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	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: GAL-MCI-301 **Title of Study:** An Open-Label Extension Study to Assess the Long-Term Safety and Tolerability of Galantamine HBr in the Treatment of Mild Cognitive Impairment		
Study Initiation/Completion Dates: 20 May 2003 to 18 May 2004		**Phase of development:** 3b
Objectives: The primary objective of this study was to evaluate the long-term safety and tolerability of galantamine hydrobromide (hereafter referred to as galantamine or GAL) in subjects with mild cognitive impairment (MCI). Long-term safety was monitored by means of adverse event (AE) reports, physical examinations, vital signs, electrocardiograms (ECGs), and laboratory evaluations. Secondary objectives were to 1) assess the long-term effects of galantamine on cognition and function, as measured by the Alzheimer's Disease Assessment Scale-cognitive portion/MCI version (ADAS-cog/MCI), and Clinical Dementia Rating (CDR), including the sum of the boxes of the CDR (CDR-SB); and 2) explore the effect of galantamine on the subjects' quality of life using the Health Survey Short Form (SF-36) and the subjects' use of health and social care services using a resource-use questionnaire.		
Methodology: Approximately 900 subjects were expected to enroll in this study. All subjects with MCI who completed a preceding 24-month double-blind study (either GAL-INT-11 or GAL-INT-18) and did not progress to dementia during the study, with dementia defined as a CDR of ≥1, and who elected to continue in this 12-month open-label extension study, were considered for enrollment. During the double-blind study, subjects received either placebo (PLA) or galantamine (GAL) treatment for 24 months. The last visit (Visit 11, Month 24) of the double-blind study was to coincide with the initial visit (Visit 1) of GAL-MCI-301. The long-term safety of galantamine tablets (8 or 12 mg twice daily) was evaluated during this open-label treatment period. All subjects, regardless of previous treatment, received open-label galantamine in escalating doses to reach a daily dosing level of either 16 or 24 mg (PLA/GAL and GAL/GAL grouping are based on treatment sequence in double-blind and open-label studies). The investigator chose the final dose based on safety and tolerability. Subjects returned for evaluation at 2, 6, and 12 months (or earlier end point) after beginning open-label galantamine treatment. Blood samples were drawn at the initial visit and at 6 and 12 months (or earlier end point) after beginning open-label galantamine to measure the concentration of glutamine synthetase, and possibly other proteins coincident with dementia, from subjects who consented to participate in this portion of the study. Originally planned for a 12-month open-label treatment period, this study was stopped prior to its scheduled end after review of the results of Studies GAL-INT-11 and GAL-INT-18.		
Criteria for Evaluation: Efficacy: Efficacy assessments were considered supplementary in this study. Cognitive and functional abilities were evaluated using psychometric scales (ADAS-cog/MCI, as well as the sum of 11 and 13 cognitive items of the Alzheimer's Disease Assessment Scale [ADAS-cog/11 and ADAS-cog/13, respectively]), global rating of dementia (CDR), and CDR-SB. Safety: Safety was based on the incidence of treatment-emergent adverse events (TEAEs) and changes from baseline of the double-blind study and from the initial visit of the open-label study in vital signs, body weight, laboratory evaluations, physical examinations, and ECGs. Outcomes Research: Results from the SF-36 Health Survey and health resource use analysis will be reported separately from this clinical study report. Pharmacoproteomics: At participating sites, blood samples were drawn from subjects who consented to measure concentrations of glutamine synthetase. Results from this analysis will be reported separately from this clinical study report.		

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Sixteen (5%) PLA/GAL and 18 (6%) GAL/GAL subjects with a CDR score ≤0.5 at the initial visit converted (CDR score ≥1.0) during the study. Two other subjects (1 PLA/GAL and 1 GAL/GAL) had a CDR score of ≥1.0 at both the initial visit and at end point. Four (3 PLA/GAL and 1 GAL/GAL) subjects had a CDR score of ≥1.0 at the initial visit but ≤0.5 at end point. A higher CDR-SB score indicates subjects with greater deterioration of global functioning. The mean change (standard deviation [SD]) from baseline for CDR-SB score at end point was -0.3 (1.53) for the PLA/GAL group and -0.2 (1.18) for the GAL/GAL group. The mean change (SD) from the initial visit for CDR-SB score at end point was -0.2 (1.19) for the PLA/GAL group compared with -0.1 (0.86) for the GAL/GAL group. For ADAS-cog/MCI (range: 0-90), higher scores indicate a lower degree of cognitive functioning. At end point, the mean changes (SD) from baseline were –1.1 (7.36) points in the PLA/GAL group and -0.6 (6.49) points in the GAL/GAL group. At end point, the mean changes (SD) from the initial visit were 1.2 (4.71) points in the PLA/GAL group and 2.2 (4.70) points in the GAL/GAL group. Results from analyses of the ADAS-cog/11 and ADAS-cog/13 subscales were consistent with the results of the ADAS-cog/MCI.

SAFETY RESULTS:

The incidence of subjects with at least 1 TEAE was 76% (PLA/GAL, 80%; GAL/GAL, 70%). The most frequently reported TEAE was nausea, occurring in 17% of all subjects and occurring more frequently in the PLA/GAL group (24%) than in the GAL/GAL group (10%). Most TEAEs were mild or moderate in severity. Three subjects (1 PLA/GAL and 2 GAL/GAL) died due to TEAEs or within 30 days after the end of treatment. Causes of death were myocardial infarction (1 PLA/GAL subject), cardiac arrest (1 GAL/GAL), and subarachnoid hemorrhage (1 GAL/GAL). Another GAL/GAL subject died more than 30 days after the last dose of study drug (cerebrovascular disorder). Only myocardial infarction was attributed as possibly related to study drug by the investigator. The incidence of subjects who had at least 1 treatment-emergent serious adverse event (SAE) was 9% (PLA/GAL, 9%; GAL/GAL, 10%). No treatment-emergent SAEs were reported by more than 2.0% of subjects overall or in either group. Treatment-emergent SAEs that occurred in at least 1.0% of subjects overall or in either group were surgical intervention and myocardial infarction. The incidence of subjects who discontinued treatment because of TEAEs was 9% (PLA/GAL, 11%, GAL/GAL, 6%). The most frequently reported TEAEs leading to study drug discontinuation were gastrointestinal (GI) disorders (5%), which occurred more frequently in the PLA/GAL group (8%) than in the GAL/GAL group (3%). The most frequently reported GI disorder TEAEs leading to discontinuation were nausea (4%) and diarrhea (1%). There were no clinically relevant concerns in physical examination findings, body weight, laboratory test results, ECG, or vital sign parameters during this study.

CONCLUSION:

The AE profile, and changes in laboratory, vital signs, physical findings, and ECG parameters, 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.

Date of the report: 24 November 2004