1 Synopsis

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Sponsor: Janssen Pharmaceutical K.K Finished Product: REMINYL® Active Ingredient: Galantamine hydrobromide	Summery tables of each study Individual study table referring to part of the Dossier Volume: Page:	(For National Authority use only)
Title of Study: Placebo-Controlled Double-Blind Comparative Study of Galantamine (R113675) in Treatment of Alzheimer's Disease		
Investigators: Total of 71 including Taku Yoshida, Department of Neuropsychiatry, Sapporo Medical University Hospital		
Study Centers: Total of 71 including the Department of Neuropsychiatry, Sapporo Medical University Hospital		
Published Literature: None		
Study Period: Date of First Informed Consent: April 11, 2001 Date of Final Observation: February 26, 2004		Phase of Development: Phase III
Objectives: To validate the efficacy and safety of galantamine (R113675) in daily dosages of 16 mg and 24 mg in the treatment of Alzheimer's disease (AD) by means of a placebo-controlled, three-arm, double-blind comparative study, and to investigate the dose-response. In addition, to investigate the similarity between the results generated in this clinical study for the efficacy and safety of galantamine in Japanese patients and the results generated for the drug in Caucasian patients in the GAL-USA-10 clinical study conducted overseas.		
Methodology (Study Design): Multicenter, placebo-controlled, randomized, double-blind, parallel-group comparative study		
No. of Patients (planned and analyzed): Target No. of Patients as Second Enrollment Cases: 390 No. of Patients as Second Enrollment Cases: 398 Efficacy Analysis Set: 390 (FAS population) Safety Analysis Set: 397		
Diagnosis (Subjects), main inclusion criteria and exclusion criteria: Subjects: Patients with mild and moderate AD. Inclusion Criteria: (1) Patients diagnosed with probable AD in accordance with the diagnostic criteria established by the NINCDS-ADRDA Study Group. (2) Patients with an MMSE score of 10-22 inclusive (at the start of the screening period). (3) Patients with an ADAS-J cog score of at least 18 (at the start of the screening period). (4) Patients judged by the investigator and subinvestigator to have gradual onset and progression (aggravation) of cognitive dysfunction during the 6 months or more prior to the start of the observation period. (5) Outpatient status. Exclusion Criteria: (1) Patients with a coexisting neurodegenerative disorder other than AD that presents as dementia. (2) Patients with cognitive dysfunction due to acute cerebral trauma caused by post traumatic brain injury or subdural hematoma, etc. (3) Patients with multi-infarct dementia or active cerebrovascular disease. (4) Patients with a clinically serious cardiovascular disease. (5) Patients taking a cholinesterase inhibitor. etc.		

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Test drug: Galantamine 4-mg tablets, 8-mg tablets and 12-mg tablets.
Control drug: Placebo (confirmed to be indistinguishable from the galantamine 4-mg tablets, 8-mg tablets and 12-mg tablets).

Doses, Method of Administration and Administration Period:

Doses:

- Galantamine 24 mg/day
- Galantamine 16 mg/day
- Placebo

Method of Administration and Administration Period:

(1) Observation period (4-week period before double-blind period)
During the observation period, the "study drug for the observation period" will be administered orally by the single-blind method at three tablets per dose, two doses per day (after breakfast and dinner).

(2) Double-blind period (22 weeks)
The study drug for Double-Blind Period I will be administered from Week 1 to Week 4. The study drug for Double-Blind Period II will be administered from Week 5 to Week 8. The study drug for Double-Blind Period III will be administered from Week 9 to Week 22. The study drugs will be administered orally at three tablets per dose, two dose per day (after breakfast and dinner).

1) Galantamine 24 mg/day group
Subjects will be given 8 mg/day from Week 1 to Week 4, 16 mg/day from Week 5 to Week 22 and 24 mg/day from Week 9 to Week 22.
2) Galantamine 16 mg/day group
Subjects will be given 8 mg/day from Week 1 to Week 4 and 16 mg/day from Week 5 to Week 22.
3) Placebo group
Subjects will be given placebo from Week 1 to Week 22.

Duration of treatment: 26 weeks

(1) Observation period (4 weeks)
(2) Double-blind period (22 weeks)

Reference therapy: None

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Criteria for evaluation:

Efficacy:

(1) Primary endpoints
   1) Change in ADAS-J cog score at final evaluation relative to that at start of double-blind period
   2) Evaluation of CIBIC plus-J at final evaluation

(2) Secondary endpoints
   1) Change in DAD score at final evaluation relative to that at start of double-blind period
   2) Change in Behave-AD score at final evaluation relative to that at start of double-blind period
   3) Change in MENFIS score at final evaluation relative to that at start of double-blind period

Safety:

(1) Subjective symptoms/objective findings (adverse events)
(2) Physical examinations (blood pressure, pulse rate), body weight, ECG, laboratory tests

Statistical Method:

(1) Definition of analysis set
   The full analysis set (FAS) treated was defined as follows.
   The analysis set was defined as subjects who were allocated the study drug after they were judged to be eligible for this study at time of registration, who were given the study drug at least once during the double-blind period, and for whom efficacy data after administration of the study drug was available.
   1) Subject background analysis set
      The FAS was used.
   2) Efficacy analysis set
      The FAS was used.
      Regarding imputation of missing data, they were treated as observed case (OC) data as follows. Data obtained within the allowable period which is fixed for each time point in advance will be used. No data will be used for missing data in the double-blind period.
   3) Safety analysis set
      All subjects given the study drug at least once during the double-blind period were included in the safety analysis.

(2) Analysis of subject background

With regard to the major factor in the patients' background and degree of the symptoms before the start of the double-blind period, distribution and basic statistical value will be figured out by parameters for each treatment group. Appropriate test will be performed (with a significance level of 15%) to investigate the balance of the subjects between the treatment groups.

(3) Efficacy analysis

1) Primary analysis

Using OC data from the primary assessments, the superiority of the test drug in a group (GAL group) comprising the 16 mg/day group and the 24 mg/day group relative to the placebo group was studied in an FAS population.

2) Secondary analyses

① Investigation of dose-response pattern

ADAS-cog was tested by one-way analysis of variance, and CIBIC plus was tested by a non-parametric test, using a contrast coefficient for the placebo group, 16 mg/day group and 24 mg/day group (-2, 1, 1). Other contrast coefficients, i.e., (-1, 0, 1), (-1, -1, 2) and (-1, 2, -1) were used out of consideration for model fidelity.

② Comparison between treatment groups

In the comparison of the placebo group and the 16 mg/day group, and comparison of the placebo group and the 24 mg/day group, analysis of variance was used for ADAS-cog, and the two-sample Wilcoxon rank sum test was used for CIBIC plus.

③ Other analyses

CIBIC subscales (DAD, Behave-AD, MENFIS) and responders were analyzed.

(4) Safety analysis

Regarding adverse events, safety was evaluated by tabulating the number of patients with AEs, the incidence, and the number of instances for each adverse event and for each group.
Regarding results of laboratory tests (hematology and blood biochemistry tests), basic statistics were calculated for test results before and after administration of the test drug and the differences between them for each test item, for each test time point and for each group, and differences were tested using the one-sample t-test.

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Summary-Conclusion:

Efficacy Results:

(1) Comparison of placebo group and GAL group
The superiority of the test drug in the GAL group relative to the placebo group was verified in terms of the two primary assessments: change in ADAS-cog scores and CIBIC plus evaluation 22 weeks after start of treatment.

(2) Comparison of placebo group and 16 mg/day group and placebo group and 24 mg/day group
In terms of change in ADAS-cog scores 22 weeks after start of treatment, no significant difference was seen between the placebo group and the 16 mg/day group, but a significant difference was seen between the placebo group and the 24 mg/day group. In the investigation of the dose-response pattern, the contribution of the contrast coefficient (-1, 0, 1) was the most significant, and a linear dose-response pattern was seen between the three groups.
On the other hand, in terms of CIBIC plus evaluation 22 weeks after start of treatment, a significant difference was seen between the placebo group and the 16 mg/day group, but no significant difference was seen between the placebo group and the 24 mg/day group. In the investigation of the dose-response pattern, the p-value of contrast coefficient (-2, 1, 1) was the smallest.
The difference between the 16 mg/day group and the 24 mg/day group in terms of the above two assessments was studied by means of subset analysis, but no factors were clearly demonstrated.

Safety Results:

The incidence of adverse events in each group was 77.7% (108/139 subjects) in the placebo group, 82.6% (109/132 subjects) in the 16 mg/day group, and 88.9% (112/126 subjects) in the 24 mg/day group. The incidence was lowest in the placebo group and highest in the 24 mg/day group.

The most commonly seen adverse events in the groups given this drug were "metabolism and nutritional disorders" and "gastrointestinal disorders" such as decreased appetite, loss of appetite, nausea and vomiting, which are thought to be associated with an acetylcholinesterase (AchE) inhibitory effect, which is the pharmacological action of the study drug. The incidence of these adverse events was high at the start of administration and when the dose was increased, but they were transitory, and none was severe.

In addition, most of the adverse events that led to discontinuation of administration were decreased appetite, loss of appetite, nausea and vomiting, which are thought to be associated with an AchE inhibitory effect, which is the pharmacological action of the study drug. Many of these occurred at the start of administration and during administration of 8 mg/day or 16 mg/day during the dose-escalation period. Almost none of the adverse events that led to discontinuation of administration at 24 mg/day was an event thought to be associated with an AchE inhibitory effect, which is the pharmacological action of the study drug. In patients in whom administration was discontinued due to nausea or vomiting, nausea or vomiting occurred multiple times before discontinuation of administration, but it resolved rapidly after discontinuation of administration.

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No clinically significant changes were seen in any of the groups in terms of laboratory tests, ECG, vital signs and body weight.

Therefore, we concluded that there was no problem with the tolerability of the study drug at 16 mg/day and 24 mg/day based on the results of this study, except for adverse events thought to be associated with an AChE inhibitory effect, which is the pharmacological action of the study drug.

Conclusions:
The results of this study confirmed that Galantamine (R113675) significantly inhibited progression of dementia symptoms in Alzheimer's disease relative to placebo within a dose range of 16 mg/day to 24 mg/day, and there were thought to be no particular problems with respect to tolerability. However, a similarity in the results of this study and the results of the GAL-USA-10 study in terms of efficacy and safety was not clearly demonstrated.

Report date: September 15,2005

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