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A Study About the Impact of Intensive Instruction on the Use of Aricept and the Reasons for Discontinuation in Patients With Alzheimer's Disease

Clinical study protocol

Protocol# ART-2013-01
(NCT01972204)

List / abbreviations and definitions of abbreviations and terms

Acronym	Expression not to be omitted (definition)
AChE	Acetylcholine esterase : acetylcholinesterase
AD	Alzheimer's disease : Alzheimer's dementia
ADL	A ctivities of D aily L iving : daily living behavior
AE	Adverse event : adverse event
BPSD	Behavioral and Psychological Symptoms of Dementia : behavioral and psychological symptoms of dementia
CRC	C linical research coordinator: test coordinator over ter
DSM	Diagnostic and Statistical Manual of Mental Disorders : Diagnostic Statistics Manual of the American Psychiatric Association
FAST	Functional Assessment Staging : Dementia severity rating scale
MMSE - J	Mini-Mental State Examination - English : Mental State Short Time Test - Japan Version
NMDA	N-methyl-D-aspartate : N methyl D aspartic acid
SAE	Serious adverse event : serious adverse event

summary

item	Contents
Study name	A Study About the Impact of Intensive Instruction on the Use of Aricept and the Reasons for Discontinuation in Patients With Alzheimer's Disease
The purpose	The purpose of this study is to examine the influence of the instruction on the use of Aricept with educational brochure on the 48-week medication persistence and to assess the reasons for discontinuation.
Examination design	Multicenter joint randomized parallel group comparison study comparative study
Target patient	Alzheimer type dementia patients Selection criteria 1) Patients meeting DSM- IV diagnostic criteria for Alzheimer's dementia 2) Patients who agreed with this research (consent from patients should be acquired as much as possible and consent from substitute is essential) 3) We agree to cooperate with this research, provide necessary patient information, patients with families or carers who can accompany at the regular visit date 4) Outpatient from home Exclusion criteria 1) Patients receiving treatment for AChE inhibitors (donepezil, galantamine, rivastigmine) , and NMDA receptor antagonists (memantine) within 4 weeks before consent acquisition 2) Patients with dyspepsil hydrochloride preparations or hypersensitivity to piperidine derivatives 3) Patients are also other test drug which has received the administration of investigational drugs within 12 weeks before the start of administration of study drug 4) Other patients whose clinical research doctor deemed inappropriate as subjects
Target case number	150 cases
Drugs used	Aricept ® products (commercially available) ・Tablets 3 mg , tablets 5 mg , tablets 10 mg Fine grain 0.5 % ・D tablets 3 mg , D tablets 5 mg , D tablets 10 mg ・Oral jelly 3 mg , Oral jelly 5 mg , Oral jelly 10 mg ・Dry syrup 1% Normally, once 3 mg 1 day as donepezil hydrochloride in adults Starting from 1 to 2 weeks 5 mg And orally administered. For advanced Alzheimer's type dementia patients, 5 mg In 4 weeks

	or more, 10 mg . Further, it should be reduced according to symptoms. Fine: Normal, for adults once a day 0.6 g Starting from 1 to 2 weeks 1.0 g And orally administered. For advanced Alzheimer type dementia patients, 1.0 g In after more than 4 weeks, 2.0 g . Further, it should be reduced according to symptoms. Dry syrup: usually, once a day for adults 0. 3 g It starts from 0 after one to two weeks. 5 g And orally administered. The high degree of Alzheimer-type dementia, 0. 5 g In 4 weeks or more, 1. 0 g . Further, it should be reduced according to symptoms.
Test method	Clinical research personnel to query the allocation group to promptly clinical research secretariat after consent from the subject has been acquired ("informed consent file" in due strengthening leadership group / Normal leadership group), the administration of Aricept ® Start. Among the study period of between 48 weeks, the subjects required date to visit (2 weeks, 12 weeks, 24 weeks, 48 weeks, increase the time from the donepezil hydrochloride 5 mg to 10 mg), examination of the provisions · Perform observation (compliance with medication, cognitive function test, adverse events , concomitant medication). Enhanced leadership group due to "informed consent file", intends line medication guidance using the "informed consent file" to the required date to subject himself and family or caregiver. If you stop taking Aricept ® medication, investigate until the reason is clear .
Evaluation items	<u>Key evaluation items</u> - Aricept ® medication continuation rate when medication after 48 weeks - Aricept ® medication discontinuation at the time of reason <u>Secondary endpoint</u> - Aricept ® factor analysis of the impact on the medication continued
analysis	Aricept ® medication continuation rate of 48 weeks compared with strengthening leadership group and the normal guidance group due to "informed consent file". Aggregates the reason at the time of Aricept ® medication discontinuation, to compare the reason for terminating between groups. In addition, the factors that affect the Aricept ® medication continuously analyzed by logistic regression analysis.
Medical institutions	15 facilities
Research period	After the Joint Ethics Committee approval to 2017 Dec.

table of contents

1. Background · Preface

Alzheimer type dementia (AD) is a progressive neurodegenerative disorder, with a decline in cognitive and memory ability, progressive disorder in daily living behavior, various symptoms of mental symptoms and behavior disorder [1] . Along with the rapid aging, the prevalence of dementia in Japan is increasing, according to the announcement of the Ministry of Health, Labor and Welfare study group in May 2013 (Representative Takashi Asada Tsukuba University), 65 years of age or older The prevalence of dementia among elderly people is estimated at 15 % , which is said to be 4.62 million at 2012 . AD is pathologically characterized by generalized cerebral atrophy and senile plaques of the cerebral cortex and neurofibrillary tangles. In addition, neurochemical studies have reported reduction of acetylcholine (ACh) mainly in forebrain and decreased activity of choline acetyltransferase which is ACh synthase, and the functional deterioration itself in intracerebral cholinergic nerve itself is the most essential "Choline hypothesis" to be said to be a pathological condition began to be cast.

Aricept ® (generic name: donepezil hydrochloride) is an acetylcholinesterase (AChE) inhibitor created by Eisai Co., Ltd. It is an AD therapeutic agent having an action of increasing ACh concentration in the brain . In Japan, in October 1999 tablets (3 mg , 5 mg) were approved for the suppression of the progress of cognitive symptoms in mild and moderate AD, and in tablets (3 mg , 5 mg) as approval, in August 2007 irrespective of severity, Suppression of progress of cognitive symptoms in all AD was recognized as efficacy and effect. With respect to the dosage form additional, fine granules in March 2001, orally disintegrating in February 2004 (D) Tablets (3 m g, 5 mg) , with the change of dosage regimen in August 2007, tablets (10 mg), D tablet (10 mg), oral jelly (3 mg , 5 mg , 10 mg) in July 2009 , and dry syrup in February 2013 .

Aricept ® once, suspended (6 weeks or 4-8 weeks) Then, the case of no treatment cognitive function that is equivalent reported [2], compliance continuation rate of Aricept ® under the actual clinical, low values (Table - 1). According to the report [3] of Watanabe et al., When carried out understanding of drug therapy with pathology and Aricept ® of AD, medication instruction classroom with the aim to improve the medication adherence of the (Aricept classroom [4]) to the patient and family, medication continuation rate although the improvement of is Ru recognized, yet, a patient of about 30% in one year has led to discontinuation. In addition, the reason that lead to medication discontinuation of Aricept ®, the details are to grasp the unknown is often a (eg. Visits and the like that are no longer), the reason for terminating also in order to address the measures for medication continuation rate improved details There is a need.

Table - 1 medication continuation rate of Aricept ® under real clinical

	Specific usage record survey A [5]	Specific usage record survey B [6]			Watanabe 's report [3]
Object	Mild	Height			Mainly mild, moderate
Example number	640 cases	824 cases			About 50 cases
period	3 months	6 months	1 year	2 years	1 year
Drug continuation rate	59.7 %	83.7 %	68.9 %	50.9 %	49.2 %
Aricept Classroom Drug continuation rate at the time of implementation					73.1 %

Eisai Co., Ltd., has been created with the patient and family that medication Aricept ® a description for the tool for caregivers "informed consent file". This tool explains the pathology of AD , the significance of medication by Aricept ® , side effects, etc. , and aims to improve the continuation rate of Aricept ® medication by deepening the understanding of patients and their families and carers .

In the present study, strengthening of medication instruction using the tool to verify the impact on the Aricept ® medication continuation rate. In addition, in subjects medication of Aricept ® has reached the stop, investigate the reason for discontinuation in more detail, you analyze the background factor.

As a result of this study, we hope to build a standard dosing guidance method for drug treatment of Alzheimer type dementia and accumulate useful information for measures to improve the medication continuity rate .

2. Purpose of clinical research

The purpose of this study is to examine the influence of the instruction on the use of Aricept with educational brochure on the 48-week medication persistence and to assess the reasons for discontinuation. To examine the influence of the instruction on the use of Aricept with educational brochure comparing to the ordinary instruction on the 48-week medication persistence and to assess the reasons for discontinuation.

3. Object

Alzheimer disease patients

3.1. Selection criteria

Target patients who meet all of the following criteria

1) Patients conforming to the diagnostic criteria for Alzheimer type dementia by DSM - IV
2) Patients who agreed with this research (consent from patients should be acquired as much as possible and consent from substitute is essential)
3) We agreed to cooperate with this research, provide subject information necessary for this research, patients with families or caregivers who can accompany at the regular visit date

Four) Outpatient from home

3.2. Exclusion criteria

Patients who conflict with any of the following will not be included in this clinical study

1) Patients AChE inhibitor within 4 weeks prior informed consent (donepezil, galantamine, rivastigmine), and are receiving medical NMDA receptor antagonists (memantine)
2) Patients with dyspepsil hydrochloride preparations or hypersensitivity to piperidine derivatives
3) Patients are also other test drug which has received the administration of investigational drugs within 12 weeks before the start of administration of study drug

Four) Other patients whose clinical research doctor deemed inappropriate as subjects

[Rationale for setting]

1) Because there is concern about the influence on the evaluation of drug continuation rate , 2) to 3) for safety consideration

4) In order to leave room for clinical research doctors to consider whether to participate in this clinical study considering the safety of the subject taking the general factors other than those mentioned above into consideration

3.3. Definition of cancellation example

During the clinical study period , Medication of Aricept ® If you need to abort occurs, if it is found that to stop the medication of Aricept ®, or when it becomes the patient was transferred, non-visit by the institutionalization and hospitalization, etc., the case became untraceable It is handled as a discontinued example. In addition, even if you change the Aricept ® to generic drugs handled as a discontinued example.

In addition, we are dealing with a subject that is not called off example with a "medication continue".

The doctor in charge of clinical research investigates the reasons for suspension (classification ① and classification ② below) until the reason becomes clear in the discontinued example and records it in the case report.

[Reason classification of ①] (1 only one selection)

1) Doctor's judgment
2) Hope and judgment of the subject himself / herself
3) Hope , judgment of family member or carer

[Reason classification of ②] (select one or more)

1) Adverse event
2) Insufficient effect
   (A) Effect on cognitive function
   (B) Effect on ADL
   (C) Effect on psychological symptoms
   (D) Other: Free description
3) Change to other oral preparations (galantamine, memantine) (1) 2) Reason for change other than 12) : Free description)

Four) Change to patch agent (rivastigmine) (1) 2) Reason for change other than 12) : Free description)

Five) Change to generic drug

6) Aricept ® drug discontinuation due to hospital entry, ward hospitalization (entry to nursing home health care facility, hospitalization of comprehensive medical system etc)

7) Withdrawal of treatment due to visiting difficulties (eg family members or carers were absent)

8) Discontinuation of therapy due to medication assistance burden increase

9) Refusal (if the subject refuses to take the test medicine and the reason is unclear)

10) Transfer , facility entry , inpatient due to hospitalization

11) Others: it corresponds to the freedom described (12 if the reason is unclear))

12) Unknown (When it becomes impossible pursuit, reason is unclear etc.)

3.4. Additional Supplementary Items in Canceled Example

Investigate the date of discontinuation and state it in the case report.

Even after discontinuation, when continuing medication for Aricept ® (for example, in case of inability to visit by transfer, facility entry , hospitalization, etc) , follow up will take place at the prescribed visit points (2 weeks, 12 weeks, 24 weeks, 48 weeks) At the time of the period, investigate the medication situation of Aricept ® by phone etc. and describe it in the case report.

If there is use of Alzheimer's type dementia treatment drug (including generic drugs) after discontinuation, as follow up, investigate the medication situation of the therapeutic medicine on the telephone etc. at 48 weeks and describe the contents in the case report .

4. Explain to the subject and obtain consent

This doctor in charge of clinical research will fully explain the content of this clinical study etc. to subjects and substitutes . Give subjects and substitutives enough time to ask questions and whether to participate in this clinical study or not before confirming that we have understood the content of this clinical study well and before starting Obtain written consent from the principal (as far as possible) and from the substitute for free participation in participation in this clinical study .

The consent document, describes the clinical research physician and agreed subjects (as possible) was carried out, Daidaku's signed or serial name seal, dating. In addition, if the CRC ・pharmacist etc complementarily explained, the cooperating person also signs,

signs, signs, and writes dates. One copy of the original shall be kept in the chart and the copy shall be given to the subject.

During this clinical study period, it can affect the willingness of subjects and Daidaku's about whether you want to join to continue to subject and Daidaku's new important information may be related to the consent of, or this clinical study, If sexual information is obtained, the clinical research representative promptly revises the consent explanation document based on the information and obtain approval from the joint ethics committee. Clinical research representatives will provide clinical research physicians with a revised consent statement . The doctor in charge of clinical research should promptly explain the information to the subject and the substitute, obtain the reconsideration by free will about the continuing participation in this clinical study, copy the copy of the consent form and the revised explanatory document to the subject .

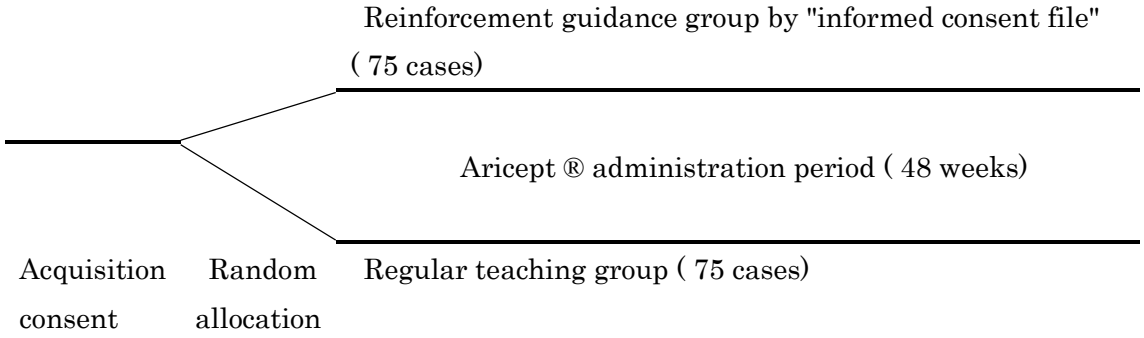
In addition, subjects and substitutes can withdraw their consent at any time even after agreeing to participate in this clinical study, and shall not suffer any disadvantage due to withdrawal of consent .

5. Clinical research method

5.1. Clinical study design

Multicenter joint randomized parallel group comparison study comparative study

5.2. Test outline



1) Taking medication by "Informed consent file" (Attachment 2)

In strengthening leadership group due to "informed consent file", during the visit of the provisions (the second week [at the time increased from donepezil hydrochloride 3 mg to 5 mg], 12 weeks, 24 weeks, 48 weeks, and the increase at the time) from the donepezil hydrochloride 5 mg to 10 mg, use the "informed consent

file", the pathology of AD, the significance of drug therapy with Aricept ®, side effects, etc. to the subject himself and family or caregiver explain.

2) Confirmation of reason for canceling medication

If medication is stopped , confirm the reason . If you did not visit the clinical research physician, CRC · pharmacist or the like to perform the investigation until the clear reason by telephone or the like.

5.3. Study participation schedule period of subjects

48 weeks

5.4. Drug information

Aricept ® products [Eisai Co., Ltd.]

1) Tablets 3 mg , tablets 5 mg , tablets 10 mg (containing 3 mg , 5 mg , 10 mg of donepezil hydrochloride in 1 tablet)
2) Fine grain 0.5 % (1.0 g contains 5 mg of donepezil hydrochloride)
3) D Tablets 3 mg, D Tablets 5 mg, (containing donepezil hydrochloride 3 mg in 1 tablet, 5 mg, 10 m g) D Tablets 10 mg
4) Oral jelly 3 mg, oral jelly 5 mg, (containing donepezil hydrochloride 3 mg, 5 mg, 10 mg in 1) oral jelly 10 mg
5) Dry syrup 1% (containing 1 mg of donepezil hydrochloride in 1.0 g)

It is possible to change the dosage form during the research period . When changing the dosage form, describe its contents in the case report.

Storage and Storage Conditions

· Storage at room temperature
· Before opening the fine grained bulk package, shield the light and preserve it.
· D tablet After opening the aluminum bag, PTP packing should be stored avoiding moisture. Rose packaging should be stored after opening the aluminum bag, shielding light and avoiding dampness.

For details see Aricept ® package insert

5.5. Dose / administration method and administration period / method of use

There line the administration of the following drug agents, to continue 48 weeks.

Once a day as donepezil hydrochloride 3 mg　Starting from 1 to 2 weeks 5 mg　And orally administered.　For advanced Alzheimer's type dementia patients, 5 mg　In 4 weeks or more, 10 mg　.　Further, it should be reduced according to symptoms.

Fine: Normal, for adults once a day 0.6 g　Starting from 1 to 2 weeks 1.0 g　And orally administered.　For advanced Alzheimer type dementia patients, 1.0 g　In after more than 4 weeks, 2.0 g　.　Further, it should be reduced according to symptoms.

Dry syrup: usually, once a day for adults 0. 3 g　It starts from 0 after one to two weeks. 5 g　And orally administered.　The high degree of Alzheimer-type dementia, 0. 5 g　In 4 weeks or more, 1. 0 g　.　Further, it should be reduced according to symptoms.

In addition, if the dose of donepezil hydrochloride is increased or decreased in the range up to 10 mg at the discretion of the doctor in charge of clinical research , the study is continued .

5.6.　Assignment method

Assignment managers prepare subject individually allocated envelopes of random assignment of 240 cases of study treatment (including 90 preliminary cases) beforehand and provide them to the clinical research secretariat .　Clinical research staff will promptly refer to the clinical research secretariat to allocate examination treatment of the subject in the registration form after consent from the subject is acquired .　Clinical research Secretariat, in advance based on the allocation table that was created, and notifies the allocation group that is described in the allocation table by young turn to clinical research personnel.　When notifying the assignment, the Clinical Research Secretariat promptly transmits " registration date ", " date of consent acquisition", "subject identification code", "facility name", " name of clinical research staff who made the notification " fill in the allocation record file, stores.

After the subject of allocation query, clinical research personnel, for subjects having acquired the consent, store to create a subject identification code table.　In the subject ID code table, fill in the subject name, gender, consent acquisition date, medical record number, subject ID code.　The assignment treatment group notified from the clinical research secretariat shall be entered in the subject identification code table promptly after notification .

5.7.　Regulations on concomitant medication (therapy)

1) Concomitant medication (therapy)

Not applicable

2) Combination prohibited drug (therapy)

· AChE inhibitors (galantamine , rivastigmine)

3) combination restriction drug (therapy)

Not applicable

4) Combination caution drug (therapy)

Use it with caution when using it.

· Sucamethonium chloride hydrate

It may potentiate muscle relaxant action.

· Choline activator, cholinesterase inhibitor

There is a possibility that the choline stimulating action such as the vagus nerve stimulating action is enhanced.

· Itraconazole, erythromycin, etc., quinidine sulfate hydrate etc.

It may inhibit the metabolism of this drug and potentiate its action.

· Carbamazepine, dexamethasone, phenytoin, phenobarbital, rifampicin etc.

It may promote the metabolism of this drug and reduce its action.

· Central anticholinergic agent, atropine anticholinergic agent

This drug and anticholinergic agent may interfere with each other and reduce the respective effects.

Non-steroidal anti-inflammatory analgesics

It may cause peptic ulcers.

For details see Aricept ® package insert

6. Evaluation item

6.1. Key evaluation items

1) Compliance continuation rate when Aricept ® administration after 48 weeks

2) The reason at the time of Aricept ® medication discontinuation

6.2. Secondary objectives

1) In each group, the analysis of the factors that affect the Aricept ® medication continues

[Subject background factor]

- years of education (number of years)

· Same residence family (Yes No)

· Caregiver background (relationship, sex, age, nursing care experience, watch over / day)

· Nursing care classification (7 categories)

· In-home service (availability, type [free description] , frequency / month)

· Severity : FAST (7 steps)

· MMSE-J total score

· MMSE-J item scores

· Daily independence degree of elderly with dementia (9 ranks)

· Concomitant medications (antipsychotic drugs, antiepileptic drugs, antidepressants, sleep inducing drugs, Chinese herbal medicines etc.)

· Number of concomitant drugs (number)

· BPSD (delusions, hallucinations, excitement, depression · discomfort, anxiety, euphoria, irresponsible · indifference, depression suppression, irritability · instability, presence or absence of abnormal behavior)

[Factors after commencement of research]

· MMSE-J total score change

· MMSE-J The amount of change in each item score

· Average compliance (90 % or more, 70 % or more and less than 90 % , 30 % or more and less than 70 % , 10 % or more and less than 30 %, less than 10 %)

· Addition (presence or absence) of antipsychotic drugs, antiepileptic drugs, antidepressants, sleep inducing drugs, Chinese herbal medicines etc. during the research period

· Addition of memantine during the research period (presence / absence)

2) Safety assessment

· Adverse events

Side effects

item	Clinical the study start date	Administration start date	2 weeks ※ 1	12 weeks ※ 2	24 weeks ※ 2	48 weeks ※ 2 Or Canceled ※ 4	Donepezil hydrochloride when increasing from 5 mg to 10 mg * 5
Acquisition consent	○						
Subject background	○						
Medication compliance			○	○	○	○	○
Medication instruction by 'informed consent file' ※ 3		○	○	○	○		○
Cognitive function test * 6 (MMSE-J)		Δ		Δ	Δ	Δ	Δ
Adverse event			○	○	○	○	○
Use of concomitant medication		○	○	○	○	○	○

7. Observation / inspection items and schedule

7.1. Observation and inspection schedu

Table - 2 Administration and Inspection Schedule

※ 1 Increase from 3 mg to 5 mg of donepezil hydrochloride . The week before the allowable range.

※ 2 Allow 2 weeks before and after .

※ 3 It is implemented in the reinforcement guidance group by "informed consent file" . (Attachment 2)

* 4 Detailed confirmation of the reason for termination is carried out . If you do not visit the hospital, doctor in charge of clinical research, CRC · pharmacist etc investigate until the reason is clarified by telephone etc.

※ 5 It is carried out in advanced Alzheimer's type dementia. From donepezil hydrochloride 5 mg to 10 mg

Is increased.

* 6 When implementation is possible, at the start of administration and at 12 weeks. Furthermore, it is also carried out to the extent possible, at 24 week, 48 week, when stopping, and when increasing from 5 mg to 10 mg of donepezil hydrochloride .

7.2. Observation and inspection items

7.2.1. Subject background

Investigate the following items at the start of clinical research and fill in the case report.

· Subjects Background: gender, date of birth or age, years of education (number of years), family member (presence or absence), caregiver background (relationship, gender, age, presence or absence of nursing experience, watching time / day), requiring long-term care division (7 categories) , in- home service (presence / absence, type [free description] , frequency / month)

· Consent of examinee and substitutee : date of consent acquisition , subject identification code

· Disease period: morbidity period, severity FAST Attachment 3) (7th step) , Daily life independence of elderly people with dementia Attachment 4) (9 ranks) ,

Total score of each MMSE-J and each item score, BPSD (delusions, hallucinations, excitement, depression · discomfort, anxiety, euphoria,

excitement / indifference, depression suppression, irritation / instability, abnormal behavior)

· Complications: Name of the afflicted disease at acquiring consent

· Concomitant medication: drug name

7.2.2. View

When administered after 2 weeks, when 12 weeks, at week 24, at 48 weeks or when stopped, and examined the following items during increase from donepezil hydrochloride 5 mg to 10 mg, to fill in the case report form.

1) Medication compliance

The doctor in charge listens to subject compliance and evaluates in the following five stages.

① medication 90 % or more ② medication 70 % or more and less than 90 % ③ medication 30 % or more and less than 70 %

④ medication 10 % or more and less than 30 % ⑤ medication taking less than 10 %

2) Cognitive function test

Examine the total score and each item score of MMSE- J . If practicable, perform at the beginning of administration and at 12 weeks. Furthermore, it is also carried out to the extent possible, at 24 week, 48 week, when stopping, and when increasing from 5 mg to 10 mg of donepezil hydrochloride .

3) Adverse event

9.2 See record of adverse events

Four) Use of concomitant medication

Investigate the drug name. For memantine, we investigate dose and dosing period.

8. End of research , suspension and suspension

8.1. The end of the study

Regarding treatment after completion of this clinical study, we will leave it to the judgment of the attending physician based on the state of the subject .

In the case where the clinical study has been completed in the exemplary medical institutions, research responsible physician based on the provisions of the medical institution, the length and Tokushukai group Co Ethics Committee schematic and terminated that the medical institutions of this clinical study results .

8.2. Stop-interruption in the research

During this clinical study progresses, if it is forced to change, such as stop-interrupted or this clinical study implementation plan of the clinical studies for the following reasons, research investigators length of quickly its contents and the reasons of medical institutions Contact. The responsible physician shall promptly report the relevant information to the head of the medical institution and the Joint Ethics Committee in writing.

1) If drug safety agent used, the critical information on the effectiveness obtained
2) When it is judged that it is necessary to change this clinical study implementation plan due to the occurrence of serious adverse event
3) When it is judged that recruitment of subjects is difficult and it is obviously difficult to achieve the number of cases planned

9. Adverse events and pregnancy information , other events

9.1. Definition

Definitions of adverse events (AE) and serious adverse events (SAE) are shown below.

9.1.1. Adverse event (AE)

The adverse event occurs during this clinical study period to a subject in medicine agent is administered, (including abnormal abnormal laboratory values) any undesirable or unintended sign is that the event, and this clinical study Whether or not there is a cause-and-effect relation does not matter. Including worsening of the original disease, deterioration of complications.

9.1.2. Serious adverse events (Serious adverse event: SAE)

The serious adverse events, of any medical events that occur when drug agent is administered (both doses), refers to the following event.

1) Those that resulted in death
2) Threatening life
3) Those in need of extension of hospitalization or hospitalization / treatment period
4) Persistent or serious malfunction
5) Congenital abnormality has come

6) Other serious medical events

Medical judgment that medical or surgical treatment is required to expose subjects to crisis or not to result in any of the above, even if death, life-threatening events, or events requiring hospitalization are not occurred Is considered a serious adverse event.

9.2. Record of adverse events

Clinical research physician is, this clinical study for a new adverse events occurring after the start, the event name , serious category (serious, non-serious), severity (mild, moderate, severe) , the expression date, treatment , outcome date (or outcome date confirmed) , outcome (recovery, there has been recovery sequelae, light, non-recovery, death, unknown) and this clinical study causal relationship between (no relation, related Oh might Rukamo , probably related Yes) In the case report.

For abnormal variations in clinical laboratory values judged clinically important by a doctor in charge of clinical research , fill out the case report along with the basis.

Regarding the causal relationship between adverse events and this clinical study , fill in the case report the basis of the judgment.

(1) Causality relationship with this clinical study

1) No relation:

There is no reasonable causal relation between this drug administration and adverse event. (There is no temporal rationality between this drug administration and adverse events, or it is thought that the factors of patients, such as concomitant drugs and original diseases and complications, are greatly influenced by patients.)

2) There may be relevance :

There is a possibility of a reasonable causal relationship between this drug administration and an adverse event. (There is temporal rationality between this drug administration and the adverse event expression and the possibility of a causal relationship with this drug is considered even when considering factors of patients such as concomitant drugs and original diseases and complications Conceivable.)

3) Probably related :

There is a high possibility of a reasonable causal relationship between this drug administration and an adverse event. (There is temporal rationality between this drug administration and the adverse event expression and the possibility of a causal relationship with this drug is

considered even when considering factors of patients such as concomitant drugs and original diseases and complications A similar adverse event is admitted by re - administration.

(2) Severity of Adverse Events

1) Mild: degree of discomfort, but not affecting normal daily activities

2) Moderate: degree of disruption to normal daily activities due to discomfort

3) High level : incapacity or enough to normal daily activities becomes impossible, it was deprived of the activity capacity state

If the severity of an adverse event changes, record the heaviest one.

9.3. Report of serious adverse events

This clinical study regardless of presence or absence of a causal relationship between, if serious adverse events were expressed, investigator physician , after taking prompt and appropriate treatment of safety in the first priority, immediately the medical Report to the chief of the institution.

Brief description of the adverse events, the reason is judged to be severe , the test subject identification code , investigator physician , clinical research name and day 1 of administration , causality (drug agents and clinical studies determined steps) shall describe . In addition, the adverse event will be notified to the joint clinical research institution.

In addition, prepare a serious adverse event report and contact the clinical research secretariat (submission of a copy) . In addition, when unexpected serious adverse events related to this clinical study occur, the status and results of response will be announced and reported to the Minister of Health, Labor and Welfare, etc.

9.4. Reporting of pregnancy information

If you perceive the information about the pregnancy is , the study investigators report on pregnancy and to create, clinical research secretariat to contact the (Submission of copy) . Study principal investigator, and follow-up to the outcome of birth, spontaneous abortion, abortion, etc. pregnancy is known, after the proven outcomes of pregnancy, to create a report on the outcome of pregnancy, clinical research secretariat to contact the (A copy of the Submit) . If the outcome of pregnancy is spontaneous abortion, abortion, congenital anomaly, perinatal mortality, treat it as a serious adverse event, in addition

to a report on the outcome of pregnancy, together with a serious adverse event report create.

9.5. Report of other events

Excessive amount of administration If you perceive the information related to the research principal investigator excessive amount of administration report on the Create, clinical research secretariat to contact the (Submission of copy) .

9.6. Expected adverse events

Please refer to the Aricept ® package insert for the content and rate of occurrence of anticipated adverse events .

9.7. Report to the manufacturer of the drug concerned

The clinical research secretariat submits the following report (copy) to Eisai Co., Ltd., the manufacturer of the drug.

· Serious adverse event report
· Report on pregnancy and report on pregnancy outcome
· Report on overdosage

Ten. Implementation period

Joint Ethics Committee approval after ~ 201 5 years 6 May 3 1 day

Registration period: Joint Ethics Committee approval later - 2014 years 3 Tsuki 31 days

Patient Out Last : 2015 year 3 Tsuki 3 1 day

Statistical analysis: ~ 2015 years 5 May 3 1 day

Summary reporting: ~ 2015 years 6 May 3 0 days

11. Statistical analysis

11.1. Analysis target group

Obtaining informed consent to the procedure noncompliance with examples, all analyzes target excluded from. Aricept ® medication continuation rate , Aricept ® medication discontinuation at the time of the reason for the analysis of, the full analysis (Full Analysis Set : FAS) and the target group which is adapted to study implementation plan (Per Protocol Set : PPS) providing a . FAS is also a one-time study drug is administered has been a subject of the population. PPS shall be a group excluding cases of inappropriate selection / exclusion criteria from FAS and examples of use of

prohibited concomitant medications . In addition, safety on the analysis is , even study drug was administered once a subject of the population.

11.2. Analysis of main evaluation items

48 weeks Aricept between ® medication continuation rate the due to "informed consent file" strengthening leadership group and the normal guidance in group 2 performs a comparison of rates between the groups (two-tailed test, the p-= 0.05 , with respect to the following statistical tests Similarly). We also compare intergroups independently in the medication continuation rate for each Visit [2 nd week, 12 th week, 24 th week] .

Aricept ® medication discontinuation during aggregates the reason of, between the groups stop reason to compare .

11.3. Secondary assessment analysis of the item

In each group, Aricept ® medication continues to affect the factors by logistic regression analysis to analyze (Factors, 6.2 2) reference). In addition, we compare the influence of factors among groups (points which are multiple selections are not considered) .

11.4. Analysis of safety

Subjects who are included in this clinical study and whose test drugs have been administered at least once are subject to safety analysis.

All adverse events are indicated and serious adverse events are separately counted. Drugs agents adverse events observed after administration administration group by type of adverse events for each, categorical adverse events was calculated expression rate, a comparison between groups (adverse events by type, categorical statistical analysis Performed by the data center prior to) .

11.5. Other

In addition to the predetermined analysis plan , additional exploratory analysis is performed as necessary, such as comparison between transition patterns of the clinical state after incorporation into the study , as necessary.

12. Number of target cases and setting basis

Total 150 cases

[Rationale for setting]

In one year's observation results [3], which showed the influence on the continuation rate of the medication instruction class (Aricept class) in patients with Alzheimer's type dementia [3], the continuation rate of the group not taking medication instruction was 0.49 (95% confidence limit 0.36 - 0.61), but in the advising instruction classroom the continuation rate was 0.73 (95% confidence limit 0.60 to 0.85). Point estimation of these continuation rate values the group to the detectability 0. 8 as when determining the number of necessary cases, 1 group 64 becomes example. Table 3 shows representative values within the confidence limits of the continuity rate of each group and the number of necessary cases for the point estimate. Based on the consideration of the number of these necessary cases and the number of new patients with Alzheimer type dementia in the Tokushu Association Hospital group, the number of target cases was set to 150 cases .

Table - 3 Calculation of the number of necessary examples in the interval estimation range of the medication continuation rate of non-medication / guidance group (detection power = 0.8)

		Medication instruction group						
		0.6	0.65	0.7	0.73	0.75	0.8	0.85
Clothes agents non finger Guiding group	0.35	62	43	31	26	twenty four	18	14
	0.4	97	62	42	35	31	twenty three	17
	0.45	173	96	61	48	41	29	twenty two
	0.49	321	150	85	64	54	37	26
	0.5	388	170	93	70	58	39	27
	0.55	1534	376	163	111	89	54	36
	0.6	-	1471	356	206	152	82	49

13. Ethical matters

13.1. Rules to Observe

This all persons involved in the clinical study, "World Medical Association Declaration of Helsinki" (2008 year 10 May revised edition) and "Ethical Guidelines for

Clinical Research" (ending 20 years the Ministry of Health, Labor and Welfare Notification No. 415 in accordance with the issue).

13.2. Creation and revision of explanatory documents / consent documents

The research responsible doctor prepares agreement documents etc. to be used to obtain consent to participate in this clinical study from subjects and substitutes, and revises them if necessary. An agreement explanation document / agreement document that has been created or revised shall be used after review by the Joint Ethics Committee in advance .

The consent document shall include the following items. However, do not describe such as to induce subjects intentionally.

1) Participation in this clinical study is optional
2) Do not accept disadvantageous response by not agreeing to participate in this clinical study
3) Subject or substitute etc shall be able to retract the consent document given by himself without being disadvantaged at any time
Four) Reason for being selected as a subject
Five) Significance, purpose, method and duration of this clinical study
6) Research responsibility doctor the name of such and job title
7) It predicted the clinical study result of this clinical study expected benefit from participating in and Possible risks and entail unpleasant condition, the clinical study correspondence after completion
8) Subject and by the hope of such Daidaku person, personal information protection and of other subjects this clinical study carried out of in that there is no hindrance to the range, this clinical study plan and this clinical study is possible to obtain or view the documentation on how to What you can do
9) The possibility of providing the results of this clinical research to other agencies after judging by the Joint Ethics Committee about the handling of personal information, the name of the institution of the providing destination, reasonable use purpose at the destination, etc.
10) This clinical study that there is a possibility that the intellectual property rights, such as is produced by the achievements of and in the case of intellectual property rights or the like has been produced of the right attribution
11) The results of this clinical study may be published after making it impossible to identify subjects
12) Method of storage and use of samples and storage period

13) this clinical research funding sources involved in, conflict of interest that may occur and research investigator relationships with related organizations such as
14) Presence or absence of compensation accompanying this clinical study
15) Information on inquiries, contact information of contacts such as complaints

13.3. Ethics committee review

Prior to the implementation of this clinical study , the Joint Ethics Committee , at the Joint Ethics Committee, the content of the clinical study implementation plan, consent explanation document, case report, other materials required by the Joint Ethics Committee, ethical, scientific and medical From the viewpoint of validity and investigative responsibility doctor 's eligibility etc, conduct the examination after the Joint Ethics Committee approves the implementation of clinical research .

In addition, this clinical study throughout the period, the document which is the subject of a joint ethics committee of examination is added, updated or revised if it is (minor add, update or revised except for) , and year 1 times, the progress of clinical research as well as the occurrence of adverse events in with are also intended to be subject to review in the same way.

13.4. Audit

If the audit by the Joint Ethics Committee and regulatory agencies is conducted before, during or after the completion of this clinical study , it shall be accepted.

14. Money Payment and Health Damage Compensation , Funding Source for Clinical Studies

14.1. Medical expenses during this clinical study

This clinical study for the treatment to be performed on the subject during the participation period , is subject to the health insurance subject to join, the co-payment amount is the subject of the burden.

14.2. Payment of money to subjects

This clinical research by which to participate in the research, there is no possibility to receive the burden costs.

14.3. Funding sources and conflicts of interest in clinical research

The source of contribution of this clinical research fund is Eisai Co. , Ltd. In addition, this clinical for the conflict of interest situation of the study investigator, line the information disclosure required in the Conflict of Interest Committee Joint Ethics Committee intends .

14.4. Compensation

If health damage occurs in this clinical study , health insurance will be used for treatment costs. To prepare for compensation and liability incurred in this clinical study, research researcher and research sharing doctor join clinical research insurance.

15. About personal information and other rights

15.1. Protection of privacy

Joint Ethics Committee this ongoing clinical studies or after the end, documents related to the implementation, serious adverse events reports and case report form the investigation of such Kotogaa that is, this time, the contents of which can identify an individual offer It is not done .

In addition, those who participate in this clinical research shall not leak information on the subject's privacy, which was learned by viewing the source material, to third parties .

15.2. By signing a consent form, you will approve browsing

This clinical study participants of, materials , etc. to view it is that, for these officials imposed a duty to protect the secrets are . Patients By signing this consent document, approved the view that the made .

15.3. On cases where intellectual property rights etc. arise

This clinical study if the from the results intellectual property rights or the like is generated, the rights Eisai Co., Ltd. belong to, this clinical study to participate in the participating institutions, such as research investigators, and the patient is not to have that right.

15.4. About viewing original material

This clinical study material about how the subject is hope and if, personal information protection and of other subjects this clinical study carried out of in that there is no

hindrance to the range, be obtained or browsing is possible . However, it desires to browse and since the protection of personal information described above , such as for a variety of procedures or clinical studies practitioner and clinical studies conference of the exemplary tissue lines the Ukoto . As a result, there are cases in which it takes time to present the material and only a part of the desired material is presented.

16. Save the document

16.1. Documents anonymity of

Materials concerning this clinical study of all subjects who got consent shall be specified by concatenable anonymous subject identification code given at the time of registration . The correspondence table specifying the subject and the subject identification code is strictly managed by the research responsible doctor.

16.2. Storage of documents

Essential documents related to the implementation of this clinical study (a copy of the application document, a notice from the hospital director, a copy of various applications and reports, a copy of the subject identification code list, consent form, case report etc, Documents or records necessary to ensure sexuality, etc.). Also, when discarding materials , they shall be made anonymous. Researchers should take steps to prevent these documents from being accidentally or promptly destroyed.

Storage location : Each medical institution

Responsible Officer: Research Researcher

Retention period: 5 years after clinical study is over

17. Publication of research results

The results of this clinical study will be published as a paper or conference presentation. Also, at the time of publication, personal information of the subject shall not be leaked to a third party.

18. Clinical research implementation system

1) Clinical research representative

Kamei Toritome	Shonan virtue meeting hospital	Fujisawa Zhuzhou	Nerve within the Department of	Hospital length	0466 - 35 - 1177

[Operation] We will conduct this clinical study and oversee the whole clinical research.

2) Collaborators

Satoshi Takahashi Medical Law Humanities Association Tokyo Headquarters Drug Delegation

[Operation] Perform adjustment work of participating facilities.

3) Statistical analysis director / assignment manager

Toru Uoi Director Aurolink Co., Ltd.

[Operation] Perform statistical analysis and prepare analysis plan / analysis report. Specification design of the allocation table , creation / storage of the allocation table .

4) Data center

AUROLINK Inc.

Yubinbango 101-0054 Nishikicho Kanda, Chiyoda-ku, Tokyo 3-21 Chiyoda Platform Square 1186

TEL : 03 - 6666 - 0018 FAX : 0 3 - 6666 - 0018

[Operation] Implement data management.

5) Clinical research secretariat

Future Medical Research Center, Inc.

Hiroyoshi Yamaji (Representative of the Research Bureau)

Yubinbango 102 - 0083 Kojimachi, Chiyoda-ku, Tokyo 1-8-7 Eminabiru 3 floor

TEL : 03 - 3263 - 4801 FAX : 0 3 - 3263 - 4802

[Operation] We perform general support activities of this clinical research , and central registration / assignment work .

6) implementation facilities and research officer

See Attachment 1

19. References

1) Cummings JL. Alzheimer's disease. N Engl J Med. 2004 Jul 1; 351 (1): 56-67.

2) Dement Geriatr Cogn Disord. Homma A , Imai Y, Tago H, et al. Long-term safety and efficacy of donepezil in patients with severe Alzheimer's disease: results from a 52 - week, open - label, multicenter, extension study in . 2009 ; 27 (3) : 232-23 9 .

3) Watanabe N , Yamamura K , Suzuki Y, et al. Pharmacist-based Donepezil Outpatient Consultation Service to improve medication persistence. Patient Prefer Adherence. 2012 ; 6 : 605-611.

Four) Keiko Yamamura Supervised Aricept Class Text
Available from: http://www.aricept.jp/helpful/art_classroom.html

Five) Akira Honma . Alzheimer's disease patients ADL respect of donepezil hydrochloride effective and discontinuations prognosis (Aricept special survey) . Geriatr Med. 2009 ; 47 (8): 1047-1059.

6) Akira Honma . Advanced Alzheimer's disease donepezil hydrochloride for 10 mg / safety and efficacy of daily administration (Aricept (R) specific-use results surveys) . Geriatr Med. 2013 ; 51 (3): 309-342.