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-18 **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: Bengt Winblad, M.D. – Huddinge University Hospital, Stockholm, Sweden		
Publication (Reference): None		
Study Initiation/Completion Dates: 19 April 2001 – 4 December 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). 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 Argentina, Australia, Belgium, Canada, the Czech Republic, Israel, Spain, and the United States. Subjects were randomized to receive 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 1,062 randomized. Of these, 1,019 subjects were analyzed for efficacy (Intent-to-Treat [ITT] Analysis Set) and 1,058 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); and 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); and 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 higher degree of attention performance.

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 the 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 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 the change from baseline in ADAS-cog/MCI scores at Months 12 and 24 (LOCF data). The mean changes (SD) from baseline were -0.4 (5.87) and -0.6 (6.54) points for the galantamine group compared with -0.5 (6.05) and -0.7 (6.85) for the placebo group at Months 12 (p=0.927) and 24 (p=0.969), 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=0.619). Eighty-six (17%) of 498 galantamine subjects converted compared with 107 (21%) of 511 placebo subjects. Galantamine treatment was not statistically different from placebo in maintaining global functioning, assessed by the change from baseline in CDR-SB scores at Months 12 and 24 (LOCF data). The mean changes (SD) from baseline were 0.3 (1.29) and 0.4 (1.40) points for the galantamine group and 0.3 (1.26) and 0.6 (1.48) points for placebo at Months 12 (p=0.662) and 24 (p=0.056), respectively. Galantamine treatment was statistically superior to placebo in improving attention performance, assessed by the change from baseline in DSST scores at Month 24 (p=0.020) but not at Month 12 (LOCF data). There were no differences in treatment effect between the galantamine and placebo groups for the measured efficacy end points: ADCS-ADL/MCI, ADAS-cog/11, and ADAS-cog/13 scores at Months 12 or 24. In the subgroup of subjects with a NYU Immediate Recall test score ≤1, galantamine was statistically superior to placebo in the change from baseline at Month 24 in CDR-SB scores (p=0.013). In the subgroup with a NYU Delayed Recall score of 4-5, galantamine was statistically superior to placebo with regard to the rate of conversion to dementia by Month 24 (9% vs. 26%; p=0.017). In the subgroup with a Delayed to Immediate Recall ratio of >1.0-1.5, galantamine treatment approached statistical significance compared with placebo in the rate of conversion to dementia (10% vs. 16%; p=0.058); 12% of placebo subjects converted by Month 24 vs. 4% of galantamine subjects.

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EFFICACY RESULTS (continued)

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 or 24 mg/day was well tolerated in subjects with MCI. The adverse event profile and changes in laboratory, vital sign, and ECG parameters, and observed physical findings 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 88% (placebo, 86%; galantamine, 90%). The most frequently reported event was nausea (19%), which was reported more often for galantamine (29%) than placebo (9%) subjects. Most treatment-emergent adverse events were mild to moderate in severity. Seven galantamine and no placebo subjects died due to treatment-emergent adverse events during double-blind treatment or within 30 days after the end of treatment. With the exception of sudden death, which was reported for 2 subjects, no specific event leading to death was reported for more than 1 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 (placebo, 21%; galantamine, 19%). Injury was the most common treatment-emergent serious adverse event, occurring in 2% of all subjects (galantamine, 2%; placebo, 2%). Discontinuations due to treatment-emergent adverse events were higher in the galantamine group (23%) than placebo (10%). The most frequently reported event leading to discontinuation was nausea (4%), which occurred more frequently in galantamine subjects (8%) than placebo (1%). There were no clinically relevant concerns in any physical examination finding or body weight, laboratory test results, ECG, or vital sign parameters during double-blind treatment.

Open-Label Treatment Period

During open-label galantamine treatment, 137 (77%) of 177 subjects had at least 1 treatment-emergent adverse event (PLA/GAL, 72%; GAL/GAL, 85%). The most frequently reported treatment-emergent adverse events were injury (14%). Four subjects (all GAL/GAL) died during the open-label treatment period or within 30 days after the end of open-label treatment. The causes of death were pneumonia (1 GAL/GAL subject), pneumonia and respiratory insufficiency (1 GAL/GAL subject), anemia, asthenia, and colon carcinoma (1 GAL/GAL), and malignant gastrointestinal neoplasm (1 GAL/GAL subject). No adverse events leading to death were considered by the investigator to be related to study drug administration. Forty-two (24%) of 177 subjects (PLA/GAL, 22%; GAL/GAL, 27%) reported 1 or more treatment-emergent serious adverse events during the open-label galantamine period. The most frequently reported treatment-emergent serious adverse events were pneumonia (3%), and atrial fibrillation, fall, injury, syncope, and vomiting (each 2%). All treatment-emergent serious adverse events reported in this study were considered by the investigators to be either doubtfully related or unrelated to galantamine. Fourteen (8%) of 177 subjects (PLA/GAL, 9%; GAL/GAL, 7%) had treatment-emergent adverse events that led to discontinuation of open-label galantamine treatment. The most frequently reported adverse events leading to discontinuation were tremor (2 PLA/GAL subjects), pneumonia (2 GAL/GAL), vomiting (2 GAL/GAL), malignant gastrointestinal neoplasm (1 PLA/GAL and 1 GAL/GAL), and nausea (1 PLA/GAL and 1 GAL/GAL). There were no clinically relevant concerns in any physical examination finding or body weight, laboratory test results, ECG, or vital sign parameters during open-label treatment.

SYNOPSIS (CONTINUED)

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CONCLUSION:

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). Galantamine, administered as a twice-daily flexible-dosing regimen of 16 or 24 mg/day for 24 months, was not significantly better than placebo in maintaining global functioning or cognition in subjects with MCI or delaying clinical conversion of MCI to dementia.

The adverse event profile, as well as changes in laboratory parameters, vital signs, 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: 17 June 2004