SYNOPSIS

Name of Sponsor: Xian-Janssen Pharmaceutical Ltd.

Name of Finished product: galanthamine tablets
Name of Active Ingredient: galanthamine hydrobromide

Protocol no: CR005803

Title of study: a randomized, double-blind, active-controlled, variable-dose, multi-center study to compare the efficacy and safety of galanthamine hydrobromide tablets and donepezil tablets in the treatment of mild to moderate Alzheimer's disease

Principal investigator: Professor Zhang Zhenxin, Department of Neurology, Peking Union Medical College Hospital (1, Shuaifuyuan, Dongcheng District, Beijing 100730)

Literature (references): none

Start/end date: March 26, 2004 - February 4, 2005

Clinical trial phase: Phase III

Research purposes: the major purpose of this study is to evaluate the efficacy and safety of the new drug galanthamine hydrobromide tablets (16 and 24 mg/day) in the treatment of mild to moderate Alzheimer's disease (AD) and provide the required clinical basis for the registration of this product in China.

Research methods: this study is a randomized, double-blind, active-controlled, variable-dose, multi-center clinical trial for evaluating the efficacy and safety of galanthamine hydrobromide in the treatment of mild to moderate AD patients through non-inferiority comparison to presently marketed donepezil tablets.

The study includes a screening period, a single-blind wash-out period and a double-blind wash-out period. Initially, patients underwent a screening period (first visit) of no more than two weeks for the selection of those eligible for assessment. Patients who were currently taking other marketed drugs for dementia only needed to discontinue the drug before screening (first visit) and did not need to receive wash-out, and then entered the single-blind wash-out period (second visit), or else directly entered the baseline period (third visit). The single-blind wash-out period lasted four weeks during which subjects took a placebo, twice daily. The double-blind treatment period (third to seventh visits) lasted 16 weeks, during which subjects who still met the selection/exclusion criteria at baseline were randomized into the galanthamine group and the donepezil group with a ratio of 1:1, and administered twice daily. A 16-week variable-dose treatment was then performed. The dose adjustment was conducted during the previous 9-12 weeks, and the dose was then fixed at 16 mg/day or 24 mg/tablet after the 12th week. The detailed dose is shown as follows:

	The galanthamine group	The donepezil group
Wash-out period		
Week -4 - 0	Placebo	Placebo
Double-blind treatment period		
Week 0 - 4	8mg/day	5mg/day
Week 5 - 8	16mg/day	5mg/day
Week 9 - 12*	16-24mg/day	5-10mg/day
Week 13 - 16	16-24mg/day	5-10mg/day

*The dose was fixed at a certain level within the specified range according to the tolerance of subjects at the end of week 12

Subject number: 233 cases of patients from nine hospitals in China, of which 198 cases completed the trial and 35 cases were withdrawn from the trial.

Diagnosis and major selection criteria: out-patients or in-patients with probable Alzheimer's disease diagnosed according to NINCDS-ADRDA criteria, 40-90 years old, no gender limitation, baseline MMSE scores of 10-24 points (including 10 and 24), had a permanent caregiver during the trial, and the legal representatives of the caregiver and subject should sign the informed consent form. Patients with other neurodegenerative disorders, organic brain diseases or vascular dementia were excluded.

The name, dosage, medication and batch number of test drug: galanthamine tablets, 4 mg/tablet and 8 mg/tablet, Lot No. 04032452 and 04021648, valid until March 2006 and February 2006, respectively. Oral administration, twice daily. See research methods for the doses used in the trial.

The name, dosage, medication and batch number of reference drug: donepezil, 5 mg/tablet, lot number 5817182 and 3116903, valid until January 2005 and September 2006, respectively. Oral administration, once daily. See research methods for the doses used in the trial.

SYNOPSI (CONTINUED)

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Treatment duration: total 16 weeks.

Evaluation criteria:

Efficacy:

Clinical efficacy was assessed with three scales: ADAS-cog (Alzheimer's Disease Assessment Scale - Cognitive), ADCS-ADL (Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory), and NPI (Neuropsychiatric Inventory). The evaluation was performed at baseline (third visit), and after 6 (fifth visit) and 16 (seventh visit) weeks of treatment. The primary outcome measure was the change in ADAS-cog/11 scores from the baseline to the end of the trial (at week 16).

The ADAS-cog/11 was the primary outcome measure, which includes 11 items of function evaluation, namely, immediate word recall, naming objects and fingers, commands, constructional praxis, ideational praxis, orientation, word recognition, remembering test instructions, spoken language ability, word-finding difficulty in spontaneous speech, and comprehension. A higher ADAS-cog score indicates a poorer cognitive function. According to the difference of abilities reflected, these items are classified into six classes: items 3 and 5 reflect "operation" ability; items 1, 2 and 7 reflect "memory" ability; item 6 reflects "orientation" ability; item 4 reflects "visual-spatial" ability; items 9, 10 and 11 reflect "language" ability; and items 8 and 12 reflect "attention" ability.

ADCS-ADL is a 23-item inventory to assess comprehensive activities of daily living by patients with mild to moderate AD. Each item in the inventory is scored 0-3 or 0-7 points in accordance with the difference of questions, with the highest score of 78 points. A higher score indicates a more strong learning ability. The ADCS-ADL is classified into two classes: basic activities of daily living, including items 1, 2, 3, 4, 5, 6, 15 and 18, and advanced activities of daily living, including other items in item 23.

NPI covers 12 neuropsychiatric disturbances in AD patients: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavior disturbances, and appetite and eating abnormalities. Each neuropsychiatric symptom may be present or absent (0 points). The severity of each manifestation is classified into 3 grades (1-3 points): mild, moderate and severe. The frequency of each manifestation is classified into 4 grades (1-4 points): occasional, regular, frequent and very frequent. The NPI score for each manifestation is calculated by multiplying frequency and severity (the highest score = 12). The total NPI score is the sum of the 12 symptom product scores (the highest score = 144). A higher NPI score indicates a poorer performance.

Safety:

Adverse events, clinical laboratory tests, vital signs, and electrocardiogram etc. were included. Adverse events and serious adverse events were gathered from all those reported by subjects or observed by researchers during the period between the beginning research-related step and the last medication, and their nature, severity, treatment, outcome and causal relationship with the drug used were recorded. Clinical laboratory tests, physical examination, and electrocardiogram determination were conducted during the screening period (first visit), at baseline (third visit), and at the end of trial (seventh visit).

Statistical methods:

Within FAS population, PP population and subpopulations, primary endpoint outcomes were analyzed using two methods: the non-inferiority *t*-test and the Two-way ANOVA test. Under the circumstances of considering the center, Two-way ANOVA test was adopted to evaluate whether there was a difference in therapeutic efficacy between the two groups. Additionally, the correlation between primary endpoint outcomes and subpopulation were analyzed. Secondary outcome measures were analyzed by using the Two-way ANOVA test or a CMH test controlling for center to evaluate whether there was a difference in therapeutic efficacy between the two groups.

SYNOPSIS (CONTINUED)

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Summary-Conclusion

Efficacy results:

AD patients treated with galanthamine and donepezil for 16 weeks displayed significantly improved cognitive function that were evaluated with the ADAS-cog/11 scale; galanthamine was superior to donepezil in improving the ADAS-cog/11 scores.

All outcome measures were based on full analysis set (FAS). The analysis on the primary outcome measure showed that cognitive function was improved in both the galantamine group and the donepezil group. After treatment for 16 weeks, the improvement (decline) in ADAS-cog/11 scores from baseline in the galanthamine group and the donepezil group was 5.4±6.4 and 4.0±7.3, respectively, indicating that galanthamine is superior to donepezil in improving the ADAS-cog/11 scores though this superiority showed no statistical significance ($p = 0.0984$).

The results from the analysis of secondary outcome measures, which were based on subgroup analysis and improvement of the ADAS-cog/11, as well as ADCS-ADL score and NPI score, also supported those obtained from primary outcome measure analysis.

After treatment for 16 weeks, the effective rates (the decline in ADAS-cog/11 scores from baseline to endpoint is greater than 0) obtained through ADAS-cog/11 evaluation in the galantamine group and the donepezil group were 82% and 78%, respectively. The percentage of subjects with a decline in ADAS-cog/11 scores greater than 4, 7 and 10 points in the galantamine group (58%, 39% and 24%, respectively) was also higher than those in the donepezil group (49%, 35% and 18%, respectively). At the end of treatment, the number of subjects with a decline in ADAS-cog/11 scores greater than 20 points in the galantamine group (78%) were more than those in the donepezil group (58%) ($p = 0.015$). In addition, galanthamine was significantly superior to donepezil in improving the language ability of subjects after treatment for 16 weeks ($p = 0.035$).

The ADCS-ADL evaluation indicated, after treatment for 16 weeks, activities of daily living in AD patients were maintained in both the galantamine group and the donepezil group, and showed statistically significant improvement in some aspects (meeting, reading and hobbies).

The neuropsychiatric symptoms (NPI) of AD patients were improved in both the galantamine group and the donepezil group after treatment for 16 weeks. Moreover, galanthamine was significantly superior to donepezil in improving night-time behavior disturbances ($p = 0.012$). Overall, treatment with both galantamine (16-24 mg/day) and donepezil (5-10 mg/day) for 16 weeks can improve the cognitive function, activities of daily living and neuropsychiatric symptoms in AD patients.

Safety results:

The maximum recommended dose (24 mg/day and 10 mg/day, respectively) was reached in most of the subjects treated with galanthamine (69%) and donepezil (61%) at the end of the trial. During the trial, the types and incidence rates of adverse events occurred were similar between the galanthamine group (44 %) and the donepezil (47%). The commonly seen adverse events with an incidence rate no less than 5% were mainly digestive system or nervous system symptoms, such as nausea, vomiting and dizziness. The incidence rate of digestive system symptoms (moderate to severe) in the galanthamine group (10%) was lower than that in the donepezil group (23%), showing statistical significance. Most of these adverse events occurred during the trial were mild to moderate, transient, and could be quickly alleviated after stopping medication or giving symptomatic treatment.

Three cases of SAE (one case in the galanthamine group and two cases in the donepezil group) were present during the trial, and two cases might be associated with the drug used. No deaths occurred. The drug-associated SAE in the galanthamine group was thrombocytopenia while that in the donepezil group was acute drug-induced liver injury. After treatment, subjects were back to normal.

Similar results were obtained in vital signs, physical examination and electrocardiogram between the two treatment groups, and no clinical safety concerns were noted. The changes discovered in medical examination were identical to those occurred in the elderly population.

Overall, variable doses of galanthamine (16-24 mg/day) are well tolerated in AD patients. The safety and tolerability of galanthamine are similar to those of donepezil. For the tolerability in the digestive system, galanthamine is superior to donepezil in the incidence rate and severity of adverse reactions.

Conclusion:

Galanthamine tablets (16-24 mg/day) are safe and effective in the treatment of mild to moderate Alzheimer's disease.

Reporting date: May 30, 2005

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