1. Synopsis

<table>
<tr><td>Sponsor:
Janssen Pharmaceutical K.K.</td><td rowspan="3">Summary table of the study
Individual study table referring to part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority use only)</td></tr>
<tr><td>Finished Product: REMINYL®</td></tr>
<tr><td>Active ingredient:
Galantamine hydrobromide</td></tr>
<tr><td colspan="3">Title of Study:
Placebo-controlled confirmation study of galantamine (R113675) for Alzheimer type dementia</td></tr>
<tr><td colspan="3">Investigators:
Total of 91 including Yoshihisa Hatakeyama, Department of Neuropsychiatry, Sapporo Medical University Hospital</td></tr>
<tr><td colspan="3">Study Centers:
Total of 83 centers (91 departments) including the Department of Neuropsychiatry, Sapporo Medical University Hospital</td></tr>
<tr><td colspan="3">Published Literature: None</td></tr>
<tr><td colspan="2">Study period:
Date of First Informed Consent: January 26, 2006
Date of Final Observation: September 19, 2008</td><td>Phase of Development:
Phase III</td></tr>
<tr><td colspan="3">Objectives:
To assess the efficacy and safety of galantamine 16 mg/day and 24 mg/day in 24-week administration to patients with mild to moderate Alzheimer type dementia in a placebo-controlled double-blind comparative study. As primary endpoints for efficacy, Alzheimer's disease assessment scale Japan -cognitive subscale (ADAS-J cog) and Clinician's interview-based impression of change-plus Japan (CIBIC plus-J) were employed.</td></tr>
<tr><td colspan="3">Methodology (Study Design):
This study was planned as a multicenter, placebo-controlled, randomized, double-blind, parallel-group comparison study.
The primary registration was conducted for subjects whose eligibility was confirmed based on the results of screening tests at the start of run-in period (4 weeks prior to the start of double-blind period), and the study drug for the run-in period (placebo tablets) was administered to them for 4 weeks in a single-blind study. Subsequently, the secondary registration was conducted only for the subjects whose eligibility was confirmed based on the obtained survey and assessment results, and they were randomly assigned to the galantamine 24 mg/day treatment group (GAL 24 mg/day group), galantamine 16 mg/day treatment group (GAL 16 mg/day group), or placebo treatment group (placebo group). As for the study drug for the double-blind period (galantamine or placebo), 3 tablets were orally administered to the subjects twice daily, after breakfast and after supper for 24 weeks by the double-dummy method.</td></tr>
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Number of subjects (planned and analyzed):

Target number of subjects: 558 subjects to be registered for secondary registration
(Placebo group 186 subjects, GAL 16 mg/day group 186 subjects, GAL 24 mg/day group 186 subjects)

Analyzed:

Full analysis set (FAS): 574 subjects (Placebo group 191 subjects, GAL 16 mg/day group 191 subjects, GAL 24 mg/day group 192 subjects)

Per protocol set (PPS) -ADAS: 455 subjects (Placebo group 158 subjects, GAL 16 mg/day group 152 subjects, GAL 24 mg/day group 145 subjects)

PPS-CIBIC: 457 subjects (Placebo group 159 subjects, GAL 16 mg/day group 155 subjects, GAL 24 mg/day group 143 subjects)

Safety population: 580 subjects (Placebo group 194 subjects, GAL 16 mg/day group 192 subjects, GAL 24 mg/day group 194 subjects)

Diagnosis and major inclusion criteria:

(1) Patients diagnosed as having probable Alzheimer's disease (AD) in accordance with the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Work Group criteria.
(2) Patients with a Mini-Mental State Examination (MMSE) score of 10 to 22 inclusive at the start of run-in period and at the start of double-blind period.
(3) Patients with a total ADAS-J cog score of at least 18 at the start of run-in period and at the start of double-blind period.
(4) Patients with a score of at least 1 for orientation and word recall on ADAS-J cog at the start of run-in period and at the start of double-blind period.
(5) Patients with a score of at least 1 for orientation of place and orientation of time on Mental Function Impairment Scale (MENFIS) at the start of run-in period and at the start of double-blind period.
(6) Patients in whom gradual development or progression (worsening) of cognitive dysfunction was observed by the investigator or subinvestigator 6 months or longer prior to the start of run-in period.
(7) Outpatients status
(8) Patients with the same caregiver who can provide information necessary for assessment by CIBIC plus-J and manage administration with the investigational product, and accompany the patient at hospital visits during the study period.
(9) Patients who have given informed consent in writing (the legal representative's consent must be obtained, and the subject's consent should be obtained as long as possible)

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Investigational product, dosage and administration:

Investigational product

Type	Galantamine 4 mg tablets	Galantamine 8 mg tablets	Galantamine 12 mg tablets	Placebo (4 mg) tablets	Placebo (8 mg) tablets	Placebo (12 mg) tablets
Composition	Contains galantamine 4 mg per tablet	Contains galantamine 8 mg per tablet	Contains galantamine 12 mg per tablet	Contains no galantamine per tablet	Contains no galantamine per tablet	Contains no galantamine per tablet
Manufacturing sites	Active Ingredient: Janssen Pharmaceutica (Belgium), Product: Janssen Farmaceutici SpA (Italy), Packaging: Bushu Pharmaceuticals Ltd. (Japan)					

Dosage and Administration:

1. Run-in period
   The study drug for the run-in period (placebo tablets) was orally administered twice daily after breakfast and after supper for 4 weeks prior to the start of double-blind period.

2. Double-blind period
   The study drug for the double-blind period (galantamine tablets or placebo tablets) was orally administered twice daily after breakfast and after supper for 24 weeks.

Dosages in treatment groups

Placebo group:
Placebo (1 placebo 4 mg tablet, 1 placebo 8 mg tablet and 1 placebo 12 mg tablet per administration) was administered over Weeks 1-24.

GAL 16 mg/day group:
For Weeks 1-4, galantamine 8 mg/day (1 galantamine 4 mg tablet, 1 placebo 8 mg tablet and 1 placebo 12 mg tablet per administration) was administered, and for Weeks 5-24, galantamine 16 mg/day (1 placebo 4 mg tablet, 1 galantamine 8 mg tablet and 1 placebo 12 mg tablet per administration) was administered.

GAL 24 mg/day group:
For Weeks 1-4, galantamine 8 mg/day (1 galantamine 4 mg tablet, 1 placebo 8 mg tablet and 1 placebo 12 mg tablet per administration) was administered, and for Weeks 5-8, galantamine 16 mg/day (1 placebo 4 mg tablet, 1 galantamine 8 mg tablet and 1 placebo 12 mg tablet per administration) was administered, and for Weeks 9-24, galantamine 24 mg/day (1 placebo 4 mg tablet, 1 placebo 8 mg tablet and 1 galantamine 12 mg tablet per administration) was administered.

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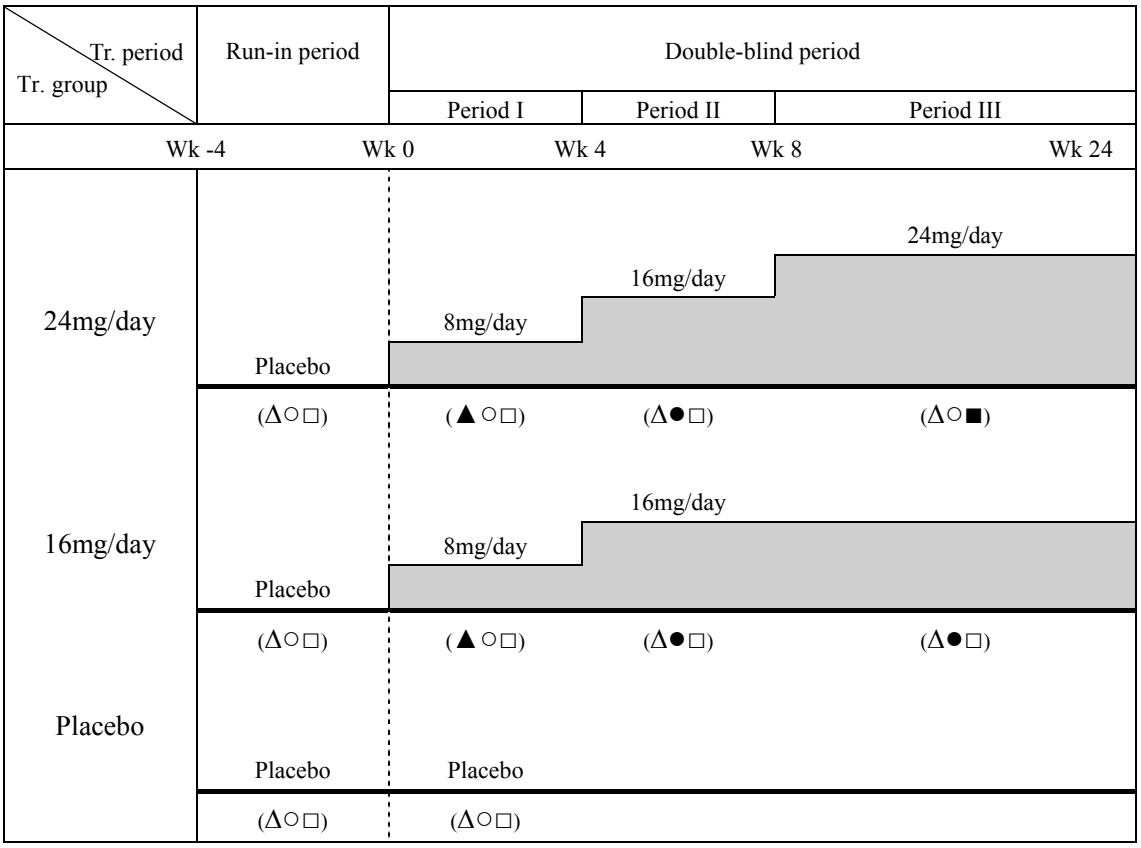

Tablets used

	4 mg Tab.	8 mg Tab.	12 mg Tab.
Galantamine	▲	●	■
Placebo	Δ	○	□

Duration of trial:
(1) Run-in period (4 weeks)
(2) Double-blind period (24 weeks)
(3) Follow-up period (1 week)

Criteria for evaluation:
Efficacy endpoints: ADAS-J cog, CIBIC plus-J
Safety endpoints: Adverse events, blood pressure, pulse rate, body weight, laboratory examinations, 12-lead electrocardiograms

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Statistical Method:

(1) Efficacy

1) ADAS-J cog

For change from baseline at the final assessment (at Week 24), an analysis of covariance (ANCOVA) was conducted using the baseline score as a covariate. A test of therapeutic efficacy was conducted using contrast coefficients of [-2, 1, 1] for the placebo group, GAL 16 mg/day group and GAL 24 mg/day group. Only when a statistically significant difference was detected at a 5% significance level, comparisons of LS means of placebo group vs. GAL 16 mg/day group and placebo group vs. GAL 24 mg/day group were conducted.

The LS means and the standard error were shown for each group, and the difference in LS means compared with the placebo group and the 95% confidence interval of the difference were calculated.

2) CIBIC plus-J

Distributions of 7 grades in the global assessment were shown, and data of the GAL 16 mg/day group and GAL 24 mg/day group were combined, and a comparison with the placebo group was conducted using the Wilcoxon rank-sum test. Only when a statistically significant difference was detected at a 5% significance level, comparisons of placebo group vs. GAL 16 mg/day group and placebo group vs. GAL 24 mg/day group were conducted using the Wilcoxon rank-sum test.

(2) Safety

Adverse events that newly occurred or worsened in the double-blind period were considered Treatment-Emergent Signs and Symptoms (TESS), and the following analyses were conducted for TESS. In addition, analyses were also conducted for adverse events that newly occurred or worsened in the run-in period or later.

- The number of subjects with events, the incidence and the number of events were totalized for each adverse event. The adverse events were totalized based on the System Organ Classes (SOC) and Preferred Terms (PT) in the Japanese version of the Medical Dictionary for Regulatory Activities (MedDRA/J) published by ICH.
- In tantalization of the number of subjects with events, if the same event occurred in the same subject more than once, the events were totalized using the following priority levels:
  For the severity, 1. Severe, 2. Moderate, 3. Mild; for the seriousness, 1. Serious, 2. Non-serious; and for causal relationship, 1. Very likely, 2. Probable, 3. Possible, 4. Doubtful, 5. Not related.
- Adverse events whose relationship with the investigational product could not be ruled out (“Doubtful”, “Possible”, “Probable”, “Very likely”) were handled as “adverse reactions”, and the tabulation was conducted in the same manner as adverse events.

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Summary-Conclusion:

Efficacy results:

Regarding the primary endpoint -- change in ADAS-J cog score from baseline at final assessment, significantly superior results were observed in the GAL 16 mg/day group and GAL 24 mg/day group compared with the placebo group ($p=0.0113$ and $p < 0.0001$, ANCOVA), and the ADAS-J cog score improved with the increase in dose. On the other hand, in CIBIC plus-J scores at final assessment, there were no statistically significant differences in the GAL 16 mg/day group and GAL 24 mg/day group compared with the placebo group. When temporal fluctuations of CIBIC plus-J scores were examined, at Week 16 or later the percentage of worsening was lower in the GAL 16 mg/day group and GAL 24 mg/day group than in the placebo group. In the assessment of subscales of CIBIC plus-J -- DAD and MENFIS, it is suggested that the GAL 16 mg/day group and GAL 24 mg/day group did not worsen the scores compared with the placebo group.

In a responder analysis of ADAS-J cog scores, the percentage of responders was higher in the galantamine treatment groups than in the placebo treatment group, and the percentage increased with the increase in dose.

The percentage of responders who showed an improvement in ADAS-J cog score by at least 4 points and were assessed as “No change in symptoms” or better in CIBIC plus-J scores was 15.7% (30/191) in the placebo group, 19.9% (38/191) in the GAL 16 mg/day group, and 24.5% (47/192) in the GAL 24 mg/day group, and the responders increased with the increase in dose.

From the above results, in CIBIC plus-J scores, the efficacy of galantamine compared with placebo could not be confirmed, but in ADAS-J cog scores, the efficacy of galantamine compared with placebo was confirmed. In the responder analysis of ADAS-J cog scores and in the responder analysis of ADAS-J cog and CIBIC plus-J scores, the percentage of responders increased with the increase in dose of galantamine, and therefore galantamine was considered effective for the treatment of patients with mild to moderate Alzheimer type dementia.

Safety results:

The incidences of adverse events were higher in the GAL 16 mg/day group and GAL 24 mg/day group compared with the placebo group, but most of the events were mild or moderate ones. The adverse events suggesting that inhibition of acetylcholinesterase (AchE), a pharmacological effect of galantamine, may have been involved are anorexia, decreased appetite, nausea, vomiting, diarrhoea, and weight decreased. The incidence of these events was higher in the GAL 16 mg/day group and GAL 24 mg/day group compared in the placebo group.

In adverse events by onset time, all the treatment groups showed slightly higher incidences of adverse events at the induction phase – Week 1, and at the dose escalation period – Week 5 and Week 9 compared with other times, but the next week, the incidence decreased in all the treatment groups. This trend was also observed in the placebo group, but more clearly observed in the GAL 16 mg/day group and GAL 24 mg/day group.

In this study, 1 patient of the GAL 16 mg/day group died of respiratory failure, but the relationship with the investigational product was assessed as doubtful. There was no difference among the treatment groups in terms of serious adverse events and adverse events that led to discontinuation of treatment.

For patients with mild to moderate Alzheimer type dementia, we employed the dose titration that was started with galantamine 8 mg/day followed by dose escalation of 8 mg/day up to 24 mg/day every 4 weeks. The tolerability in this dose titration method was good, and no significant problem with the safety was likely based on the above results.

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Conclusions:

The efficacy of galantamine for the treatment of mild to moderate Alzheimer type dementia was assessed using ADAS-J cog and CIBIC plus-J scores as primary endpoints. As a result, in ADAS-J cog scores, the GAL 16 mg/day group and GAL 24 mg/day group were significantly superior to the placebo group, and the ADAS-J cog score improved as the dose increased. On the other hand, in CIBIC plus-J scores, the GAL 16 mg/day group and GAL 24 mg/day group did not show a statistically significant difference from the placebo group. However, from fluctuations of DAD and MENFIS (subscales of CIBIC plus-J) and results of the responder analysis of ADAS-J cog and CIBIC plus-J scores, galantamine was shown to be effective for the treatment of mild to moderate Alzheimer type dementia compared with placebo.

Regarding the safety in 24-week administration with galantamine started at 8 mg/day followed by dose titration by 8 mg/day up to 24 mg/day every 4 weeks, adverse events that might be attributable to AchE inhibition occurred more often compared with the placebo group. The severity in most of the adverse events was mild or moderate, and the tolerability was good. There was no particular finding to be noted from a viewpoint of safety.

From the above results, galantamine is considered to be an effective drug for the treatment of mild to moderate Alzheimer type dementia, having no problem with safety.

Date of reporting: February 27, 2009

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