SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: RAZADYNE™ (formerly 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.: CR004240
Title of Study: An Analysis of Mortality in Subjects who Participated in Three Studies of Galantamine in Mild Cognitive Impairment

Study Initiation/Completion Dates: 13 July 2004 to 24 March 2005	**Phase of development:** 3b

Objectives: Although mortality was low in the pooled double-blind mild cognitive impairment (MCI) studies GAL-INT-11 and GAL-INT-18, a greater number of deaths were initially recorded in the galantamine treatment group (13/1026 subjects) compared to placebo (1/1022 subjects) in the double-blind period. Because preliminary evidence showed that some subjects may have discontinued the study and then died, the objective of the current study was to ascertain the vital statuses of all subjects who were randomly assigned and treated in Studies GAL-INT-11 and GAL-INT-18.

Methodology: This was a retrieved dropout study of subjects who participated in 3 previous studies: GAL-INT-11, GAL-INT-18, and the open-label extension study GAL-MCI-301. Investigators attempted to contact subjects with missing vital status data or their informants. In most cases, when an informant did not provide informed consent, a subject could not be contacted, or contact with the subject or informant was not necessary per the health authority; medical/death records or death registers were consulted to determine if a death occurred and, if so, the cause and date of death.

Criteria for Evaluation: If a subject was found to have died, the investigator recorded the cause of death and the adverse events leading to death based upon a review of medical records, autopsy records, and/or death certificates.

Statistical Methods: Interim analyses were conducted and reported in the following documents: the European Union Pharmacovigilance Working Party response document dated 29 December 2004, and the Swedish Medical Products Agency (MPA) Response Document dated 29 December 2004, and the MPA Response Documents dated 16 February 2005 and 28 March 2005. Data were combined from the databases of CR003145, CR002014, CR005947, and CR004240. The analysis set consisted of the 2,048 subjects who were randomly assigned to treatment in the CR003145 and CR002014 studies. All analyses of mortality data were based on the data from the combined and separate subject cohorts in CR003145 and CR002014, and were done for the following 3 time periods: the double-blind period, the 24-month period (intent-to-treat [ITT] analysis), and all-available data. In the double-blind period analysis and the 24-month period analysis, a subject's survival time was censored at the end of the periods. All analyses were based on a subject's randomized treatment assignment in either CR003145 or CR002014. For each time period, Kaplan-Meier survival curves were derived, and the numbers of deaths and subjects at risk by 3-month interval were summarized. Survival analyses were performed on mortality data using the log-rank procedure for the p values, relative risks, and 95% confidence intervals (CIs). A graph of the cumulative relative risks (and CIs) of mortality by 3-month intervals for all available data was generated to examine any delayed increase in mortality risk associated with galantamine.

An assessment of fatal adverse events in the double-blind period (+2 days) of Studies CR003145 and CR002014

associated with causes of death was conducted. A blinded clinical assessment of subject data was conducted for the identification of any treatment-emergent adverse events that occurred during the double-blind period and were related to the subject's cause of death recorded in Study CR004240. These fatal adverse event cases were analyzed using the log-rank procedure while censoring other death cases.

Cox proportional hazard regression models were employed to examine the effect of baseline risk factors and mortality and the interaction between the treatment and individual risk factors. In addition, Cox regression analyses were performed to examine the effect of each of the following factors on mortality and the interaction with treatment: cardiovascular, psychiatric, and pulmonary adverse events that occurred during the double-blind period as a time-dependent variable, the number of cardiovascular and pulmonary risk factors at baseline, and the Chronic Disease Index (CDI) score. The CDI score was calculated for each subject based on the RxRisk model (formerly CDI), a validated pharmacy-based case-mix classification system developed to assess disease burden.

A case-control analysis was conducted by matching each of the 17 death cases, that occurred within 30 days of the last dose of double-blind study medication, to 2 control cases based on gender, age (±4 years), and treatment

SYNOPSIS (CONTINUED)

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duration. Cases and controls were examined by 2 physicians in a blinded fashion to determine whether certain clinically important risk factors (prespecified) were present. These case-control data were analyzed using a conditional logistic regression model.

SUMMARY - CONCLUSIONS: The overall mortality rate in the MCI studies was unexpectedly low and not likely to be generalizable to the Alzheimer's disease (AD) and AD with cerebrovascular disease (AD+CVD) populations. Notably, a well-accepted regulatory definition of mortality is the number of deaths and fatal adverse events occurring while subjects are exposed to study drug during the double-blind period. Using this definition there were 20 deaths directly related to previous adverse events in the galantamine group compared with 13 in the placebo with (RR [95% CI] = 1.54, [0.78, 3.04]). Analyzing the estimated relative risk of mortality over time, the separation in death rates of the placebo and galantamine treatment groups is apparent at both 3 and 6 months of exposure in these MCI studies, whereas there was no difference in death rates between placebo and galantamine treatments during non-MCI placebo-controlled studies up to 6 months. These findings suggest that the mortality rates from the MCI studies cannot be generalized to the non-MCI populations previously studied (AD, AD+CVD, and vascular dementia).

Based on all available follow-up data, which includes data up to 1539 days from the start of the double-blind study medication, the relative risk (95% CI) is 1.24 (0.84, 1.83). Based on an intent-to-treat analysis at 24 months from the start of the double-blind study medication, the relative risk (95% CI) is 1.70 (1.00, 2.90); the 95% CI includes unity. With extended follow-up and more complete capture of the data, the relative risk tends to move towards unity compared with the results seen in the double-blind period and the results at 24 months (+30 days) follow-up. This tendency toward the null is clearly not a result of the increasing likelihood that subjects will eventually die, since the overall cumulative mortality for all follow-up data was still relatively low (102/2048 subjects; 5.0%).

Most subjects died outside of the double-blind period and subjects randomized to placebo who had an adverse event were more likely to drop out early in the trial than subjects randomized to galantamine. Assessment of all adverse events during the double-blind period that were associated with death confirms that mortality of the randomized cohort was under-recorded in the double-blind studies. Of 13 deaths associated with adverse events that began while subjects were taking double-blind placebo, only 1 death had been recorded in the double-blind period. Of 20 deaths associated with adverse events that began while subjects were taking double-blind galantamine, 12 deaths had been recorded in the double-blind period.

Analyses of cardiovascular and pulmonary risk factors indicated an increased risk of mortality, regardless of treatment, in subjects with baseline cardiovascular conditions . The case-control analysis did not identify any treatment risk effect with respect to baseline drugs, EKG, cardiac status, or pulmonary status of the 17 patients (14 galantamine, 3 placebo) who died within 30 days of discontinuing study medication.

In conclusion, the results of GAL-GOG-3002 confirm that overall mortality in the MCI studies was lower than expected. The difference in deaths initially recorded during the double-blind portion of the trials can be explained to a large degree by the greater drop out of subjects from the placebo arm than from the galantamine arm prior to death. This explanation is supported by the finding that the numbers of deaths and fatal adverse events that occurred during the double-blind periods were 13 in the placebo group compared with 20 in the galantamine group, a difference which is not statistically significant. The lack of significant mortality risk is further supported by the same serious adverse event rates in the galantamine and placebo groups (19%).

Date of the report: 30 June 2005

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