SYNOPSIS

NAME OF SPONSOR/COMPANY: JANSSEN PHARMACEUTICA N.V. NAME OF FINISHED PRODUCT: RAZADYNE™ (formerly REMINYL®) NAME OF ACTIVE INGREDIENT(S): Galantamine	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: CR012118

Title of Study: Placebo-controlled evaluation of galantamine in the treatment of Alzheimer's disease: a cardiac safety study

Study Initiation/Completion Dates: Start: 14 May 1999 – End: 21 October 1999	**Phase of development:** III

Objectives: To investigate effect of galantamine on heart rate and PR intervals and detect any cardiac arrhythmias and conduction disturbances in patients with Alzheimer's disease treated with a rapid dose escalation of galantamine followed by 2 weeks of treatment at 32 mg per day.

Methodology: This was a 6-week, double-blind, parallel group, placebo-controlled trial of galantamine to evaluate cardiac safety using weekly titration to 32 mg (as opposed to subsequently recommended 4-week titration to 16-24 mg daily). Patients with Alzheimer's disease were randomized to either placebo or galantamine up to 32 mg daily (4 mg b.i.d. in Week 1, 8 mg b.i.d. in Week 2, 12 mg b.i.d. in Weeks 3-4, and 16 mg b.i.d. in Weeks 5-6). Dosage could be reduced from 16 mg b.i.d. to 12 mg b.i.d. during the first 3 days of the 32 mg/day dosing period, if a patient could not tolerate the higher dose.

Number of Subjects: Planned sample size was 120; 139 patients enrolled: 69 were randomized to receive placebo and 70 to receive galantamine.

Diagnosis and Main Criteria for Inclusion: Outpatients with probable Alzheimer's disease by NINCDS-ADRDA criteria, with mild-moderate dementia, MMSE score from 11 to 24, a responsible caregiver, and CT or MRI within one year.

Treatment:

Form - dosing route	matching tablets – oral				
Medication/dose	placebo	galantamine 4 mg	galantamine 8 mg	galantamine 12mg	galantamine 16 mg
Batch number (expiration date)	98I07/F4 (Sep-01)	98H06/F5 (Aug-00)	98D30/F8 (Apr-00)	98A06/F9 (Jan-00)	97B27/F10 (Feb-00)

Criteria for Evaluation: Holter monitors and ECGs were used to measure cardiac parameters at baseline, end of Week 2 (first dose of 12 mg b.i.d.), at the end of Week 4 (first dose of 16 mg b.i.d.) and Week 6 (after 2 weeks of 24 or 32 mg/day; maximum tolerated dose). The primary study parameters were hourly mean heart rates and PR intervals during each 24-hour Holter monitoring periods; 24-hour mean, maximum, and minimum heart rates and PR intervals during each of the 24-hour Holter monitoring periods; and the occurrence of conduction disturbances and cardiac arrhythmias. Safety was also assessed on the basis of the incidence of treatment-emergent adverse events and changes in physical examination findings, vital sign and ECG measurements, and laboratory evaluations. Pharmacokinetic blood levels were tested.

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Statistical methods:

Variable	Method
Holter data (Heart rate and PR interval)	Descriptive statistics of hourly heart rate and PR interval; 24-hour mean, minimum and maximum; 95% confidence intervals (CI) around mean changes from baseline; number and percent of patients with cardiac arrhythmia, conduction disturbances.
Adverse events	Number and percent of patients with AE by treatment group
Laboratory results	Descriptive statistics of means and SE of means; number and percent of patients exceeding normal limits at each timepoint; number of patients with potentially clinically important changes from baseline.
Vital signs, body weight, ECG	Descriptive statistics of mean and change from baseline and SE of means; t-tests; 95% CI around mean difference; number and percent of patients with potentially clinically important changes from baseline
Galantamine trough plasma concentration	Descriptive statistics by each dosage regimen
PK/PD analyses	Linear regression or graphic presentation of relationship between plasma concentration and variables of interest

SUMMARY – CONCLUSIONS

PRIMARY PARAMETER RESULTS: Holter data available from 68 placebo-treated and 70 galantamine-treated patients revealed no significant differences in heart rate or PR interval. At Weeks 4 and 6 there a slight decrease from baseline of approximately 2 bpm in 24-hour mean heart rate in the galantamine group. At Week 6 there was a slight decrease from baseline in mean PR interval obtained by Holter monitoring in the placebo group and a slight increase in the galantamine group: -0.5 and 4.7 msec in the placebo and galantamine groups respectively. The differences between groups did not appear to be clinically significant at any of the time points. There were no statistically significant changes in calculated ECG intervals at Weeks 2 and 4. Although there was a difference between treatment groups at Week 6 for change from baseline QT and QTc intervals, the mean QTc interval decreased in galantamine-treated patients. These changes were not felt to be clinically meaningful. The incidence of QTc lengthening appeared similar in both groups: 9.0% in the placebo group and 10.6% in the galantamine group. Only 3 patients (2 in the placebo group and 1 in the galantamine group) had increases greater than 60 msec and no individuals had QTc intervals greater than 500 msec. The overall occurrence of any new abnormality detected by Holter monitoring was similar in the two groups: 53% of placebo patients and 49% of galantamine patients. There were 4 patients in the placebo group and 4 in the galantamine group with second or third degree heart block; all cases were transient. At Week 2, pauses greater than 2 seconds were more common in galantamine (9%) than in placebo-treated (3%) patients.

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SAFETY RESULTS: The incidence of patients with at least 1 treatment-emergent adverse event was 58.0% in the placebo group and 75.7% in the galantamine group The most common adverse events in the galantamine group were nausea (27.1% galantamine, 4.3% placebo), dizziness (25.7% galantamine, 5.8% placebo), vomiting (14.3% galantamine, 0 placebo) and diarrhea (11.4% galantamine, 5.8% placebo). Treatment was discontinued in 18.6% patients in the galantamine group due to an adverse event, mainly nausea (7.1%); vomiting, headache and anorexia were less frequent causes of termination (2.9%) each. Adverse events caused treatment discontinuation in 2 (2.9%) placebo patients (diarrhea and abnormal hepatic function). Two (2.9%) patients in the placebo group and 4 (5.7%) patients in the galantamine group were reported to have serious adverse events. Although no deaths occurred during the trial or within 30 days following discontinuation of study medication, 1 patient in the galantamine group died of lymphoma (considered unrelated to study medication) 32 days after discontinuing the study.

PHARMACOKINETIC, PHARMACODYNAMIC RESULTS: Galantamine kinetics appeared to be linear in a dose range of 16 to 32 mg daily. There was a dose proportional increase in mean trough galantamine concentrations at steady state. No apparent relationship could be observed between plasma concentrations and ECG parameters of heart rate, PR interval, QRS interval and QTcB interval. The data showed no relationship between galantamine steady-state trough concentrations and vital signs heart rate, but an increase in steady-state trough galantamine concentrations might be associated with a minor increase in vital sign heart rate change from baseline. No apparent trend was observed between mean, minimum, or maximum heart rate or PR interval from the 24-hour Holter monitoring recording and galantamine trough concentrations at steady state at Week 6. Incidences of adverse events of syncope, falls, anorexia, bradycardia, and nausea as well as serious adverse events were associated with similar galantamine concentration ranges to those observed in patients without those adverse events.

CONCLUSIONS: Galantamine had no clinically significant effect, as shown by Holter monitoring, on heart rate or the PR interval at any of the doses tested in this study. The 32 mg dose is not a currently approved dose. There was no clinically significant effect on ECG intervals, or on the incidence of heart block or ventricular arrhythmia. However, pauses greater than 2 seconds were more common in galantamine than in placebo-treated patients during the titration period. Therefore, caution is advised when using the medication in patients with sick sinus syndrome or known cardiac conduction disturbance. Particular attention is warranted during the titration period when the majority of pauses occurred in this trial. The adverse events that occurred during this trial were otherwise typical of cholinesterase inhibitors and no unexpected adverse events were reported.