

Efficacy and Safety of Carisbamate in Patients with Diabetic Neuropathy or Postherpetic Neuralgia: Results from 3 Randomized, Double-Blind Placebo-Controlled Trials

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■ **Abstract:** The results of 3 proof-of-concept studies to evaluate carisbamate's efficacy and safety in treating neuropathic pain are presented. In studies 1 (postherpetic neural-

gia, $n = 91$) and 2 (diabetic neuropathy, $n = 137$), patients received carisbamate 400 mg/day or placebo for 4 weeks and then crossed over to the other treatment for 4 weeks. In study 3 (diabetic neuropathy, higher carisbamate doses), patients ($n = 386$) were randomized (1:1:1) to receive either carisbamate 800 mg/day, 1200 mg/day, pregabalin 300 mg/day or placebo for 15 weeks. Primary efficacy end point was the mean of the last 7 average daily pain scores obtained on days the study drug was taken, for all 3 studies. Least square mean (95% CI) differences between carisbamate and placebo groups on the primary end point were as follows: study 1: -0.512 ($-1.32, 0.29$) carisbamate 400 mg/day; study 2: -0.307 ($-0.94, 0.33$) carisbamate 400 mg/day; and study 3: -0.51 ($-1.10, 0.08$), carisbamate 800 mg/day; -0.55 ($-1.13, 0.04$), carisbamate 1200 mg/day; and -0.43 ($-1.01, 0.15$), pregabalin 300 mg/day. Neither carisbamate (all 3 studies) nor pregabalin (study 3) significantly differed from placebo, although multiple secondary end points showed significant improvement in efficacy with carisbamate in studies 1 and 2. Dizziness was the only treatment-emergent adverse event occurring at $\geq 10\%$ difference in carisbamate groups versus placebo (study 1: 12% vs. 1%; study 3: 14% vs. 4%; study 2: 1% vs. 2%). Carisbamate, although well tolerated, did not demonstrate efficacy in neuropathic pain across these studies, nor did the active comparator pregabalin (study 3). ■

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INTRODUCTION

Neuropathic pain may arise as a consequence of a lesion or disease affecting the somatosensory system.¹ Although many types of injury can lead to neuropathic pain, diabetes mellitus and postherpetic neuralgia (PHN) are among the most important causes.² Postherpetic neuralgia, a chronic pain syndrome that occurs after the healing of rash in herpes zoster,³ is reported to occur in as many as 1 million people every year in the United States.^{4,5} Epidemiologic data suggest that 26% to 47% of patients with diabetes have diabetic peripheral neuropathy (DPN),^{6–8} and approximately one half of these individuals have pain.^{7,9} For many patients with these underlying disorders, pain relief is limited by modest efficacy or by significant adverse effects associated with currently available agents.¹⁰

Carisbamate (S-2-O-carbamoyl-1-o-chlorophenyl) is a novel neurotherapeutic agent with an unknown mechanism of action that demonstrated efficacy in preclinical epilepsy and pain models.^{11–14} In clinical studies, for the treatment of epilepsy,^{15–19} essential tremor,²⁰ and migraine,^{21,22} carisbamate was generally well tolerated. However, no efficacy is established for non-neuropathic pain indications tested. Because signaling pathways disrupted in neuropathic pain and epilepsy can overlap, carisbamate presents the potential to complement current neuropathic pain therapies.

We present the data from 3 exploratory studies conducted to assess carisbamate's efficacy, safety, and tolerability in the treatment of neuropathic pain. Studies 1 and 2 were randomized, double-blind, placebo-controlled, proof-of-concept studies that evaluated efficacy and tolerability of carisbamate treatment in patients with PHN (study 1) and DPN (study 2) in a crossover paradigm of 4-week treatment periods. Study 3 was a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and tolerability of higher doses of carisbamate in patients with DPN over 15 weeks. Data from these studies are presented together, because the overall results provide comparative information and summarize experience more effectively than individual reports of trials with different study designs and patient populations. The combined results may also provide greater insight into the challenges of developing a product for neuropathic pain treatment.

METHODS

Patients

In study 1, patients (aged 18 to 85 years), diagnosed with PHN on the basis of a history of varicella zoster rash (shingles) and persistent pain for at least 6 months after the healing of the rash, and who experienced neuropathic pain on a daily basis for 3 months before screening were enrolled. The populations of studies 2 and 3 included patients (aged 18 to 75 years) with diabetic mellitus (type 1 or type 2) and symptoms of DPN in the distal extremities confirmed by history and findings on neurologic examination for at least 1 year (study 2) or 6 months (study 3) before study entry and lower extremity pain due to DPN on a nearly daily basis for the previous 3 months; hemoglobin A1c (HbA1c) levels $\leq 10\%$ (study 2), $\leq 11\%$ (study 3); and stable diabetic medications for 3 months and willing to discontinue all pain medications except acetaminophen 1000 mg/day.

Registration: These studies are registered at ClinicalTrials.gov. NCT00492323 (study 1), NCT00501202 (study 2), NCT00870454 (study 3).

Across all 3 studies, to be eligible for random assignment into the double-blind treatment phase, patients needed to have documented daily average pain assessments for a total of at least 5 days during the baseline period and mean daily average pain scores of 5 (studies 1 and 2) or 4 (study 3) on a 11-point numerical pain rating scale ("0" = no pain to "10" = worst pain imaginable) during the baseline period.

The main exclusion criteria in all 3 studies included poor response to 3 or more medications (treated for ≥ 1 month) for neuropathic pain; use of tricyclic antidepressants or coumadin (warfarin); past neurolytic treatment; or use of herbal topical creams or ointments for pain relief within 48 hours, capsaicin within 6 months, or systemic corticosteroids within 3 months of the baseline period. Additional exclusion criteria included clinically important medical disorders and patients in need of continued treatment with an antiepileptic drug. For all studies, women of childbearing potential were to have been practicing an effective method of birth control and not to have been pregnant at the time of screening or during study participation.

The protocols for the studies were approved by the independent ethics committee or institutional review board at each study site, and the study was conducted in

accordance with the ethical principles that have their origin in the Declaration of Helsinki and in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the respective protocols. All patients or their legally acceptable representatives provided written informed consent before their participation.

Study Design

All 3 studies were randomized, double-blind, multicenter studies (study 1: 24 sites in the United States; study 2: 35 centers in the United States; study 3: 67 sites across 11 countries). Studies 1 and 2 were placebo-controlled, 8-week crossover studies (Figure 1). Each period was 4 weeks in duration separated by a blinded washout period (the duration of the washout period for an

individual was dependent upon the half-life of any prohibited medication taken and lasted up to 14 days). Study 3 was a placebo- and active-controlled, parallel-group study (Figure 1). In all 3 studies, study drug was administered orally in equally divided doses twice daily, with or without food. Patients reported their pain scores in the evening, using an interactive voice response system. Rescue medication (acetaminophen not more than 1000 mg/day) was allowed, but was not to be taken for at least 3 hours before reporting daily pain and sleep interference assessments.

Efficacy and Safety Assessments

Patients rated their average daily pain intensity on an 11-point (0 = no pain to 10 = worst pain) numerical rating scale (NRS). The primary efficacy variable was the mean of the last 7 average daily pain scores on days

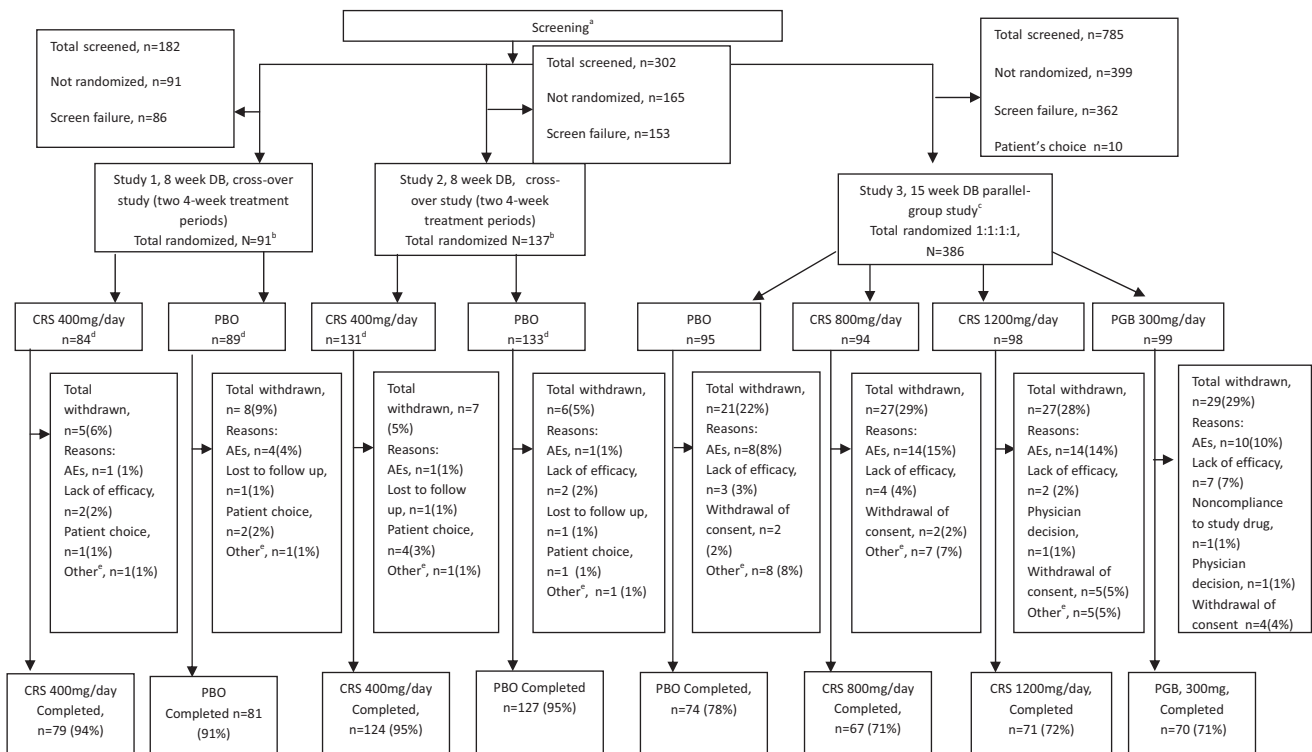


Figure 1. Patient accounting for all the 3 studies (ITT population) PBO–placebo; PGB–pregabalin; CRS–carisbamate; DB–double-blind; ITT–intent-to-treat; ^aDuration of screening period: study 1 and study 2, 9 days; study 3, 28 days; ^bIncludes 7- to 14-day washout period in between treatment periods. Four patients (study 1 [$n = 1$], study 2 [$n = 3$]) withdrew during washout period; In treatment period 1, patients were randomized to receive CRS 400 mg/day or PBO, and in treatment period 2, patients were crossed over to the other treatment. ^cThe double-blind treatment phase in study 3 included a 3-week titration period (patients were given the assigned treatment or titrated to the best-tolerated dose) followed by a 12-week maintenance period and a post-treatment phase (including a follow-up visit [within 7-14 days] and telephone contact [30 to 33 days] after the last dose of study drug). The study drug was down titrated in the post-treatment phase, and the patients were allowed to take adjunctive pain medications as clinically indicated. ^dIn each treatment group, the number of patients includes those randomized as well as those crossed over to the subsequent treatment. ^eOther reasons: study 1 – not willing to take the study drug and personal reasons; study 3 – due to personal reasons, inability to comply with study procedures, site misunderstood fatty liver to be exclusionary and withdrew patient for that reason.

the study drug was taken, in the first 4-week treatment period in studies 1 and 2 and over the 15 weeks in study 3. The key secondary end points for studies 1 and 2 included the mean of the last 7 average daily pain scores of the treatment period, current daily pain scores, maximum daily pain scores, and sleep interference scores. In study 3, the key secondary end points included the mean of the last 7 daily maximum DPN pain and sleep interference scores. Responder rates assessed in all 3 studies were defined as 30% and 50% reductions from baseline in the mean of the last 7 daily average pain scores of the treatment period. Safety assessments included recording the frequency, severity and duration of all treatment-emergent adverse events (TEAEs), and their relationship to the study medication, physical examinations, vital signs, and laboratory parameters.

Statistical Analysis

A 2-sample t-test was used for the calculation of the sample size to provide 80% power, with a 2-sided 5% type I error to detect a treatment difference of 1.5 points (study 1, approximately 42 patients) and 1.3 points (study 2, approximately 120 patients) on pain intensity scale between the carisbamate groups and placebo, based on data from treatment period 1. In study 3, the sample size calculation assumed a standard deviation of 2.4 and a 10% withdrawal rate and was estimated to provide approximately 80% power, with a 2-sided 5% type I error, to detect a 1-point treatment difference in the primary efficacy end point between any of the carisbamate dose groups and placebo, as well as at least 80% power to detect a 20% difference in responder rate between any of the carisbamate dose groups and placebo, assuming a 25% responder rate in the placebo group. The primary end point analysis in all the 3 studies and key secondary end points for study 3 were conducted using an analysis of covariance (ANCOVA) model with treatment and country as factors and baseline daily pain scores as the covariate. The key secondary end points in studies 1 and 2 were analyzed using a mixed effects model with center, period, sequence and treatment as fixed effects, baseline as covariate, and patient as a random effect, based on data from both treatment periods. The responder rates were calculated using the Cochran–Mantel–Haenszel statistics stratified by center for studies 1 and 2 (using the data from the first treatment period) and stratified by country in study 3. McNemar’s test was used for calculating the responder rates using data from both treatment periods

in studies 1 and 2. In study 3, a gate-keeping approach was used to adjust for multiple comparisons. The 1200 mg/day dosage group was compared with the placebo group as the first step. If this was statistically significant at $P = 0.0499$ level, the 800 mg/day dosage group was tested vs. the placebo group. The results of pregabalin 300 mg/day vs. placebo were also reported. In addition to the primary analysis, a mixed model repeated measures (MMRM) analysis was performed on the primary efficacy end point. The MMRM analysis included the fixed, categorical effects of treatment, country, study week, and treatment-by-study week interaction, as well as the continuous, fixed covariates of baseline score, baseline score-by-study week interaction. An unstructured covariance structure was used to model the within-patient errors. In all 3 studies, the efficacy analysis was conducted in the intention-to-treat (ITT) population (all randomized patients who had at least 1 baseline and postbaseline efficacy measurement) and the safety assessments in the safety population (all randomized patients who received at least 1 dose of the study drug). In study 3, the last observation carried forward approach was used in the efficacy analysis, and the baseline value was carried forward for the patients in the ITT population who did not have a postbaseline value. In addition, in studies 1 and 2, the completers’ population (all randomized patients who completed both treatment periods with at least 4 pain assessments recorded during the last 7 days of each) was used for analyzing data from both treatment periods.

RESULTS

Patient Disposition

In study 1, of the 91 randomly assigned patients, 83 (91%) completed the first 4 weeks, and 76 (84%) completed the entire 8 weeks. In study 2, of the 137 patients randomized, 130 (95%) completed the first 4 weeks, and 121 (88%) completed the entire 8 weeks (Figure 1). The retention rates of patients who completed both treatment periods were very high in both studies 1 and 2. In study 3, of the 386 randomized patients, 74 (78%) patients in the placebo group, 67 (71%) patients in the carisbamate 800 mg/day group, 71 (72%) in the carisbamate 1200 mg/day group, and 70 (71%) patients in the pregabalin treatment group completed the double-blind treatment phase. Across all 3 studies, the study completion and early withdrawal rates were similar for the treatment groups. Adverse

events were reported as the most common reason for early withdrawal; the incidence was slightly higher in the placebo group (4%) versus 400 mg/day carisbamate group (1%) in study 1, and in 800 mg/day carisbamate (15%) and 1200 mg/day carisbamate treatment groups (14%) vs. pregabalin (10%) and placebo (8%) in study 3 (Figure 1).

Demographics and baseline characteristics were consistent and well matched across treatment groups within each study and across all 3 studies except for a higher percentage of women in treatment sequence B (placebo→carisbamate) than A (carisbamate→placebo) in studies 1 and 2 and baseline diabetic treatment in study 3 (Table 1). In study 3, the number of patients using insulin were 7 (7.1%) in the 1,200 mg/day carisbamate group and 18 (18.2%) in the 300 mg/day pregabalin group, and those using both insulin and oral agents were 9 (9.6%) in the 800 mg/day carisbamate group and 19 (20.0%) in the placebo group. The population was predominately white ($n = 218$, 57%) or Asian ($n = 102$, 26%) in study 3 and predominantly white in study 1 (82%) and study 2 (74%).

Primary Efficacy

In each study, the mean of the last 7 average daily pain scores on days the study drug was taken was not significantly different in the active treatment groups from placebo (all $P > 0.05$; primary end point; Table 2; Figure 2). A high placebo response occurred in study 3,

and even pregabalin did not separate from placebo (Table 2). The results of the MMRM analysis were consistent with that observed for the primary efficacy analysis in this study. There was no clear clinical evidence of carryover effects observed in studies 1 and 2. In study 3, the dropout rates in the active treatment groups were approximately 2 to 3 times higher than the 10% anticipated rate. However, the placebo-subtracted last observation carried forward treatment effect among the dropouts was favorable (carisbamate 800 mg/day $[-0.2]$, carisbamate 1200 mg/day $[-1.4]$, pregabalin 300 mg/day $[-0.5]$) and did not negatively affect the primary analysis results.

Secondary Efficacy

Forest plots for key secondary end points from studies 1 and 2 showed results that, although favoring carisbamate 400 mg/day, were not significantly different from placebo (Figure 2). A significant difference between carisbamate and placebo was observed in study 2 in the combined treatment period analysis for both the mean of the last 7 average daily DPN pain scores for days on which study drug was taken ($P = 0.006$; Table 2, Figure 2) and the 30% responder rate ($P = 0.033$; Table 3, Figure 2). In study 3, carisbamate 800 mg/day treatment group had the highest percentage of patients with 30% and 50% response rates (Table 3). However, the placebo group also had high responder rates in this study (Table 3). In study 3, the 1200 mg/

Table 1. Demographics and Baseline Characteristics in All the 3 Studies

	Study 1		Study 2		Study 3				Total (All Patients) ($n = 386$)
	CRS↔PBO ($n = 47$)	PBO↔CRS ($n = 44$)	CRS↔PBO ($n = 67$)	PBO↔CRS ($n = 70$)	PBO ($n = 95$)	CRS 800 mg/ day ($n = 94$)	CRS 1200 mg/ day ($n = 98$)	PGB 300 mg/ day ($n = 99$)	
Sex, n (%)									
Men	21 (44.7)	13 (29.5)	45 (67.2)	36 (51.4)	57 (60.0)	53 (56.4)	56 (57.1)	59 (59.6)	225 (58.3)
Women	26 (55.3)	31 (70.5)	22 (32.8)	34 (48.6)	38 (40.0)	41 (43.6)	42 (42.9)	40 (40.4)	161 (41.7)
Race, n (%)									
White	40 (85.1)	35 (79.5)	50 (74.6)	51 (72.9)	56 (58.9)	51 (54.3)	57 (58.2)	54 (54.5)	218 (56.5)
Black or African American	3 (6.4)	7 (15.9)	14 (20.9)	16 (22.9)	7 (7.4)	10 (10.6)	9 (9.2)	12 (12.1)	38 (9.8)
Asian	2 (4.3)	2 (4.5)	0	1 (1.4)	27 (28.4)	24 (25.5)	24 (24.5)	27 (27.3)	102 (26.4)
Other or multiple or not reported	2 (4.3)	0 (0)	3 (4.5)	2 (2.85)	5 (5.3)	9 (9.6)	8 (8.2)	6 (6.1)	28 (7.3)
Age (years)									
18 to <65, n (%)	16 (34)	18 (41)	44 (65.7)	45 (64.3)	72 (75.8)	74 (78.7)	74 (75.5)	79 (79.8)	299 (77.5)
≥ 65, n (%)	31 (66)	26 (59)	23 (34.3)	25 (35.7)	23 (24.2)	20 (21.3)	24 (24.5)	20 (20.2)	87 (22.5)
Mean (SD)	65 (14.9)	66 (12.0)	58 (10.04)	59 (10.90)	58 (9.25)	57 (8.89)	59 (8.30)	57 (9.31)	58 (8.94)
Baseline BMI (kg/m^2)									
Mean (SD)	28.5 (5.0)	29.5 (5.9)	33.5 (7.13)	33.5 (6.36)	30.8 (6.84)	32.1 (9.35)	31.6 (7.62)	31.0	31.4 (8.06) [†]

CRS, carisbamate; PBO, placebo; PGB, pregabalin; BMI, body mass index.

* $n = 98$.

[†] $n = 385$.

Table 2. Changes in the Last 7 Average Daily Pain Scores on Days the Study Drug was Taken

	PHN Pain Scores in Study 1		DPN Pain Scores in Study 2		DPN Pain Scores in Study 3			
	PBO	CRS 400 mg/day First Treatment Period	PBO	CRS 400 mg/day	PBO	CRS 800 mg/day	CRS 1200 mg/day	PGB 300 mg/day
<i>n</i>	43	46	70	66	95	94	98	99
BS, mean (SD)	6.72 (1.21)	6.57 (1.11)	6.79 (1.38)	6.76 (1.27)	6.45 (1.30)	6.64 (1.59)	6.20 (1.47)	6.61 (1.67)
Last 7 daily pain scores								
Mean (SD)	5.60 (1.90)	5.02 (2.00)	5.78 (1.98)	5.46 (2.03)	4.69 (2.17)	4.27 (2.40)	3.98 (2.08)	4.34 (2.23)
<i>P</i> value treatment minus PBO		0.21		0.34		0.087	0.067	0.147
LSM difference		-0.51		-0.31		-0.51	-0.55	-0.43
95% CI		-1.32; 0.30		-0.94; 0.33		-1.10; 0.08	-1.13; 0.04	-1.01; 0.15
Completion of both treatment periods					NA	NA	NA	NA
<i>N</i>	75	75	102	102				
BS, mean (SD)	6.65 (1.18)	6.65 (1.18)	6.90 (1.32)	6.90 (1.32)				
Last 7 daily pain scores								
Mean (SD)	5.08 (2.19)	4.97 (2.06)	5.73 (2.22)	5.36 (2.24)				
<i>P</i> value minus PBO		0.3		0.006*				
LSM difference		-0.18		-0.38				
95% CI		-0.52; 0.16		-0.64; -0.11				

BS, baseline; CRS, carisbamate; PBO, placebo; LSM, least square means; PHN, postherpetic neuralgia; DPN, diabetes-related peripheral neuropathy.

**P* <0.05 significant.

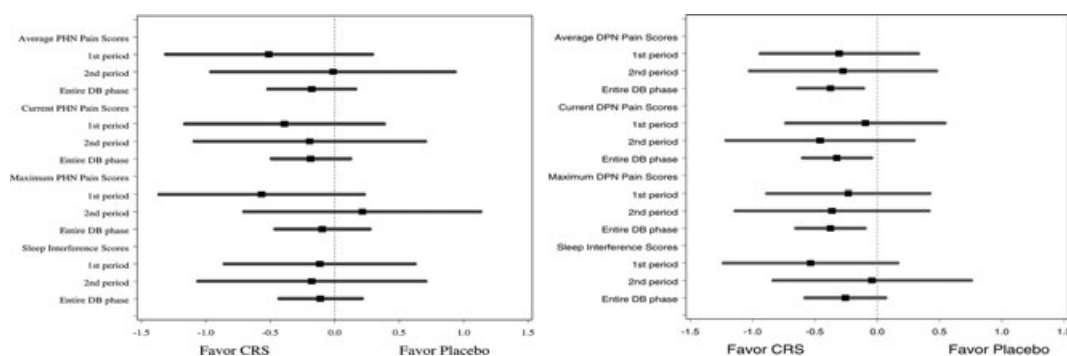


Figure 2. Forest plots of primary and key secondary efficacy variables in studies 1 (PHN) and 2 (DPN) CRS-carisbamate; PHN—postherpetic neuralgia; DPN—diabetes-related peripheral neuropathy; in the forest plots, the clinically evaluable analysis set was used (intent-to-treat population for treatment periods 1 and 2 and completer patient population for the entire double-blind phase). LSM (least square mean) and 95% confidence interval for the treatment difference were used to prepare these plots.

day carisbamate group significantly differed from placebo on the least square mean treatment difference of the last 7 daily DPN pain scores (-0.70 ; $P = 0.029$), but neither the 800 mg/day carisbamate (-0.43 ; $P = 0.181$) nor 300 mg/day pregabalin (-0.49 ; $P = 0.129$) did. Sleep interference pain scores were not significantly different between the active treatment groups versus placebo in any of the 3 studies. However, in studies 1 and 2, they slightly favored carisbamate versus placebo (Table 4).

Safety

The overall incidence of TEAEs was highest in study 3 and was comparable for placebo and carisbamate (Table 5). The most frequently reported TEAEs

included dizziness, headache, nausea, and nasopharyngitis with a higher incidence reported in the carisbamate treatment group versus placebo in study 1, and nausea, upper respiratory tract infection, and headache in study 2, with similar incidences reported in carisbamate and placebo treatment groups (Table 5). The most frequently reported TEAEs in study 3 included the following: dizziness in patients receiving carisbamate, which was also reported in a higher incidence in the pregabalin treatment group compared with placebo, somnolence in patients receiving pregabalin treatment, and constipation in patients receiving placebo treatment. In study 3, there was a higher incidence of peripheral edema and hyperglycemia TEAEs reported in the pregabalin treatment group than in carisbamate groups (Table 5). However, glycemic control as monitored by HbA1c

Table 3. Responder Rates (30% and 50%) in All 3 Studies

	Study 1		Study 2		Study 3			
	PBO	CRS 400 mg/day	PBO	CRS 400 mg/day	PBO	CRS 800 mg/day	CRS 1200 mg/day	PGB 300 mg/day
30% responder rates								
First treatment period (n)	43	46	70	66	95	94	98	99
Responders, n (%)	10 (23)	15 (33)	10 (14)	18 (27)	45 (47)	53 (56)	53 (54)	49 (50)
P value vs. PBO		0.275		0.078		0.220	0.357	0.809
Both treatment periods (n)	75	75	102	102	NA	NA	NA	NA
Responders, n (%)	24 (32)	28 (37)	22 (22)	32 (31)				
P value vs. PBO		0.371		0.033*				
50% responder rates								
First treatment period (n)	43	46	70	66	95	94	98	99
Responders, n (%)	4 (9)	9 (20)	5 (7)	8 (12)	26 (27)	32 (34)	32 (33)	32 (32)
P value vs. PBO		0.123		0.322		0.342	0.459	0.475
Both treatment periods (n)	75	75	102	102	NA	NA	NA	NA
Responders, n (%)	14 (19)	15 (20)	12 (12)	18 (18)				
P value vs PBO		0.782		0.134				

PBO, placebo; CRS, carisbamate; PGB, pregabalin; NA, not applicable.
*P <0.05 significant.

was stable over time for all treatment groups in study 3. The number of patients with at least 1 serious adverse events in study 3 was higher in the placebo group ($n = 8$, [8.6%]) compared with carisbamate (both 800 and 1200 mg/day, $n = 7$ [3.6%]) and pregabalin ($n = 3$, [3.1%]) active treatment groups. There were no deaths reported in studies 1 and 2. In study 3, 1 death due to carcinoma of the lung occurred in the placebo group after completion of the double-blind treatment phase and 91 days after administration of the last dose of the study drug. A higher incidence of clinically significant weight gain $\geq 7\%$ during the double-blind treatment phase occurred for pregabalin ($n = 7$, [7%]) compared

with either carisbamate 800 mg/day ($n = 3$ [3%]) or carisbamate 1,200 mg/day ($n = 2$ [2%]) treatment groups in study 3. One patient (1%) in the 800 mg/day carisbamate group and 2 (2%) patients in the 300 mg/day pregabalin group in study 3 reported disturbance in attention. In study 3, alanine aminotransferase (ALT) elevations ≥ 3 times upper limit normal (ULN) occurred in 2 patients in the carisbamate 800 mg/day group (one of these patients had a confounding factor related to the prohibited use of nonsteroidal anti-inflammatory drugs). Both TEAEs resolved without sequelae. There were no ALT elevations reported in studies 1 and 2.

Table 4. Changes in the Last 7 Daily Sleep Interference Pain Scores in All 3 Studies

	Study 1		Study 2		Study 3			
	PBO	CRS 400 mg/day	PBO	CRS 400 mg/day	PBO	CRS 800 mg/day	CRS 1200 mg/day	PGB 300 mg/day
	First Treatment Period				15-Week Double-Blind Treatment Phase			
n	43	46	69	66	93	94	97	97
BS, mean (SD)	4.63 (2.62)	4.75 (2.35)	5.36 (2.52)	5.44 (2.38)	5.26 (2.27)	5.19 (2.46)	4.80 (2.23)	5.19 (2.38)
Last 7 daily scores*								
Mean (SD)	3.49 (2.71)	3.53 (1.99)	4.15 (2.68)	3.70 (2.44)	3.36 (2.55)	3.08 (2.47)	2.78 (2.09)	2.86 (2.16)
P value vs. PBO		0.754		0.133		0.404	0.252	0.108
LSM difference		-0.12		-0.54		-0.24	-0.33	-0.46
95% CI		-0.86; 0.62		-1.24; 0.17		-0.81; 0.33	-0.89; 0.23	-1.02; 0.10
Completion of both treatment periods					NA	NA	NA	NA
n	75	75	102	102				
BS, mean (SD)	4.66 (2.52)	4.66 (2.52)	5.58 (2.44)	5.58 (2.44)				
Last 7 daily scores								
Mean (SD)	3.10 (2.48)	3.10 (2.26)	3.87 (2.60)	3.62 (2.51)				
P value vs. PBO		0.493		0.121				
LSM difference		-0.11		-0.26				
95% CI		-0.44; 0.21		-0.58; 0.07				

BS, baseline; PBO, placebo; CRS, carisbamate; NA, not applicable; PGB, pregabalin; LSM, least square means.
*Last observation carried forward approach was used for the calculation of the values in study 3.

Table 5. Treatment-Emergent Adverse Events in All 3 Studies

Body System or Organ Class	Study 1		Study 2		Study 3				
	PBO (N = 88) n (%)	CRS 400 mg/day (N = 82) n (%)	PBO (N = 133) n (%)	CRS 400 mg/day (N = 129) n (%)	PBO (N = 93) n (%)	CRS 800 mg/day (N = 94) n (%)	CRS 1200 mg/day (N = 98) n (%)	CRS Total (N = 192) n (%)	PGB 300 mg/day (N = 98) n (%)
TEAE	32 (36)	37 (45)	71 (53)	65 (50)	60 (65)	67 (71)	70 (71)	137 (71)	61 (62)
Drug-related TEAE	13 (15)	22 (27)	24 (18)	19 (15)	24 (26)	36 (38)	34 (35)	70 (37)	31 (32)
Serious TEAE	0	0	3 (2)	2 (2)	8 (9)	4 (4)	3 (3)	7 (4)	3 (3)
TEAE leading to discontinuation	5 (6)	1 (1)	2 (2)	1 (1)	8 (9)	14 (15)	14 (14)	28 (15)	10 (10)
TEAEs reported in at least 5% of the patients in any of the 3 studies									
Dizziness	1 (1)	10 (12)	2 (2)	1 (1)	4 (4)	13 (14)	13 (13)	26 (14)	9 (9)
Headache	6 (7)	10 (12)	8 (6)	7 (5)	7 (8)	12 (13)	9 (9)	21 (11)	4 (4)
Somnolence	1 (1)	3 (4)	1 (1)	1 (1)	1 (1)	6 (6)	10 (10)	16 (8)	10 (10)
Nausea	1 (1)	7 (9)	9 (7)	5 (4)	3 (3)	7 (7)	9 (9)	16 (8)	2 (2)
Diarrhea	0 (0)	2 (2)	3 (2)	2 (2)	1 (1)	6 (6)	6 (6)	12 (6)	2 (2)
Constipation	0 (0)	1 (1)	3 (2)	1 (1)	6 (6)	1 (1)	2 (2)	3 (2)	2 (2)
Urinary Tract Infection	2 (2)	1 (1)	5 (4)	8 (6)	7 (8)	4 (4)	4 (4)	8 (4)	5 (5)
Nasopharyngitis	3 (3)	5 (6)	2 (2)	2 (2)	2 (2)	1 (1)	6 (6)	7 (4)	2 (2)
Fatigue	0 (0)	2 (2)	3 (2)	2 (2)	2 (2)	4 (4)	6 (6)	10 (5)	3 (3)
Edema peripheral	0 (0)	2 (2)	4 (3)	1 (1)	2 (2)	1 (1)	0 (0)	1 (1)	7 (7)
Hyperglycemia	0 (0)	0 (0)	1 (1)	0 (0)	2 (2)	3 (3)	3 (3)	6 (3)	7 (7)

CRS, carisbamate; PBO, placebo; PGB, pregabalin; TEAEs, treatment-emergent adverse events.

DISCUSSION

Across studies, carisbamate treatment did not significantly differ from placebo on the primary efficacy end point, and sensitivity analyses were confirmatory. Some trends toward improved efficacy were seen, however, in both studies 1 and 2. This trend was especially notable for several key end points in study 2, which included older diabetic patients with DPN who had significant medical comorbidities. Significant differences were seen versus placebo in the combined treatment period of study 2 in the average daily pain scores on days the study drug was taken and the 30% responder rate. The crossover confirmation design was selected in studies 1 and 2 to improve the accuracy of the effect estimate and to reduce sample size. The first period was selected for primary end point analysis to ensure that there was no potential even for mild carryover effect that could confound the primary assessment. There was no clear evidence of carryover effects or significant second-period dropouts observed in either study.

Study 3 explored the benefits of higher doses (800 mg/day and 1200 mg/day) of carisbamate given for a longer duration (15 weeks) in the treatment of patients with DPN. Neither carisbamate dose nor pregabalin (300 mg/day; active control) differed significantly from placebo on the primary efficacy end point. The treatment effect was about half of the target assumed in the sample size determination. The only significant difference compared with placebo was observed with carisbamate 1200 mg/day in the last 7 average daily DPN pain scores.

Pregabalin was used as an active control in study 3 to determine the sensitivity of clinical end points in the study and establish safety and tolerability of carisbamate relative to an available marketed therapy. Implementation of an active control was necessary because of an assumed increase in the placebo response due to the parallel design, the multiple centers, and long duration (15 weeks) of the trial. Previous neuropathic pain trials showed parallel-group designs to be associated with a greater placebo response,²³ and it also appears the relative risk of failure increases with longer study durations.²⁴ An increase in number of study sites has been reported to increase placebo response in antipsychotic studies.^{25,26} A recent meta-analysis report suggests that a reduced placebo response and larger sample sizes are some of the factors that contribute to positive outcomes in neuropathic pain trials.²³ In study 3, the sample size calculation assumed 25% of patients on

placebo would have a 30% improvement in their numerical rating scale (30% responder rate). However, at the end of the study, it was observed that nearly double that number (47%) responded to placebo treatment, which thus effectively lowered the power of the trial.

The placebo response in study 3 was in fact higher than the rates seen for earlier shorter-term studies conducted for pregabalin,^{27,28} but similar to a 12-week placebo-controlled pregabalin study,²⁹ consistent with the expected higher placebo response in longer trials, and thus not unique to this study with carisbamate.

The mechanics of analgesic clinical trial designs are such that even high dropout rates can render trials uninterpretable.³⁰ In study 3, the dropout rates in the active treatment groups were approximately 2 to 3 times higher than our pretrial prediction of 10%. However, the placebo-subtracted LOCF treatment effect among the dropouts was favorable, and thus, the dropout rates did not negatively affect the primary analysis results. Carisbamate up to 1200 mg/day also failed to establish conclusive efficacy in epilepsy studies when used adjunctively in patients with partial onset seizures: although efficacy was demonstrated in a large dose-ranging phase 2 clinical trial,¹⁷ mixed results were obtained in 2 later-phase 3 trials.¹⁸ The neuropathic pain studies reported here were initiated before the results of the epilepsy trials were known, and study 3 was ongoing when the sponsor decided to halt development of the epilepsy program for carisbamate. Given the limitations discussed above and the failure of the active comparator to differentiate from placebo in study 3, the results of these 3 studies have to be interpreted cautiously. Despite the suggestion of a dose proportional improvement in pain seen across the 2 DPN studies, the overall effect size did not show a robust efficacy signal in DPN.

In general, carisbamate was well tolerated, with no new or unexpected safety concerns in these neuropathic pain populations, as compared with previous epilepsy trials.¹⁷⁻¹⁹ In the epilepsy studies, ALT elevations (≥ 3 ULN) were reported at higher carisbamate doses of 800, 1200, and 1600 mg/day.^{17,19} In the current studies, only 2 patients in the carisbamate 800 mg/day group in study 3 had ALT elevations ≥ 3 ULN, both of which resolved without any sequelae. Both carisbamate- and pregabalin-treated groups showed similar discontinuation rates, and pregabalin's tolerability was consistent with earlier studies.^{27,28,31,32} Adverse events particularly relevant in the diabetic population such as weight gain, somnolence, and peripheral edema occurred less frequently

with carisbamate than pregabalin. However, some gastrointestinal adverse events as well as dizziness were more frequently reported with carisbamate than with pregabalin.

CONCLUSIONS

Carisbamate was well tolerated in these studies. The small effect sizes may have contributed to the compromised results in these failed studies: neither the active control pregabalin nor carisbamate had an effect that was significantly different than that seen with placebo. Carisbamate was favored over placebo on some secondary end points.

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Study 1

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Study 3

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