SYNOPSIS

Name of Sponsor/Company Johnson & Johnson Pharmaceutical Research & Development	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Name of Finished Product Carisbamate Name of Active Ingredient(s) (S)-2-O-carbamoyl-1-O-chlorophenyl-ethanol	Volume: Page:	
Protocol No.: RWJ-333369-MIG-2001		
Title of Study: A randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study of the efficacy of RWJ-333369 in the prophylaxis of migraine		
Principal Investigator: Roger K. Cady, M.D. - Primary Care Network, Inc, [redacted] USA		
Publication (Reference): None		
Study Period: 09 March 2002 to 07 February 2006		**Phase of Development:** 2
Objectives: Primary: to evaluate efficacy and safety of 3 doses carisbamate vs placebo in migraine prophylaxis and explore dose-response relationships. Secondary: explore effects of migraine on pain, vitality, psychological stress, and social, role, and cognitive function using Headache Impact Test-6™ (HIT-6); assess effect of study drug cessation on migraine frequency		
Methodology: Pre-treatment phase: 4-week baseline period in which migraine attacks counted for qualifying for double-blind phase. Double-blind phase: 2-week dose titration period followed by 12-week maintenance period. Post-treatment phase: 1–week dose taper followed by 3 weeks observation. Subjects randomly assigned to receive 100 mg, 300 mg, 600 mg/day carisbamate or placebo with doses increased to target during titration period. Migraine attacks counted in accordance with Committee on Proprietary Medicinal Products (CPMP) guidelines. HIT-6 administered at baseline and at study completion.		
Number of Subjects (planned and analyzed): Planned enrollment was approximately 300 subjects. Actual number randomized was 323 subjects, with 316 subjects receiving at least 1 dose of study drug and 226 subjects completing. Intent-to-Treat population (efficacy analysis) all subjects with a baseline and postbaseline efficacy value. Safety population: all subjects who received at least 1 dose of study drug		
Diagnosis and Main Criteria for Inclusion: To be included, subjects between 18 and 65 years of age were required to have a history of migraine conforming to the 2003 International Headache Society criteria, and a retrospective 3-month history of 3-12 migraines/month and ≤15 headache days/month. Subjects required a prospective 4-week washout of all migraine prophylaxis medications before entering the study.		
Test Product, Dose and Mode of Administration, Batch No.: Carisbamate 100 mg, 300 mg, 600 mg capsules administered orally once daily.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo encapsulated to be identical to carisbamate 100-mg capsules		
Duration of Treatment: Approximately 22 weeks (4-week baseline, 14-week double-blind, 4 week post-treatment evaluation)		
Criteria for Evaluation: Pharmacokinetics: Plasma concentrations of carisbamate were measured in samples obtained on Day 14/Visit 3; Day 42/Visit 4; Day 70/Visit 5; Day 98/Visit 6. Efficacy: Primary variable: Percent reduction in average monthly migraine frequency (using 48-hour rule) from baseline to end of double-blind phase. Secondary endpoints: (1)Percent responders (≥50% reduction from baseline); (2)percent reduction from baseline in average monthly migraine days; (3)percent reduction in average monthly migraine days with use of rescue medication; (4)percent reduction in average monthly migraine frequency using the 24-hour rule; (5)time of onset of treatment effect for the primary efficacy variable; (6)percent change from baseline to post-treatment 28-day interval in average monthly migraine frequency; (7)change from baseline in total HIT-6 score Safety: Adverse events, laboratory test values (hematology, chemistry, urinalysis), lipid profile values, fasting blood glucose values, ECG readings, vital signs, physical examination findings, neurological examination findings Pharmacogenomics: Subjects could voluntarily consent to have blood obtained for pharmacogenomic analysis		

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Statistical Methods: Study powered to detect difference of 28% in percent reduction fro baseline in average monthly migraine frequency between carisbamate and placebo. Sample size calculation based on 2-sample rank test and Bonferroni multiple-adjustment procedure. Descriptive statistics used for calculation of plasma concentration of carisbamate with no formal statistical comparisons between doses. Each dose group was compared with placebo for the primary efficacy variable using the Wilcoxon rank-sum statistical test stratified by center. The Hochberg multiple comparison procedure was used to ensure a Type 1 error of no more than 5%. Response rate was analyzed by Mantel-Haenszel statistics stratified by center. The change from baseline in HIT-6 scores was summarized by treatment group. Adverse events (AEs) were coded by the Medical Dictionary for Regulatory Activities (MedDRA). For each treatment group, the percent of subjects in each category were summarized with special attention paid to subjects with severe or serious AEs or discontinuations due to AEs. Laboratory test , vital signs, physical examination, and neurological examination data were summarized by descriptive statistics. Cardiovascular safety evaluated by descriptive statistics and frequency tabulations. Tables included shifts from baseline. Variables evaluated included heart rate, PR interval, QRS interval, QT interval, QTcB, QTcF, pulse, blood pressure. QTc values tabulated for absolute values and relation to baseline to detect individual QTc changes.

SUMMARY – CONCLUSIONS: PHARMACOKINETICS: Data were consistent with that from previous studies. The mean concentration of carisbamate was highest within the first 4 hours after dose administration and declined over the next 4 to 12 hours

Carisbamate Concentrations In Plasma
(Study 33369-MIG-2001: Pharmacokinetics Analysis Set)

Daily Dose	Interval (h)	N	Mean	SD	Min	Max
100 mg	0-1.99	38	1.51	0.68	Blq	2.67
	2-3.99	46	1.43	0.67	Blq	2.85
	4-5.99	11	1.07	0.59	Blq	1.89
	6-7.99	5	1.24	0.58	0.75	2.20
	8-9.99	11	1.25	0.35	0.62	1.76
	10-12	20	0.82	0.46	Blq	1.75
300 mg	0-1.99	38	5.60	2.42	Blq	12.5
	2-3.99	50	5.39	2.61	Blq	12.0
	4-5.99	20	4.13	3.09	Blq	9.97
	6-7.99	10	4.59	2.08	2.51	8.88
	8-9.99	15	2.81	1.96	Blq	5.96
	10-12	18	3.00	1.35	Blq	4.96
600 mg	0-1.99	27	8.90	2.46	2.92	13.1
	2-3.99	38	7.24	3.67	Blq	14.7
	4-5.99	5	5.87	3.96	Blq	9.79
	6-7.99	5	5.89	0.95	4.74	7.30
	8-9.99	17	5.97	3.13	Blq	12.9
	10-12	27	4.47	2.08	Blq	7.45

Blq: Below limit of quantitation
N=the number of concentrations per interval.

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SUMMARY - CONCLUSIONS

PHARMACOKINETICS: Data were consistent with that from previous studies. The mean concentration of carisbamate was highest within the first 4 hours after dose administration and declined over the next 4 to 12 hours

EFFICACY RESULTS: There were no statistically significant differences between any carisbamate (at any dose) and placebo for any of the primary or secondary variables. Percent reduction from baseline in average monthly migraine frequency (primary endpoint) was 37% (placebo), 33% (carisbamate 100 mg), 27% (carisbamate 300 mg), and 35% (carisbamate 600 mg) ($p \geq 0.567$). There was no evidence of efficacy for migraine prophylaxis for any of the treatment groups.

SAFETY RESULTS: The number of subjects experiencing adverse events and serious adverse events was similar in the placebo- and carisbamate-treated subjects. The most frequently reported event for carisbamate-treated subjects was fatigue that appeared to be dose-related.

At least 1 serious adverse event was reported in each group: for 1% (1/78) of the placebo group and for 3% (6/238) of the combined carisbamate groups (4% [3/81] 100 mg/day, 3% [2/80] 300 mg/day, and 1% [1/77] 600 mg/day).

The only treatment emergent serious adverse event that occurred in more than 1 subject overall or in any treatment group was appendicitis (2 subjects in the 300 mg/day group).

Subjects With Adverse Events/Reactions (Double-Blind Phase)
(Study 33369-MIG-2001: Safety Analysis Set)

	Placebo (N= 78) n (%)	Carisbamate (N=238) n (%)
One or more adverse events/reactions	58 (74)	183 (77)
One or more serious adverse events/reactions	1 (1)	6 (3)
Deaths	0	0
Discontinued due to adverse events/reactions	10 (13)	31 (13)

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Incidence Of Treatment-Emergent Adverse Events (TEAEs) In ≥5% Of Subjects In Any Treatment Group By Preferred Term Sorted By Incidence
(Study 33369-MIG-2001: Safety Analysis Set)

Preferred Term	Placebo (N=78) n (%)	R369[a] 100 mg (N=81) n (%)	R369[a] 300 mg (N=80) n (%)	R369[a] 600 mg (N=77) n (%)	Total R369[a] (N=238) n (%)
Subjects with TEAEs	58 (74)	58 (72)	64 (80)	61 (79)	183 (77)
Fatigue	5 (6)	10 (12)	14 (18)	17 (22)	41 (17)
Nasopharyngitis	9 (12)	10 (12)	9 (11)	11 (14)	30 (13)
Nausea	6 (8)	7 (9)	5 (6)	9 (12)	21 (9)
Back Pain	1 (1)	6 (7)	4 (5)	2 (3)	12 (5)
Diarrhoea	2 (3)	6 (7)	2 (3)	3 (4)	11 (5)
Dizziness	3 (4)	3 (4)	2 (3)	6 (8)	11 (5)
Somnolence	4 (5)	3 (4)	3 (4)	2 (3)	8 (3)
Abdominal Pain Upper	2 (3)	1 (1)	2 (3)	4 (5)	7 (3)
Vomiting	2 (3)	1 (1)	2 (3)	4 (5)	7 (3)
Hepatic Enzyme Increased	0	1 (1)	1 (1)	4 (5)	6 (3)
Migraine	5 (6)	2 (2)	2 (3)	2 (3)	6 (3)
Insomnia	4 (5)	2 (2)	1 (1)	1 (1)	4 (2)

[a] R369 = RWJ-333369 (carisbamate)
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

CONCLUSION: Carisbamate was safe and well tolerated in all treatment groups. Only 1 adverse event, fatigue, was dose-related and appeared more frequently than in the placebo group. Discontinuation due to adverse events was low and similar to placebo. With respect to the primary efficacy measure, percent reduction in monthly migraine frequency for carisbamate versus placebo, there was no evidence of efficacy, nor was there a trend indicative of efficacy for any active treatment arm. The findings for secondary efficacy were consistent with those for primary efficacy.

Issue Date of the Clinical Study Report: 18 May 2007

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