SYNOPSIS

Issue Date: 1 APRIL 2011
Document No.: EDMS-ERI-22225251:1.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development
Name of Finished Product	Carisbamate
Name of Active Ingredient(s)	S-2-O-carbamaoyl-1-*O*-chlorophenyl-ethanol

Protocol No.: 333369NPP2003

Title of Study: A Randomized, Double-Blind, Placebo- and Active-Controlled Study of Carisbamate in the Treatment of Neuropathic Pain in Diabetic Peripheral Neuropathy Followed by a Blinded Extension Phase

EudraCT Number: 2008-008753-33

Coordinating Principal Investigator: Timothy Smith, MD

Publication (Reference): None

Study Period: 31 March 2009 to 19 July 2010

Phase of Development: 2b

Objectives: The primary objective of this study was to evaluate the efficacy, safety, and tolerability of 800 and 1,200 mg/day of carisbamate compared with placebo in reducing the average daily pain in subjects with chronic diabetic peripheral neuropathy (DPN). The secondary objectives of this study were to:

- Evaluate the impact of 800 and 1,200 mg/day of carisbamate compared with placebo on pain symptoms, functional health status (including physical and social functioning) and well being, rescue medication use, and sleep interference
- Evaluate global assessments of improvement and severity from the subject's perspective
- Characterize the population PK of carisbamate in subjects with DPN
- Evaluate long-term safety of carisbamate in subjects with DPN

The exploratory objectives of this study were to:

- Explore effects of 800 and 1,200 mg/day of carisbamate on the impact of pain severity and interference with activities of daily living, changes in sleep dimensions and daytime somnolence, and medical resource utilization (MRU) including work activity assessment
- Compare descriptively the safety and efficacy of 800 and 1,200 mg/day of carisbamate with pregabalin 300 mg/day

Methods: This was a randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter study with an optional blinded extension phase in subjects with a diagnosis of chronic neuropathic pain associated with DPN. The study consisted of a pretreatment phase (including a screening, washout, and baseline period), a double-blind treatment phase (with a titration and a fixed-dose period), and an optional blinded extension phase with carisbamate 400 to 1,200 mg/day or pregabalin 150 to 300 mg/day, as well as a posttreatment phase (including a follow-up visit and telephone contact). The duration of the study, excluding the pretreatment phase, was approximately 58 weeks for subjects who entered the extension phase and approximately 19 weeks for those subjects that did not enter the extension phase.

During the screening period (Visit 1) subjects were screened within 28 days prior to the planned first dose of the study drug to determine their eligibility to participate in the study. During the washout period (Visit 1A) of up to 7 days, subjects discontinued all prohibited medications. Prohibited medications with the potential to cause withdrawal symptoms were to be tapered and discontinue before the washout period.

If a prohibited medication was taken during the washout period, the washout period would restart beginning after the last dose of the prohibited medication. Beginning with the baseline period (Visit 2), which lasted at least 7 days, subjects documented the use of rescue medication (acetaminophen) taken each day in the Interactive Voice Response System (IVRS) and recorded daily pain and sleep interference assessments and also reported their responses to 5 additional questions about sleep during Days –7 through –1. Subjects who had documented daily DPN pain assessments (ie, evening ratings for pain over the past 24 hours) for at least 5 days in the baseline period, and had a mean Daily Average Pain score of at least 4 on an 11-point scale (0=no pain to 10=worse pain imaginable) during the baseline period could enter the double-blind treatment phase.

At Visit 3 (Day 1), during the double-blind treatment period, subjects were randomly assigned in a 1:1:1:1 ratio to carisbamate 800 mg/day, carisbamate 1,200 mg/day, pregabalin 300 mg/day, or placebo. Subjects were titrated to the assigned treatment, or to the best tolerated dosage over a period of 3 weeks per the dosing schedule. Rescue medication (acetaminophen no greater than 1,000 mg/day) was allowed throughout the study. From Day 22, subjects were to remain on their last dose of the titration period (ie, either the assigned dosage or the best tolerated dosage if the subject experienced tolerability issues at the assigned dosage). No further dosage adjustment was allowed. Immediately after intake of the evening dose of the study drug, subjects were to call the IVRS to report their pain and sleep interference assessments as well as use of rescue medication.

A pharmacogenomic blood sample was collected on Day 1 from subjects who consented separately to the pharmacogenomic component of the study (where local regulations permitted). Subject participation in pharmacogenomic research was optional.

At baseline and at the time points specified, subjects completed the following efficacy assessments:

- Neuropathic Pain Symptom Inventory (NPSI)
- Subject Global Impression of Change (SGIC; not completed at baseline)
- Subject Global Impression of Severity (SGIS)
- Short-Form Health Survey (SF-36)
- Brief Pain Inventory (BPI)
- Medical Outcomes Study (MOS) Sleep Scale (Acute version)

Venous blood samples (approximately 2 mL) were collected on Days 8, 22, 78, and 106 for measurement of trough and postdose plasma concentrations of carisbamate.

Those subjects who did not enter the blinded extension phase returned to the study center for a posttreatment visit (Visit 14) within 7 to 14 days after the final visit of the double-blind treatment phase for safety and efficacy evaluations (or within 7 days of the last dose of study drug for subjects who withdrew early from study). For the subjects who participated in the extension phase, the posttreatment visit following blinded extension was scheduled at Visit 14 (or within 7 to 14 days after the final visit of the extension phase). During the posttreatment phase, subjects were allowed to take pain medications as clinically indicated, while study treatment was down titrated.

All subjects who opted to enter the blinded extension phase of the study received treatment with carisbamate or pregabalin in a blinded fashion. Subjects previously treated with carisbamate or with placebo received treatment with carisbamate 400 to 1,200 mg/day, titrated to their individually best dosage, and those previously treated with pregabalin received treatment with pregabalin 150 to 300 mg/day, titrated to their individually best dosage. All carisbamate and pregabalin daily doses were given in a twice-daily regimen. Subjects continued to record daily pain assessments and the use of rescue medication throughout the blinded extension phase and daily sleep interference assessments up to Visit 13 for 7-day blocks prior to study visits in their IVRS.

Subjects who withdrew from the study during a scheduled visit had all evaluations performed for that visit except patient-report outcome questionnaires (NPSI, SGIC, SGIS, SF-36, BPI, MOS, and MRU) and

returned 7 to 14 days after the last dose of study drug for end-of-treatment/early withdrawal (Visit 14) procedures. Subjects who withdrew between scheduled visits returned to the site for a taper kit then had a final follow-up posttreatment visit (Visit 14) within 7 to 14 days after the last dose of study drug.

An external independent Data Safety Monitoring Board (DSMB) was established to monitor the safety data on a quarterly, ongoing basis, to ensure the continuing safety of the subjects enrolled in this study. The DSMB consisted of experts in the fields of pain, hepatology, cardiovascular disease, and statistics. The interim safety data was analyzed by an external independent statistical group. The DSMB met quarterly to review interim data. After the review, the DSMB made recommendations regarding whether any actions regarding the clinical study were needed to be taken to ensure the safety of the subjects. Additional information, including the responsibilities and procedures of the DSMB, is provided in the DSMB Charter.

An interim analysis was conducted to obtain efficacy and safety information necessary for decision-making to determine whether to initiate future studies or consider early termination of this study. The interim analysis cohort included at least the first 55 subjects in each treatment group who completed the 7 weeks of double-blind treatment. The interim analysis included all randomized subjects who received at least 1 dose of study drug and had safety assessments.

Number of Subjects (planned and analyzed):

Planned: A total of approximately 360 subjects were planned to be enrolled in the study.

Analyzed: A total of 386 subjects were randomly assigned in a 1:1:1:1 ratio to 1 of the 4 treatment groups: 94 subjects to 800 mg/day carisbamate, 98 subjects to 1,200 mg/day carisbamate, 99 subjects to 300 mg/d pregabalin, and 95 subjects to placebo. All 386 subjects were included in the intent-to-treat (ITT) analysis set; 383 subjects were included in the safety analysis set (all subjects who received at least 1 dose of study drug and had safety information available; 94, 98, 98, and 93 subjects, respectively, in the 4 treatment groups).

Diagnosis and Main Criteria for Inclusion: Men or women between 18 and 75 years of age, inclusive, with the presence of diabetes mellitus (type 1 or type 2) and the presence of symptoms of diabetes-related painful peripheral neuropathy in the distal extremities for at least 6 months prior to study entry and the pain symptoms attributable to DPN who experienced lower extremity pain due to diabetic neuropathy on a nearly daily basis for the previous 3 months were eligible for enrollment into the study. The subjects also had to have hemoglobin A1c (HbA_{1c}) levels $\leq$11%, a stable diabetic treatment regimen (including oral hypoglycemics, insulin, or diet) for 3 months before screening, and had to be willing to discontinue treatment for chronic pain with antiepileptic drugs (including gabapentin or pregabalin), opioids or opioid-containing analgesics, or selective norepinephrine reuptake inhibitors or tricyclic antidepressants for any indication.

Test Product, Dose and Mode of Administration, Batch No.: Study drug was administered orally in equally divided doses twice daily, with or without food. Study drug was supplied as carisbamate wet granulation tablets containing 200 or 400 mg of active drug, and matching placebo tablets.

Reference Therapy, Dose and Mode of Administration, Batch No.: Pregabalin was supplied as 75- and 150-mg overencapsulated capsules and matching placebo capsules.

Duration of Treatment: The duration of the study, excluding the pretreatment phase, was approximately 58 weeks for subjects who entered the extension phase, and approximately 19 weeks for those subjects that did not enter the extension phase.

Criteria for Evaluation: Efficacy was evaluated by daily pain assessments, NPSI, SF-36, sleep assessments, the MOS Sleep Scale, SGIS, SGIC, BPI, and MRU, including work/activity assessment. Venous blood samples (approximately 2 mL) were collected on Days 8, 22, 78, and 106 for measurement of trough and postdose plasma concentrations of carisbamate. A pharmacogenomic blood sample (10 mL) was collected to allow for pharmacogenomic research, as necessary (where local regulations permitted).

Safety was evaluated by the monitoring of frequency and severity of adverse events (AEs); clinical laboratory tests (hematology, serum chemistry, and urinalysis); 12-lead electrocardiograms (ECGs); vital sign measurements; and physical (including body weight and height) and neurologic examinations.

A DSMB was established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study.

Statistical Methods:

Sample Size Determination: Approximately 90 subjects were planned to be randomly assigned to each of the treatment groups. Based on the data from previous studies (333369NPP2002), the sample size calculation assumed a standard deviation (SD) of 2.4 and a 10% withdrawal rate. The planned sample size was estimated to provide approximately 80% power, with a 5% 2-sided type I error, to detect a 1-point treatment difference in the primary efficacy endpoint between any of the carisbamate dosage groups and placebo. The planned sample size also provided at least 80% power to detect a 20% difference in responder rate between any of the carisbamate dosage groups and placebo, assuming a 25% responder rate in the placebo group.

Efficacy Analysis: Three analysis sets were used for the efficacy analyses: the all randomized subjects analysis set, the ITT population, and the safety analysis set. The primary endpoint was analyzed using an analysis of covariance (ANCOVA) model, with treatment and country as factors and mean baseline daily pain scores as the covariate. The primary analysis was to compare each of the carisbamate dosage groups with placebo based on the treatment effect estimated from the ANCOVA model. Since the study was not planned to be stopped for efficacy superiority, no type I error inflation was introduced. Nevertheless, a 0.0001 of type I error will be allocated to the interim analysis. The final primary analysis was therefore analyzed at a 2-sided 0.0499 level.

In addition to the primary analysis, a mixed-model repeated measures (MMRM) analysis and other sensitivity analyses were performed on the primary efficacy endpoint. The primary endpoint was also summarized descriptively using the subgroups age, body mass index (BMI), and geographic region.

Key secondary endpoints that were analyzed included responder rate, response distribution curves, the mean of the last 7 Daily Maximum DPN Pain scores, and the mean of the last 7 Daily Sleep Interference scores. Other secondary endpoints included changes from baseline in NPSI, SF-36, and SGIS; SGIC; and the use of rescue medication. The exploratory efficacy endpoints that were analyzed included BPI, sleep assessments and MOS Sleep Scale, and MRU and work/activity assessments.

Pharmacokinetics: The concentrations of carisbamate in plasma samples collected during the study were listed by subject ID number, treatment group, and the time since the last dose. The population PK analysis based on the carisbamate plasma concentration-time data that was described in the protocol was not performed since additional studies with carisbamate for the treatment of DPN will not be conducted.

Safety Analysis: All subjects who were randomly assigned to the treatment and received at least 1 dose of the study drug were included in the safety analysis. Baseline for all clinical laboratory evaluations, vital sign measurements, and 12-lead ECGs was defined as the last evaluation done before study drug administration. Safety was evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, physical and neurologic examination results, vital sign measurements, and 12-lead ECGs from baseline through the posttreatment phase of the study. The incidence of AEs and changes in clinical laboratory parameters were summarized descriptively by treatment group.

RESULTS:

STUDY POPULATION: A total of 386 subjects were randomly assigned in a 1:1:1:1 ratio to 1 of the 4 treatment groups: 94 subjects to 800 mg/day carisbamate, 98 subjects to 1,200 mg/day carisbamate, 99 subjects to 300 mg/d pregabalin, and 95 subjects to placebo. Of the 386 randomized subjects, 282 (73%) completed the double-blind treatment phase. Withdrawal rates were similar among the active treatment groups. The main reason for withdrawal was withdrawal due to AEs, which had a higher rate for the active treatment groups compared with placebo.

Most subjects were male (58.3%) and white (56.5%); 26.4% of subjects were Asian and 9.8% of subjects were black. Subject age ranged from 27 to 75 years old, with a mean age of 57.6 years. A total of 22.5% of subjects were 65 years of age or older.

EFFICACY RESULTS: All efficacy analyses are based on the ITT analysis set.

Primary Efficacy Endpoint: The primary efficacy endpoint was the mean of the last 7 Daily Average DPN Pain scores of the double-blind treatment phase on days study drug was taken (last observation carried forward [LOCF] analysis). The baseline value was carried forward for ITT subjects who did not have a postbaseline value.

The estimated placebo-subtracted treatment effect was -0.55 for 1,200 mg/day carisbamate and -0.51 points for 800 mg/day carisbamate (Table 1). The estimated placebo-subtracted treatment effect was -0.43 points for 300 mg/day pregabalin. None of the comparisons with placebo were statistically significant.

Table 1: Average Daily DPN Pain Scores: Primary Efficacy Analysis
(Study CARIS-NPP-2003: Intent-To-Treat Analysis Set)

	PBO (N=95)	CRS 800 mg/day (N=94)	CRS 1200 mg/day (N=98)	PGB 300 mg/day (N=99)
Baseline				
N	95	94	98	99
Mean (SD)	6.45 (1.298)	6.64 (1.594)	6.20 (1.473)	6.61 (1.674)
Median (Range)	6.29 (4.2;9.6)	6.43 (4.0;10.0)	6.00 (3.9;10.0)	6.40 (3.7;10.0)
Mean of the last 7 daily pain scores (primary endpoint) [LOCF]				
N	95	94	98	99
Mean (SD)	4.69 (2.165)	4.27 (2.404)	3.98 (2.078)	4.34 (2.232)
Median (Range)	4.57 (0.7;9.9)	4.29 (0.0;10.0)	3.86 (0.0;10.0)	4.00 (0.0;10.0)
LS Mean(SE)	4.63 (0.234)	4.12 (0.235)	4.09 (0.229)	4.20 (0.227)
95% CI for LS Mean	(4.2;5.1)	(3.7;4.6)	(3.6;4.5)	(3.8;4.6)
Carisbamate vs. Placebo (Primary Comparison)				
P-value		0.087	0.067	
Diff. of LS Means (SE)		-0.51 (0.299)	-0.55 (0.296)	
95% CI		(-1.101;0.075)	(-1.128;0.038)	

Based on ANCOVA model with treatment and country as factors and mean baseline daily pain scores as the covariate.
P-values are adjusted for multiple comparisons using the step-down closed testing procedure.
The 95% confidence intervals are unadjusted for multiplicity.
PBO=Placebo, CRS=Carisbamate, PGB=Pregabalin.

Key Secondary Efficacy Analyses: The secondary endpoints in this study were as follows:

- Responder rates and response distribution curves, based on the primary efficacy endpoint
- Maximum Daily DPN Pain scores
- Daily Sleep Interference Pain scores

Except for responder rates, no multiplicity adjustments were made for any secondary endpoint analysis.

The 30% responder rates were 56%, 54%, 50%, and 47% for the 800 mg/day carisbamate, 1,200 mg/day carisbamate, 300 mg/day pregabalin, and placebo groups, respectively. The 50% responder rates were 34%, 33%, 32%, and 27%, respectively. No comparison with placebo was statistically significant.

The estimated placebo-subtracted treatment effect for the mean of the last 7 Maximum Daily DPN Pain scores was -0.43 for 800 mg/day carisbamate, -0.70 for 1,200 mg/day carisbamate, and -0.49 for 300 mg/day pregabalin. The comparison of 1,200 mg/day carisbamate with placebo was statistically significant (p=0.029).

The estimated placebo-subtracted treatment effect for the mean of the last 7 Daily Sleep Interference Pain scores was -0.24 for 800 mg/day carisbamate, -0.33 for 1,200 mg/day carisbamate, and -0.46 for 300 mg/day pregabalin. There were no statistically significant differences versus placebo.

Other Secondary Efficacy Analyses: The mean decrease in NPSI Total Intensity Score at the end of the double-blind treatment phase was -16.3 for 800 mg/day carisbamate, -15.0 for 1,200 mg/day carisbamate, -13.4 for 300 mg/day pregabalin, and -17.0 for placebo. There were no discernible differences in change from baseline between the 4 treatment groups.

For SF-36, the bodily pain scale showed the greatest mean change from baseline (5.3 to 6.8 across the 4 treatment groups), but there were no differences noted among the treatment groups. Although the mean change from baseline was smallest for placebo for 7 of the 10 scores, there was no discernible pattern among the active treatment groups, and the differences among treatment groups were small.

A total of 78.8% to 81.1% of subjects in each treatment group received rescue medication at some point during the double-blind treatment phase, with no difference among treatment groups.

There were no differences among the treatment groups in SGIS or SGIC.

SAFETY RESULTS:

Summary of All Adverse Events: A total of 62.2% to 71.4% of subjects in each treatment group experienced at least 1 TEAE (Table 2). Fewer subjects discontinued due to an AE in the placebo group (8.6%) than in the active treatment groups (10.2% to 14.9%), although more subjects had an SAE in the placebo group (8.6%) than in the active treatment groups (3.1% to 4.3%).

Table 2: Overall Summary of TEAEs - Double-Blind Phase
(Study CARIS-NPP-2003: Safety Analysis Set)

	------ PBO -----	CRS 800 mg/day	CRS 1200 mg/day	--- CRS Total --	PGB 300 mg/day
	(N=93)	(N=94)	(N=98)	(N=192)	(N=98)
Subjects with at Least One TEAE, n (%)	60 (64.5)	67 (71.3)	70 (71.4)	137 (71.4)	61 (62.2)
Subjects with at Least One Serious TEAE, n (%)	8 (8.6)	4 (4.3)	3 (3.1)	7 (3.6)	3 (3.1)
Subjects with at Least One TEAE Leading to Study Discontinuation, n (%)	8 (8.6)	14 (14.9)	14 (14.3)	28 (14.6)	10 (10.2)
Subjects with at Least One TEAE Related to Study Medication (a), n (%)	24 (25.8)	36 (38.3)	34 (34.7)	70 (36.5)	31 (31.6)
Subjects with at Least One Severe TEAE, n (%)	9 (9.7)	5 (5.3)	6 (6.1)	11 (5.7)	4 (4.1)

TEAE = treatment-emergent adverse event
(a) Study drug relationships of possible, probable, and very likely are included in this category
PBO=Placebo, CRS=Carisbamate, PGB=Pregabalin.

The most frequently occurring TEAE in subjects receiving carisbamate was dizziness (14% for 800 mg/day and 13% for 1,200 mg/day; Table 3). Nausea and diarrhea were also reported more frequently with carisbamate (7% and 6%, respectively, for 800 mg/day carisbamate; 9% and 6%, respectively, for 1,200 mg/day carisbamate). Somnolence was the most frequent adverse event for subjects receiving 300 mg/day pregabalin (10%). The only TEAE that occurred more frequently with the active treatments than with placebo (with a ≥10% between-group difference) was dizziness (14% and 13% for 800 mg/day and 1,200 mg/day, respectively, of carisbamate, 9% for 300 mg/day pregabalin, and 4% for placebo).

Table 3: Treatment-Emergent Adverse Events in at Least 5% of Subjects in Any Treatment Group by Body System and Preferred Term - Double Blind Phase
(Study CARIS-NPP-2003: Safety Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	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 (%)
Total no. subjects with adverse events	60 (65)	67 (71)	70 (71)	137 (71)	61 (62)
Nervous System Disorders	15 (16)	28 (30)	28 (29)	56 (29)	22 (22)
Dizziness	4 (4)	13 (14)	13 (13)	26 (14)	9 (9)
Headache	7 (8)	12 (13)	9 (9)	21 (11)	4 (4)
Somnolence	1 (1)	6 (6)	10 (10)	16 (8)	10 (10)
Gastrointestinal Disorders	15 (16)	22 (23)	22 (22)	44 (23)	16 (16)
Nausea	3 (3)	7 (7)	9 (9)	16 (8)	2 (2)
Diarrhoea	1 (1)	6 (6)	6 (6)	12 (6)	2 (2)
Constipation	6 (6)	1 (1)	2 (2)	3 (2)	2 (2)
Infections and Infestations	22 (24)	15 (16)	23 (23)	38 (20)	17 (17)
Urinary Tract Infection	7 (8)	4 (4)	4 (4)	8 (4)	5 (5)
Nasopharyngitis	2 (2)	1 (1)	6 (6)	7 (4)	2 (2)
General Disorders and Administration Site Conditions	7 (8)	14 (15)	13 (13)	27 (14)	14 (14)
Fatigue	2 (2)	4 (4)	6 (6)	10 (5)	3 (3)
Oedema Peripheral	2 (2)	1 (1)	0	1 (1)	7 (7)
Metabolism and Nutrition Disorders	7 (8)	9 (10)	8 (8)	17 (9)	11 (11)
Hyperglycaemia	2 (2)	3 (3)	3 (3)	6 (3)	7 (7)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Most TEAEs were mild or moderate in severity, with no differences seen among treatment groups. For most system organ classes, the majority of TEAEs in each treatment group were considered to be not related or doubtfully related to study drug. For nervous system disorders and gastrointestinal disorders, a higher number of subjects experienced TEAEs in each treatment group that were considered to be possibly, probably, or very likely related to study drug. For nervous system disorders, TEAEs that were considered to be possibly, probably, or very likely related to study drug were seen more frequently in the active treatment groups (18 subjects [19%] in the 800 mg/day carisbamate group, 20 subjects [20%] in the 1,200 mg/day carisbamate group, and 16 subjects [16%] in the 300 mg/day pregabalin group) than in the placebo group (11 subjects [12%]). For gastrointestinal disorders, TEAEs that were considered to be possibly, probably, or very likely related to study drug were seen more frequently in the carisbamate dosage groups (15 subjects [16%] in the 800 mg/day group and 13 subjects [13%] in the 1,200 mg/day group) than in the 300 mg/day pregabalin group (9 subjects [9%]) or the placebo group (10 subjects [11%]).

Deaths: One subject ([redacted] in the placebo group died after completion of the double-blind treatment phase, of carcinoma of the right lung; death occurred 91 days after the last dose of study drug.

Serious Adverse Events: The frequency of SAEs was comparable among the active treatment groups (3% to 4%), with a higher incidence (9%) for the placebo group. With the exception of pneumonia in 2 subjects in the 300 mg/day pregabalin group, no preferred term was associated with more than 1 SAE in any treatment group; no preferred term was associated with more than 2 SAEs in the study.

Adverse Events Leading to Discontinuation: The rates of discontinuation due to TEAEs were slightly higher in the carisbamate groups (15% and 14% for 800 mg/day and 1,200 mg/day, respectively) than for 300 mg/day pregabalin (10%) or placebo (9%). The most frequent TEAEs leading to discontinuation were dizziness, nausea, and somnolence, with a slightly higher incidence in the carisbamate groups (2%, 3%, and 2%, respectively, for 800 mg/day and 5%, 2%, and 3%, respectively, for 1,200 mg/day) than for 300 mg/day pregabalin (1%, 1%, and 1%, respectively) or placebo (1%, 0, and 0, respectively).

Other Relevant Adverse Events: One subject (1%) in the 800 mg/day carisbamate group and 2 subjects (2%) in the 300 mg/day pregabalin group reported cognition-related TEAEs (disturbance in attention). The subject in the 800 mg/day carisbamate group was withdrawn for this AE.

Incidence rates for somnolence were higher for the active treatment groups (6%, 10%, and 10% for 800 mg/day carisbamate, 1,200 mg/day carisbamate, and 300 mg/day pregabalin) than for placebo (1%). No somnolence event was serious. Somnolence TEAEs led to discontinuation for 5 subjects (3%) in the carisbamate groups (2% for 800 mg/day and 3% for 1,200 mg/day) and 1 subject (1%) in the 300 mg/day pregabalin group.

The highest incidence of peripheral edema occurred in the 300 mg/day pregabalin group (7%), compared with 1% for 800 mg/day carisbamate, 0 for 1,200 mg/day carisbamate, and 2% for placebo. No peripheral edema event was serious. Peripheral edema led to discontinuation for 2 subjects in the 300 mg/day pregabalin group, and 1 subject each in the 800 mg/day carisbamate and placebo groups.

Three subjects experienced a weight-related TEAE, including 1 subject each in the 800 mg/day carisbamate group (weight decreased), 300 mg/day pregabalin group (weight increased), and placebo group (weight increased). Seven subjects in the 300 mg/day pregabalin group experienced a weight gain ≥7% during the double-blind treatment phase, compared with 3 subjects in the 800 mg/day carisbamate group, 2 subjects in the 1,200 mg/day carisbamate group, and 1 placebo subject.

Clinical Laboratory Evaluation: With the exception of glucose, abnormally high or low clinical laboratory levels were seen in 3 or fewer subjects in any treatment group for any parameter. All of the mean changes from baseline in hematology, serum chemistry, and urinalysis values (including ALT and AST) were small and were similar across the 4 treatment groups.

Laboratory Values of Special Interest: There were 2 cases, both in the 800 mg/day carisbamate group, of ALT elevations at or above ≥3 times ULN that recovered without sequelae. In one case, there was a confounding factor relating to the use of disallowed medication (NSAID); in the second case, the subject normalized once study medication was discontinued.

Hemoglobin A1c values were stable over time in all treatment groups, with no TEMA values seen. Mean HbA_{1c} values from baseline to endpoint decreased slightly in all 4 treatment groups (-0.24, -0.10, -0.03, and -0.09 mmol/L for the 800 mg/day carisbamate, 1,200 mg/day carisbamate, 300 mg/day pregabalin, and placebo groups, respectively).

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSIONS: In this study, no statistically significant effect was observed either for carisbamate or for the active comparator pregabalin on the primary efficacy outcome; the study failed in assay sensitivity. Overall, the treatment difference from placebo was modest for carisbamate and for pregabalin and was about half of the target assumed in the sample size determination.

There was no clear dose response between 800 and 1,200 mg/day, and it is unlikely that higher dosages would result in an increased effect.

In general, carisbamate was well tolerated, with no new or unexpected safety concerns. A slightly higher incidence of some events, eg, dizziness and nausea, was seen in the carisbamate dosage groups than in the pregabalin or placebo groups, as well as a slightly higher rate of discontinuation due to TEAEs. On the other hand, there was less peripheral edema and weight gain in the carisbamate dosage groups. The frequency of SAEs was lower in the active treatment groups than in the placebo group, and the 1 death occurred in the placebo group. Two cases of ALT elevations, both in the 800 mg/day carisbamate group, recovered without sequelae.

Disclaimer

Disclaimer Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.