SYNOPSIS

NAME OF SPONSOR/COMPANY: Janssen-Cilag EMEA NAME OF FINISHED PRODUCT: Reminyl® NAME OF ACTIVE INGREDIENT(S): Galantamine (R113675)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: GAL-MVD-301 **Title of Study:** Long-term Safety and Efficacy of Galantamine in Patients with Alzheimer's Disease or Vascular/Mixed Dementia.		
Principal Investigator: Multicenter study		
Publication (Reference): JRF, Clinical Research Report GAL-MVD-301, May 2007 (EDMS- PSDB-4156603:2.0)		
Study Initiation/Completion Dates: 11 October 2002 / 1 November 2004		**Phase of development:** IIIB
Objectives: The primary objective of this trial was to document the long-term response and safety of galantamine in subjects with Alzheimer's Disease or vascular dementia or AD with cerebrovascular disease.		
Methodology: This was a 24-month, open-label trial in which treatment with 12 mg b.i.d. galantamine was evaluated for patients coming from the clinical trials GAL-INT-13 and GAL-INT-14. These two trials were 1-year follow-up studies of the GAL-INT-6 trial in which subjects received placebo or galantamine. Safety was assessed by periodic physical examination, vital signs, ECG (only for patients with vascular dementia or AD with cerebrovascular disease) and adverse event reports. The ADAS-cognitive scale, MMSE and DAD scale were used to document long-term efficacy. Patients who completed the last visit in GAL-INT-13 or GAL-INT-14 more than 4 weeks before entering this trial, could enter the trial at Visit 2 if they had used galantamine 12 mg b.i.d. in the period between the trials (only a period of maximum 4 weeks without galantamine was accepted). Patients were seen at 6 monthly intervals. Total treatment duration with galantamine over the different trials (GAL-INT-6, GAL-INT-13 or GAL-INT-14, GAL-MVD-301) was 4 to 6 years.		
Number of Subjects (planned and analyzed): Planned: 100 Analyzed: 33		
Diagnosis and Main Criteria for Inclusion: • Diagnosed with Alzheimer's disease (when enrolled previously in GAL-INT-13) or vascular dementia or AD with cerebrovascular disease (when enrolled previously in GAL-INT-14). • Subjects who had completed Visit 3 in GAL-INT-13 or GAL-INT-14 no more than 9 months before entering this trial, and had used galantamine 12 mg b.i.d. since their participation in the previous trial, with the exception of maximum 4 weeks without galantamine. • Subjects (or their legal guardians or legal representatives) and their primary caregiver had to give informed consent for the participation in the trial, according to procedures required by individual countries. If during the trial, the primary caregiver changed (e.g. if patient was institutionalized), the new caregiver had to complete the caregiver's informed consent form. • Subjects had to be in good health, as determined by medical history and complete physical examination.		
Test Product: galantamine (R113675) **Dose:** 12 mg b.i.d. (In case a patient had not taken galantamine for 3-7 days, the patient had to take 4 mg galantamine b.i.d. for one week, then 8 mg galantamine b.i.d. the next week, and afterwards he/she continued with 12 mg b.i.d. If galantamine had not been taken for more than 7 days, the standard 4-weekly dose escalation, starting from 4 mg b.i.d., was used) **Mode of Administration:** oral tablets **Batch No.:** Not applicable		

SYNOPSIS (CONTINUED)

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Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable		
Duration of Treatment: Patients received galantamine for a period of two years during this trial. As this was a follow-up trial of GAL-INT-13 and GAL-INT-14, total duration of treatment with galantamine was 4 to 6 years (trial GAL-INT-6 included).		
Criteria for Evaluation: Efficacy: • Alzheimer's Disease Assessment, cognitive subscale (ADAS-cog) • Disability Assessment for Dementia (DAD) • Mini-Mental State Examination (MMSE) Safety: • Adverse events • Vital signs • ECG (only for subjects with vascular dementia or AD with cerebrovascular disease) • Physical examination		
Statistical Methods: Intent-to-treat analysis; descriptive statistics; frequency tabulations; two sided Wilcoxon signed-ranks test		

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Overall, the mean (SD) total ADAS-cog score increased from 24.4 (12.30) at baseline of the current trial (GAL-MVD-301) to 32.8 (15.60) at treatment endpoint, corresponding to a mean change from baseline of 8.4 (11.46), which was statistically significant ($p < 0.001$). The mean ADAS-cog score increased from 18.6 (7.60) at baseline of the first trial (GAL-INT-6) to 32.8 (15.60) at treatment endpoint. This increase corresponded with a mean change from baseline of the first trial of 14.1 (12.34), which was statistically significant ($p < 0.001$).

The mean total ADAS-cog score at baseline of the first trial (GAL-INT-6) was 18.6 (7.60). The mean increase from baseline of the first trial in total ADAS-cog score was 14.1 (12.34) at treatment endpoint, which was statistically significant ($p < 0.001$). Mean changes from baseline of the first trial that were statistically significant ($p < 0.001$) were noted at Years 3 (5.8 [9.12]), 3.5 (8.2 [9.27]), and 4 (7.4 [8.93]), while a mean change at Year 5 was 15.6 (12.51). At Month 7.5, a statistically significant mean decrease in total ADAS-cog score from baseline of 2.4 (4.36) was noted ($p = 0.002$). These increases in ADAS-cog score versus baseline of the current and first trial indicate a general worsening over time, which was strongest between Year 4 and Year 5.

Overall, the mean (SD) total DAD score at baseline of the current trial was 67.6 (28.40). At treatment endpoint, mean total DAD score had decreased to 47.8 (33.27), corresponding to a mean change from baseline of the current trial of -19.7 (28.06), which was statistically significant ($p < 0.001$). Mean changes from baseline of the current trial in DAD score were generally small at Years 3.5 and 4 (-5.7 [19.59] and –10.6 [18.51], respectively, $p \leq 0.038$). At Year 5 mean change from baseline was -22.8 (30.52) at treatment endpoint. This mean change was statistically significant ($p < 0.001$).

The mean total DAD score at baseline of the first trial (GAL-INT-6) was 82.8 (18.39). The mean decrease from baseline of the first trial in ADAS-cog score was -34.9 (29.31) at treatment endpoint, which was statistically significant ($p < 0.001$), also corresponding to a general worsening. Statistically significant mean changes from baseline of the first trial ($p \leq 0.030$) were noted at Years 1.5, 2, 2.5, 3, 3.5, 4, and 5. These decreases versus baseline of the current and first trial indicate a general worsening, which was strongest between Year 4 and Year 5.

Overall, the mean (SD) MMSE score at screening of the first trial (GAL-INT-6) was 21.6 (3.11). At treatment endpoint, mean MMSE score had decreased to 13.5 (6.68), corresponding to a mean change from screening of the first trial of –7.9 (5.91), which was statistically significant ($p < 0.001$). This indicates a general worsening over time. The observed decreases in mean MMSE score at the different time points were statistically significantly ($p \leq 0.016$), except at Year 1 ($p = 0.992$).

The majority of subjects (97%) had a worsening in MMSE score at treatment endpoint. The percentage of subjects with response to treatment was low at all time points. No subjects with unchanged MMSE score were reported at treatment endpoint.

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SAFETY RESULTS:

Adverse Events Reported by ≥ 5 Subjects During the Current Trial by Decreasing Incidence (Regardless of Severity and Causality)

Preferred term, n (%)	**All subjects** **N = 33**
Urinary tract infection	13 (39.4)
Injury	7 (21.2)
Hematuria	5 (15.2)
Insomnia	5 (15.2)
Pneumonia	5 (15.2)

In total, 97% of the subjects experienced at least one AE that started during the current trial. Severe AEs were reported in 30% of the subjects. None of the subjects were reported with an AE considered at least possibly related to the study medication during this trial. Overall, the most commonly reported AEs were those belonging to the system organ classes "body as a whole - general disorders" (52%), "urinary system disorders" (49%), "gastrointestinal system disorders" (42%), "central and peripheral nervous system disorders" (33%), and "psychiatric disorders" and "respiratory system disorders" (30% each). The most commonly reported AE was urinary tract infection, reported in 39% of the subjects.

Two deaths were reported during this trial resulting from AEs encephalopathy and cerebral hemorrhage. Sixty-four percent of the subjects experienced a SAE of which the SAEs belonging to the system organ classes "body as a whole - general disorders" and "urinary system disorders" were the most commonly reported (18% each). During the current trial, 15% of the subjects had an AE leading to discontinuation. None of the AEs leading to discontinuation were observed in >1 subject.

Overall, no clinically relevant changes in vital signs and ECG were noted. Across all body systems and time points after baseline of the current trial, 97% of the subjects showed treatment-emergent abnormal physical findings of which neurological abnormalities were the most common, reported by 25 subjects.

CONCLUSION:

When administered as 12 mg b.i.d., galantamine is generally safe and well tolerated.

Galantamine can be considered to have a positive effect on the chronic, progressive deterioration of cognitive function and daily living activities in subjects with dementia in this trial. Based on published data, a more rapid deterioration of these efficacy parameters may be expected in similar subjects on placebo or on no treatment.

Date of the report: 4 May 2007