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-COG-3002 (Interim Analysis)

Title of Study: An Analysis of Mortality in Subjects Who Participated in Three Studies of Galantamine in Mild Cognitive Impairment (MCI)

Study Initiation/Completion Dates: 13 July 2004 - ongoing	**Phase of development:** 3b

Objective: In the pooled double-blind 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 (2/1022 subjects). Since 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 subjects who were randomized and treated in Studies GAL-INT-11 and GAL-INT-18 that were not recorded during the course of these clinical studies.

Methodology: This was an observational study of subjects who participated in 3 previous studies: GAL-INT-11, GAL-INT-18, and the open-label extension study GAL-MCI-301. The sponsor provided the investigators with a list of the case report form (CRF) identification number, date of birth, and initials of subjects who enrolled at their site and whose vital status was unknown. The investigators were to contact the subjects or their informants to obtain informed consent and to collect the subject's vital status. If a subject did not provide informed consent, documentation of contact with the subject was to suffice as evidence that the subject was alive. If an informant did not provide informed consent or a subject could not be contacted, medical or death records or death registers were to be consulted when necessary to determine if a death occurred and, if so, the cause and date of death.

Number of Subjects in the Interim Analysis: Of a total of 2048 subjects (placebo, 1022 subjects; galantamine, 1026 subjects) originally randomized in Studies GAL-INT-11 and GAL-INT-18, vital status data for 1800 subjects (placebo, 895 subjects; galantamine, 905 subjects) have been collected and are part of this interim analysis.

Criteria for Evaluation: If a subject has died, the investigator was to record on the CRF the cause of death and adverse events leading to death based upon a review of medical and autopsy records and death certificates.

Statistical Methods: The reasons for death were coded using the World Health Organization Adverse Reaction Terminology (WHOART) preferred terms and summarized within body system for each randomized treatment group. The analysis set consisted of all subjects in the safety populations in GAL-INT-11 and GAL-INT-18. Kaplan-Meier analyses are provided for the time course of deaths by treatment and the number of subjects at risk based on an intent-to-treat analysis at 24 months (plus 30-day follow-up period per protocol) from the start of double-blind study medication as well as an intent-to-treat analysis of all available follow-up data, which includes data up to 1254 days from the start of double-blind study medication. The relative risk (RR), p-value, and 95% confidence interval (CI) around the RR were presented. The clinical characteristics of all fatal cases were examined, including relevant medical history and other adverse events for each subject.

SUMMARY – CONCLUSIONS

SAFETY RESULTS:

- Based on the originally recorded mortality rates in the pooled MCI studies, the relative risk (95% CI) of mortality in the galantamine treatment group compared to placebo (hazard ratio) during the double-blind phase was 4.86 (1.76, 13.40). Based on the data retrieved to date as part of this interim analysis, the RR (95% CI) of mortality for the double-blind phase of the MCI studies is 3.04 (1.26, 7.32).

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS (Continued)

SAFETY RESULTS (Continued):

- Based on an intent-to-treat analysis at 24 months (plus 30-day follow-up period per protocol) from the start of double-blind study medication, the relative risk (95% CI) (galantamine relative to placebo, hazard ratio) based on the log-rank test is 1.73 (1.00, 2.98); it is noteworthy that the 95% confidence interval includes unity, although these studies were not designed with adequate statistical power to compare mortality. In this analysis, the separation in death rates of the placebo and galantamine treatment groups becomes apparent within the first 3 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 of 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 (Alzheimer's disease [AD], Alzheimer's disease with cerebrovascular disease, and vascular dementia).
- Based on an intent-to-treat analysis of all available follow-up data, which includes data up to 1254 days from the start of double-blind study medication, the relative risk (95% CI) (galantamine relative to placebo, hazard ratio) based on the log-rank test is 1.20 (0.80, 1.79); again, it is noteworthy that the 95% confidence interval includes unity, although these studies were not designed with adequate statistical power to compare mortality. In addition, with extended follow-up and more complete capture of the data, the relative risk tends to move toward the null compared to the results seen in the double-blind period and the results at 24 months (+30 days) follow-up. Further, this tendency toward the null is clearly not a result of the increasing likelihood that subjects will eventually die, since the overall cumulative mortality at 39 months of follow-up was still relatively low (96/2048 subjects; 4.7%).
- The overall incidence of serious adverse events was the same for placebo and galantamine treatment groups (19%). For both the 24 month (+30 days) data and all available data, the adverse events leading to death in the "as randomized" galantamine group were distributed among multiple body systems, confirming the all-causes mortality observed when only data from the double-blind phases of the studies were considered. Many subjects who had cardiovascular causes of death had other adverse events associated with death and multiple cardiovascular risk factors in their medical histories.

CONCLUSIONS:

Preliminary results from this ongoing retrieved dropout study indicate that the estimated relative risk of mortality for galantamine in these trials tends to move toward parity. Although at this time an increased estimated risk of mortality in the population studied in GAL-INT-11 and GAL-INT-18 is still apparent, the addition of data from the retrieved dropout analysis shows that it is becoming smaller than that originally recorded and indicates a decreasing hazard over time. A final report of all available follow-up mortality data from the MCI studies will be made available at the earliest possible opportunity following completion of this study.

DISCUSSION:

Based on a review of all AD studies conducted to date, there is no evidence of increased risk of mortality in patients with AD treated with galantamine. The increased risk of mortality that is evident in the first 6 months of the MCI studies is not seen in pooled AD studies of 6 months duration.

The difference in recorded mortality in 2 studies of subjects with mild cognitive impairment is not fully explainable based on this interim analysis. However, it is important to note that the incidence of serious adverse events was equal in the placebo and galantamine groups and that the overall mortality rate was low. Furthermore, there are indications of biased dropout early in the study since subjects in the placebo group who experienced a serious adverse event were twice as likely to drop out than their counterparts on galantamine.

Date of the report: 20 January 2005