SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Carisbamate NAME OF ACTIVE INGREDIENT(S): S-2-O-carbamaoyl-1-O-chlorophenyl-ethanol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: RWJ-333369-EPY-2003

Title of Study: A Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy, Safety, and Tolerability of RWJ-333369 as Adjunctive Therapy in Subjects with Refractory Partial Seizures

Coordinating Investigator: Edward Faught, M.D. - University of Alabama, [redacted]; USA

Publication (Reference): None

Study Initiation/Completion Dates: 14 February 2005 - 24 May 2006	**Phase of development:** 2

Objectives: The primary objective was to evaluate the efficacy, safety, and tolerability of 4 daily doses of carisbamate (100, 300, 800, and 1,600 mg) as adjunctive treatment of refractory partial epilepsy in subjects who were between 18 and 70 years of age, inclusive. Additional objectives were to evaluate the population pharmacokinetics of carisbamate.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study with 4 phases: 1) a baseline phase, including an 8-week prospective baseline; 2) a double-blind treatment phase, including a 4-week dose titration period and a 12-week maintenance period; 3) a post-treatment phase for subjects who did not wish to enter the open-label extension phase; and 4) an open-label extension phase including a double-blind conversion period. The first 3 phases comprised study RWJ-333369 EPY-2003; the fourth phase constitutes study RWJ-333369-EPY-2006. This report presents results from the first 3 phases; results from the open-label extension phase (Study RWJ-333369 EPY-2006) will be reported separately.

Eligible subjects were randomly assigned to receive either placebo or 1 of 4 daily dosages of carisbamate (100, 300, 800, or 1,600 mg) equally distributed among treatment arms. During the 4-week titration period, subjects had their dosage increased weekly until the target dosage was attained. Following the 12-week maintenance period, subjects had the option of a 3-week taper and discontinuation of study drug, or a 3-week blinded transition to open-label treatment with carisbamate (Study RWJ-333369 EPY-2006). Efficacy and safety assessments were performed and samples for pharmacokinetic analysis were collected at regular intervals throughout the study. An Internal Safety Committee (ISC) met during the study to ensure the safety of the subjects and monitor any clinically relevant trends.

Number of Subjects (planned and analyzed): Approximately 500 subjects were planned and 537 subjects were entered into this study. Investigators at 101 centers in 12 countries participated.

Diagnosis and Main Criteria for Inclusion: Men and women between 18 and 70 years of age, inclusive. Subjects must have experienced at least 6 complex partial and/or secondarily generalized and/or simple partial motor seizures during an 8-week prospective baseline, without a seizure-free interval >4 weeks any time during those 8 weeks, despite appropriate doses of no more than 3 (preferably no more than 1 or 2) concomitant antiepileptic drugs (AEDs).

Test Product, Dose and Mode of Administration, Batch No.: The target doses of carisbamate were 100, 300, 800, and 1,600 mg per day, administered in 2 equally divided doses with or without food. Carisbamate was formulated in tablets of 50 mg (Batch No, PD1294; exp 5/06), 100 mg (PD1295; exp 5/06), 200 mg (PD1297; exp 6/06), and 400 mg (PD1299, PD1301, PD1303; exp 6/06), with identical-appearing placebo comparators for each tablet size (Batch Nos. PD1339, exp 12/09; PD1340, exp 12/09; PD1341, exp 12/09; PD1343, exp 12/09; respectively).

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Carisbamate NAME OF ACTIVE INGREDIENT(S): S-2-O-carbamoyl-1-O-chlorophenyl-ethanol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: Double-blind treatment included a 4-week dose titration period and a 12-week maintenance period. Subjects not entering Study RWJ-333369-EPY-2006 tapered and discontinued study drug over a 3-week period. Subjects entering Study RWJ-333369-EPY-2006 replaced double-blind study drug with open-label carisbamate over a 3-week period. After 12 months of open-label treatment, subjects were re-evaluated. Those who benefited from carisbamate treatment could continue treatment at the discretion of the investigator, until it was available by prescription, or until the program was terminated by the sponsor.

Criteria for Evaluation:

Pharmacokinetics:

Antiepileptic Drugs: Plasma concentrations of the concomitant AEDs (oxcarbazepine [OXC], phenytoin [PHT], phenobarbital [PB], topiramate [TPM], carbamazepine [CBZ], valproic acid [VPA], and lamotrigine [LTG]) were determined at baseline (Visits 1 and 3) and during steady-state concomitant treatment with RWJ-333369 (Visits 6, 7, and 8). Plasma concentrations of concomitant AEDs could be determined during the remainder of the double-blind treatment phase if the investigator believed that symptoms of toxicity might have been related to concomitant AEDs, rather than to the study drug.

Carisbamate: At Visits 6, 7, and 8, carisbamate concentrations in plasma were measured and summarized using descriptive statistical methods. Planned population pharmacokinetic analyses will be performed after pooling concentration-time data from the present study and previous Phase 1 and 2 studies. The results from these latter analyses will be presented in a separate report.

Efficacy: Efficacy was evaluated based on counts of seizures occurring during the pretreatment baseline and the double-blind titration and maintenance phases. The subject diaries were the source of all seizure count data. The primary efficacy variable was the percent reduction in seizure frequency (average monthly seizure rate) of complex partial and/or secondarily generalized and/or simple partial motor seizures during the double-blind treatment period, relative to the pretreatment baseline. Secondary efficacy variables for the double-blind treatment period were: 1) the percentage of subjects with ≥50% reduction from baseline in seizure frequency (average monthly seizure rate) of complex partial and/or secondarily generalized and/or simple partial motor seizures, 2) the percent reduction from baseline in secondarily generalized tonic-clonic (GTC) seizure frequency (average monthly seizure rate), and 3) the percentage of subjects who become seizure-free (all seizure types) during the last 8 weeks of the double-blind treatment period.

Safety: Safety was assessed by the frequency, severity, and timing of adverse events, as well as by clinical laboratory test values, 12-lead ECG recordings, vital sign measurement, and physical and neurologic examinations.

Pharmacogenomics: Pharmacogenomic results will be presented in a separate report.

Statistical Methods: The analysis of the primary efficacy variable (percent reduction in seizure frequency of complex partial and/or secondarily generalized and/or simple partial motor seizures during the double-blind treatment period, relative to the pretreatment baseline) compared each carisbamate dose group with placebo using the Wilcoxon test statistics stratified by pooled analysis center. For the primary efficacy analysis, pairwise comparisons were adjusted for multiplicity to control 2-sided type 1 error. For the secondary efficacy variables, each carisbamate dose group was compared to placebo at a 2-sided 0.05 level. For percent reduction, the pairwise treatment comparisons were analyzed using Wilcoxon test statistics stratified by pooled analysis center. For responder rate and seizure freedom, Mantel-Haenszel statistics stratified by pooled analysis center were performed. There was no multiple comparisons adjustment for secondary variables. An interim analysis was conducted to obtain efficacy and safety information for planning new carisbamate studies. This included demographic and baseline characteristics, efficacy, and safety data from the first 266 randomized subjects with data through Week 8 (n=264).

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Carisbamate NAME OF ACTIVE INGREDIENT (S): RWJ-333369	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

- The mean concentrations of carisbamate in plasma were highest within the first 4 hours after dosing and declined during the following 4 to 12 hours. As expected, the mean concentrations over the 12-hour dosing interval increased with an increase in the daily regimen of carisbamate. These pharmacokinetic results are consistent with those reported previously.

EFFICACY RESULTS:

- Carisbamate 300 mg/day, 800 mg/day, and 1,600 mg/day doses were effective in reducing seizure frequency in a highly refractory epilepsy population.
- Carisbamate dosages of 300 mg/day and 1,600 mg/day were associated with superior overall response rate ($p \leq 0.01$; $p=0.069$ for the 800 mg/day dose).
- The dosages chosen in this study were successful in characterizing a dose response curve, in which 100 mg/day was not statistically superior to placebo ($p=0.079$), while the broad range from 300 mg/day up to 1,600 mg/day showed similar reduction in seizures.
- The reduction in seizures adjusted for placebo was similar between subjects treated with versus without enzyme inducers in subjects receiving 300 mg/day and above.
- Doses of carisbamate of 300 mg/day, 800 mg/day, and 1,600 mg/day were effective in reducing the frequency of all quantifiable seizure types compared with placebo ($p<0.01$ for each of these doses).

SAFETY RESULTS:

- Overall, carisbamate was safe at all dosage levels tested and was well tolerated up to 800 mg/day.
- Discontinuations and dose reductions due to adverse events (AEs) were generally comparable to placebo for dosages of 100 mg/day and 300 mg/day, but increased for 800 mg/day (discontinuations only) and 1,600 mg/day (both).
- Rates of serious adverse events were greater for placebo than for carisbamate overall.
- There were no deaths.
- Clinically significant elevations of liver enzymes were observed in 4 subjects (1 at 800 mg/day and 3 at 1,600 mg/day). These elevations normalized after discontinuation of study drug.
- There were no other patterns of clinically significant abnormalities for laboratory evaluations. Although changes were observed in platelets and lipids, there were small and interpreted as not clinically significant.
- There was an effect of carisbamate on QTcF interval shortening, but the clinical significance of this finding is not clear given the greater incidence of cardiac AEs in the placebo treatment group compared to treatment.
- There were no significant effects on vital signs or body weight.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Carisbamate NAME OF ACTIVE INGREDIENT(S): RWJ-333369	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

CONCLUSION:

The results of this multicenter, randomized, double-blind, placebo controlled, parallel-group study demonstrate carisbamate was safe and effective in the treatment of partial onset seizures compared with placebo. Doses of 300 mg, 800 mg, and 1,600 mg daily were effective in reducing seizure frequency. There was no additional clinically significant gain in efficacy in 800 mg and 1,600 mg daily relative to the 300 mg daily dose. Given the results on discontinuation, adverse events, and safety parameters indicating a dose-dependent increase in these events, particularly at the highest dose of 1,600 mg/day, the dosage with the optimal benefit-risk is in the 300 mg/day range. The 100-mg dose has been established as a statistically and clinically ineffective dose.

Date of the report: 26 March 2007

SYNOPSIS

Issue Date: 18 January 2011

Document No.: EDMS-ERI-20678935:1.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	To be determined
Name of Active Ingredient(s)	carisbamate

Protocol No.: 333369-EPY-2006

Title of Study: A double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy, safety, and tolerability of RWJ-333369 as adjunctive therapy in subjects with refractory partial seizures.

EudraCT Number: 2004-002069-19

NCT No.: NCT00228969

Clinical Registry No.: N/A

Coordinating Investigator: William Rosenfeld, MD. The Comprehensive Epilepsy Care Center for Children and Adults, [redacted], USA.

Study Center(s): Argentina (5 sites), Belgium (4 sites), Brazil (4 sites), Bulgaria (3 sites), France (5 sites), Hungary (5 sites), Netherlands (2 sites), Poland (13 sites), Russia (13 sites), Spain (5 sites), UK (5 sites), USA (29 sites).

Publication (Reference): None

Study Period: 14 February 2005 - 17 June 2010.

Phase of Development: 3

Objectives: The objective of this study was to provide long-term efficacy, safety, and tolerability data of carisbamate as adjunctive therapy in subjects with medically refractory seizures.

Methodology: Protocol 333369EPY2003/2006 was divided into a double-blind period (EPY2003) and an open-label long-term extension period (EPY2006). Subjects who completed the double-blind treatment phase were eligible to be enrolled into the open-label extension study after a 3-week double-blind conversion period. During the open-label extension, the dosage of carisbamate could be increased to a maximum of 1200 mg/day under the final protocol, provided that (a) the subject continued to have uncontrolled seizures, (b) the subject had no adverse events that would preclude a dosage increase, and (c) the subject had a total bilirubin level within the normal range, and an alanine aminotransferase (ALT) level that did not exceed 1.5 times the upper limit of normal (ULN) before each increase. The target dose was 400 to 800 mg/day at the discretion of the investigator and according to the therapeutic response. During the open-label extension, subjects returned to the study center at 1, 3, 6, 9, and 12 months. After 12 months of participation in the open-label extension phase, subjects were reevaluated every 3 months and those benefiting from carisbamate therapy continued the study at the discretion of the investigator, until the drug was available by prescription or until the clinical program was terminated by the sponsor.

Number of Subjects (planned and analyzed): Approximately 500 men and women with refractory partial onset seizures who had met the inclusion and exclusion criteria were to be enrolled in this study. Four hundred-twenty subjects entered EPY2006 and were included in the safety population, and 419 subjects were included in the intent-to-treat (ITT) population.

Diagnosis and Main Criteria for Inclusion: Subjects were men or women, between 18 to 70 years, inclusive, weighing ≥40 kg. They must have been diagnosed with epilepsy for at least 1 year, with a history of partial onset seizures, and concomitant treatment with 1 to 3 antiepileptic drugs with doses stable over the past month. Women of childbearing potential must have had a negative pregnancy test, and have agreed to use adequate birth control. Subjects with a history of any nonepileptic seizures, major psychiatric disorder, or suicidal behavior over the past 2 years were to be excluded from study participation. Amendment INT-8 (dated 20 October 2009) updated the inclusion and exclusion criteria to ensure that subjects with a history (at any time in their life) of Stevens Johnson Syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, or various symptoms of drug-related rash, were not allowed to enter EPY2006, or if already enrolled, were withdrawn from the study. Since all subjects had entered the study prior to Amendment INT-8, none were withdrawn for this reason.

Test Product, Dose and Mode of Administration, Batch No.: Subjects receiving open-label treatment were switched from the direct compression tablet formulation to the same dosage of the wet granulation tablet formulation. RWJ-333369 direct compression formulation tablets were supplied in formulations containing 50 mg, 100 mg, 200 mg, or 400 mg of active drug. RWJ-333369 wet granulation tablets were supplied in formulations containing 50 mg, 100 mg, 200 mg, 400 mg, or 600 mg of active drug. The tablets for both formulations differed in size and appearance according to the amount of active drug.

333369-EPY-2006 Study Drug Information

CRS Tablet Strength	Lot Number	Expiry Date
50 mg	PD2924	31-Jul-10
100 mg	9AG8143-X	31-Jan-11
200 mg	8EG5672-X	31-May-10
	8HG6575-X	31-Aug-10
	9AG8139-X	31-Jan-11
400 mg	8HG6577-X	31-Aug-10
	9CG8827-X	31-Mar-11
600 mg	8EG5878-X	31-May-10

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: Open-label studies were to run until carisbamate was approved for adjunctive use in the treatment of POS, or until development for this indication had been terminated by the sponsor. Following the results of CARISEPY-3013, and J&JPRD's decision no longer to pursue this indication, EPY2006 was discontinued, as per protocol. In the present study, all subjects who discontinued as a result of this per protocol ending are considered "completers".

Criteria for Evaluation: Efficacy was evaluated based on seizures counts, which were recorded in subject diaries. Seizure frequency was calculated as the actual seizure count divided by the number of days in the period, multiplied by 28 (ie, normalized to 28 days). The percent reduction was calculated as 100*[B-D]/B, where B is the seizure frequency in the baseline period, D is seizure frequency during the study, and reductions in seizure frequency yield a positive value.

Safety was evaluated at 1, 3, 6, 9, 12 months, and then every 3 months by examining the incidence and severity of adverse events; evaluation of laboratory safety (hematology, serum chemistry, serum lipid profile and urinalysis); 12-lead ECGs, vital signs; physical and neurological examination.

Statistical Methods: The ITT analysis set was defined as subjects who provided seizure diary data for at least 1 visit in the open-label extension. Efficacy was evaluated for subjects in the ITT analysis set, based on counts of all POS, which included all simple partial motor, complex partial, and/or secondarily generalized seizures. Summary statistics were provided for percent reduction in seizure frequency (average monthly seizure rate) of POS and responder rate, defined as the proportion of subjects with ≥50% reduction from baseline in seizure frequency (average monthly seizure rate) of POS (planned

analyses), and for percent reduction from baseline to the last 6 months of the open-label phase in seizure frequency, and the seizure-free rate in the last 6 months of the open-label phase (post hoc analyses).

The safety analysis set was defined as subjects who received at least one dose of carisbamate in the open-label extension. Modal dose treatment group was defined by assigning a dose category (carisbamate <400 mg, 400 to <600 mg, 600 to 800 mg, >800 to 1000 mg, >1000 to 1200 mg, or >1,200 mg) to each daily dose during the open-label extension, and then assigning the most frequent dose category as the modal dose for the subject. Safety data were summarized, and descriptive statistics were calculated.

RESULTS:

STUDY POPULATION:

Summary of Subject Retention in the OL Phase (All Extension Subjects)
(Study 333369-EPY-2006: Open Label Extension Population Analysis Set)

Subject Completed Treatment/trial Reason for Withdrawal/termination	CRS <400 mg (N=29) n (%)	CRS 400-<600 mg (N=55) n (%)	CRS 600-800 mg (N=248) n (%)	CRS >800-1000 mg (N=20) n (%)	CRS >1000-1200 mg (N=31) n (%)	CRS >1200 mg (N=37) n (%)	Total (N=420) n (%)
Completed	5 (17)	21 (38)	93 (38)	2 (10)	0	1 (3)	122 (29)
Withdrawn	24 (83)	34 (62)	155 (63)	18 (90)	31 (100)	36 (97)	298 (71)
Subject choice(subject withdrew consent)	9 (31)	15 (27)	90 36)	8 (40)	13 (42)	9 (24)	144 (34)
Lost to follow-up	1 (3)	2 (4)	4 (2)	1 (5)	0	1 (3)	9 (2)
Adverse event	7 (24)	6 (11)	13 (5)	0	1 (3)	4 (11)	31 (7)
Pregnancy	0	0	2 (1)	0	0	0	2 (<1)
Death	0	2 (4)	0	1 (5)	0	1 (3)	4 (1)
Other	7 (24)	9 (16)	45 (18)	8 (40)	17 (55)	21 (57)	107 (25)
Unknown *	0	0	1 (<1)	0	0	0	1 (<1)

Note: Percentages calculated with the number of subjects in each group as denominator.
* Subject [redacted] stopped treatment on [redacted] however the reason for withdrawal was not provided.
CRS = Carisbamate.
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Of the 420 subjects who entered EPY2006, 50% were women, and most (97%) were white. The median age of subjects who entered EPY2006 was 37 years (range, 17 to 69 years) upon enrollment into the double-blind treatment phase (EPY2003). The median duration of epilepsy prior to double-blind treatment baseline was 21 years (range, 0 to 58 years). The most common seizure type at baseline was complex partial seizures (82%). The demographic and baseline characteristics of all subjects who entered the open-label extension phase were similar across the modal dose groups.

The majority of subjects (approximately 72%) were treated within the target dose range of 400 to 800 mg/day during EPY2006. Thirty-seven subjects received carisbamate at modal dosages greater than 1200 mg/day, despite the maximum dose in the final protocol of 1200 mg/day. Under the original protocol, the maximum dosage was 1600 mg/day. The majority (95%) of subjects who entered EPY2006 were treated with carisbamate for ≥3 months: 66% for ≥1 year; 47% for ≥2 years; 36% for ≥3 years; 21% for ≥4 years. Total subject exposure across all dose groups was 906.5 subject years, including 779.8 subject years for those subjects treated within the target dose range of 400 to 800 mg/day.

EFFICACY RESULTS: During the open-label extension phase, subjects experienced a median 44.6% decrease from baseline in POS frequency (average monthly [28-day] seizure rate), and 43.4% of subjects met the responder criteria. During the last 6 months of treatment in the open-label extension phase, median decrease from baseline in monthly POS frequency (44.4%) was similar to that observed throughout the study. Few subjects (5.2%) remained seizure free in the last 6 months of the open-label extension phase.

SAFETY RESULTS:

Overall Summary of TEAEs in the OL Phase (Safety)
(Study 333369-EPY-2006: Safety Analysis Set)

	CRS <400 mg (N=29) n (%)	CRS 400-<600 mg (N=55) n (%)	CRS 600-800 mg (N=248) n (%)	CRS >800-1000 mg (N=20) n (%)	CRS >1000-1200 mg (N=31) n (%)	CRS >1200 mg (N=37) n (%)	Total (N=420) n (%)
Total TEAEs	27 (93)	49 (89)	212 (85)	15 (75)	23 (74)	28 (76)	354 (84)
Related TEAEs[a]	20 (69)	25 (45)	110 (44)	10 (50)	9 (29)	13 (35)	187 (45)
Serious TEAEs	5 (17)	11 (20)	55 (22)	4 (20)	1 (3)	8 (22)	84 (20)
Related Serious TEAEs[a]	1 (3)	3 (5)	4 (2)	0	0	2 (5)	10 (2)
TEAEs leading to discontinuation	7 (24)	6 (11)	13 (5)	0	1 (3)	4 (11)	31 (7)
TEAEs leading to dose adjustment or temporary stop	9 (31)	14 (25)	52 (21)	6 (30)	4 (13)	5 (14)	90 (21)

[a] Study drug relationships of possible, probable, and very likely are included in this category
CRS = Carisbamate; TEAE = treatment-emergent adverse event
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The most frequently reported TEAE across all dose ranges were headache (34%), dizziness (18%), somnolence (12%), nasopharyngitis (12%), and nausea (11%). The incidence of subjects with TEAEs was comparable across all modal dose groups.

Seven deaths were reported during the open-label extension phase: 4 subjects were withdrawn from the study due to death, and 3 subjects died following completion of or previous withdrawal from the open-label extension phase. The adverse events that resulted in death were considered by the investigator to be not related or of doubtful relationship to study drug, with the exception of sudden unexplained death in epilepsy (Subject [redacted] which was considered to be possibly related to study drug.

Eighty-four (20%) subjects across all dose ranges reported treatment-emergent serious adverse events during EPY2006. The most frequently reported serious adverse events across all dose ranges were convulsion (4%) and epilepsy (2%). Thirty-one (7%) subjects across all dose ranges experienced TEAE that led to discontinuation from the open-label extension phase of the study. Ninety (21%) subjects experienced TEAE that led to dose adjustment or temporary interruption of the study drug.

Fifty-three (13%) subjects across all dose ranges reported cardiovascular TEAE during EPY2006, the most frequent of which were peripheral oedema (3%), palpitation (2%), and chest pain (2%). Five of the subjects who died had potentially cardiovascular-related adverse events. Across all modal dose ranges, 15 (4%) subjects experienced hepatic TEAE, 1 subject reported a suicidality-related TEAE, and 9 (2%) subjects experienced cognitive TEAE. No events related to abuse potential were reported.

Six subjects, 1 in each modal dose range of <400 mg/day, 400 to <600 mg/day, >1000 to 1200 mg/day, and >1200 mg/day, and 2 in the modal dose range of 600 to 800 mg/day, reported treatment-emergent ALT increase of >3 times ULN. One subject in the modal dose range of 600 to 800 mg/day and 1 subject in the modal dose range of <400 mg/day reported treatment-emergent AST increase of >3 times ULN. There were no patterns of clinically significant abnormalities for laboratory, vital signs, or ECG parameters.

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

CONCLUSION(S): The results of this study demonstrate that carisbamate maintained a reduced frequency of POS in subjects who continued into an open-label extension period. There was no evidence for changes proportional to modal doses in adverse events, serious adverse events, discontinuations due to adverse events, or clinical laboratory, vital sign, or ECG abnormalities in subjects who continued into an open-label extension period.

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