SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: RAZADYNE™ / 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.: CR004366

Title of Study: A Study of Galantamine HBr as an Adjunctive Treatment to Atypical Antipsychotic Medications in Outpatients with Schizophrenia and Associated Cognitive Defects

Study Initiation/Completion Dates: 06 May 2003 – 28 February 2005	**Phase of development:** 2

Objectives: This exploratory study evaluated the effects of administering extended-release (ER) galantamine hydrobromide (HBr) (16 and 24 mg once daily; fixed dose) or placebo to outpatients with schizophrenia who were on a stable regimen of the atypical antipsychotic medications risperidone, quetiapine, olanzapine, aripiprazole, or ziprasidone, alone or in combination. The impact of adjunctive galantamine therapy on the following measures was explored: continuing positive, negative, and general symptoms of schizophrenia; cognitive deficits associated with schizophrenia; and the overall severity of the illness. The safety and tolerability of adjunctive galantamine to atypical antipsychotic medications was assessed, and the plasma concentrations of galantamine were determined.

Methodology: This randomized, double-blind, placebo-controlled, parallel-group, multicenter, pilot study was conducted at 15 centers in the United States and Canada. Approximately 100 subjects were to be randomly assigned to 3 groups to receive study drug for 8 weeks (on 7 consecutive days per week). The placebo group received placebo daily for 8 weeks. The 8-mg galantamine group received galantamine ER 8-mg daily for 8 weeks. The 16-mg galantamine group received galantamine ER 8-mg daily for 1 week, followed by galantamine ER 16-mg daily for 7 weeks. Randomization into the 8-mg galantamine group was subsequently discontinued and a 24-mg galantamine group was added. The 24-mg galantamine group received galantamine ER 8-mg daily for 1 week, followed by galantamine ER 16-mg daily for 1 week, followed by a galantamine ER 24-mg daily for 6 weeks.

During Visits 2, 3, and 4, efficacy and safety evaluations were performed and samples for pharmacokinetic analysis were collected. Between Visits 2, 3, and 4, study site personnel contacted the subjects by telephone at designated time points to record adverse events and concomitant medications, and to review the study drug dosing schedule.

All statistical tests were interpreted at the 5% significance level, unless otherwise specified. Missing data were imputed using the last observation carried forward (LOCF). Changes from baseline were summarized by treatment group and for between-group differences with descriptive statistics. For most efficacy measures, an analysis of covariance (ANCOVA) was performed to compare the changes between the galantamine and placebo groups. Clinical Global Impression (CGI) change scores were analyzed by the analysis of variance (ANOVA) method.

Criteria for Evaluation:

Efficacy: Efficacy was evaluated by the changes from baseline to Week 8 for Positive and Negative Syndrome Scale (PANSS), CGI (severity [CGI-S] and improvement [CGI-I] subscales), and Brief Assessment of Cognition in Schizophrenia (BACS) scores, as well as the Lexical and Semantic Fluency Test (LSFT) and 3 computerized tests (Continuous Performance Test, CPT; Reaction Time Test, RTT; and Finger Tapping Test, FTT). Concentrations of nicotine and cotinine in the blood were measured at Visits 2 and 4 to determine changes in nicotine use during the study.

Safety: Safety was assessed on the basis of the incidence of treatment-emergent adverse events and changes from baseline to Week 8 in physical examination findings, vital sign and electrocardiogram (ECG) measurements, laboratory evaluations, and the Simpson-Angus Extrapyramidal Side Effects Scale - Abbreviated (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS).

Pharmacokinetic/Pharmacodynamic Relationships: Trough plasma concentrations of galantamine were determined at baseline and at Visits 3 (Week 4, Day 28) and Visit 4, Final Visit (Week 8, Day 56 or Early Withdrawal). Plasma concentrations of prolactin were determined at Visits 2, 3, and 4. The relationship between trough plasma concentration of galantamine and prolactin concentrations was explored graphically.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: RAZADYNE™ / 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)

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

The total PANSS score change from baseline to Week 8 results show no statistical significance for any of the galantamine groups (8-, 16-, or 24-mg) compared with placebo based on treatment comparison at the nominal 5% level (p=0.760, p=0.433, and p=0.983, respectively). The total BACS score change from baseline to Week 8 results show no statistical significance for any galantamine group (8-, 16-, or 24-mg) compared with placebo based on treatment comparison at the nominal 5% level (p=0.282, p=0.131, and p=0.887, respectively). The CGI-S score change from baseline to Week 8 results show no statistical significance for any galantamine group (8-, 16-, or 24-mg) compared with placebo based on treatment comparison at the nominal 5% level (p=0.259, p=0.998, and p=0.722, respectively).

SAFETY RESULTS:

The incidence of subjects with at least 1 treatment-emergent adverse event was 60% in the placebo group and 64% in the combined galantamine group (8-mg, 50%; 16-mg, 63%; and 24-mg, 68%). The most frequently reported treatment-emergent adverse event in galantamine subjects was psychosis, which occurred at a similar incidence in the galantamine (combined, 9%; 8-mg, 10%; 16-mg, 10%; and 24-mg, 9%) and placebo (7%) groups. Most treatment-emergent adverse events reported were mild or moderate in severity. No deaths were reported during study treatment or within 30 days of the last dose of study drug. The incidence of subjects with at least 1 treatment-emergent serious adverse event was 9% in the combined galantamine group (8-mg, 10%; 16-mg, 17%; and 24-mg, 3%) compared with 10% in the placebo group. The only treatment-emergent serious adverse events that occurred in 2 or more subjects overall or in any group were psychosis (placebo, 2 [7%]; 8-mg, 1 [10%]; 16-mg, 3 [10%]; and 24-mg, 0 subjects) and suicide attempt (placebo, 0; 8-mg, 0; 16-mg, 2 [7%]; and 24-mg, 1 [3%] subjects). The incidence of subjects with an adverse event leading to permanent discontinuation of study drug was 10% in the placebo group compared with 16% in the combined galantamine group. A higher incidence of subjects in the 16-mg group (27%) discontinued treatment because of a treatment-emergent adverse event than in the 8-mg (10%) or 24-mg (9%) galantamine groups. The most frequently reported treatment-emergent adverse events leading to study drug discontinuation in galantamine subjects were psychiatric disorders (11%), which occurred more frequently in the 16-mg galantamine group (20%) than in the 8-mg (10%) or 24-mg galantamine (3%) groups. Psychiatric disorders leading to study drug discontinuation occurred in 3% of placebo subjects. The most frequently reported psychiatric disorder leading to discontinuation in galantamine subjects was psychosis (5%). No subjects in the placebo group experienced psychosis leading to discontinuation.

There were no clinically relevant changes in physical examination findings, body weight, laboratory test results, ECG, or vital sign parameters. There were no statistically significant differences between any galantamine group and placebo in the change from baseline in SAS, AIMS, or BARS scores.

Overall, galantamine appeared to be generally safe and well tolerated in this population of schizophrenic subjects.

PHARMACOKINETIC/PHARMACODYNAMIC RESULTS:

Mean trough plasma galantamine concentrations in this study were similar to those seen in elderly subjects and healthy volunteers. Although trough plasma galantamine concentrations appeared to increase in a dose-proportional manner, the overall incidence of adverse events was not affected. Small sample sizes and wide variability in female subjects preclude any definitive conclusions; overall, the data suggest that galantamine had little effect on dopamine-prolactin release or inhibition within the hypothalamic-adenohypophyseal axis. Cotinine levels increased for all treatment groups, including placebo during the study, an indication that nicotine exposure during the study did not vary significantly between treatment groups and did not differentially affect the action of galantamine.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: RAZADYNE™ / 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)

CONCLUSION:

There was no evidence of beneficial effects of galantamine on overall cognitive performance in this schizophrenic subject population. No consistent improvements were detected on assessments of psychotic symptom severity or on a global measure of change. Galantamine appeared to be generally safe and well tolerated in this population. Plasma galantamine concentrations were similar to those seen in healthy young and elderly subjects.

Date of the report: 13 December 2005

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.