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.: GAL-INT-11

Title of Study: A Randomized Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Galantamine in Subjects With Mild Cognitive Impairment (MCI) Clinically at Risk for Development of Clinically Probable Alzheimer's Disease

Coordinating Investigator: Steven DeKosky, M.D. - University of Pittsburgh - Alzheimer Disease Research Center, Pittsburgh, PA; USA.

Publication (Reference): None

Study Initiation/Completion Dates: 23 April 2001 - 18 November 2003	**Phase of development:** 3b

Objectives: The primary objectives were to assess the ability of galantamine compared with placebo to 1) improve cognition and global functioning in subjects with mild cognitive impairment (MCI) at the end of 12 months (as measured by the Alzheimer's Disease Assessment Scale adapted to MCI [ADAS-cog/MCI] and the Clinical Dementia Rating Sum of the Boxes [CDR-SB]) and 2) delay conversion to dementia (as measured by a change in Clinical Dementia Rating [CDR] score from 0.5 to ≥1.0) at the end of 24 months. The global severity of dementia was assessed using the CDR scale. Secondary objectives were to evaluate the effects of galantamine on subjects with regard to the activities of daily living and attention, using the Alzheimer's Disease Cooperative Study-Activities of Daily Living adapted to MCI (ADCS-ADL/MCI) and the Digit Symbol Substitution Test (DSST), as well as scores for the 11 and 13 subitems of the ADAS (ADAS-cog/11 and ADAS-cog/13, respectively). The ability of galantamine to slow serial magnetic resonance imaging (MRI)-determined rate of brain/hippocampal atrophy compared with placebo was also assessed. Safety 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 Austria, Canada, Finland, France, Germany, the Netherlands, Poland, Sweden, Great Britain, and the United States. Subjects were randomized to placebo or galantamine in a double-blind fashion for 24 months. Subjects in the galantamine group received 4 weeks of galantamine 4 mg twice daily (b.i.d.), followed by 4 weeks of galantamine 8 mg b.i.d. Based on safety and tolerability, the galantamine dose could be increased to 12 mg b.i.d. at Month 2, and could be reduced to 8 mg b.i.d. at Month 3. The dose chosen at the end of Month 3 was fixed for the remainder of the study.

Number of Subjects (planned and analyzed): 780 subjects planned for enrollment with 995 randomized. 898 subjects were analyzed for efficacy (Intent-to-Treat [ITT] Analysis Set) and 990 were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Men or women outpatients ≥50 years of age with gradual clinical decline of cognitive ability consistent with MCI (CDR score = 0.5 and memory score ≥0.5), impairment of activities of daily living insufficient for diagnosis of dementia, and a New York University (NYU) Paragraph Recall test with delayed recall score ≤10.

Test Product, Dose and Mode of Administration, Batch No.: Galantamine 4- (F047), 8- (F048), and 12-mg (F049) tablets were administered orally b.i.d. Batch Nos. 00G12/F047 (exp 7/03); 01B01/F047 (exp. 2/04); 01C08/F047 (exp 4/04); 02C14/F47 (exp 5/05); 00H01/F048, 00H02/F048, 00H08/F048 (exp 8/03); 00J10/F048, 00J12/F048 00J13/F048 (exp 11/03); 00K28/F048, 00K29/F048 (exp 01/04); 00H22/F049, 00H24/F049, 00H25/F049 (exp 8/03); 00H23/F049, 00H28/F049, 00H29/F049 (exp 10/03); 00L01/F049, 00L05/F049 (exp 1/04); 01B02/F049 (exp 02/04); 01C13/F049, 01D03/F049, and 01D04/F049 (exp. 05/04).

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo tablets (F004), identical in appearance to test product, were administered orally b.i.d. Batch Nos. 00G07/F004, 00G10/F004, 00G11/F004, 00G12/F004, 00G13/F004, 00G14/F004 (exp 7/03); 00I20/F004 (exp 9/03); 00I21/F004, 00I28/F004, 00I26/F004, 00J03/F004 (exp 10/03); 01C05/F004 (exp 3/04); 01C07/F004 (exp 4/04); and 01C06/F004 (exp 5/04).

Duration of Treatment: Study drug was administered for 24 months.

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Criteria for Evaluation:

Efficacy: Efficacy was evaluated by CDR, ADAS-cog/MCI, CDR-SB, ADCS-ADL/MCI, DSST, ADAS-cog/11, and ADAS-cog/13 measurements at baseline and Months 3, 6, 9, 12, 15, 18, 21, and 24. The primary efficacy analyses were to compare galantamine with placebo with respect to 1) the change in ADAS-cog/MCI and CDR-SB scores (measures of memory/cognition and global improvement) from baseline to Month 12 and 2) the number and percent of subjects who converted from MCI to dementia (CDR ≥1.0) by 24 months. The secondary efficacy analyses were to compare galantamine with placebo with respect to change in ADAS-cog/MCI, CDR-SB, ADCS-ADL/MCI, DSST, ADAS-cog/11, and ADAS-cog/13 scores (measures of functionality, attention, and cognition) from baseline to Month 24. Lower ADAS-cog/MCI, ADAS-cog/11, and ADAS-cog/13 scores indicate a lesser degree of cognitive impairment; higher CDR-SB scores indicate greater deterioration of global functioning; higher ADCS-ADL/MCI scores indicate a lesser degree of impairment of daily functioning; and higher DSST scores indicate a higher degree of attention performance. Efficacy also was assessed using MRI measurements to determine the rate of brain/hippocampal atrophy.

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

Statistical Methods: Changes in ADAS-cog/MCI and CDR-SB scores were analyzed using analysis of covariance (ANCOVA) models with treatment, analysis center (pooled centers), and baseline value as factors. Similar techniques were applied to secondary DSST, ADAS-cog/11, ADAS-cog/13, and ADCS-ADL/MCI analyses. The number and percent of subjects who converted from MCI to dementia were analyzed using the log-rank test procedure, accounting for subjects who discontinued prematurely. To account for discontinued subjects, Kaplan-Meier curves were used to estimate the percentage of conversion by Month 24. The relative risk of conversion was estimated using the Cox's proportional hazard ratio model. Categorized DSST scores (<85 vs. ≥85 and ≤100 vs.>100) were analyzed using the Cochran-Mantel-Haenszel (CMH) test for general association controlling for analysis center. Primary efficacy analysis was based on last-observation-carried-forward (LOCF) analysis for the ITT analysis set. Adverse events were coded using a World Health Organization Adverse Reaction Terminology (WHOART) dictionary maintained by the sponsor. Safety results were analyzed using descriptive statistics.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Double-Blind Treatment Period: Galantamine treatment was not statistically different from placebo in improving cognition, assessed by change from baseline in ADAS-cog/MCI scores at Months 12 and 24 (LOCF data). At Months 12 and 24, the mean changes (SD) from baseline were -0.6 (5.55) and -1.2 (6.08) points in the galantamine group compared with -0.3 (5.22) and -0.7 (6.17) points for placebo (p=0.231 and 0.166), respectively. Galantamine treatment was not statistically different from placebo with regard to conversion of MCI to dementia (change in CDR score from 0.5 to ≥1.0) by Month 24 (p=0.146). Fifty-nine (13%) of 442 galantamine subjects converted by Month 24 compared with 83 (18%) of 452 placebo subjects. Galantamine treatment was statistically superior to placebo in maintaining global functioning, as assessed by the change from baseline in CDR-SB scores at Months 12 and 24 (LOCF data). Mean changes (SD) from baseline were 0.1 (1.06) and 0.3 (1.29) points in the galantamine group compared with 0.3 (1.28) and 0.4 (1.45) points in the placebo group at Months 12 (p=0.024) and 24 (p=0.028), respectively. Galantamine treatment was statistically superior compared with placebo in improving attention, assessed by change in DSST scores from baseline at Month 12 (LOCF data). At Months 12 and 24, the mean changes (SD) from baseline were 2.3 (12.76) and 2.0 (13.71) points in the galantamine group compared with 0.6 (14.05) and 1.0 (15.47) points in the placebo group (p=0.009 and 0.079, respectively). There were no differences in treatment effect between the galantamine and placebo treatment groups for the measured efficacy end points: ADCS-ADL/MCI, ADAS-cog/11, or ADAS-cog/13 scores at Months 12 or 24.

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EFFICACY RESULTS:

Double-Blind Treatment Period (continued): Galantamine treatment was statistically superior to placebo with regard to the rate of atrophy in whole-brain volume at Month 24 but not hippocampal atrophy. The mean (SD) rate of brain volume atrophy was 0.619 (0.535) %/year for placebo compared with 0.413 (0.517) %/year for galantamine (p=0.003), corresponding to a 33% reduction in the rate of whole brain atrophy. In the subgroup of subjects who had >3 years since the onset of cognitive problems, galantamine was statistically superior to placebo in the change from baseline in ADAS-cog/MCI score at Month 24 (p=0.034) and in the rate of whole brain atrophy (p=0.019). Galantamine treatment also approached statistical significance compared with placebo in the change from baseline in CDR-SB scores at Months 12 and 24 for this subgroup (p=0.051 and 0.075, respectively) and with regard to conversion to dementia by Month 24 (p=0.081). In the subgroup with a NYU Delayed Recall score ≤1, galantamine treatment was statistically superior to placebo in the change from baseline in ADAS-cog/MCI score at Months 12 and 24 (p=0.007 and 0.020, respectively) and in the rate of whole brain atrophy (p=0.050). A numerical trend in favor of galantamine was observed compared with placebo with regard to conversion to dementia by Month 24 for this subgroup (p=0.070). Galantamine treatment was also statistically superior compared with placebo, assessed by change in ADAS-cog/MCI scores from baseline, for the following subgroups: NYU Delayed Recall score from 2 to 3 at Month 24 (p=0.045); NYU Immediate Recall score from 2 to 3 at Month 12 (p=0.010); NYU Immediate Recall score >5 at Month 24 (p=0.043); and Delayed to Immediate Recall ratio of ≤0.5 at Months 12 (p=0.038) and 24 (p=0.007). Galantamine treatment was also statistically superior or approached statistical significance compared with placebo treatment, assessed by change in CDR-SB scores from baseline at Months 12 and 24 for the following subgroups: women (p=0.042 and 0.053, respectively); presence of first degrees relative with AD status – yes (p=0.012 and 0.048); smoking status – no (p=0.040 and 0.075); and Delayed to Immediate Recall ratio of >0.5-1.0 (p=0.012 and 0.010). Galantamine treatment was also statistically superior to placebo treatment, assessed by brain atrophy rates from baseline at Month 24 for the following subgroups: men (p<0.001); >2-3 years since onset of cognitive problems (p=0.030); presence of first degrees relative with AD status – no (p=0.005); smoking status – no (p=0.002); NYU Immediate Recall score of 4-5 (p=0.019); NYU Delayed Recall scores of 4-5 and >5 (p=0.074, and 0.054, respectively); and Delayed to Immediate Recall ratio of >0.5-1.0 and >1.5 (p=0.077 and 0.014, respectively).

Open-Label Treatment Period: Subjects began open-label galantamine treatment at various time points. Therefore, no conclusions were drawn from efficacy assessments during the open-label treatment.

SAFETY RESULTS:

Overall, galantamine administered in a flexible-dosing regimen of 16 mg/day or 24 mg/day was well tolerated in subjects with MCI. The adverse event profile, as well as changes in laboratory, vital sign, and ECG parameters, and observed physical findings for galantamine in this study was similar to those of 16 and 24 mg/day galantamine in previous double-blind, placebo-controlled studies in subjects with Alzheimer's disease (AD).

Double-Blind Treatment Period: The incidence of subjects with at least 1 treatment-emergent adverse event during double-blind treatment was 89% (placebo, 88%; galantamine, 90%). The most frequently reported event was nausea (22%), which was reported more often for galantamine (30%) than placebo (13%) subjects. Most treatment-emergent adverse events were mild to moderate in severity. Six galantamine and 1 placebo subject died due to treatment-emergent adverse events during the double-blind treatment period. The most common causes of death were suicide (2 galantamine subjects) and myocardial infarction (2 galantamine subjects). Other causes of death were bronchial carcinoma and sudden death (1 galantamine subject), cerebrovascular disorder and syncope (1 galantamine subject), and arrhythmia and cardiac arrest (1 placebo subject). No events leading to death were attributed to study drug. The incidence of subjects with at least 1 treatment-emergent serious adverse event was similar in both treatment groups (galantamine, 18%; placebo, 17%). The most frequently reported treatment-emergent serious adverse events were injury (placebo, 1%; galantamine, 2%) and surgical intervention (placebo, 2%; galantamine, 1%).

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SAFETY RESULTS:

Double-Blind Treatment Period (continued): Discontinuations due to treatment-emergent adverse events were higher in the galantamine group (21%) than placebo group (9%). The most frequently reported treatment-emergent adverse events leading to discontinuation were nausea (4%) and diarrhea (2%), which occurred more frequently in the galantamine group (8% and 2%, respectively) than placebo (each 1%). There were no clinically relevant concerns in any physical examination findings, body weight or laboratory test results, ECG, or vital sign parameters during double-blind treatment.

Open-Label Treatment Period: The incidence of subjects with at least 1 treatment-emergent adverse event during open-label treatment was 81% and 83% in the PLA/GAL and GAL/GAL groups, respectively. The most frequently reported treatment-emergent adverse event was nausea (15%), which occurred more frequently in the PLA/GAL (16%) than the GAL/GAL (13%) group. Most treatment-emergent adverse events were mild to moderate in severity. Five subjects (2 GAL/GAL and 3 PLA/GAL) died during the open-label treatment period. The causes of death were angina pectoris and pneumonia (1 PLA/GAL subject), cerebral hemorrhage (1 PLA/GAL), myocardial infarction (1 GAL/GAL), cardiac failure (1 GAL/GAL), and ovarian carcinoma (1 PLA/GAL). No events leading to death were attributed to study drug. The incidence of subjects reporting at least 1 treatment-emergent serious adverse event during the open-label treatment period was 21% (PLA/GAL, 23%; GAL/GAL, 19%). The most frequently reported treatment-emergent serious adverse events were fall, surgical intervention, myocardial infarction, angina pectoris, injury, arthritis, and cardiac failure (each occurred in 2% of all subjects). One PLA/GAL subject had serious events (aggressive reaction and urinary tract infection) considered at least possibly related to study drug. Twelve (9%) subjects had treatment-emergent adverse events that led to discontinuation of open-label galantamine treatment (PLA/GAL, 11%; GAL/GAL, 6%). The most frequently reported treatment-emergent adverse events leading to discontinuation were nausea (2%; all PLA/GAL subjects) and myocardial infarction (2%; all GAL/GAL subjects). There were no clinically relevant concerns in any physical examination findings, body weight or laboratory test results, ECG, or vital sign parameters during open-label treatment.

CONCLUSIONS:

The study results did not meet the objectives of statistically significant outcomes in both symptomatic end points at Month 12 (change from baseline in ADAS-cog/MCI and CDR-SB) and disease progression at Month 24 (change in CDR score from 0.5 to ≥1.0), however, numerical trends in favor of galantamine were observed. Galantamine, administered as a twice-daily flexible-dosing regimen of 16 or 24 mg/day for 24 months, was significantly better than placebo in maintaining global functioning in subjects with MCI. Galantamine treatment was not significantly different from placebo in maintaining cognition or delaying clinical conversion of MCI to dementia. Whole brain atrophy, but not hippocampal atrophy, was significantly reduced by galantamine treatment.

The adverse event profile, as well as changes in laboratory, vital sign, and ECG parameters, and observed physical findings in subjects with MCI who were treated with galantamine were similar to those of subjects with probable AD treated with galantamine (16 or 24 mg/day) in previous double-blind, placebo-controlled, and open-label studies. However, the imbalance in the number of deaths between galantamine and placebo during the double-blind period is of significant concern and requires further evaluation.

Since preliminary evidence indicated that some subjects may have discontinued the double-blind MCI studies and then died, a retrieved dropout study, GAL-COG-3002, is currently being conducted to determine the mortality status of all subjects over the 2-year duration of the MCI studies. The results of GAL-COG-3002 are expected to provide a definitive determination of the mortality rate in the MCI studies. An interim analysis of this study has been performed, and a synopsis describing the results is also posted on this website. Based on the interim analysis of data, the revised incidence of mortality in the double-blind phase of the pooled GAL-INT-11 and GAL-INT-18 studies is currently 5/1022 (0.5%) in the placebo group and 15/1026 (1.5%) in the galantamine group.

Date of the report: 11 June 2004