C_{max} with G-GR doses (r^2 = 0.998 and 0.998, respectively). This

Table 1. Mean (± SD) gabapentin plasma and urinary PK parameters following a single oral dose of G-GR or G-IR at 600 mg following a meal containing 1000 calories with 50% of calories from fat.

PK parameter	Neurontin® 2 × 300 mg n = 15	G-GR6 2 × 300 mg n = 15	G-GR8 2 × 300 mg n = 16	G-GR8 1 × 600 mg n = 16
AUC_t (ng·h/ml)	46800 ± 9130	45800 ± 13300	43200 ± 12700	48800 ± 13200
AUC_∞ (ng·h/ml)	47400 ± 9130	46600 ± 13400	43900 ± 12700	49600 ± 13100
C_{max} (ng/ml)	4810 ± 900	3070 ± 690	3200 ± 760	3190 ± 610
t_{max} (h)*	4.0 (2.5 – 5.0)	5.0 (2.5 – 12)	5.0 (4.0 – 12)	5.0 (5.0 – 12)
$t_{½}$ (h)	5.9 ± 1.3	5.9 ± 1.4	5.7 ± 1.1	5.6 ± 1.7
CL_R (ml/min)	118 ± 35	110 ± 32	113 ± 33	118 ± 38
A_e (%)	53 ± 10	48 ± 12	47 ± 13	54 ± 14

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*Median (min – max).

Ae: Amount of gabapentin excreted in the urine; AUC_t: Area under the plasma concentration–time curve from 0 to last detectable concentration; AUC_∞: Area under the plasma concentration–time curve from 0 to infinity; CL_R: Renal clearance; C_{max}: Maximum plasma concentration; G-GR: Gastroretentive gabapentin tablets; PK: Pharmacokinetic; SD: Standard deviation; t_{max}: Time to C_{max}; ½: Half-life.

Table 2. Dose proportionality of G-GR tablets (600 mg) between 600 and 2400 mg administered as a single dose following a 500 – 600 calorie meal with 40% of the calories from fat (mean ± SD).

PK parameter	1 × 600 mg (n = 19)	2 × 600 mg (n = 19)	3 × 600 mg (n = 19)	4 × 600 mg (n = 19)
AUC_∞ (ng·h/ml)	37624 ± 11910	66383 ± 21806	95147 ± 2755	113334 ± 32397
Relative bioavailability to 600 mg (%)*	100	94 (74, 105)	87 (71, 101)	80 (64, 91)
C_{max} (ng/ml)	2962 ± 775	4933 ± 1051	6686 ± 1748	7847 ± 2102
Relative C_{max} to 600 mg (%)*	100	88 (74, 98)	77 (66, 88)	69 (58, 77)
t_{max}‡ (h)	6 (4 – 10)	6 (3 – 12)	6 (4 – 12)	7 (3 – 10)

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*Mean (90% CI).

‡Median (min – max).

CI: Confidence interval; G-GR: Gastroretentive gabapentin tablets; PK: Pharmacokinetic; SD: Standard deviation.

¶ p-Values not adjusted for multiple comparisons for secondary end points as per statically analysis plan.

improvement in dose proportionality is likely due to the slower input rate of gabapentin from the G-GR tablets and implies that bioavailability is not compromised at higher doses with G-GR tablets.

4.3 Food effect

The fat and caloric content of a meal has a pronounced effect on gastric residence time of gastroretentive tables, such as G-GR, as was demonstrated in the GI-transit studies discussed above, and hence may also affect the bioavailability of gabapentin delivered from G-GR tablets. The effect of food on the bioavailability of gabapentin administered as G-GR was investigated in 22 subjects. Following an overnight fast of at least 10 h the subjects were fed either a high fat meal (945 calories ~ 50% of calories from fat) or a low fat meal (836 calories ~ 30% calories from fat). Within 30 min of the start of the meals, the subjects were administered one 600 mg G-GR tablet. In the third arm of the study, the subjects were administered one G-GR tablet while continuing to fast [29].

Gabapentin bioavailability, measured as $AUC_{0\text{-inf}}$, was significantly greater after the high fat meal (53173 ± 15377 ng·h/ml, $p < 0.01$) and the low fat meal (32435 ± 12468 ng·h/ml, $p < 0.01$) compared with fasting (24430 ± 12478 ng·h/ml). In addition, gabapentin bioavailability was significantly greater after the high fat meal compared with the low fat meal ($p < 0.01$). As with AUC, C_{max} was also greater after the high fat meal (4002 ± 805 ng/ml, $p < 0.01$) and low fat meal (2902 ± 749 ng/ml, $p < 0.01$) compared with fasting (2175 ± 923 ng/ml). In addition, gabapentin C_{max} was significantly greater after the high fat meal compared with the low fat meal ($p < 0.01$). Furthermore, the low and high fat meals prolonged the t_{max} by approximately 3 and 6 h, respectively, compared with the fasting state. These data demonstrate the necessity to administer G-GR tables with a meal.

The recommended dose for treating PHN is 1800 mg once daily (QD). At steady state the relative bioavailability of the 1800 mg dose is 87% of the single 600 mg dose examined in the dose proportionality study, which is in agreement

with the dose proportionality study (Section 4.2). This decrease in bioavailability is not likely to be clinically significant as it is within the US Food and Drug Administration (US FDA) criteria for bioequivalents.

4.4 Steady state PK

The objective of this study was to compare the PK of G-GR with G-IR at steady state and to investigate the accumulation potential by comparing exposure to gabapentin between steady state and a single dose administration. Twenty-four healthy volunteers were enrolled and 21 completed all the study arms. G-GR, 600 mg tablets, were administered for 5 days as either three tablets QD following the evening meal (1000 calories 50% from fat) or asymmetrical as one tablet after breakfast (1000 calories 50% from fat) and two tablets after the evening meal, 12 h apart. These dosing regimens of G-GR were compared with G-IR 600 mg tablets given TID at 6 h intervals beginning in the morning [30].

The gabapentin plasma concentration–time profiles for the three dosing regimens are illustrated in **Figure 2**. The QD dosing results in lower daytime gabapentin plasma concentrations compared with G-IR TID and the asymmetrical G-GR dosing regimen. When compared with G-IR the QD dosing of G-GR tablets resulted in similar means ratio of the AUC_{0-24} 93% (90% confidence interval (CI): 87 – 100%), while the observed C_{max} means ratio was somewhat greater 112% (90% CI: 103 – 121%). The C_{min} means ratio for G-GR QD was lower when compared with G-IR, 71% (90% CI: 64 – 79%). The asymmetrical dosing of G-GR tablets resulted in a similar AUC_{0-24} compared with G-IR with a means ratio of 102% (90% CI: 95 – 109%), while the C_{max} values were slightly lower with a means ratio of 94% (90% CI: 87 – 101%). C_{min} for asymmetrical G-GR dosing was higher compared with G-IR, with a mean ratio of 153% (90% CI: 138 – 169%). T_{max} was extended by 6 h for the G-GR QD and 4 h for the asymmetrical dosed G-GR compared with the G-IR t_{max} of about 2 h. There was no accumulation of gabapentin with repeated administration.

These data demonstrate that the bioavailability of once-daily dose of 1800 mg gabapentin delivered from the G-GR tablets was maintained with a reduced dosing frequency compared with G-IR administered TID, which substantiates the observation of efficacy of G-GR for the treatment of PHN (see below).

5. Efficacy and tolerability

The efficacy and tolerability of G-GR was evaluated in one 4-week Phase II study [31] and two 10-week Phase III studies [32,33], which were double-blind, randomized, well-controlled trials in PHN patients. Study protocols were approved by institutional review boards and conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice. Each patient provided written informed consent before undergoing any study procedure. For ethical reasons all the studies employed an enrichment design as patients were excluded from the study if they had previously not responded to treatment for PHN with gabapentin at doses > 1200 mg/day or pregabalin at doses > 300 mg/day, had experienced dose-limiting adverse effects that prevented titration of gabapentin to an effective dose, or were hypersensitive to gabapentin. A similar enrichment design was previously used in the G-IR study reported by Rice and Maton [6] and the pregabalin studies for PHN [34-36]. Other exclusion criteria included neurolytic/neurosurgical treatment for PHN, severe pain from causes other than PHN, use of injected anesthetics or steroids within 30 days of baseline, immunocompromised state, creatinine clearance < 50 ml/min, gastric reduction surgery, history of substance abuse within the past year or any skin condition that could alter sensation in the area affected by the neuropathy. In all G-GR studies, patients were titrated up to 1800 mg in 2 weeks starting at 300 mg/day (day 1), 600 mg/day (day 2), 900 mg/day (days 3 – 6), 1200 mg/day (days 7 – 10) and 1500 mg/day (days 11 – 14). The primary efficacy end point was the least square (LS) mean change in the average daily pain (ADP) score from baseline to end of study treatment (week 4 for Phase II study, Week 10 for the Phase III studies). Key secondary efficacy end points included the proportion of patients with at least a 30 and 50% decrease in pain score, changes from baseline to end point in average daily sleep interference score (SIS), changes from baseline to each week in APD and SIS, and end of study assessment of Clinician Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC). Adverse events (AEs) were recorded throughout the study by direct questioning, laboratory tests and physical examination of the patients.

5.1 Phase II study (31, clinicaltrials.gov identifier: NCT00712439)

In the 4-week study, 158 PHN patients who had experienced pain for at least 3 months after healing of acute herpes zoster skin rash and had a baseline ADP score of ≥ 4 on a 0 (no pain) to 10 (worst pain possible) Numerical Rating Scale (NRS) were randomized to receive G-GR 1800 mg QD with the evening meal, asymmetrical G-GR (600 mg AM with breakfast, 1200 mg PM with the evening meal) or placebo. The type of meal was not specified. Missing data were inputted using the last observation carried forward (LOCF) method, defined as the average of the last seven available observations. Analysis of the primary efficacy parameter were performed at the $\alpha = 0.025$ significance level owing to two pairwise comparisons between each G-GR treatment and the placebo. The statistical tests used for the baseline variables and secondary efficacy parameters were performed at the $\alpha = 0.05$ significance level. All tests were two-sided.

There was a numerically greater decrease in the LS mean change in ADP score from baseline to end of study in both G-GR groups compared with placebo and a numerically

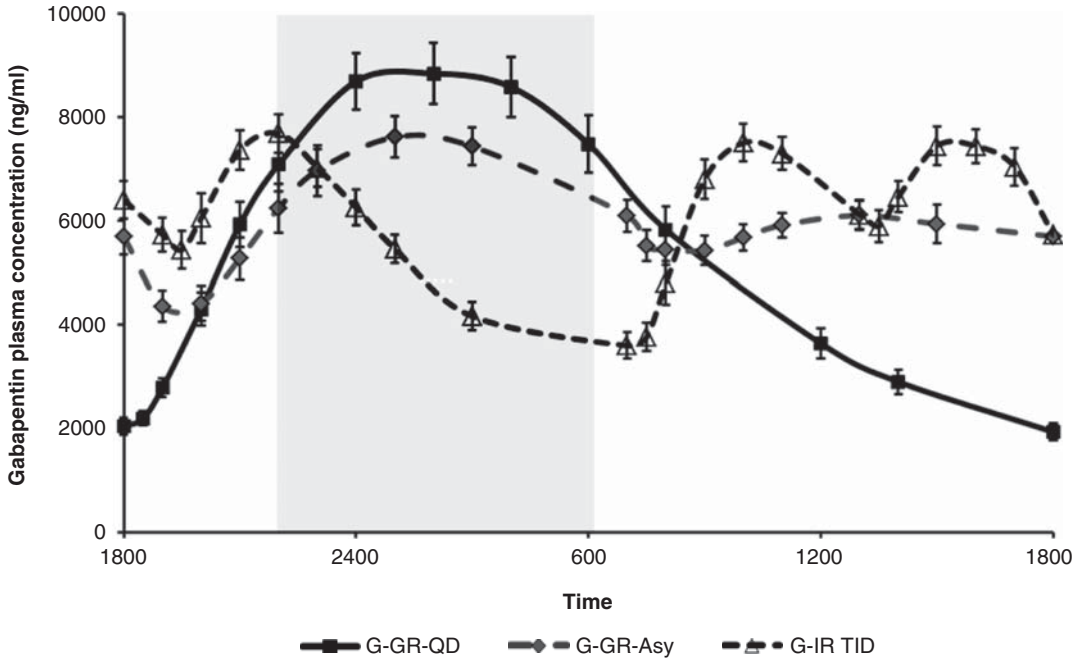

Figure 2. Mean (± standard error of the mean (SEM)) steady-state plasma concentration–time profiles of gabapentin following administration of G-GR 1800 mg once daily with the evening meal, G-GR dosed asymmetrical (600 with breakfast and 1200 mg with the evening meal) and G-IR dosed at 6 h intervals starting at 07:00 h during the day. The gray shaded box represents the nighttime period.

G-GR-Asy: Gastroretentive gabapentin tablets dosed asymmetrically; G-GR-QD: Gastroretentive gabapentin tablets once daily; G-IR TID: Gabapentin immediate-release three times per day.

greater percentage of patients in the G-GR groups had a ≥ 50 and 30% decrease in ADP score from baseline to end of study compared with placebo (**Table 3**). However, these differences were only significant in the asymmetrical G-GR group (**Table 3**). Improvement in pain scores were observed as early as the first week and continued for the duration of the treatment with the asymmetrical G-GR being significant ($p < 0.05$) throughout and the G-GR QD group being significant at week 1. There was a significantly greater decrease in the LS mean changes in SIS in both G-GR groups compared with placebo (**Table 3**). The changes in SIS were significantly different from placebo as early as week 1 and throughout the study for both G-GR groups. Approximately, 35, 52 and 25% of the patients in the G-GR QD, asymmetrical G-GR and placebo groups, respectively, were rated as very much or much improved for the CGIC (**Table 3**). For the PGIC about 33, 41 and 21% of the patients rated their PHN as very much or much improved in the G-GR QD, asymmetrical G-GR and placebo groups, respectively (**Table 3**).

Common AEs in the G-GR QD, asymmetrical G-GR and placebo groups were dizziness, 22.2, 11.3 and 9.8% and somnolence, 9.3, 7.5 and 7.8%, respectively.

The results of this study demonstrated that G-GR administered asymmetrically twice daily was significantly more effective than placebo in treating pain associated with PHN. Additionally, there was a trend toward greater efficacy with the G-GR once-daily treatment compared with placebo. Therefore, both dosing regimens were advanced to Phase III studies.

5.2 Phase III studies

5.2.1 First Phase III study (33, clinicaltrials.gov identifier: NCT00335933)

In the first 10-week study, 407 patients with post-zoster pain for ≥ 3 months and a baseline ADP ≥ 4 on a 0 – 10 NRS were randomized to receive either G-GR, 1800 mg total daily dose, administered QD with the evening meal, or as an asymmetrical divided dose with breakfast and the evening meal, or placebo. As in the Phase II study, the type of meal was not specified. Missing data for the primary end point were imputed using the baseline observation carried forward (BOCF) method. For this analysis if a patient completed the efficacy treatment period and completed all daily pain scores during the last 7 days of treatment, the end point was the mean pain scores over the last 7 days. If a patient discontinued the efficacy treatment prematurely, the end point was equal to the average baseline pain score. If a patient completed the efficacy treatment period but had missing data during the last week, the missing data were replaced by the average baseline score and the end point was equal to the mean of imputed pain scores and the actual recorded pain scores. LOCF analyses were

Table 3. Efficacy results from the Phase II study (intent-to-treat population).

	G-GR-QD (n = 46)	G-GR-Asy (n = 50)	Placebo (n = 51)	p-Value¶ vs. placebo	
				G-GR-QD	G-GR- Asy-
LOCF ADP score*	-1.9 (-2.5, -1.4)	-2.2 (-2.8, -1.7)	-1.3 (-1.9, -0.7)	0.089	0.014
Difference from placebo	-0.64 (-1.38, -0.10)	-0.95 (-1.71, -0.20)			
LOCF average daily SIS*	-1.9 (-2.5, -1.4)	-2.3 (-2.9, -1.7)	-1.2 (-1.8, -0.6)	0.048	0.006
Difference from placebo	-0.78 (-1.55, -0.01)	-1.12 (-1.91, -0.33)			
LOCF 50% responder rate‡	25.5%	28.8%	11.8%	0.072	0.032
LOCF 30% responder rate‡	43.6%	48.1%	31.4%	0.195	0.083
PGIC (very much or much improved)	32.7%	40.8%	20.8%	0.181	0.033
CGIC (very much or much improved)	34.6%	52.3%	25.0%	0.319	0.007

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*Change from baseline to end of study in least square mean (95% CI).

‡Percentage of patients with at least a 50% reduction in ADP score from baseline to end of study.

§Percentage of patients with at least a 30% reduction in ADP score from baseline to end of study.

ADP: Average daily pain; CGIC: Clinical global impression of change; CI: Confidence interval; G-GR-Asy: Asymmetrical gastroretentive gabapentin tablets divided dose (600 mg AM, 1200 mg PM); G-GR-QD: Gastroretentive gabapentin tablets once daily (1800 mg PM); LOCF: Last observation carried forward; PGIC: Patient global impression of change; SIS: Sleep interference score.

¶p- values not adjusted for multiple comparisons for secondary end points as per statically analysis plan.

Table 4. Efficacy results for the first Phase III study (intent-to-treat population).

	G-GR-QD (n = 134)	G-GR-Asy (n = 135)	Placebo (n = 131)	p-Value¶ vs. placebo	
				G-GR-QD	G-GR-Asy
BOCF ADP score*	-1.9 (-2.3, -1.4)	-1.7 (-2.1, -1.3)	-1.4 (-1.8, -1.0)	0.110	0.255
Difference from placebo	-0.43 (-0.95, 0.10)	-0.30 (-0.82, 0.22)			
Rash resolved < 6 months*,‡	-2.0 (-2.9, -1.1)	-2.2 (-3.0, -1.3)	-2.4 (-3.3, -1.6	0.478	0.677
Difference from placebo	0.44 (-0.79, 1.67)	0.25 (-0.95, 1.46)			
	n = 27	n = 29	n = 30		
Rash resolved ≥ 6 months*,‡	-2.0 (2.4, -1.6)	-1.8 (-2.2, -1.4)	-1.4 (-1.8, -0.9)	0.040	0.148
Difference from placebo	-0.61 (-1.18, -0.03)	-0.43 (-1.01, 0.15)			
	n = 107	n = 106	n = 101		
LOCF ADP score*	-2.3 (-2.7, -1.9)	-2.1 (-2.5, -1.7)	-1.7 (-2.1, -1.3)	0.032	0.154
Difference from placebo	-0.58 (-1.12, -0.05)	-0.39 (-0.92, 0.15)			
BOCF average daily SIS*	-2.0 (-2.4, -1.6)	-1.6 (-2.0, -1.2)	-1.4 (-1.8, -1.0)	0.015	0.363
Difference from placebo	-0.62 (-1.11, -0.12)	-0.23 (-0.72, 0.27)			
LOCF average daily SIS*	-2.5 (-2.9, -2.1)	-2.0 (-2.4, -1.6)	-1.6 (-2.0, -1.2)	0.001	0.152
Difference from placebo	-0.86 (-13.6, -0.37)	-0.36 (-0.85, 0.13)			
BOCF 50% responder rate§	27.6%	30.4%	22.9%	0.379	0.167
LOCF 50% responder rate§	36.6%	34.1%	27.5%	0.113	0.244
PGIC (very much or much improved)	44.0%	38.3%	27.6%	0.008	0.084
CGIC (very much or much improved)	47.2%	38.3%	27.6%	0.002	0.081

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*Change from baseline to end of study in least square mean (95% CI).

‡*Post hoc* analysis

§Percentage of patients with at least a 50% reduction in ADP score from baseline to end of study.

¶p-Values not adjusted for multiple comparisons for secondary end points as per statically analysis plan.

ADP: Average daily pain; BOCF: Baseline observation carried forward; CGIC: Clinician global impression of change; CI: Confidence interval; G-GR-Asy: Asymmetrical gastroretentive gabapentin tablets (600 mg AM, 1200 mg PM); G-GR-QD: Gastroretentive gabapentin tablets once daily (1800 mg PM); LOCF: Last observation carried forward; PGIC: Patient global impression of change; SIS: Sleep interference score.

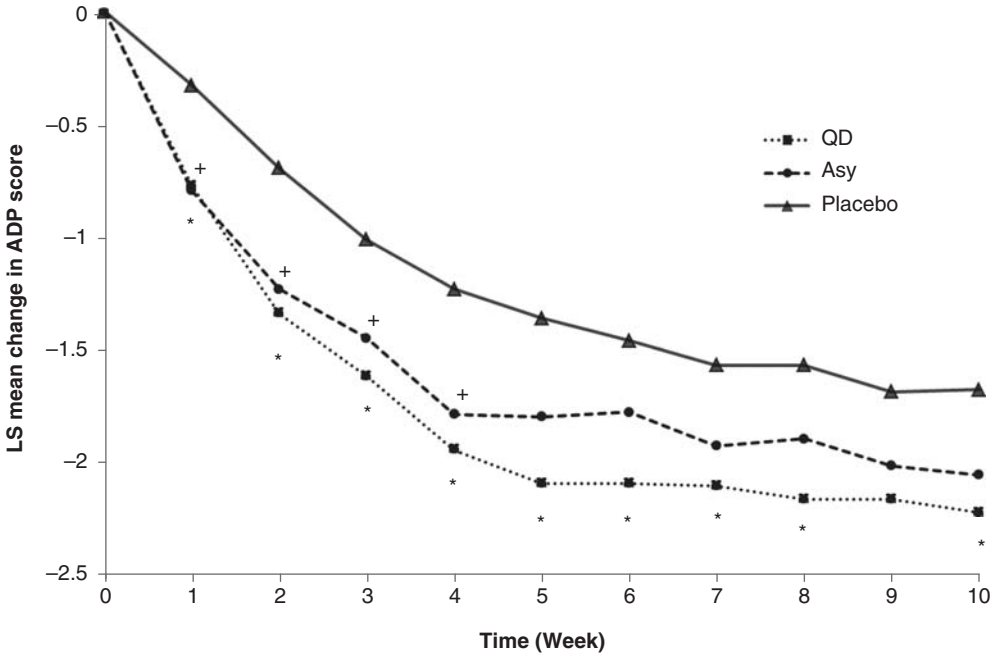

Figure 3. Least squares (LS) mean change from baseline in weekly LOCF average daily pain (ADP) score for the first Phase III study.

*p < 0.035 compared with placebo for the QD (p values not adjusted for multiple comparisons for secondary end points as per statically analysis plan).

+p < 0.038 compared with placebo for the asymmetrical dosing.

QD: 1800 mg of G-GR dosed once daily with the evening meal; Asy: asymmetrical dosing of G-GR (600 mg with breakfast, 1200 mg with the evening meal).

performed as sensitivity analyses. Statically analysis was carried out as outline above for the Phase II study.

Between-group differences for the BOCF ADP primary end point did not reach statistical significance for either G-GR group (**Table 4**). However, in a *post hoc* BOCF analysis of patients who had their rash resolved 6 months or more prior to study entry, the ADP score reduction was significantly larger in the G-GR QD group ($p = 0.040$) compared with placebo, while patients who had their rash resolved less than 6 months prior to study were not different from placebo (**Table 4**). For the asymmetrical G-GR group, differences between treatment groups were not significant in either subgroup (**Table 4**). In contrast to the Phase II study, the G-GR QD group had an improvement in pain scores at week 1, which continued through week 8 and at week 10, while the asymmetrical G-GR group was only improved through week 4 (**Figure 3**), as was the case in the Phase II study. Significant improvements in the SIS compared with placebo also were observed in the G-GR QD group, but not in the asymmetrical G-GR group (**Table 4**). Additionally, the SIS was significantly improved compared with placebo throughout the study for the G-GR QD groups ($p < 0.002$) but only at weeks 1, 2 and 4 for the asymmetrically G-GR group ($p < 0.05$). For the CGIC the G-GR QD group was significantly improved compared with placebo while the asymmetrical G-GR was not (**Table 4**). Similar results were also obtained for the PGIC (**Table 4**).

Among gabapentin G-GR treated patients, 12 and 11% withdrew due to AEs compared with 11% for placebo. The most common AE causing withdrawal was dizziness (2 and 3%) in the G-GR QD and asymmetrical G-GR groups, respectively. Treatment-related AEs in the G-GR treated groups occurred in 31% of patients. The most common AEs in the QD, asymmetrical and placebo groups included dizziness (10, 15 and 3%), headache (4, 7 and 5%), somnolence (3, 7 and 2%) and peripheral edema (5, 5 and 0%), respectively.

In contrast to the 4-week Phase II study, this larger and longer Phase III study demonstrated greater efficacy in the G-GR once-daily group based on many of the secondary end points than in the asymmetrical G-GR group. Additionally, the subgroup *post hoc* analysis identified the duration of PHN prior to study entry as a potentially important factor as there was no difference in the decrease in ADP score between the active groups and placebo in the subgroup with PHN for less than 6 months. This may be due to a large degree of spontaneous resolution of PHN between 3 and 6 months, as previously reported in a vaccine study where PHN resolved in about 44% of patients in the placebo group between 3 and 6 months after the healing of herpes zoster lesions [37].

Table 5. Efficacy results for the second Phase III study (intent-to-treat population).

	G-GR-QD (n = 134)	Placebo (n = 131)	p-Value vs. placebo
BOCF ADP score*	-2.1 (-2.4, -1.8)	-1.6 (-1.9, -1.3)	0.013
Difference from placebo	-0.49 (-0.88, -0.11)		
LOCF ADP score*	-2.4 (-2.7, -2.1)	-1.9 (-2.2, -1.5)	0.007
Difference from placebo	-0.55 (-0.96, -0.15)		
BOCF average daily SIS*	-2.3 (-2.6, -2.0)	-1.6 (-1.9, -1.3)	< 0.001
Difference from placebo	-0.70 (-1.07, -0.35)		
LOCF average daily SIS*	-2.5 (-2.9, -2.1)	-1.6 (-2.0, -1.2)	0.001
Difference from placebo	-0.84 (-1.22, -0.46)		
BOCF 50% responder rate‡	29.5%	22.6%	0.094
LOCF 50% responder rate‡	36.8%	25.7%	0.011
BOCF 30% responder rate§	47.7%	37.4%	0.027
LOCF 30% responder rate§	55.5%	42.2%	0.005
PGIC (very much or much improved)	42.7%	33.5%	0.043
CGIC (very much or much improved)	44.1%	33.9%	0.027

*Change from baseline to end of study in least square mean (95% CI).

‡Percentage of patients with at least a 50% reduction in ADP score from baseline to end of study.

§Percentage of patients with at least a 30% reduction in ADP score from baseline to end of study.

ADP: Average daily pain; BOCF: Baseline observation carried forward; CGIC: Clinician global impression of change; CI: Confidence interval; G-GR-QD: Gastroretentive gabapentin tablets once daily (1800 mg PM); LOCF: Last observation carried forward; PGIC: Patient global impression of change; SIS: Sleep interference score.

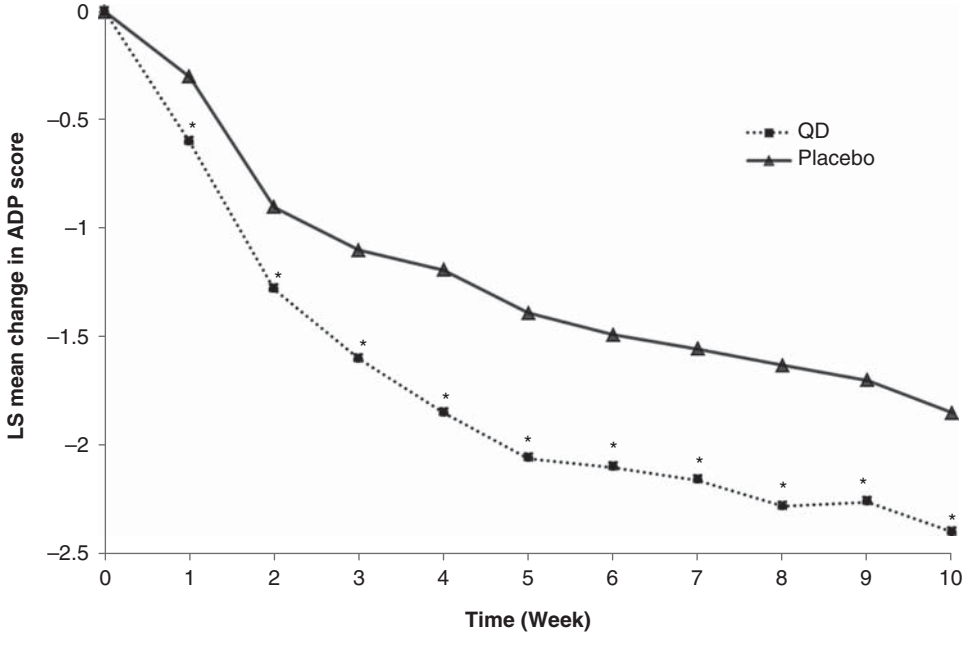

Figure 4. Least squares (LS) mean change from baseline in weekly LOCF average daily pain (ADP) score for the second Phase III study.

*p < 0.002 compared with placebo.

QD: 1800 mg of G-GR dosed once daily with the evening meal.

5.2.2 Second Phase III study (32, clinicaltrials.gov identifier: NCT00636636)

Since the results of the first Phase III study demonstrated better efficacy and tolerability in the QD group compared with the asymmetrically dosed group, the second 10-week study compared G-GR, 1800 mg administered QD with the evening meal, with placebo in 452 patients with post-zoster pain for ≥ 6 months and < 5 years, and a baseline ADP score ≥ 4 on a 0 – 10 NRS. Similar to the previous efficacy studies, the type of meal was not specified. Missing data for

the primary end point were imputed using the BOCF method as outlined above, while LOCF was used for sensitivity analyses. A hierarchical statistical paradigm dependent on a statistically significant primary outcome, performed at = 0.05 was used for the analyses of PGIC and CGIC simultaneously at the = 0.05/2 = 0.025, two-sided significance level. If either test was statistically significant, the analysis on average daily SIS was performed at the = 0.05, two-sided significance level.

There was a significantly greater decrease in the primary end point, BOCF LS mean ADP score from baseline to end of study, in the G-GR QD group compared with placebo (**Table 5**). Forty-eight percent of patients treated with G-GR demonstrated a 30% or more reduction in LS mean ADP scores compared with 37% of placebo patients (**Table 5**). Significant improvement in pain scores (BOCF and LOCF) were observed as early as the week 1 and continued for the full 10 weeks of the efficacy treatment (**Figure 4**). Forty-three percent of the G-GR QD patients reported feeling much or very much improved on the PGIC compared with 34% of the placebo patients (**Table 5**). Results were similar for the CGIC (**Table 5**). The reduction in the SIS using BOCF imputation was greater for the G-GR group than for placebo (**Table 5**). Additionally, the SIS was improved as early as week 1 and throughout the study compared with placebo. However, because of the sequential hierarchical paradigm, these comparisons were not considered statistically significant.

AEs leading to withdrawal occurred in 8.6 and 4.3% of the G-GR and placebo groups, respectively, with the only AE leading to discontinuation in more than 2% of the patients being dizziness (2.3%) in the G-GR group. The most common AEs (≥ 2% of patients) with a higher incidence in G-GR-treated patients than in placebo were dizziness (11.3 vs. 1.7%), somnolence (5.4 vs. 3.0%), headache (4.5 vs. 3.9%), nausea (4.5 vs. 3.0%) and peripheral edema (3.2 vs. 1%). All incidences of these AEs were mild or moderate, with no severe AEs reported.

6. Conclusion

Gabapentin is a first-line treatment for PHN, a disease predominantly present in the elderly, who often take one or more other medications for concomitant conditions [4,5]. Since gabapentin is absorbed by a saturable low-capacity transporter expressed primarily in the upper small intestine, and because it has a short elimination half-life (5 – 7 h), TID dosing of the IR product is required. This TID dosing may adversely affect patient adherence and may be the cause of the high incidence of dizziness and somnolence associated with the rapid rise in gabapentin plasma levels after each dose and/or higher plasma concentrations during the waking hours. The gastroretentive properties and gradual release of gabapentin from G-GR tablets as demonstrated in the PK studies resulted in significant benefit in the relief of PHN in a controlled clinical study (second Phase III) with once-daily administration of 1800 mg. This was demonstrated as a rapid and sustained reduction in ADP scores as well as a reduction in SIS. This reduction in ADP score (-2.4 LOCF) was similar in magnitude to what has been reported for IR formulations of gabapentin (-2.2 LOCF) administered three times per day (600 mg TID) in a study of similar design, which also had an enriched population (i.e., subjects were excluded if they failed to respond to gabapentin at doses > 1200 mg/day, had experienced dose-limiting adverse effects that prevented titration of gabapentin to an effective dose or were hypersensitive to gabapentin) [6]. G-GR was well tolerated with a low incidence of dizziness and somnolence, the AEs most commonly associated with gabapentin therapy.

7. Expert opinion

Gabapentin is absorbed primarily in the upper small intestine via an active uptake transporter that is saturable at clinically relevant dosages of gabapentin. IR formulations of gabapentin release the drug within about 30 min, leading to a concentration of gabapentin in the small intestine that saturates the transporter, especially at higher, therapeutic doses. Consequently, the IR formulation of gabapentin must be dosed more frequently at lower unit doses. By contrast, the gastroretentive technology takes advantage of the normal physiology of the stomach in the fed state to retain the G-GR tablet in the stomach for a much longer time (8 – 10 h) and allowing for gradually release of gabapentin over a prolonged time (10 h). This combination of a longer gastroretention and prolonged release of gabapentin results in a lower concentration of gabapentin in the small intestine, less saturation of the transporter and the ability to administer the recommended 1800 mg dose of gabapentin as a once-daily evening dose. The once-daily administration of the GR formulation with the evening meal has been demonstrated to be efficacious and well tolerated in a randomized placebo-controlled Phase III (second study) clinical study for the treatment of PHN.

Pain due to PHN has been reported to increase throughout the day and to peak in the evening [38]; therefore, taking the full dose of G-GR once daily with the evening meal results in higher gabapentin concentrations when pain may be the greatest. This is likely to ameliorate the evening pain and allow the patients to have a better night's sleep. Additionally, the gradual release of gabapentin over 10 h along with the evening dosing of G-GR may have contributed to the favorable tolerability profile observed with G-GR. Although no studies that directly compare G-GR and G-IR have been performed, the rates of dizziness and somnolence reported in a clinical study of similar design and patient population with G-IR (1800 mg/day, 600 mg TID) were considerably higher than what has been observed for G-GR (dizziness, 31% (number need to harm (NNH) = 5) vs.11% (NNH = 12); somnolence, 17% (NNH = 9) vs. 4% (NNH = 100)) [6]. A possible

explanation for the lower AE incidence observed with G-GR may have to do with administration in the evening resulting in peak levels of gabapentin occurring about ~ 8 h after dosing when the patient is likely to be asleep. By contrast, peak concentrations of gabapentin with G-IR therapy occur multiple times during the waking hours. Moreover, during the day when the patient may need to be active and pain scores are lower [38], the lower gabapentin plasma concentration with G-GR may be less likely to cause dizziness and/or somnolence.

The primary efficacy end point data for the G-GR Phase III studies is presented using both LOCF and BOCF imputation for missing data. In recent years, the US FDA has required that BOCF be used to determine a difference from placebo for the primary end point in PHN studies. However, previous published studies of G-IR and pregabalin of similar design in PHN reported the primary efficacy end point of reduction in ADP using LOCF imputation [6,34-36,39]. Thus, when comparing across studies, the absolute reductions in pain score observed for the active arms in the G-GR studies (-2.3 to -2.4) with QD dosing are similar to the G-IR (-2.1 to -2.3) and pregabalin (-1.2 to -2.7) studies. This is also true for the secondary end points such as responder rates, PGIC and CGIC. Additionally, most of these studies were of shorter length (7-8 weeks) than the G-GR studies which may have affected the placebo response. It has previously been reported that the placebo group responses in neuropathic pain studies increase as a function of trial length [40,41]. These two factors become apparent in the first Phase III study with G-GR as the LOCF change for baseline to end of study is positive. Additionally, both the BOCF and LOCF change from baseline to week 7 are also significant. These data indicate that once-daily G-GR is as efficacious as other drugs (G-IR and pregabalin) in well-controlled clinical studies that work by the same mechanism that involves the $\alpha 2\delta$ subunit of voltage-dependent calcium channels in neuronal tissue to reduce pain in PHN [6,34-36,39].

The clinical studies reported in this manuscript were of an enriched design such that patients were excluded if they failed to respond to gabapentin at doses > 1200 mg/day or pregabalin at doses > 300 mg/day, had experienced dose-limiting adverse effects that prevented titration of gabapentin to an effective dose, or were hypersensitive to gabapentin. The gabapentin IR study by Rice and Maton [6] employed a similar enriched design as well as the pregabalin studies [34-36]. However, in clinical practice patients who would not have been treated in the controlled clinical studies are likely to be treated with G-GR, especially those who have not previously tolerated IR gabapentin or failed to respond to it. To address this, a study is currently ongoing to assess the safety and effectiveness of once-daily G-GR in clinical practice. The only exclusion criteria are patients who are pregnant or nursing mother, are hypersensitive to gabapentin or have an estimated creatinine clearance of < 30 ml/min or are in hemodialysis.

In summary, the improved adherence with once-daily dosing, the favorable tolerability profile, the lack of drug–drug interactions and the fact that the recommended 1800 mg/day dose can be reached within 2 weeks make G-GR a valuable new addition for treating PHN.

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Declaration of interest

C Chen and VE Cowles are employees of Depomed, Inc. CE Argoff has served as a consultant and speaker for Endo Pharmaceuticals, Pfizer, PriCara (Janssen), Lilly, Forest Laboratories, King Pharmaceuticals®, Inc. Neurogesx and Depomed, Inc., and as a consultant for Vertex, Bristol-Myers Squibb, Gruenenthal, Covidien, Shinoghi Pharmaceuticals, Zogenix, Solvay Pharmaceuticals and Nuvo Research, and has received grant support from Endo Pharmaceuticals, Pfizer, Neurogesx, Lilly and Forest Laboratories. All studies were funded by Depomed, Inc.

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