SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: REMINYL® NAME OF ACTIVE INGREDIENT(S): Galantamine HBr (R113675)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: CR006037

Title of Study: Placebo-Controlled Evaluation of Galantamine in the Treatment of Alzheimer's Disease: Safety and Efficacy of a Controlled-Release Formulation

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Publication (Reference): None

Study Initiation/Completion Dates: 08 February 2001 - 15 July 2002. **Phase of development:** 3b

Objectives: The primary objective of this study was to evaluate the safety and efficacy (as measured by Alzheimer's Disease Assessment Scale: sum of 11 cognitive items [ADAS-cog/11] and Clinician's Interview Based Impression of Change – Plus Caregiver Input [CIBIC-plus]) of a flexible dosing regimen (16 or 24 mg/day) of galantamine controlled-release (CR) compared with placebo in subjects with mild to moderate Alzheimer's disease. Secondary objectives were to evaluate the effects of galantamine CR and immediate-release (IR) treatment on those subjects with regard to the activities of daily living and behavior, using the Alzheimer's Disease Cooperative Study -Activities of Daily Living (ADCS-ADL) and the Neuropsychiatric Inventory (NPI) scores, as well as ADAS-cog/13, ADAS-cog/10, and ADAS-cog/mem scores, and to estimate the difference in effect between the galantamine-CR and -IR treatment groups. Safety of galantamine CR 16 or 24 mg/day, compared with that of placebo and galantamine IR 8 or 12 mg twice daily (b.i.d.), was assessed using adverse event reports, physical examinations, vital signs, electrocardiograms (ECGs), and laboratory evaluations.

Methodology: This double-blind, parallel-group, placebo-controlled, flexible-dose study was conducted in the U.S., Australia, Canada, South Africa, and New Zealand. Following a 4-week, single-blind, placebo run-in period, subjects were randomized to receive placebo, galantamine IR, or galantamine CR in double-blind fashion for 26 weeks. Subjects in the galantamine treatment groups received 4 weeks of galantamine CR 8 mg q.d. or IR 4 mg b.i.d., followed by 4 weeks of galantamine CR 16 mg q.d. or IR 8 mg b.i.d. Based on safety and tolerability, the galantamine dose could be increased to CR 24 mg q.d. or IR 12 mg b.i.d. at Week 8, and could be reduced to CR 16 mg q.d. or IR 8 mg b.i.d. at Week 12. The dose chosen at the end of Week 12 was fixed for the remainder of the study.

Number of Subjects (planned and analyzed): 885 subjects planned enrollment with 965 subjects randomized, treated, and analyzed for safety. 925 subjects were analyzed for efficacy (Intent-to-Treat [ITT] Analysis Set).

Diagnosis and Main Criteria for Inclusion: Male or female outpatients, including subjects living in residential homes for the elderly and day patients, with mild to moderate Alzheimer's disease based on National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria who had an onset between ages 40 and 90 years and an MMSE score of 10 to 24 and an ADAS-cog/11 score of ≥18.

Test Product, Dose and Mode of Administration, Batch No.: Galantamine CR 8-, 16-, and 24-mg pellet-filled capsules were administered orally once daily; Batch Nos 00I11/F055 (exp 9/02), 00I12/F056 (exp 9/02), and 00I13/F057 (exp 9/02), respectively.

Reference Therapy, Dose and Mode of Administration, Batch No.: Galantamine IR 4-, 8-, and 12-mg encapsulated tablets were administered orally twice daily; Batch Nos 00I29/F059 (exp 9/02), 00I30/F060 (exp 9/02), and 00I30/F061 (exp 9/02), respectively. Placebo capsules were administered orally twice daily; Batch Nos 00G25/F058 (exp 7/02), and 01A15/F058 (exp 1/03). All preparations were identical in appearance, taste and smell.

Duration of Treatment: Following a 4-week placebo run-in period, study drug was administered for 26 weeks.

Criteria for Evaluation:

Efficacy: Efficacy was evaluated by the ADAS-cog/11, CIBIC-plus, ADCS-ADL, and NPI measurements at

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Efficacy (continued): baseline and at Weeks 8, 12, and 26. The primary efficacy analysis was to compare galantamine CR with placebo with respect to change in ADAS-cog/11 scores from baseline to Week 26 and CIBIC-plus scores at Week 26. The secondary efficacy analysis was to compare galantamine CR with placebo with respect to change in ADCS/ADL, NPI, ADAS-cog/13, ADAS-cog/10, and ADAS-cog/mem scores from baseline to Week 26. Comparisons for efficacy measurements between galantamine IR and placebo and between galantamine CR and IR were also to be considered secondary. To investigate the general reproducibility of the results for the efficacy endpoints in this study compared to those in the GAL-USA-10 study, the following exploratory analyses were performed: the CIBIC-plus data by screening MMSE scores ranging from 10 to 22 for all centers and for U.S. centers only (with pooling for small centers). In addition, composite responder analyses were performed based on a combination of defined changes in ADAS-cog/11, CIBIC-plus and ADCS-ADL at Week 26.

Safety: Safety was based on the incidence of treatment-emergent adverse events and on changes from baseline in physical examinations, vital sign and ECG measurements, and laboratory evaluations.

Statistical Methods: The changes in the ADAS-cog/11 score were analyzed using analysis of variance (ANOVA) models with treatment and country (U.S. vs. non-U.S.) factors. The linear contrasts on the LS Means of the treatment effects were used to perform the between-group comparisons. The Cochran-Mantel-Haenszel (CMH) test using modified ridit scores, derived from rank scores (the Van Elteren test) controlling for country (U.S. vs. non-U.S.) effect, was applied to compare the distributions between each pair of the treatments for the CIBIC-plus score. Similar ANOVA techniques were applied to secondary ADAS-cog/13, ADAS-cog/10, ADAS-cog/mem, ADCS-ADL, and NPI analyses. The percentages of responders for ADAS-cog/11 and CIBIC-plus were analyzed using the CMH test. The primary efficacy analysis was based on the observed case (OC) data for the ITT analysis set. Last observation carried forward (LOCF) analysis for the ITT analysis set and classical ITT (CITT) analysis for the all randomized subject analysis set were also performed. Adverse events were coded using a WHOART dictionary maintained by the sponsor. Changes from baseline in vital signs and ECG measurements were evaluated using descriptive statistics and paired t-test (within groups).

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: Treatment with galantamine CR and IR led to statistically significant improvements in the primary efficacy endpoint (ADAS-cog/11) compared with placebo at Week 26. Both galantamine CR and IR treatments were numerically better but not statistically different from that of the placebo group in maintaining global function assessed by CIBIC-plus scores at Week 26. The trend of CIBIC-plus responders was in favor of both galantamine treatment groups (about 61%) over placebo (about 57%). Results from the LOCF and CITT analyses supported these results.

Primary Efficacy Pararmeters (Observed Case Data) at Week 26
(Study GCR00603: ITT Subjects Analysis Set, Excluding Data From 1 U.S. Site)

Change in Baseline in ADAS-cog/11 Score at Week 26			CIBIC-plus scores at Week 26, n (%)			
				Placebo	GAL-IR	GAL-CR
PLACEBO	GAL-IR	GAL-CR		(N=259)	(N=240)	(N=246)
Mean ± SE	Mean ± SE	Mean ± SE	Markedly improved	3 (1)	3 (1)	3 (1)
(N=248)	(N=227)	(N=240)	Moderately improved	9 (3)	14 (6)	14 (6)
1.3 ± 0.36	-1.8 ± 0.42	-1.4 ± 0.34	Mildly improved	41 (16)	36 (15)	43 (17)
	(p<0.001)[a]	(p<0.001)[a]	No change	94 (36)	93 (39)	90 (37)
			Mildly worse	70 (27)	67 (28)	69 (28)
			Moderately worse	36 (14)	25 (10)	23 (9)
			Markedly worse	6 (2)	2 (1)	4 (2)
					(p=0.223)[b]	(p=0.086)[b]

[a]Comparison of each galantamine group with placebo.
[b]Comparison with placebo using Van Elteren controlling for country effect (U.S. vs non-U.S.)

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EFFICACY RESULTS (continued): The results for the secondary efficacy endpoints of ADCS-ADL score, responder analyses, and ADAS-cog subscale scores were supportive of the results observed for the primary efficacy endpoints. Subjects in the galantamine CR treatment group maintained daily functioning, based on the change from baseline in ADCS-ADL score at Week 26, statistically significantly better than those in the placebo group, while maintenance of daily functioning for subjects in the galantamine-IR treatment was numerically better than those for the placebo group (mean difference: galantamine CR vs. placebo = 2.4 [p=0.003]; galantamine IR vs. placebo = 1.4 [p=0.088]). Based on the change from baseline in NPI scores at Week 26, treatment response for the both galantamine groups were numerically better but not statistically different from placebo (mean difference: galantamine CR vs. placebo = -0.7: galantamine IR vs. placebo = -1.3). The results for change from baseline in the ADAS subscale scores (ADAS-cog/13, ADAS-cog/10, and ADAS-cog/mem) and ADAS-cog/11 responder analyses were supportive of the ADAS-cog/11 results for the intent-to-treat population. There were no differences in treatment effect between the galantamine-CR and -IR treatment groups for any of the measured efficacy endpoints: ADAS-cog/11, CIBIC-plus, ADCS-ADL, NPI, and ADAS subscale scores.

Exploratory Analyses: The results from analyses on ADAS-cog/11, CIBIC-plus, and ADCS-ADL in subjects with screening MMSE scores ranging from 10 to 22 for all centers and for U.S. centers only (with pooling for small centers), and composite responder analyses supported the effectiveness of galantamine CR treatment over placebo. These findings were similar to the efficacy results for galantamine IR over placebo observed in the GAL-USA-10 study.

SAFETY RESULTS: In part due to the flexible dosing design employed in this study, a greater number of subjects in the galantamine-CR group (66%) reached a final dose of galantamine 24 mg/day than in the galantamine-IR group (61%). This could have contributed to the relative higher incidences of adverse events in the galantamine-CR compared to the galantamine-IR group. The number of subjects with at least 1 adverse event was 79%, 72%, and 70% in the galantamine-CR and -IR and placebo groups, respectively. The most frequently reported adverse event was nausea, occurring in 12% of all subjects and occurring more frequently in the galantamine treatment groups than in the placebo group (galantamine CR: 17%; galantamine IR: 14%; placebo: 5%). Cholinergic-related adverse events were transient in duration and most likely related to the initiation of upward dose titration. Fewer episodes of nausea or vomiting occurred in the galantamine-CR group than in the -IR group during the first 8 weeks. This may reflect better gastrointestinal tolerability of galantamine CR over IR during the early phase of dose escalation.

Eight deaths occurred either during double-blind treatment or within 30 days after the end of treatment (galantamine CR: 5; galantamine IR: 1; placebo: 2). None of the deaths were attributed to study medication. The number of subjects reporting at least 1 serious adverse event was similar among the treatment groups (galantamine CR: 11%; galantamine IR: 12%; placebo: 11%). The most common serious adverse events were injury, surgical intervention, fall, pneumonia, syncope, fever, and cerebrovascular disorder reported by at least 1% of all subjects. The number of subjects who discontinued treatment because of adverse events was slightly higher in the galantamine treatment groups than in the placebo group (galantamine CR: 9%; galantamine IR: 7%; placebo: 5%). The most frequently reported adverse event leading to discontinuation was nausea. Overall, the adverse event profiles for galantamine CR and IR were similar in this study and were consistent with that reported for galantamine IR in a previous double-blind, placebo-controlled clinical study of similar design. There were no clinically relevant concerns in findings for vital signs, laboratory findings, ECGs, body weight, or physical examination.

CONCLUSIONS:

Galantamine CR, administered as a once-daily flexible dosing regimen of 16 or 24 mg/day, was demonstrated to be safe and effective for the treatment of mild to moderate Alzheimer's disease.

Date of the report: 31 January 2003

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