SYNOPSIS

Name of Sponsor/Company	Janssen Pharmaceutical K.K.
Name of Finished Product	REMINYL®
Name of Active Ingredient(s)	Galantamine hydrobromide

Issue Date: 18 October 2013

Protocol No.: JNS023-JPN-02

Title of Study: Evaluation of Efficacy and Safety of Galantamine in Patients With Dementia of Alzheimer's Type Who Failed to Benefit From Donepezil

Investigators: Total of 12 including Ken Nagata

Study Center(s): Total of 12 centers (12 departments) including Department of Neurology, Research Institute for Brain and Blood Vessels-Akita, Akita Prefectural Hospital Organization

Published Literature: None

Study Period: 5 September 2011 (Date of informed consent for first subject) to 12 June 2013 (Date of last observation for last subject)

Phase of Development: Phase 4

Type of Study: Post-marketing clinical study

Objectives:

Primary objectives: The efficacy and safety of galantamine 16 to 24 mg/day for 24 weeks in patients with mild to moderate dementia of Alzheimer's type who failed to benefit from donepezil were evaluated in patients who switched from donepezil. Efficacy was evaluated on the Alzheimer's Disease Assessment Scale Japan-cognitive subscale (ADAS-J cog).

Secondary objectives: Efficacy in patients who switched from donepezil was evaluated on the Clinical Global Impression-Change (CGI-C) scale.

Methodology:

This was a multicenter, open-label, single-arm, non-randomized study in subjects with dementia of Alzheimer's type who had a diagnosis of mild to moderate (Mini-Mental State Examination [MMSE] score 10 to 22) probable Alzheimer's disease (AD) in accordance with diagnostic criteria of the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) study group and failed to benefit from donepezil. Subjects were treated with galantamine at a flexible dose of 16 or 24 mg/day for 24 weeks in accordance with the dosing regimen specified in the protocol.

The study agent was orally administered twice daily (preferably after morning and evening meals) for 24 weeks during the treatment period. During the dose escalation period, the study treatment was started with a dose of 8 mg/day (2 × 4 mg), and the dose was escalated to 16 mg/day (2 × 8 mg) at 4 weeks. Dose escalation up to 24 mg/day (2 × 12 mg) was allowed after 8 weeks (flexible dose period) depending on the symptom; however, dose escalation was allowed after subjects were treated at the same dose for at least 4 weeks. Dose reduction to 16 mg/day was allowed in subjects treated at a dose escalated to 24 mg/day if treatment at 24 mg/day became difficult because of a safety or tolerability problem. Re-escalation after the reduction to 16 mg/day was allowed after subjects were treated at the reduced dose for at least 4 weeks. The follow-up period was 1 week after completion or discontinuation of the study treatment in the treatment period and adverse events were investigated during this period.

Number of Subjects (planned and analyzed):

Planned:
Target number of subjects for enrollment; 125
Number of subjects analyzed; 97

Analyzed:
Number of subjects enrolled; 102
Full Analysis Set (FAS); 100
Safety Population (SP); 102

Diagnosis and Criteria for Inclusion:

Inclusion criteria

Subjects who fulfilled the following criteria were included in the study:

1. Subjects who had a diagnosis of probable AD in accordance with the diagnostic criteria of the NINCDS-ADRDA study group.
2. Subjects who had an MMSE score between 10 and 22 at screening.
3. Subjects who received a stable dose of donepezil 5 mg for at least 6 months before screening.
4. Subjects who had progression (worsening) of impaired cognitive function observed at least 6 months before screening and response to donepezil that was considered inadequate by the investigator or subinvestigator.
5. Outpatients.
6. Subjects who had a same caregiver who was capable of providing information required to assess CGI-C, managing the administration of the study agent and accompanying the subject to the study site throughout the study period.
7. Subjects who were considered by the investigator or subinvestigator to have no clinically significant problems in physical examination, medical history, vital signs, and 12-lead electrocardiography at screening. Subjects may have abnormalities in these examinations that are expected from the underlying disease in the study population.
8. Subjects who were medically stable on the basis of the laboratory tests at screening. If any result of serum chemistry, hematology, or urinalysis that was abnormal or out of the reference range, the subject could be included only if the result was considered not clinically significant by the investigator or subinvestigator, or the subject was considered appropriate and reasonable as the subject of the study. This decision was recorded in the subject's source documents.
9. Subjects who provided written informed consent.

Test Product, Dose and Mode of Administration, and Lot Nos.:

Study agents and lot Nos.:

Formulation	JNS023 4 mg tablet	JNS023 4 mg tablet for re-escalation	JNS023 8 mg tablet	JNS023 12 mg tablet
Composition	1 tablet contains 5.1 mg of galantamine hydrobromide (4 mg of galantamine)		1 tablet contains 10.3 mg of galantamine hydrobromide (8 mg of galantamine)	1 tablet contains 15.4 mg of galantamine hydrobromide (12 mg of galantamine)
Production code	0011A	0011B	0010A	0003C
Expiration date	March 2014		April 2014	August 2013
Dosage form	Orally disintegrating tablet			

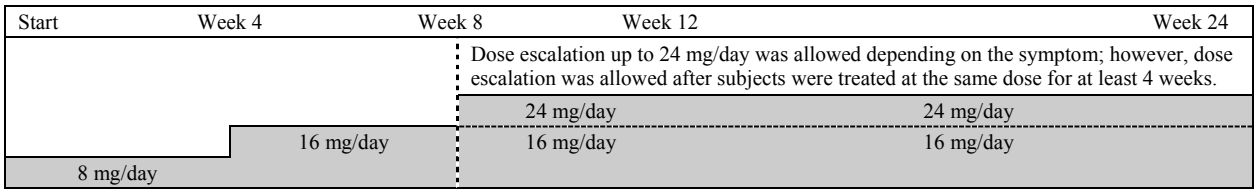
Dose and method of administration:

Method of administration;

The study agent was orally administered twice daily (preferably after morning and evening meals) for 24 weeks during the treatment period. The study agent was allowed to be taken without water.

The study treatment was started with a dose of 8 mg/day (2 × 4 mg), and the dose was escalated to 16 mg/day (2 × 8 mg) at Week 4. Dose escalation up to 24 mg/day (2 × 12 mg) was allowed after Week 8 depending on the symptoms; however, dose escalation was allowed after subjects were treated at the same dose for at least 4 weeks. Dose reduction to 16 mg/day was allowed in subjects treated at a dose escalated to 24 mg/day if treatment at 24 mg/day became difficult because of a safety or tolerability problem. Re-escalation after the reduction to 16 mg/day was allowed after subjects were treated at the reduced dose for at least 4 weeks.

Dose; Flexible dose of 16 or 24 mg/day as the maintenance dose



Study Duration:

Treatment period, 24 weeks; follow-up period, 1 week

Criteria for Evaluation:

Efficacy variables:

a. Primary endpoint: Change from baseline in ADAS-J cog at the end point
b. Secondary endpoints: CGI-C at the end point and percentage of responders with improved ADAS-J cog at the end point (subjects with ADAS-J cog score decreased from baseline)

Safety variables:

Adverse events, laboratory tests (hematology, serum chemistry, and urinalysis), 12-lead electrocardiography, vital signs (blood pressure and pulse rate), weight

Statistical Methods:

1. Analysis sets

a. FAS

The analysis set for efficacy was the FAS. The FAS was defined as subjects who received the study agent at least once and was evaluated for efficacy (ADAS-J cog) at baseline and at least 1 time point after receiving the study agent.

b. SP

The SP was defined as subjects who received the study agent at least once.

2. Efficacy analysis

The following analyses were performed in the FAS. Missing values were imputed by the last observation carried forward (LOCF) method. Analyses were also performed using only data obtained at each evaluation time (data from observed cases [OCs]). Two-sided 95% confidence intervals (CIs) were calculated.

a. Primary endpoint

· ADAS-J cog

Descriptive statistics and 2-sided 95% CI were calculated for the change from baseline in ADAS-J cog at the end point. To visualize the change during the study period, changes from baseline to evaluation times were graphically illustrated. The changes were also graphically illustrated with the improvement of the symptom upward. Descriptive statistics and 2-sided 95% CI were calculated for the change from baseline in ADAS-J cog at each evaluation time point (Weeks 4, 8, 16, and 24).

b. Secondary endpoints

· CGI-C

For the end point, the frequency distribution of CGI-C results (very much improved, much improved, minimally improved, unchanged, minimally worse, much worse, very much worse) was tabulated and the proportion of subjects whose symptoms were considered unchanged or better and its 2-sided 95% CI were calculated. CGI-C results were similarly analyzed for each evaluation time point (Weeks 4, 8, 16, and 24).

· Percentage of responders

A responder was defined as a subject with improved ADAS-J cog (subject with an ADAS-J cog score decreased from baseline by ≥0 point). The percentage of responders and its 2-sided 95% CI were calculated for the end point. The percentage of responders was similarly analyzed for each evaluation time point (Weeks 4, 8, 16, and 24).

3. Safety analysis

Treatment-Emergent Signs and Symptoms (TESS) were defined as adverse events that newly occur or worsen after starting the study treatment. The following analyses were performed for TESS.

· Adverse event terms were written using the Medical Dictionary for Regulatory Activities/J (MedDRA/J) and tabulated by system organ class (SOC) and preferred term (PT).
· If the same event occurred more than once in the same subject, the greatest severity (in order from severe, moderate, to mild), the greatest seriousness (in order from serious to non-serious), and the strongest causal relationship (in order from very likely, probable, possible, doubtful, to not related) were used when tabulating the event.
· An adverse event related to the study agent (the relationship was doubtful, possible, probable, or very likely) was handled as an adverse reaction. Such events were tabulated as with adverse events.
· Adverse events, serious adverse events, and adverse events that led to discontinuation or interruption of the study treatment were also tabulated by severity, time of onset, and dose at time of onset.

Results (summary) – Conclusions:

Study population:

Of the 127 subjects who provided informed consent, 102 were enrolled and all these subjects took the study agent at least once. Of the 102 subjects, 87 (85.3%) underwent the 24-week evaluation and completed the study.

Of the 102 subjects, 15 (14.7%) discontinued the study during the treatment period. The most common reason for discontinuation was safety reasons (adverse events) (11 subjects). The SP included all the 102 subjects who took the study agent at least once. The FAS included 100 subjects, excluding 2 who did not undergo the ADAS-J cog evaluation after study treatment from the SP.

Of all subjects, 32.4% (33/102 subjects) were male, and 67.6% (69/102 subjects) were female. The mean (SD) age was 79.3 (6.90) years. The mean (SD) age of onset of dementia of Alzheimer's type was 75.4 (6.86) years. The mean (SD) MMSE score and ADAS-J cog score at baseline were 17.6 (3.09) and 22.24 (7.765), respectively. The median duration of treatment with donepezil was 1.67 years, ranging from 0.5 to 8.4 years.

Efficacy results:

1. Primary endpoint

The ADAS-J cog score decreased (improved) from baseline. The mean (SD) change from baseline in the ADAS-J cog score at the end point was -2.05 (4.531) (95% CI = -2.95 to -1.15).

The ADAS-J cog score decreased (improved) throughout the treatment period, indicating that the effect of improving the cognitive function was maintained. The mean change from baseline in ADAS-J cog at each evaluation time point (LOCF) was -1.76 (95% CI = -2.47 to -1.06) at Week 4, -1.59 (95% CI = -2.45 to -0.73) at Week 8, -1.71 (95% CI = -2.53 to -0.90) at Week 16, and -2.05 (95% CI = -2.95 to -1.15) at Week 24. The results from OCs were similar to the results obtained by the LOCF method.

2. Secondary endpoints

a. CGI-C

Clinical symptoms were improved and progression of symptoms was delayed. The percentage of subjects whose symptoms were unchanged or improved at the end point compared with the symptoms at baseline was 87.0% (95% CI = 78.8% to 92.9%). Of these subjects, 3.0% (3/100 subjects) had very much improved symptoms, 15.0% (15/100 subjects) had much improved symptoms, 32.0% (32/100 subjects) had minimally improved symptoms, and 37.0% (37/100 subjects) had unchanged symptoms, compared with baseline.

The percentage of subjects with unchanged or improved symptoms remained 86% or higher throughout the treatment period. The frequency distribution of CGI-C at each evaluation time point (LOCF) showed that the percentage of subjects with unchanged or improved symptoms was 94.0% (95% CI = 87.4% to 97.8%) at Week 4, 91.0% (95% CI = 83.6% to 95.8%) at Week 8, 86.0% (95% CI = 77.6% to 92.1%) at Week 16, and 87.0% (95% CI = 78.8% to 92.9%) at Week 24. The percentage of subjects with unchanged symptoms decreased from Weeks 4 to 24, and the percentage of subjects with minimally improved symptoms tended to increase. The results from OCs were similar to the results obtained by the LOCF method.

b. ADAS-J cog responders

The percentage of ADAS-J cog responders at the end point was 70.0% (95% CI = 60.0% to 78.8%). Of these responders, 37.0% showed a decrease (improvement) of ≥0 points and <4 points, 15.0% showed a decrease of ≥4 points and <7 points, 16.0% showed a decrease of ≥7 points and <10 points, and 2.0% showed a decrease of ≥10 points.

The percentage of ADAS-J cog responders at each evaluation time point (LOCF) was 68.0% (95% CI = 57.9% to 77.0%) at Week 4, 71.0% (95% CI = 61.1% to 79.6%) at Week 8, 71.0% (95% CI = 61.1% to 79.6%) at Week 16, and 70.0% (95% CI = 60.0% to 78.8%) at Week 24. The percentage of ADAS-J cog responders remained 68% or higher throughout the treatment period from after Week 4. The results from OCs were similar to the results obtained by the LOCF method.

The above results show that cognitive function and overall clinical symptoms improved in patients who switched from donepezil. It was therefore concluded that oral galantamine 16 to 24 mg/day for 24 weeks was effective in patients with mild to moderate dementia of Alzheimer's type who failed to benefit from donepezil.

Safety Results:

1. Adverse events

The incidence of adverse events during the treatment period was 65.7% (67/102 subjects, 157 events). The incidence of adverse events related to the study agent was 30.4% (31/102 subjects, 50 events).

The most common adverse events (incidence ≥5%) that occurred during the treatment period were nasopharyngitis (14.7%, 15 subjects, 24 events), nausea (5.9%, 6 subjects, 8 events), and diarrhea (5.9%, 6 subjects, 6 events). The most common adverse event (incidence ≥5%) related to the study agent was nausea (5.9%, 6 subjects, 8 events).

The adverse events considered associated with the inhibition of acetylcholinesterase (AChE), a pharmacological action of galantamine, other than nausea and diarrhea, were decreased appetite (3.9%, 4 subjects, 5 events), vomiting (3.9%, 4 subjects, 5 events), and weight decreased (1.0%, 1 subject, 1 event).

Most adverse events were mild or moderate in severity. The incidence of severe adverse events was 2.9% (3/102 subjects, 3 events), and these events were influenza, inflammation, and weight decreased. All these events were resolved or resolving.

The overall incidence of adverse events by time of onset tended to be higher when the initial dose of 8 mg/day was escalated to 16 mg/day or the dose of 16 mg/day was escalated to 24 mg/day, but the incidence did not tend to increase with time. A similar trend was seen for the incidence of gastrointestinal disorders (SOC).

The overall incidence of adverse events by dose at onset tended to be slightly higher with the maintenance dose of 16 or 24 mg than with the initial dose of 8 mg. Of the common adverse events, the incidence of nasopharyngitis was higher with the maintenance dose than with the initial dose. The incidence of gastrointestinal disorders, such as nausea, diarrhea, and vomiting, tended to be higher with the maintenance dose than with the initial dose. It should be noted that the difference in the observation duration between the initial dose and the maintenance dose needs to be considered to interpret these results.

The overall incidence of adverse events did not differ greatly depending on the sex. Overall, the incidence of adverse events by donepezil treatment duration tended to be slightly higher with a donepezil treatment duration of ≥3 years than <1 year or ≥1 year and <3 years. A similar trend was seen for the incidence of gastrointestinal disorders (SOC).

No deaths were reported. Serious adverse events occurred in 6.9% (7/102 subjects, 8 events) during the treatment period and were 1 event each of rotator cuff syndrome, gastric ulcer hemorrhage, myocardial ischemia, gastric cancer, influenza, inflammation, decreased appetite, and dementia Alzheimer's type. The serious adverse events related to the study agent were gastric ulcer hemorrhage, inflammation, decreased appetite, and dementia Alzheimer's type. The serious adverse events that occurred during the treatment period were resolved or resolving, except myocardial ischemia (not resolved). A causal relationship with the study agent was ruled out for 1 serious adverse event (gastric cancer) that occurred during the follow-up period and 1 serious adverse event (rhabdomyolysis) that occurred after the end of the follow-up period. These events were resolved.

The incidence of adverse events that led to discontinuation of the study treatment was 9.8% (10/102 subjects, 11 events). The only adverse event that led to the discontinuation of study treatment in ≥2 subjects was delirium (2.0%, 2 events).

The incidence of adverse events that led to treatment interruption was 4.9% (5/102 subjects, 8 events). The only adverse event that led to treatment interruption in ≥2 subjects was vomiting (2.0%, 2 events).

2. Laboratory tests, ECG, blood pressure, pulse rate, body weight

No clinically significant changes were seen in the laboratory test values, vital signs (blood pressure and pulse rate), or body weight. A laboratory test-related adverse event that occurred during the treatment period was 1 event of mild blood creatine phosphokinase increased in 1 subject, and a causal relationship with the study agent was ruled out for the event. The study treatment was interrupted in this subject, and the event was resolved. One event of severe weight decreased occurred in 1 subject and was related to the study agent. The study treatment was discontinued in this subject, and the event was resolving.

No remarkable changes were observed over time in the ECG parameters (PR, QRS, QT, and QTc intervals). An abnormal ECG-related adverse event categorized in investigations (SOC) was 1 event of mild electrocardiogram ST segment depression in 1 subject, and a causal relationship with the study agent was ruled out for the event. The event was resolved.

The above results indicated that galantamine administered at an initial dose of 8 mg/day and at a maintenance dose of 16 or 24 mg/day for 24 weeks was well tolerated in subjects who switched from donepezil, and no safety concerns were noted in the subjects

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Note: The study refers to a post-marketing clinical study.

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