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

NCT02787746

July 15, 2015

Informed Consent Form

A single-arm multicenter clinical study on the safety and efficacy of donepezil hydrochloride tablets in the treatment of Alzheimer's disease

Informed Consent Form

We are here to introduce you to participate in a single-arm multicenter (post-marketing) clinical study of the safety and efficacy of donepezil hydrochloride tablets in the treatment of Alzheimer's disease. This clinical study is a clinical observation of a medicine that has been on the market for many years, and before deciding whether to participate, it is necessary for you to understand the purpose of the study, the study medication, the possible benefits and risks to you, what you are expected to do in the study, and your rights as a subject.

1. Project Introduction

The name of this study is: A single-arm multicenter clinical study on the safety and efficacy of donepezil hydrochloride tablets in the treatment of Alzheimer's disease. The study you are participating in is a clinically validated study of a medicine that has been on the market for many years.

Donepezil hydrochloride tablets (trade name: Aricept) is manufactured by Eisai (China) Pharmaceutical Co., Ltd. and was approved by the State Food and Drug Administration in 2007 (Approval No. H20050978) for the treatment of mild-to-moderate Alzheimer's disease, which is also widely used all over the world.

The purpose of this study is to evaluate the safety and efficacy of donepezil hydrochloride tablets in the treatment of Alzheimer's disease, and to systematically accumulate the safety data of donepezil hydrochloride tablets in clinical practice in China, to better serve the general population of patients.

The study used a single-arm design without a control group; therefore, all patients received Aricept, and the medication regimen was consistent with routine clinical care. The specific medication method is as follows: once a day, 2 tablets at a time. Take it orally at night before going to bed (after breakfast for patients with insomnia). If subjects cannot tolerate 10mg, they may return to the 5mg dose, with a second dosage of 10mg after 4 weeks of use; if the second dosage of 10mg is not tolerated, returning to 5mg or discontinuing the drug will be considered as discontinuation of the study. The overall treatment period is 20 weeks.

You will be required to have a total of 3 visits, one at baseline, 4 weeks after maintaining the 10mg dose, and 20 weeks after maintaining the 10mg dose, and safety need be observed at any time during the medication. The following things you need to do with your doctor during each visit:

Visit 1 (baseline): sign informed consent after learning about the study; General information collection: filling in demographic data, allergy history, medical history inquiry, recording of concomitant diseases, combined medications, etc.; vital signs measurement; relevant scale scoring; laboratory tests; Syphilis, folic acid, vitamin B12, thyroid function T3, T4 tests; Brain MRI (should include axial and coronal position, which can be exempted with previous brain MRI with diagnostic reference value, but should have a detailed image description); Electrocardiographic examination（ECG）

Visit 2 (within 7 days after the 10-mg dose was maintained for 4 weeks): vital signs

were measured; Relevant scale scores; APOE genotyping was performed. Blood biochemical tests; ECG

Visit 3 (within 7 days after the 10-mg dose was maintained for 20 weeks): vital signs were measured; Relevant scale scores; Laboratory tests; ECG

Inclusion and exclusion criteria are as follows:

Inclusion criteria

The age ranged from 50 to 85 years old, both male and female,

Patients with a diagnosis of Alzheimer's disease consistent with the 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 for probable AD), with mild to moderate AD as assessed with a Mini-Mental State Examination (MMSE) score (a score range of 0 to 30, with higher scores indicating better cognitive function) of between 10 and 24 (inclusive), Modified Hachinski Ischemia Scale (MHIS)$\leqslant$4, Activity of daily life scale (ADL) $\geqslant$23, and Hamilton Depression Scale (HAMD) <7 at screening. The diagnosis of AD should also be supported by magnetic resonance imaging (MRI) scans (medial temporal lobe atrophy, Fazekas scale of white matter lesions $\leqslant$2 within 6 months prior to the screening).

Have been taking donepezil 5 mg/day for at least 4 weeks before the screening,

Have an exclusive caregiver,

Be ambulatory or ambulatory aided by a walker or cane,

Have good eyesight and hearing,

Could cooperate with the examination and treatment.

Subjects volunteered and had a guardian sign an informed consent form.

Exclusion criteria

Patients with vascular dementia, other types of dementia or with other psychiatric or neurological disorders (e.g., delirium, depression, Parkinson’s disease, etc.).

Patients with type I diabetes, obstructive lung disease or asthma, vitamin B12 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])

Epilepsy or head trauma resulting in unconsciousness that occurred in the two years prior to the screening.

Patients with hematologic diseases (such as anemia, granulocytes, leukemia, etc.), tumor, neoplasms within 2 years prior to the screening.

Patients with a history of alcohol dependence and drug abuse.

Patients with known hypersensitivity to medicines or foods.

Patients taking anticholinergic agents or antihistaminic agents.

Current use of anticholinergic drugs (e.g., atropine, ipratropium bromide, pirenzepine, isopropyl atropine, anisodamine, scopolamine, hexamethylene diamine, succinylcholine) or antihistamine drugs (e.g., chlorphenamine, loratadine, proglumide, famotidine).

Patients who had been hospitalized continuously for more than 3 months before the screening.

2. Research units and qualifications of personnel

This clinical study was led by Xuanwu Hospital of Capital Medical University and Beijing Friendship Hospital affiliated to Capital Medical University. More than 20 research centers nationwide participated in this clinical study. The principal investigator of this study is Professor Jia Jianping. Researchers have rich clinical experience and through the GCP training, has the high academic level.

3. Possible benefits of participating in this study

Your benefits from this study include that your condition may be improved or slower degeneration, you will receive good medical services during the study, and your participation will also contribute to the systematic accumulation of safety data of the drug in clinical use in China which will make more patients with Alzheimer's disease (AD) will have access to better treatment.

4. Possible discomfort and risks to you from the study

All possible drug adverse reaction. The most common adverse reactions of Aricept® include diarrhea, muscle spasms, fatigue, nausea, vomiting, and insomnia. The following is a list of adverse reactions in addition to individual cases according to the organ, system, and frequency of occurrence. [The frequency of adverse reactions was defined as extremely common (≥1 in 10), common (≥1 in 100, < 1 in 10), uncommon (≥1 in 1,000, < 1 in 100), and rare (≥1 in 10,000, < 1 in 1,000).]Extremely common: diarrhea, nausea, headache; Common: common cold, anorexia, vomiting, rash, itching, hallucinations, irritability, aggressive behavior, fainting, vertigo, insomnia, gastrointestinal dysfunction, muscle cramps, urinary incontinence, fatigue, pain, accidental injury; Uncommon: epilepsy, bradycardia, gastrointestinal bleeding, gastric and duodenal ulcer, slight increase in serum creatine kinase concentration; Rare: extrapyramidal symptoms, sinoatrial block, atrioventricular block, abnormal liver function, including hepatitis. In general, the adverse reactions of the study were mostly tolerable, and the study sites and sponsors would provide corresponding support and treatment. In general, the risks were manageable.

5. Contingency plans to be taken in the event of an emergency during the study

If you experience any discomfort during the clinical study, new changes in your condition, or any unexpected situation, regardless of whether it is related to the drug, you should promptly notify your doctor in charge, he/she will make a judgment and medical treatment. Your doctor in charge and the hospital will do their best to prevent any possible risks associated with this study.

If an adverse event occurs during a clinical study, your study physician will provide you with support and treatment. You will be compensated appropriately depending on the circumstances of your injury and relevant laws and regulations.

6. Other matters requiring your cooperation

Please follow the instructions of the responsible doctor of the study. If you need other treatment (including medication), please contact your responsible study doctor in advance.

About drug combination:

CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, and erythromycin) and CYP2D6 inhibitors (e.g., quinidine, fluoxetine), which inhibit the metabolism of donepezil, were prohibited during the study.

During the study period to ban the use of enzyme inducers (e.g., rifampicin, sodium phenytoin, carbamazepine) and alcohol.

Anticholinergic drugs such as neuromuscular blocking agents (succinylcholine, neostigmine), cholinergic agonists (pilocarpine), or beta-blockers (atenolol, propranolol hydrochloride) were prohibited during the study.

All concomitant medications used during the study period should be consulted before administration.

Please according to the appointment to see a doctor. you may be reimbursed $100 for transportation costs with invoice after each visit.

7. Your rights and obligations

1) Rights

The study doctor will introduce you to the study drug and the study arrangement, and participation is completely voluntary.

The study doctor will report to you all events relevant to you so that you can decide at any time whether to continue participating.

If you have any questions, you can call or speak directly to the study physician.

You may refuse to participate in the study or withdraw from the study at any time during the study, without affecting your relationship with your doctor, your medical care, or any other loss of benefits.

2) Obligations

Adhere to the principle of voluntary participation and sign the informed consent form before the start of the study. Please follow the unified arrangement of the research doctor and cooperate with the research doctor to complete the research task. Please do not use other drugs without authorization during the study. If you must use them, please consult your research doctor in advance.

You need to go to the hospital in time during the study follow-up.

8. Reasons for terminating your participation in the study

1) The study physician determined that you would not benefit from the study.
2) You did not take the medication as directed by your study physician.
3) There is a potential risk of harm to your health during the study.

If the above occurs, the study physician has the right to terminate your participation in the study without your consent.

9. Confidentiality

Your records will be safeguarded and treated in confidence. Only authorized personnel can access your records. At the same time, we allow the ethics committee to review your records, but it won't appear in your name and identification.

10. Protocol approval and conduct

The trial protocol was approved by the ethics committee of the primary investigator's institution. If there is any violation of the study protocol during the trial, you can directly complain to the Ethics Committee of Xuanwu Hospital at 010-83198935.

Signed Informed Consent

Study Name: A single-arm multicenter clinical study on the safety and efficacy of donepezil hydrochloride tablets in the treatment of Alzheimer's disease
Sponsor: Eisai (China) Pharmaceutical Co., Ltd
SFDA approval number: H20050978
Centre for the study of Numbers: _____

Subject Consent Statement:

I have read the above description of the study and had the opportunity to discuss it with physicians and ask questions. All my questions were satisfactorily answered. I am aware of the risks and benefits that may arise from participation in this study. I know in the study is voluntary, I confirm that has sufficient time to consider, and understand:

I can always ask the doctor for more information.

I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights and interests will not be affected.

I also knew that if I withdrew from the study, especially for medical reasons, it would be in my best interests and the best interests of the study if I informed my doctor of any changes in my condition and completed the physical and physical examinations.

Because of illness change if I need to take any other medication, I will consult the doctor in advance and tell the doctor afterwards. I have obtained a signed and dated copy of the informed consent form.

I volunteered to participate in this study.

Signature of subjects: _____ **Date:** _____
Contact number: _____
Signature of guardian of subject: _____ **Date:** _____
Relationship with the subject: _____ **Contact number:** _____

The study physician declares:

I confirm that the details of the study have been explained to the subject (and/or the subject's legal representative) so that he or she is fully aware of the above, including his or her rights and possible benefits and risks; Participants were given time to consider and make a decision to participate in the study and a copy of their signed informed consent form was provided.

The doctor signature: _____ **Date:** _____
Contact number: _____