SYNOPSIS

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

Protocol No.: CR002011

Title of Study: A Randomized, 26-Week, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Galantamine in the Treatment of Dementia Secondary to Cerebrovascular Disease

Coordinating Investigator: Alexander Auchus, M.D. – Case Western Reserve University, University Memory and Aging Center, Cleveland, Ohio; USA

Publication (Reference): none

Study Initiation/Completion Dates: 19 August 2001 - 28 August 2003	**Phase of Development:** 3

Objectives: The primary objective was to evaluate the efficacy of galantamine (8 or 12 mg twice daily [b.i.d.]) compared with placebo on cognition, as measured by the Alzheimer's Disease Assessment Scale: sum of 11 cognitive items (ADAS-cog/11) and activities of daily living, as measured by the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) Inventory. Secondary objectives were to evaluate effects of galantamine on global clinical assessment (Clinician's Interview Based Impression of Change – Plus Caregiver Input [CIBIC-plus]), behavior (Neuropsychiatric Inventory [NPI]), and other cognitive scores (ADAS-cog/13, ADAS-cog/10, and ADAS-cog/mem). The effect of galantamine on executive function was assessed using the EXIT-25 scale (performed only at sites in English-speaking countries that were initiated under the original CR002011 protocol). Safety was assessed by monitoring of adverse events, electrocardiograms (ECGs), physical examinations, vital signs, body weight, and laboratory tests. Information on the pharmacokinetics of galantamine and on health/social care resource use was collected during the study.

Methodology: This double-blind, parallel-group, placebo-controlled, flexble-dose study was conducted in 21 countries. Following a 4-week, single-blind, placebo run-in period, subjects were randomized to receive placebo or galantamine (8 or 12 mg b.i.d., flexible dosage after initial dose escalation) in a double-blind fashion for 26 weeks. Efficacy assessments: ADAS-cog/11, ADCS-ADL Inventory, CIBIC-plus, NPI, EXIT-25, ADAS-cog/13, ADAS-cog/10, and ADAS-cog/mem measured at baseline and at Weeks 8, 12, and 26. Safety assessments: treatment-emergent adverse event (TEAE), physical examinations, vital signs, body weight, ECGs, laboratory evaluations.

Number of Subjects (planned and analyzed): 780 subjects planned enrollment. 786 subjects were randomized, treated, and analyzed for safety. The efficacy analysis included 740 subjects in the modified intent-to-treat [MITT] analysis set and 767 in the intent-to-treat [ITT] analysis set.

Diagnosis and Main Criteria for Inclusion: Male or female outpatients with mild to moderate vascular dementia based on National Institute of Neurological and Communicative Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria who had onset between ages 40 and 90 years, an MMSE score of 10 to 26 (inclusive), and an ADAS-cog/11 score of ≥12. Subjects must have had the opportunity to perform certain activities of daily living.

Test Product, Dose and Mode of Administration, Batch No.: Galantamine 4-mg (Batch Nos. 00G12/F047, 01B01/F047), 8-mg (Batch Nos. 00J16/F048, 00J11/F048, 00J10/F048), and 12-mg (Batch Nos. 00L06/F049, 01B05/F049, 00L04/F049) tablets administered orally b.i.d. All tablets were identical in appearance, taste, and smell.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo 0-mg (Batch Nos. 99F01/F004, 99F02/F004, 00I27/F004, 00I22/F004, 00I25/F004, 00I26/F004, and 00J04/F004) tablets were administered orally b.i.d. Placebo tablets were identical to galantamine tablets 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: Pharmacokinetics: Plasma samples were assayed for galantamine concentration using a validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) method. Results from the pharmacokinetic analyses will be reported separately from the clinical study report.

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Efficacy: Efficacy was evaluated using ADAS-cog/11, ADCS-ADL Inventory, CIBIC-plus, NPI, EXIT-25, ADAS-cog/13, ADAS-cog/10, and ADAS-cog/mem measurements at baseline and Weeks 8, 12, and 26. The primary efficacy variables were the changes from baseline in ADAS-cog/11 and ADAS-ADL Inventory scores at Week 26. The secondary efficacy variables were the CIBIC-plus score at Week 26, the trichotomized CIBIC-plus score at Week 26, the percentage of ADAS-cog/11 responders and composite (ADAS-cog/11 and ADCS-ADL) responders at Week 26, and changes from baseline at Week 26 in NPI, NPI caregiver's distress, ADAS-cog/13, ADAS-cog/10, ADAS-cog/mem, and EXIT-25 scores. A trichotomized scale for CIBIC-plus scores was defined based on the following categories: "improved" (score of 1 to 3), "no change" (4), or "worsened" (5 to 7). ADAS-cog/11 responder analysis was performed based on the change from baseline in ADAS-cog/11 scores at Week 26 (4 categories of responders were defined: change ≤ 0, ≤ -4, ≤ -7, and ≤ -10). Composite responder analysis was performed based on a combination of defined changes from baseline in ADAS-cog/11 (change ≤ -4) and ADCS-ADL (change ≥ 0) scores at Week 26. EXIT-25 was assessed only in subjects from countries with English as the primary language. Results from health resource use analysis will be reported separately.

Safety: Safety was based on the incidence of treatment-emergent adverse events and changes from baseline in physical examinations, vital signs, body weight, ECGs, and laboratory evaluations. Data about serious adverse events, including death, were collected up to 30 days after a subject's last dose of study drug.

Statistical Methods: Primary efficacy: For the change in ADAS-cog/11 score and in ADCS-ADL score, analyses were based on the MITT last observation carried forward (LOCF) data. The ITT analysis and the observed case analysis were also performed. An analysis of covariance (ANCOVA) model was used to compare the least square (LS) mean scores between treatments. This model included treatment, analysis center (pooled center), and baseline score as factors. The difference between treatment groups in LS means and the 95% confidence intervals around the difference were calculated. Secondary efficacy: The MITT analysis set with the LOCF approach was used in all secondary efficacy analyses. In addition, the CIBIC-plus score was also analyzed based on the ITT analysis set and observed case. An ANCOVA model similar to that used for the primary variables was applied to the secondary analyses of the change from baseline in ADAS-cog/10, ADAS-cog/13, ADAS-cog/mem, NPI, NPI distress, and EXIT-25 scores. The Cochran-Mantel-Haenszel (CMH) test using rank scores and controlling for analysis center effect was used to assess the effect of treatment on CIBIC-plus and trichotomized CIBIC-plus scales. The percentages of responders for ADAS-cog/11 and composite responders were analyzed using the CMH test for general association controlling for analysis center. Safety: Adverse events were coded using a World Health Organization Adverse Reaction Terminology (WHOART) dictionary maintained by the sponsor. Changes from baseline in vital signs, body weight, ECGs, and laboratory evaluations were summarized using descriptive statistics and frequencies calculations.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: A statistically significant difference ($p<0.001$) favoring galantamine treatment was detected between treatment groups in the mean change from baseline in ADAS-cog/11 score at Week 26 in the primary MITT LOCF analysis. The mean change (SD) was –1.8 (5.94) in the galantamine group and -0.3 (6.32) in the placebo group. By this measure, compared to placebo, galantamine treatment is associated with improvement in cognitive ability in individuals with probable vascular dementia. The ADAS-cog/11 responder analyses at Week 26 are consistent with this result. Similar results were obtained from the analysis of ADAS-cog/11 based on the ITT analysis set and observed case. Based on results of the analysis of the change in the ADCS-ADL score at Week 26 (MITT LOCF data) galantamine treatment was not associated with a significant difference compared to placebo in the ability to perform activities of daily living ($p=0.783$). The mean change (SD) was 0.7 (8.81) in the galantamine group and 1.3 (9.37) in the placebo group. Results from additional ITT and observed case analyses of the change in the ADCS-ADL score were consistent with those for the primary MITT LOCF analysis. No significant difference in the percentage of ADAS-cog/11 and ADCS-ADL composite responders at Week 26 was observed between treatment groups ($p=0.353$). Based on the 7-point CIBIC-plus score at Week 26, an improvement in global clinical assessment was associated with galantamine treatment compared to placebo; the difference approached statistical significance ($p=0.069$). Similar results were observed based on the trichotomized CIBIC-plus scale ($p=0.062$); 38% of subjects in the galantamine group improved in global clinical assessment versus 33% in the placebo group. Observed case analysis was consistent with that for the MITT LOCF data for the CIBIC-plus scale, and comparable

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results were obtained using the ITT analysis set. For the secondary efficacy variables of ADAS-cog/13, ADAS-cog/10, and ADAS-cog/mem, results were consistent with those for ADAS-cog/11; compared to placebo, galantamine treatment was associated with statistically significant improvement from baseline at Week 26 in cognitive ability ($p<0.01$). For the NPI behavioral scale, the difference in change from baseline at Week 26 was not statistically significant between the treatment groups ($p=0.086$). The galantamine group exhibited a slight worsening in score from baseline (mean change [SD] of 0.6 [10.62]) at Week 26 compared with a slight improvement for the placebo group (-1.2 [10.07]). At Week 26, the mean change (SD) from baseline in EXIT-25 was –2.4 (4.56) in galantamine- and –1.4 (5.00) in placebo-treated subjects. The difference between treatment groups at Week 26 was statistically significant ($p=0.041$) in favor of galantamine treatment, indicating that galantamine treatment was beneficial to aspects of executive function. The improvements in EXIT-25 score may reflect an effect on subjects with subcortical damage to cholinergic projections to frontal regions.

SAFETY RESULTS:

The adverse event information obtained in this study is consistent with the adverse event profile of galantamine established in other clinical studies and in the clinical use of galantamine for the treatment of mild to moderate Alzheimer's disease. No noteworthy between-group differences were observed in the incidence of treatment-emergent serious adverse events or deaths that occurred through 30 days after termination of study medication. The higher overall incidence of treatment-emergent adverse events in galantamine- versus placebo-treated subjects was due primarily to higher frequencies of gastrointestinal system disorders (including nausea, diarrhea, vomiting, and anorexia), psychiatric disorders (primarily insomnia), and weight decrease in galantamine-treated subjects. The higher incidence of adverse events that led to discontinuation of treatment in galantamine- versus placebo-treated subjects was due to nausea and vomiting; this led to the discontinuation only of galantamine-treated subjects.

	Placebo (N=390) n (%)	Galantamine (N=396) n (%)	Total (N=786) n (%)
Subjects who died	10 (3)	5 (1)	15 (2)
Subjects with ≥1 serious TEAE	72 (18)	80 (20)	152 (19)
Subjects with ≥1 TEAE leading to permanent stop	25 (6)	50 (13)	75 (10)
Subjects with ≥1 TEAE	278 (71)	301 (76)	579 (74)
Subjects with ≥1 TEAE that was at least possibly drug related	103 (26)	140 (35)	243 (31)

Although individual changes that were considered potentially clinically important occurred in some laboratory test values, ECG results, vital signs and body weight measurements, the incidence of these changes was low and consistent with the established safety profile of galantamine and with the age and health status of the study subjects.

CONCLUSION:

Galantamine administered up to 26 weeks was safe and well tolerated in subjects with probable vascular dementia. Galantamine treatment after 26 weeks was associated with cognitive improvement based on the ADAS-cog subscale and with improvement in executive functioning based on the EXIT-25 test.

Date of the report: 26 February 2004

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