Safety and Efficacy of Donepezil in Mild to Moderate Alzheimer's Disease: A Multi-center Single-arm Study in China

Protocol & SAP Synopsis

2016.10.09

NCT02787746

PROTOCOL TITLE	Safety and Efficacy of Donepezil in Mild to Moderate Alzheimer's Disease: A Multi-center Single-arm Study in China
STUDY SPONSOR	Beijing Friendship Hospital & Eisai (China) Pharmaceutical Co., Ltd.
STUDY PHASE	4
INDICATION	For the treatment of mild to moderate Alzheimer's disease.
PRIMARY ENDPOINT	Monitoring and recording the count and incidence of adverse events (AEs).
SECONDARY ENDPOINTS	• Monitor and record the number of patients withdrew from trial for adverse events. • Change from baseline to 20 weeks in MMSE scores. • Change from baseline to 20 weeks in ADL scores. • Correlation analysis between Apo-E genotyping and adverse events of donepezil.
STUDY DESIGN	This is a Phase 4 multi-center, single-arm, open labeling study.
SAMPLE SIZE	The main indicator of this study was the incidence of adverse events in the treatment of Alzheimer's disease with 10 mg donepezil hydrochloride tablets. According to the safety data in the comprehensive literature, the incidence of adverse events is basically between 69.4%-81%, and the expected total incidence of adverse events is about 76%, estimated with a 95% confidence interval. With reference to the research data, the width of the confidence interval for the incidence of adverse events is 8%, and the significance level is set as 0.05. The sample size is estimated to be 461 cases by using PASS11.0 software. Considering the 20% drop out rate, 554 cases are finally planned to enter the group.

ELIGIBILITY CRITERIA	Inclusion Criteria: 1. Patients between 50 and 85 years of age. 2. Patients newly diagnosed as probable AD based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria and National Institute of Neurologic and Communicative Disorders and Stroke–AD and Related Disorders Association (NINCDS-ADRDA) criteria; Mild to moderate AD with Mini-Mental State Examination (MMSE) 10-24, modified Hachinski ischaemic scale (MHIS)≤4, Activity of daily life scale (ADL)≥23, and Hamilton Depression Scale (HAMD) <7. 3. MRI image supports the diagnosis of AD (medial temporal lobe atrophy, Fazekas scale of white matter lesions≤2 within 6 months prior to the screening). 4. 5mg daily of Donepezil for at least four weeks before the screening. 5. Patient with exclusive caregiver. 6. Patient should be ambulatory or ambulatory aided by a walker or cane. 7. With good eyesight and hearing, can cooperate with the examination and treatment. Exclusion Criteria: 1. Patients with vascular dementia, other types of dementia or with other psychiatric or neurological disorders (e.g. delirium, depression, Parkinson's disease, etc.). 2. Patients with type I diabetes, obstructive lung disease or asthma, vitamin B_{12} or folic acid deficiency, thyroid dysfunction, severe liver or kidney dysfunction, severe cardiac insufficiency (congestive heart failure, myocardial infarction, sick sinus syndrome, II-III degree atrioventricular block or heart rate<50 beats/minute [bpm]). 3. Epilepsy or head trauma resulting in unconsciousness that occurred in the two years prior to the screening. 4. Patients with hematologic diseases (such as anemia, granulocytes, leukemia, etc.), tumor, neoplasms within 2 years prior to the screening. 5. Patients with a history of alcohol dependence and drug abuse. 6. Patients with known hypersensitivity to medicines or

	foods; 7. Patients taking anticholinergic agents or antihistaminic agents; 8. Patients who had been hospitalized continuously for more than 3 months before the screening.
DRUG DOSAGE AND FORMULATION	Once a day, two tablets at a time. Take it orally before bed at night (insomniacs can take it after breakfast). If the subject cannot tolerate 10 mg, he can return to the 5 mg dose, and after 4 weeks of use, increase the dose to 10 mg for the second time. If the second dose is increased to 10 mg and can not tolerate, the person who returns 5 mg or discontinues the drug is considered to be discontinued.
ROUTE OF ADMINISTRATION	Oral
TREATMENT DURATION	Use 10mg dose for 20 weeks.

PROCEDURES	Subjects conducted 3 visits at baseline (-5 to 0 days), maintained 10mg dose within 7 days after 4 weeks and maintained 10mg dose for 20 weeks ±7 days, during which the follow-ups of subjects can be increase at any time with safety of drug . Visit 1 baseline (- 5 to 0 days) 1. The purpose of this visit is to examine whether the subjects are suitable for the study. 2. The subjects and their guardians sign the informed consent form after understanding the research. 3. General information collection: fill in demographic data, inquire about allergy history, inquire about past diseases, record combined diseases and medication, etc. 4. Vital signs measurement. 5. MMSE score, MIS score, ADL score, HAMD score. 6. Laboratory inspection. 7. Syphilis, folic acid and vitamin B12 examination, thyroid function T3, T4 examination. 8. Head MRI (head MRI should include axial position and coronal position. Previous head MRI with diagnostic reference value can be exempted from this item, but it should have detailed image description). 9. ECG examination. 10. Record adverse events. 11. Record combined medication. 12. Inform the subjects to follow up within 7 days after maintaining the dose of 10mg for 4 weeks. If the subjects have any questions or abnormal conditions during this period, they can contact the researchers at any time.

	Visit 2 (maintain 10mg dose within 7 days after 4 weeks) 1. Check whether the subjects take the medicine strictly according to the clinical trial plan. 2. Vital signs measurement. 3. MMSE score, ADL score. 4. APOE genotyping test. 5. Blood biochemical examination. 6. ECG examination. 7. Record adverse events. 8. Record combined medication. 9. Instruct the subjects to follow up after being enrolled for 20 weeks. If the subjects have any questions or abnormal conditions during this period, they can contact the researchers at any time. Visit 3 (maintain 10 mg dose for 20 weeks ±7 d) 1. Check whether the subjects take the medicine strictly according to the clinical trial plan. 2. Vital signs measurement. 3. MMSE score, ADL score. 4. Laboratory inspection. 5. ECG examination. 6. Record adverse events. 7. Record combined medication.

1. STATISTICAL METHODS

1.1 Sample Size Determination

The main indicator of this study was the incidence of adverse events in the treatment of Alzheimer's disease with 10 mg donepezil hydrochloride tablets. According to the safety data in the comprehensive literature, the incidence of adverse events is basically between 69.4%-81%, and the expected total incidence of adverse events is about 76%, estimated with a 95% confidence interval. With reference to the research data, the width of the confidence interval for the incidence of adverse events is 8%, and the significance

level is set as 0.05. The sample size is estimated to be 461 cases by using PASS11.0 software. Considering the 20% drop out rate, 554 cases are finally enter the group.

1.2 Elimination criteria

1. After the clinical study started, it was found that the subjects did not meet the case inclusion criteria or the case exclusion criteria.
2. Subjects had poor compliance and never used study medication.
3. Those who seriously violate the research plan.

1.3 Analysis Populations

Full Analysis Set (FAS) refers to the ideal subject set as close as possible to the principle of intention analysis (the main analysis includes all randomized subjects). The data set is obtained by excluding all randomized subjects with the smallest and reasonable method. For the estimation of the missing values of the main variables, the last carry-forward obsevation (LOCF) was used to the point where the test data was missing, and the number of subjects who evaluated the efficacy at the end point of each group was consistent with that at the beginning of the test .

Per-Protocol Set (PPS) is composed of all cases that meet the test protocol, have good compliance (the actual dose takes 80% to 120% of the applied dose), do not take prohibited drugs during the test, and complete the contents specified in CRF.

Safety Analysis Set (SAS) is composed of all cases taking drugs at least once and having safety evaluation at least once.

1.4 Efficacy Endpoints

- Primary Efficacy Endpoints

Monitoring and recording the count and incidence of adverse events (AEs).

- Secondary Efficacy Endpoints

1. Monitor and record the number of patients withdrew from trial for adverse events.
2. Change from baseline to 20 weeks in MMSE scores.
3. Change from baseline to 20 weeks in ADL scores.
4. Correlation analysis between Apo-E genotyping and adverse events of donepezil.

1.5 Safety Endpoints

Laboratory indicators, vital signs, weight and ECG
The laboratory inspection indicators include:

1. Blood routine: red blood cell count RBC, hemoglobin HGB, platelet count PLT, white blood cell count WBC.

2. Urine routine: urine protein PRO, urine red blood cell count URBC, urine white blood cell count UWBC, urine ketone body KET.

3. Blood biochemistry: liver function (ALT, aspartate aminotransferase AST, alkaline phosphatase ALP, total bilirubin TBIL, γ-glutamyl transferase γ-GT, total protein TP), renal function (creatinine Cr , Urea nitrogen BUN), myocardial enzymes (creatine kinase CK, lactate dehydrogenase LDH), fasting blood glucose GLU, electrolytes (Na^+, K^+, Cl^-, Ca^{2+}).

1.6 Statistical Methods

Complete details of efficacy and safety analyses will be provided in a separate Statistical Analysis Plan (SAP).

1.7 Efficacy Analysis

1. Primary indicators analysis

For the incidence of adverse events, list the number of subjects with adverse events, and calculate the incidence and confidence interval, and at the same time list the number of various adverse events and their incidence and confidence interval.

2. Secondary indicators analysis

The analysis of the loss rate caused by adverse events is the same as the adverse events.

For the changes in MMSE and ADL scores, list the mean, median, standard deviation, maximum, minimum, 25%, and 75% quantiles. The paired t-test should be carried out for the scores before and after treatment to obtain 95% confidence interval of the changes before and after treatment.

1.8 Other Safety Data Analysis

For the QT interval and heart rate before and after treatment, the mean, median, standard deviation, maximum, minimum, 25%, 75% quantiles were used for statistical description, and the scores before and after treatment were paired t-tested. At the same time, the 95% confidence interval of the change value before and after treatment is obtained. Based on the predetermined MCID value, the 95% confidence interval is compared with the lower limit of the 95% confidence interval to determine whether the changes in QT interval and heart rate have clinical significance.

For vital signs, the mean, median, standard deviation, maximum, minimum, and 95% confidence intervals were used to describe the changes in vital signs at each follow-up point.

For laboratory examination and ECG, the clinical significance judgment and frequency (or frequency) of all indexes before and after treatment are made in a cross table, and the details of abnormal examination items after treatment are listed.

For quantitative laboratory test values, list the mean, median, standard deviation, maximum, minimum, 25%, 75% quantiles, and paired t-test for the scores before and after treatment to obtain 95% confidence interval of the changed value to evaluate its safety.

- **Adverse Events**

When filling out the adverse event form, the researcher should use mild, moderate, and severe to describe the intensity of the adverse event. To unify the standard, the classification of event intensity is as follows:

Moderate: To some extent affects the normal function of the subject.
Severe: Obviously affect the normal function of the subject.

- Mild: Does not affect the normal function of the subject.
- Moderate: To some extent affects the normal function of the subject.
- Severe: Obviously affect the normal function of the subject.