SYNOPSIS

Name of Sponsor/Company: Janssen Pharmaceutica, Inc. Name of Finished Product: Razadyne(TM) Name of Active Ingredient(s): Galantamine Hydrobromide	
Protocol No.: CR002002	
Title of Study: A double-blind, randomized pilot study to evaluate the effects of galantamine and donepezil on sleep and attention and gastrointestinal (GI) tolerance in patients with mild to moderate Alzheimer's disease (AD).	
Coordinating Investigator: Multicenter Study	
Publication (Reference): None	
Study Period: 5 March 2002 to 29 August 2003	**Phase of development:** 4
Objectives: The trial was designed as a pilot study with the intention of assessing multiple primary objectives. The primary objectives included an investigation of differentiation between galantamine and donepezil on sleep and attention, an exploration of methods for measuring attention in Alzheimer's Disease (AD) patients and sleep in AD patients and caregivers, and evaluation of the dose comparability between galantamine at 16 mg and donepezil at 10 mg for efficacy and GI tolerance. Secondary objectives were to assess the effects of treatment with galantamine and donepezil on safety, tolerability, and quality of life.	
Methodology: This double-blind, randomized, parallel-group trial consisted of a 2-week, single-blind run-in phase; an 8-week, double-blind assessment phase; and a variable length, double-blind extension phase designed to continue until the locking of the efficacy phase data base. Following the 2-week, single-blind run-in phase, patients were randomly assigned in a 1:1 ratio to receive either 4 mg galantamine bid (with placebo qhs) or 5 mg donepezil qhs (with placebo bid). After 4 weeks, the dose was titrated upward to either 8 mg glantamine bid (with placebo qhs) or 10 mg donepezil qhs (with placebo bid). The dose titration and dosage schedule were within the ranges specified by the package labeling for both products. Patients continued to receive study medication during an extension phase that lasted until all randomized patients completed the assessment phase and the study was unblinded (database lock). The extension phase could have lasted from 6 to 54 weeks for individual patients, depending upon the time of entry to the study.	
Number of Subjects (planned and analyzed): 60 to 90 patients were planned, 76 patients were screened, and 63 patients were randomized to treatment (31 galantamine, 32 donepezil).	
Diagnosis and Main Criteria for Inclusion: Subjects were men and postmenopausal women, aged 60 or older, who had a diagnosis of mild to moderate AD based on the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer's disease. Enrolled patients were required to have a Mini-Mental State Examination (MMSE) score that was from 10 to 24. The study also included the men and women who had taken on caregiver responsibilities for these patients.	
Test Product, Dose and Mode of Administration, Batch No.: Galantamine was orally administered as overencapsulated tablets (batch numbers F68-3844 [4 mg, Weeks 1-4] and F69-3849 [8 mg, Weeks 5-8 and extension phase]).	
Reference Therapy, Dose and Mode of Administration, Batch No.: Donepezil was orally administered as overencapsulated tablets (batch numbers F245-4076 [5 mg, Weeks 1-4] and F246-4077 [10 mg, Weeks 5-8 and extension phase]). Placebo was administered as identically-appearing overencapsulated tablets (batch number F92-3298).	
Duration of Treatment: Treatment lasted for 8 weeks, plus an extension phase that could last from 6 to 54 weeks.	
Criteria for Evaluation: Efficacy: Efficacy assessments included the Clinician's Interview-Based Impression of Change Plus Family Input (CIBIC-Plus) at baseline and Week 8 (steady-state). In addition, the patient and caregiver were assessed for actigraphy and sleep log-baseline data collected at baseline; assessment data from Weeks 4-5 (nonsteady-state) and for Weeks 7-8 (steady-state). The caregiver completed the Pittsburgh Sleep Quality Index (PSQI) for patient and self, and the Circadian Sleep Inventory for Normal and Pathological States (CSINAPS) for the patient at baseline and Weeks 5 and 8. For attention, the patient was assessed for Simple Reaction Time (SRT), Choice Reaction Time (CRT), Verbal	

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Series Attention Test (VSAT), and Stroop Test (baseline and Weeks 4 and 8). For quality of life (QOL) assessments, the caregiver completed the Alzheimer's Disease Related Quality of Life Scale (ADRQL) and the caregiver completed the Allocation of Caregiver Time Survey (ACTS) and SF-12 Quality of Life Survey at baseline and Week 8.

Safety: Safety was assessed by the recording to adverse events, physical examination and vital signs (including physical and neurological exam, vital signs, sitting blood pressure, and weight).

Statistical Methods: Because of the trial's pilot nature, ie, the limited sample size and the large number of domains, the analysis focused on identifying consistent patterns in the data rather than on tests of statistical association. The data from galantamine-treated and donepezil-treated patients and their caregivers were compared across a number of domains, including sleep, attention, QOL, other measures of efficacy, and GI tolerance.

The data were summarized in tabulations of 1) demographic and baseline characteristics including routine laboratory assessments; 2) patient disposition and accounting; 3) assessments of sleep parameters (patient and caregiver), attention, efficacy, QOL (patient and caregiver) and caregiver time allocation; and 4) safety and tolerability, including incidence rates of AEs and changes in vital signs.

All tests of significance assumed a α=0.05 with α=0.10 for interaction effects. In general, between-group comparisons of categorical data were performed with either Fisher Exact test of Cochran-Mantel-Haenszel tests, stratifying for center. The significance of the between-group differences in change from baseline was assessed with either analysis of covariance (ANCOVA) or analysis of variance (ANOVA) models. The effects in these models were treatment group and center main effects and their interaction. Baseline scores served as covariates. Other models were used that had additional covariates as needed, and non-parametric tests were employed for the attention CRT and SRT variables based on prior experience with the CDR computer testing model and galantamine. No adjustment for multiplicity was performed because this pilot study was intended to explore multiple endpoints.

SUMMARY - CONCLUSIONS

The mean patient ages were 76.5 years and 77.8 years for the galantamine and donepezil treatment groups, respectively. The percentage of women in the galantamine group was 68%; 56% of the donepezil treatment group were women. About 81% of the patients in each group were Caucasian.

The mean ages of the caregivers of patients in the galantamine and donepezil treatment groups were 67.7 years and 69.4 years, respectively. Men and women were nearly equally likely to be caregivers. The patient's spouse was the caregiver for 71% of galantamine patients and for 75% of donepezil patients.

EFFICACY RESULTS:

Sleep Patterns

Patients: For actual sleep percentage, the values for changes from baseline were small for either group at both the nonsteady-state and steady-state visits. As such, the results are difficult to interpret. Changes in the mean that were consistent with improvement were coupled with changes in the median that were consistent with deterioration. Overall, the largest mean change from baseline was a gain of 1.16% for the galantamine group at Week 5.

The patterns of change in the number of wake bouts were consistent with improvements of small magnitudes in both treatment groups throughout the assessment period. The decreases in value for number of wake bouts ranged from a loss of less than 1 to slightly more than 4 bouts, for which the largest improvement was approximately 12% from the baseline. The measures for change from baseline at the non-steady-state visit did not clearly indicate which treatment group had greater improvement in this variable. At the steady-state visit, however, the data indicate slightly greater improvement for the galantamine group. The values for change from baseline in median wake bout time were suggestive of no change for either treatment at either visit.

The pattern for PSQI was consistent with improvement in sleep quality for the galantamine group at both the nonsteady-state and steady-state visits; the pattern was consistent for improvement at the steady-state visit for the donepezil group. There was an approximately 20% improvement in the values for mean and median scores in the galantamine group at each visit, with a slight worsening (more conservatively interpreted as no change) for the donepezil group's scores at the first visit and slight improvements in these scores (although minimally less than those for the galantamine group) at the steady-state visit.

The composite sleep measure is a numeric summary of worsening sleep form all potential sources of such data within the trial. The majority of patients in the trial showed increased pathology on at least one of the components of the score, with higher percentages of patients affected at the nonsteady-state visit. This phenomenon was more pronounced in the donepezil group than in the galantamine group. Overall, the differences in score between the 2 treatments were 17.2 points at nonsteady-state and 3.5 points at steady-state. Components for which there was at least

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a 10 percentage point difference between the two treatment groups were circadian behavior (galantamine was worse) and mean wake bout time (galantamine was worse) at non-steady state, and napping (donepezil was worse), circadian disruption (galantamine was worse) and PSQI (donepezil was worse).

For adverse event reporting related to sleep, more incident adverse events related to sleep occurred in the donepezil treatment arm (5) than in the galantamine treatment arm (1). The majority of these event occurred during the efficacy phase of the trial, ie, when the sleep scales were administered. There were no SAEs related to sleep in the course of the entire trial. One patient in the donepezil treatment group discontinued because of nightmares.

Caregivers: As was observed for the patients, there were minimal changes in value from baseline for either group in the key actiwatch measures of sleep fragmentation: actual sleep percentage, number of wake bouts, and median wake bout time.

The largest magnitude of change in actual sleep percentage calculated with either measure of central tendency was a loss of 0.83%, a smaller difference than that observed for the patients. Similarly, the magnitudes of change in values for the number of wake bouts were small, ranging from a decrease of 1.6 to an increase of 0.9 bouts. Unlike the patient wake bout data, the caregiver data are suggestive of a slight numerical advantage at both visits for the galantamine group's caregivers; the patient data were suggestive of an advantage for the galantamine group at the steady-state visit only. As was observed for the patients, the values of median wake bout time for caregivers suggest that there were no change for either treatment group throughout the assessment phase.

The PSQI data for caregivers was more difficult to interpret than the patient data because of the smaller magnitudes of the changes. Although the mean changes from baseline at the nonsteady-state visit were consistent with improvement, the medians were more consistent with stability for caregivers in both groups. At the steady-state visit, however, the data were more strongly indicative of improvement. Because of the magnitude of the changes were small, determining whether either group had a greater benefit than the other is difficult.

Measures of attention

SRT: The patterns for SRT speed were consistent for improved attention, ie, decreased reaction time, for both groups throughout the assessment period. The data were consistent for greater improvement for the galantamine group at the earlier visit. However, at the later visit, the data were equivocal, with mean scores suggestive of greater improvement in the galantamine group and median scores suggesting the opposite.

The baseline mean data for SRT accuracy indicated minimal room for improvement in either group; median data gave the baseline value for accuracy as 100.00% for both groups. The largest change from baseline in mean value was a gain of 0.38% in the galantamine treatment group at the earlier visit.

CRT: The patterns for CRT speed were consistent with improved attention in both groups throughout the assessment period, with the exception of mean change from baseline for the donepezil group at the earlier visit. At the earlier visit, the data were consistent with greater improvement for the galantamine group. At the later visit, the data were inconsistent, with median scores supportive of greater improvement in the donepezil group and mean scores supportive of greater improvement in the galantamine group.

For CRT accuracy scores, the baseline data were suggestive of slightly more room for improvement than was observed in the SRT; median baseline accuracy scores were 95.00% and means scores were 92.24% in both groups. When analyzed for change from baseline, the median accuracy scores indicated no change in either group at either visit. The means were consistent with slightly better accuracy in the galantamine group at the first and the donepezil group at the second visit.

VSAT: For changes in VSAT speed, the patterns were consistent with improved attention, ie, negative numbers or greater speed, in both groups throughout the assessment period. The data were consistent with greater improvement for the galantamine treatment group at the earlier visit and the donepezil treatment group at the later visit.

For changes in VSAT sum of errors, the patterns were consistent with fewer errors in both groups throughout the assessment period. The data were consistent with fewer errors for the galantamine treatment group at the earlier visit and the donepezil treatment group at the later visit.

Stroop color naming and word reading tasks: For changes in the Stroop word score, the patterns were consistent with more words read correctly in both groups throughout the postbaseline assessments, with this pattern being more pronounced for the donepezil group. For changes in the Stroop color score, the patterns were consistent with more color symbols read correctly in both groups throughout the postbaseline assessments. This pattern was more pronounced for the galantamine treatment group at the earlier visit and for the donepezil treatment group at the later visit. For changes in the Stroop color word score, the overall patterns for galantamine and donepezil differed. The data were suggestive of improvement in color word reading in the galantamine group and deterioration in color word

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reading the donepezil group. The between-group pattern, however, was not inconsistent in the earlier visit because the values for means were suggestive of greater improvement in the galantamine group and the medians were suggestive of the opposite. At the later visit, there was a consistent pattern suggesting greater improvement for the galantamine group. For changes in the Stroop interference score, the patterns were consistent with more resistance to interference in both groups through the postbaseline assessment period. At the earlier visit, the comparative results between the groups were inconsistent, with mean scores supportive of greater improvements in the donepezil treatment group and median scores supportive of the opposite. At the later visit, the results were consistent with greater improvement for the donepezil group.

CIBIC-Plus: For global functioning on the CIBIC-Plus, the data were consistent with a larger percentage of patients showing improvement in the galantamine arm (9 patients, or 33.33%, versus 7 patients, or 24.14%, in the donepezil arm), similar percentages of patient in each arm remaining stable (18 patients, 66.67% in the galantamine group; 18 patients, 62.07% in the donepezil group). Only the donepezil group had patients demonstrating deterioration (4 patients, 13.79%).

QOL measures: For the ADRQL, there was minimal numeric change for either treatment group. The mean change from baseline scores indicated a slight improvement (0.85 points) in QOL results for patients receiving galantamine and a slight worsening (-0.20 points) in QOL results for patients receiving donepezil. The results of the analysis based on medians showed that the score of neither group changed from baseline. For the caregiver analyses (ACTS), on both caregiver measures of time spent assisting patients (the mean total minutes in a given day and the total average minutes spent per day assisting with the ADLs) the pattern was consistent with less time spent in caring for the patients by the donepezil caregivers. The data on mean change from baseline in time patient was left alone, however, indicate that the patients in the galantamine group were able to be left alone more in a given day than were the donepezil group patients. The median values were consistent with no change for either treatment group. For the SF-12 analyses, the patterns were consistent with the values for the galantamine caregivers' physical scores (PCS-12) not decreasing as much as those of the donepezil caregivers. The values for the mental scores (MCS-12) indicated improvement for the galantamine group caregivers while those for the donepezil group caregivers indicated deterioration; the difference in mean scores between the groups on the MCS-12 was 2.57 points.

SAFETY RESULTS:

Adverse events (AEs) Most frequently reported AEs (N [%]):	Galantamine (N=31)	Donepezil (N=32)
Diarrhea	1 (3.2)	5 (15.6)
Headache	2 (6.5)	3 (9.4)
Pain	2 (6.5)	3 (9.4)
Injury	2 (6.5)	2 (6.3)
Nausea	3 (9.7)	1 (3.1)
Bronchitis	3 (9.7)	0 (0)
Constipation	0 (0)	3 (9.4)
Select GI AEs:		
Nausea	3 (9.7)	1 (3.1)
Vomiting	2 (6.5)	0 (0)
Diarrhea	1 (3.2)	5 (15.6)
Anorexia	0 (0)	0 (0)
Aggregate	5 (16.1)	5 (15.6)
No. (%) with one or more AE s	25 (80.6)	24 (75)
No. (%) of deaths	1 (3.2)	0 (0)
No. (%) with one or more serious AEs	3 (9.7)	4 (12.5)
No. (%) treatment stopped due to AE	3 (9.7)	3 (9.4)

Similar percentages of patients experienced AEs over the course of the trial. During the double-blind assessment phase, a slightly higher percentage of the galantamine patients experienced AEs, 67.7% versus 53.1% in the donepezil treatment group.

Differing profiles emerged in patients from each of the treatment groups regarding the most frequently reported AEs over the course of the trial. More galantamine patients experienced nausea and bronchitis, while more donepezil patients experienced diarrhea, headache, pain, injury, and constipation. The most frequently reported AEs tended to occur in the double-blind assessment phase except for the 3 cases of constipation (all in donepezil-treated patients) and 4 cases of injury (2 patients in each group) that occurred during the extension phase. The same number of patients in each group experienced nausea, vomiting or diarrhea, a predefined gastrointestinal aggregate of symptoms commonly associated with acetylcholinesterase inhibitors, over the course of the trial. In both treatment arms, the

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investigators considered few of the AEs that resulted in patient withdrawal, warranted a "severe" rating, or were considered an SAE to be related to study treatment. Two galantamine patients withdrew because of AEs that the investigator assessed as related to study medication but not serious. One of these patients reported nausea while the other reported vomiting. Hepatic failure in a donepezil-treated patient was the only SAE considered related to a study medication by any investigator. Another donepezil-treated patient who was withdrawn had a nonserious AE, nightmares, that was considered by the investigator to be related to study medication.

One galantamine-treated patient died. Heart failure and pneumonia were listed as causes of death for this patient and were not considered to be related to study treatment by the Investigator.

The patterns for change from baseline in pulse rate were consistent decreases for both groups at the week 5 visit, with greater decrease for the donepezil group. The mean decreases were 1.56 and 4.93 bpm for the galantamine and donepezil groups, respectively; the respective median decreases were 2.00 and 4.00 bpm. During the extension phase visits, too little data were recorded for meaningful comparison. The values for change from baseline to endpoint (either completion visit or termination visit) were consistent with the Week 5 results; the values for the galantamine group were 0.54 (mean) and 0 (median) bpm and for the donepezil group were -0.52 (mean) and -2.00 (median) bpm.

CONCLUSION:

The results of this study reflect its pilot nature of small sample size. Although the data from the sleep scales and measures were not consistent regarding changes in quality of sleep in either treatment group, there was some consistency across the scales in that the changes in measures of central tendency for the galantamine treatment group tended to be more on the side of improvement than did those for the donepezil treatment group. However, one must note that these changes were small in some of the scales and not present for all measures of central tendency on all scales. The results for caregiver sleep patterns were of smaller magnitude than were observed for the patients but were still consistent with the results for the patients.

In the analyses of attention measures, each treatment group showed more improvement on the attention measures, with a consistent pattern of greater improvement in the galantamine treatment group at the earlier visit; at the later visit, more of the data points showed a consistent pattern of greater improvement in the donepezil group.

When the results for the CIBIC-Plus were analyzed, the observed deterioration in nearly 15% of the donepezil patients was unexpected, as was the greater proportion of patients on galantamine that showed improvement.

In the QOL analysis, it should be noted that the magnitudes of change were small, and the results should be interpreted cautiously. However, the results did show a pattern suggestive of galantamine having a beneficial effect on the QOL of caregivers and patients.

One patient died during the study; the Investigator considered the cause of death to be unrelated to study treatment. Both treatments were well tolerated. The numbers of patients with AEs were similar in each group throughout the trial; more AEs occurred with galantamine-treated patients during the assessment phase, and more AEs occurred during the extention phase with donepezil-treated patients. The small study population makes these results vulnerable to being difficult to reproduce.

A future trial employing the larger recommended doses for both drugs, 24 mg for galantamine and 10 mg for donepezil, might demonstrate a stronger pattern of better efficacy in each of these areas than was observed in this pilot study for galantamine.

Date of the report: 25 March 2004

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