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CLINICAL STUDY PROTOCOL

Study Protocol Number:	E2020-K082-418
Study Protocol Title:	*A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Donepezil Hydrochloride (E2020) in Patients with Dementia Associated with Cerebrovascular Disease*
Representative Sponsor:	Eisai Co., Ltd. 4-6-10 Koishikawa, Bunkyo-Ku, Tokyo 112-8088, Japan (Local license holder: Daewoong Co., Ltd., 163-3 Samseong-dong, Gangnam-gu, Seoul)
Investigational Product Name:	E2020/Aricept (donepezil hydrochloride)
Indication:	Dementia Associated with Cerebrovascular disease
Phase:	Phase 4
Approval Date:	V1.0 19 June 2012 (original protocol) V2.2 6 July 2017
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

Co-sponsor

No.	Company
1	Korean Drug Co., Ltd.
2	Dong-A Pharmaceutical Co., Ltd.
3	Myungmoon Pharm. Co., Ltd.
4	Myung-In Pharmaceutical Co., Ltd.
5	Samjinpharmaceutical Co., Ltd.
6	CJ CheilJedang Corporation
7	SK Chemicals Co., Ltd.
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14	Korea Pharma Co., Ltd.
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16	Whanin Pharmaceutical Co., Ltd.
17	Hanlim Pharm. Co., Ltd.
18	Reyon Pharmaceutical Co., Ltd.
19	Hyundai Pharm Co., Ltd.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.
E2020

Name of Active Ingredient
Donepezil hydrochloride

Study Protocol Title
A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Donepezil Hydrochloride (E2020) in patients with Dementia Associated with Cerebrovascular Disease

Investigator(s)
TBD

Site(s)
Approximately 25 centers in Korea

Study Period and Phase of Development
From June 2013 to January 2019, Phase 4

Objectives

Co-Primary objectives

- To confirm that donepezil hydrochloride (E2020) has superior efficacy compared with placebo in improving cognitive function, as measured by Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog), in patients with dementia associated with cerebrovascular disease (VaD).
- To demonstrate that donepezil hydrochloride (E2020) has superior efficacy compared with placebo in improving global function, as measured by Clinician's Interview-Based Impression of Change-plus Caregiver Input (CIBIC-plus), in patients with VaD.

Secondary objectives

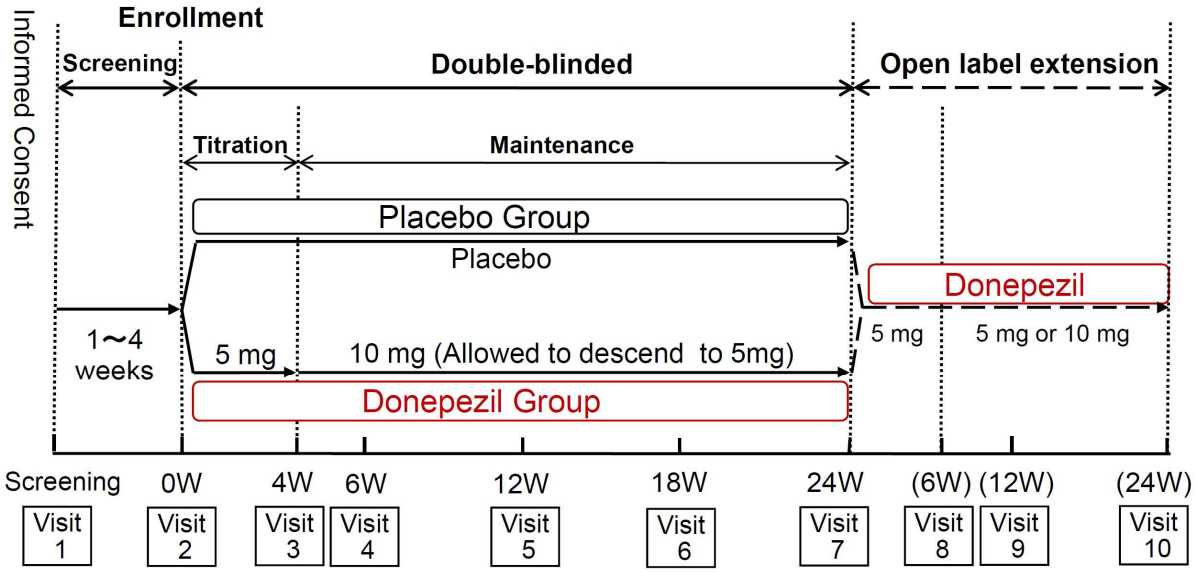
- To evaluate the efficacy (as measured by MMSE and executive function test) and safety of E2020 compared with placebo, in patients with VaD.

Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study with an open-label extension. The main part of the study consists of 2 phase; screening phase (SCR; 1 to 4 weeks), and double-blind phase (DB; 24 weeks, placebo-controlled). DB phase includes 2 periods; titration and maintenance. The duration of titration period is 4 weeks.

Prior to performing any procedures or evaluation, written informed consent will be obtained. Up to 4 weeks prior to randomization, prospective patients will be screened to confirm their diagnosis and suitability for study entry. Subjects who continue to meet all of the inclusion and none of the exclusion criteria will be randomly assigned to receive either donepezil or placebo. Donepezil or placebo will be taken once daily in the evening for the duration of their participation in the study.

Donepezil 5 mg will be administered in the titration period and then the dose will be increased to 10 mg at Week 4 (Day 28-35) according to investigator's clinical judgment. During the maintenance period, dose reduction to 5 mg/day will be permitted only when 10 mg/day is intolerable due to adverse events. In this case, the dose cannot be escalated up to 10 mg/day again.



(Open-label Extension)

Subjects, who have completed the DB phase and have consented to continue participation of the study, can be enrolled in the 24-week open-label extension phase. In this phase, treatment will be initiated at 5 mg/day, and the dose is maintained until Week 6 (Day 28-42). After assessing clinical response by examination, the dose can be increased to 10 mg/day. Dose reduction (from 10 mg/day to 5 mg/day) will be permitted when the investigator judges it difficult to continue the 10 mg/day administration. It is possible to increase the dose to 10 mg/day again. Subjects will visit the study institution at Week 6, 12, and 24.

Number of Subjects

Total 324 subjects will be randomized (162 subjects/group)

Inclusion Criteria

Patients who meet all of the following criteria will be eligible for inclusion in the study:

1. Male or female, age ≥ 40 years at the time of informed consent.
2. Possible or probable dementia associated with cerebrovascular disease as defined by NINDS-AIREN Criteria with dementia of greater than 3 months duration.
3. Radiological evidence of cerebrovascular disease.
4. Mini-Mental State Examination (MMSE) score is ≥ 10 and ≤ 24 at both Screening and Baseline.

5. Clinical Dementia Rating (CDR) ≥ 1.
6. Outpatients who are physically healthy, and ambulatory or ambulatory-aided (i.e., walker, cane or wheelchair).
7. Written informed consent (IC) is obtained from the patient (if possible) and from the patient's legal guardian prior to being exposed to any study-related procedures. Even if unable to provide written IC, the patient must assent verbally to participating in the study and the record should note this assent. The caregiver must separately provide IC for his/her own participation in the study.
8. Patients having caregivers who submit written consent to cooperate with this study, have regular contact with the patient (i.e., an average of ≥ 4 hours/day and ≥ 3 days/week), provide patients' information necessary for this study, ensure the regular administration of assigned donepezil, as well as all concomitant therapies, at the correct dose, and escort the patients on required visits to study institution.
   If, during the study, the designated caregiver relinquishes his/her responsibilities to another caregiver, the new caregiver must provide IC, and otherwise similarly qualify for inclusion in the study. If no replacement caregiver is available who meets the caregiver criteria, the subject must be discontinued from this study.
9. Patients who can visit study institution as required following with investigator's instruction.
10. Patients who have vision, hearing, speech, motor function and comprehension sufficient to be able to comply with testing procedures (glasses, contact lens, and hearing aid permissible).
11. Patients who meet prohibition/restriction of using concomitant medications before Screening.
12. Comorbid medical conditions are clinically stable prior to Baseline, unless otherwise specified. The following situations should be given particular attention;
    a. Patients with risk factors of hypertension and cardiac disease may be enrolled, provided that hypertension is well controlled by medication (supine diastolic blood pressure < 95 mmHg) and cardiac disease (*e.g. angina pectoris, congestive heart failure, or right bundle branch block*) is stable on appropriate medication for at least 12 weeks prior to Screening. Peripheral vascular disease must have been stable for 12 weeks prior to Screening. No elective surgical procedures should be planned during the course of the study (*e.g., vascular bypass procedures or coronary artery bypass surgery*).
    b. Patients with diabetes mellitus or risk factors for diabetes mellitus may be enrolled, provided that the patient's disease is stable and that there have been no recent (within 12 weeks of Screening) hospitalizations for diabetic ketoacidosis, hyperosmolar coma, or hyperglycemia. Patients with non-insulin-dependent diabetes may be enrolled if controlled on diet or oral medications. All diabetic patients must have a HbA1c concentration of ≤ 10% and a random serum glucose

concentration of ≤ 250 mg/dL at Screening.

c. Patients with risk factors of stroke may be enrolled, provided that the disease process has been stable or controlled on medication for greater than 12 weeks prior to Screening. Patients receiving anticoagulation with warfarin are eligible for inclusion in the study if the International Normalized Ratio (INR) for prothrombin time is within the therapeutic range for prophylaxis (1.4-3.0) and the dose of warfarin is stable. Patients with prosthetic heart valves, who require full anticoagulation, should have a stable (≥ 3 months) INR in the range of 2.5-3.5.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded:

1. Anti-dementia drug therapy (cholinesterase inhibitors or memantine) within 12 weeks prior to Screening.
2. Clinical and/or radiological evidence for other serious degenerative neurological disorders or neuropsychiatric disorders.

   e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob disease, dementia with Lewy Bodies, normal pressure hydrocephalus, olivopontocerebellar atrophy, multiple system atrophy, brain tumor, progressive supranuclear palsy, idiopathic seizure disorder, subdural hematoma, multiple sclerosis, active cerebral vasculitis, schizophrenia, and bipolar or unipolar depression
3. Known human immunodeficiency virus disease, neurosyphilis, or a history of significant head trauma followed by persistent neurological deficits or known structural brain abnormalities.
4. Hypothyroidism at Screening.

   Patients may be enrolled, provided that they are on a stable dose of medication for at last 12weeks prior to Screening, have normal thyroid stimulating hormone and free thyroxine at Screening, and are considered euthyroid.
5. Vitamin B12 or folate deficiency at Screening.

   Patients who are currently receiving B12 supplementation by oral or parenteral injection may be included, provided that dosing regimen has not changed for 12 weeks, plasma B12 levels are normal or above normal and there is documented evidence of continued cognitive deterioration after initiation of B12 treatment.
6. Evidence of a new TIA or stroke that occurs within 12 weeks prior to Screening, even if the symptoms are minor and do not require hospitalization, are excluded.

   These patients may subsequently become eligible for inclusion, if no new stroke or TIA is noted for 12 weeks (3 months) and all other criteria are met.
7. Supine diastolic blood pressure ≥ 95 mmHg at Screening or Baseline.
8. Complication of sick sinus syndrome, abnormal auricular and atrioventricular junction conductions (AV block, ≥ II ventricular block, etc.), or with a prolonged QT/QTc interval

(> 450 ms) as demonstrated by a repeated ECG.

9. A history of life-threatening arrhythmias (*e.g., unstable atrial flutter, unstable atrial fibrillation, ventricular tachycardia, ventricular fibrillation, or torsade de pointes*).
10. Evidence of clinically significant, severe, active, or unstable gastrointestinal, renal, hepatic, respiratory, hematological, endocrine, or cardiovascular system disease.
11. A history of malignant neoplasms (not including basal or squamous cell carcinoma of the skin) treated within 5 years prior to study entry, current evidence of malignant neoplasm, recurrent, or metastatic disease. Males with localized prostate cancer requiring no treatment would not be excluded.
12. A known or suspected history of drug or alcohol dependency or abuse within approximately the last 2 years.
13. Abnormal clinical laboratory values which are judged clinically significant by the investigator.
14. Hypersensitivity to donepezil or piperdine derivatives or any of the excipients.
15. Patients who cannot swallow or who have difficulty swallowing whole tablets, as tablets should not be broken or crushed.
16. Patients who will receive prohibited concomitant medication(s) or change dosing regimen of restricted concomitant medication(s) during this study.
17. Known plan for elective surgery that would require general anesthesia and administration of neuromuscular blocking agents, such as succinylcholine, to induce paralysis/muscle relaxation.

    Minor surgery, such as colonoscopy or cataract surgery, will be permitted as long as it does not require the use of these paralytic agents.
18. Pregnant women, lactating women, or women of child-bearing potential(< 1 year post menopausal) who don't agree to practice effective contraception (*e.g., abstinence, an intrauterine device, a double-barrier method such as condom + spermicide or condom + diaphragm with spermicide, a contraceptive implant, an oral contraceptive, or have a vasectomised partner*) throughout the entire study period and for 30 days after donepezil discontinuation, or who don't have a negative serum â-HCG test result or a negative urine pregnancy test result at Screening and Baseline.
    - All females will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (*i.e. bilateral tubal ligation, hysterectomy or bilateral oophorectomy, all with surgery at least one month before dosing*).
    - All women who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and for 30 days after donepezil discontinuation.
19. Patients who have participated in another clinical study within 12 weeks before Screening.

20. Any condition that would make the patient or the caregiver, in the opinion of the investigator, unsuitable for the study.

Study Treatment(s)

Test drug: E2020 5 mg, 10 mg tablet
Control drug: Placebo tablet (5 mg, 10 mg)

A tablet will be taken orally once daily basically in the evening.

Placebo group:

Titration: Placebo tablet matched to 5 mg tablet of donepezil
Maintenance: Placebo tablet matched to 10 mg tablet or 5 mg tablet of donepezil

Donepezil group:

Titration: 5 mg tablet
Maintenance: 10 mg or 5 mg tablet

During the Maintenance period, while patients taking 10 mg/day, dose reduction to 5 mg/day will be permitted only when the investigator judges it difficult to continue 10 mg/day administration due to an occurrence of adverse event of which the causal relationship with the donepezil is not ruled out. The dose cannot be escalated up to 10 mg/day again.

(Open-label Extension)
Until Week 6 (Day 28- 42): 5 mg tablet of donepezil
After Week 6: 10 mg or 5 mg tablet of donepezil

After Week6, the dose can be increased to 10 mg/day. Dose reduction (from 10 mg/day to 5 mg/day) will be also permitted when the investigator judges it difficult to continue the 10 mg/day administration. The dose can be escalated up to 10 mg/day again.

Duration of Treatment

Screening phase: 1-4 weeks
Double-blind phase: 24 weeks (Titration: 4 weeks, Maintenance: 20 weeks)
Open-label Extension: 24 weeks (including titration of at least 4 weeks)

Concomitant Drug/Therapy

Prohibited Concomitant Medications

12 weeks before the Screening to final day of the study

1) Anti-dementia agents (donepezil, rivastigmine, galantamine, memantine et al. except for the study drug)
2) Other investigational drugs

6 weeks before the Screening to final day of the study

3) Choline stimulants (cholinesterase inhibitor, choline agonists, except for topical agents)

3 weeks before the Screening to final day of the DB phase

4) Antiparkinsonian agents
5) Tricyclic antidepressants
6) Antipsychotics
7) Hypnotics (except for the short acting hypnotics defined as restricted concomitant drugs)
8) Nootropics (choline alfoscerate, acetyl-L-carnitine, oxiracetam et al.)
9) Gingko biloba

Restricted Concomitant Medications (The dose should be maintained)

3 weeks before the Screening to final day of the DB phase

1) Antidepressants (except for tricyclic antidepressants)
2) Anxiolytics
3) Hypnotics (short acting hypnotics; zolpidem, brotizolam, lormetazepam, rilmazafone, zopiclone, ramelteon)

Assessments

- **Efficacy Assessments**:

Primary efficacy variable:

1) Cognitive function: Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog)
2) Global function: Clinicians interview-Based Impression of Change-plus (CIBIC-plus)

Secondary efficacy variables:

1) Mini-Mental Status Examination (MMSE)
2) Executive function test (Trail making test (K-TMT-e))

- **Pharmacokinetics:** Not applicable
- **Pharmacodynamics**: Not applicable
- **Pharmacokinetic-Pharmacodynamic**: Not applicable
- **Safety**: Safety assessment will consist of determining and recording all adverse events (AEs) and serious adverse events (SAEs); laboratory evaluation for hematology, blood chemistry, and urine analysis; periodic measurement of vital signs and ECGs.

Bioanalytical Methods

Not applicable

Statistical Methods

This section summarizes Statistical Method of Core study; DB phase.

Analysis sets

The Safety Analysis Set (SAS) is the group of subjects who received at least one dose of study drug and had at least one postdose safety assessment.

The Full Analysis Set (FAS) is the group of randomized subjects who received at least one dose of study drug and had at least one postdose primary efficacy measurement.

The Per Protocol Set (PPS) is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding and will be specified in the Statistical Analysis Plan.

Efficacy analysis

The efficacy data observed from Baseline to Week 24 will be used for analysis. All statistical tests will be conducted at the significance level of 5.0% (two-tailed).

The analysis will be conducted on the FAS and PPS, using the last observation carried forward (LOCF) method to impute missing data, and the observed cases (OC) populations at Week 24 and other time points. The analysis of FAS is primary, and that of PPS is a sensitivity analysis of FAS.

Primary Efficacy Analyses:

The co-primary efficacy variables are used as follows to determine whether donepezil has superior efficacy compared to placebo:

- For ADAS-cog change from baseline to Week 24, an analysis of covariance (ANCOVA) model with baseline (covariate) and treatment (main effect) will be used for testing main effect.
- For CIBIC-plus scores, least squares (LS) mean scores at Week 24 will be compared between groups to demonstrate numerical superiority of donepezil to placebo (the difference is less than 0), using ANCOVA model with CIBIS-plus (covariate) and treatment group (main effect).

For the measurements of each visit and the change from baseline to each visit of both endpoints, descriptive statistics (median, mean, standard deviation (SD), minimum, maximum, and number of patients with non-missing data for both variable; number and percentages of each score for CIBIC-plus) will be presented. Where appropriate, least square (LS) mean, between-treatment difference in least square (LS) means, 95% confidence intervals (CIs) for the difference and p value in each visit will also be presented.

Secondary Efficacy Analysis:

MMSE and executive function test score change from Baseline to Week 24 will be analyzed using a same ANCOVA model as is described for the ADAS-cog. Other statistical inference (estimating and testing) will also be analyzed in the same way with primary analysis.

Safety analysis

The evaluation of safety parameters will be conducted on the SAS.

The incidence rates for AEs by body system, preferred term, severity, and relationship to study medication will be calculated. Individual vital signs will be descriptively summarized by treatment group and visit. Changes from Baseline to each individual post-baseline visit and to the final visit will be calculated. For clinical laboratory parameters, changes from Baseline to each visit, descriptive statistics (median, mean, standard deviation (SD), minimum, maximum, and number of patients with non-missing data) will be presented. Shift tables depicting shifts in or out of the normal range, from Baseline to the final study visit, will also be provided.

ECG data will be categorized at Baseline, and results for each subject at the end of treatment will be compared to those at Baseline. Data on other medications used by subjects during the study will be collected and summarized by therapeutic class and generic components.

Interim Analyses

Not applicable

Sample Size Rationale

The primary endpoints are the change from baseline to Week 24 (LOCF) in ADAS-cog and the measurement at Week 24 (LOCF) of the CIBIC-plus.

The estimates of these endpoints were referred from the result of subgroup (MMSE less than 24) in pooled data of previous double blind studies (E2020-A001-307 and E2020-A001-308).

The mean difference and standard deviation of the change from baseline to final visit in ADAS-cog were estimated as -2.404±5.955, using pooled data of E2020 groups (5 mg+10 mg). When the significance level was set as 5.0% (two-tailed) and statistical power as 80.0%, the subject number needed to detect statistically significant difference by 2 sample t test was calculated to be 196 (98/arm).

On the other hand, the mean difference and the standard deviation of CIBIC-plus score at the final visit were estimated as -0.261±1.162, when CIBIC-plus was regarded as continuous measurement [scored from 1 (marked improvement) to 7 (marked worsening) point]. The subject number needed to reduce the probability that donepezil is inferior to placebo in point estimate to 2.5% or less, was calculated to be 308 (154/arm).

Therefore, the subjects number required to achieve primary objectives simultaneously became 308 (154/arm). In consideration of exclusion from the analysis set (approximately 5%), the sample size was defined as 324 (162/arm).

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive subscale
AE(s)	Adverse event(s)
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
β-HCG	β-human chorionic gonadotropin
BP	Blood pressure
CBC	Complete blood count
CDR	Clinical Dementia Rating
CIBIC-plus	Clinician's Interview-Based Impression of Change-plus
CIBIS	Clinician's Interview-Based Impression of Severity
CNS	Central nervous system
CRA	Clinical research associate
CRF(s)	Case report form(s)
CRO	Contract research organization
CT	Computerized tomography
CVD	Cerebrovascular disease
DAT	Dementia of the Alzheimer type
DB	Double-blinded
ECG	Electrocardiogram
FAS	Full Analysis Set
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin A1c
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
KFDA	Korea Food and Drug Administration
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental Status Exam
MRI	Magnetic Resonance Imaging
NINDS-AIREN	National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (International Association for Research and Teaching in Neurosciences)

OLE	Open-label extension
PET	Positron emission tomography
PI	Principal Investigator
PPS	Per Protocol Set
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SAS	Safety Analysis Set
SCR	Screening
SOP	Standard operating procedure
TIA	Transient ischemic attack
VaD	Vascular dementia
V-ADAS-cog	Vascular-Alzheimer Disease Assessment Scale-Cognitive subscale

5 ETHICS

5.1 INSTITUTIONAL REVIEW BOARDS/INDEPENDENT ETHICS COMMITTEES

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with ICH E6 (Good Clinical Practice), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (e.g., change in CRA[s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC within the period in accordance with the IRB/IEC's requirements.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC within the period in accordance with the IRB/IEC's requirements and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (2008)
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Korea Good Clinical Practice (2011)

5.3 SUBJECT INFORMATION AND INFORMED CONSENT

The investigator is responsible for ensuring that no patient is subject to any study-related examination or activity before that patient has given informed consent. Written informed consent will be obtained from the patient (if possible) and from the patient's legal guardian or other representative, prior to beginning screening activities and entering the open-label extension (OLE) phase. Separate written informed consent will be provided before screening and entering OLE phase. Even if unable to provide written informed consent, the patient must assent verbally to participating in the study and the record should note this assent. The caregiver must separately give informed consent for his or her own participation in the study. If the caregiver illiterate, consent will be signified by a thumbprint or another personally identifiable method acceptable in lieu of a signature.

The patient, legal representative, and the caregiver will receive detailed information before the consent is given and the patient will receive a copy of signed document. The verbal explanation will cover all the elements specified in the written information provided for the patient. The investigator will inform the patient of the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. The patient and the caregiver must be given every opportunity to clarify any points he/she does not understand and if necessary, ask for more information. At the end of the interview, the patient and the caregiver may be given time to reflect if this is required, or if more time is requested. Patients and legal representative, and caregivers, will be required to sign and date the informed consent form. After completion, informed consent forms will be kept and archived by the investigator in the investigator's study file.

It should be emphasized that the patient, the legal representative and/or the caregiver is at liberty to withdraw their consent to participate at any time, without penalty or loss of benefits to which the patient is otherwise entitled. Patients who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact on their subsequent care.

The subject or the subject's legal representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 25 investigational site(s) in Korea.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and C&R Research which is the contract research organization are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 E2020/DONEPEZIL HYDROCHLORIDE (ARICEPT®)

Donepezil (donepezil hydrochloride, E2020, Aricept®) is a piperidine-based acetylcholinesterase (AChE) inhibitor. It has been demonstrated to be a potent and relatively specific inhibitor of AChE. In randomized clinical trials, donepezil has been shown to be effective and safe as a treatment in the management of patients with Alzheimer's disease (AD) and Vascular dementia (VaD). Currently, donepezil is approved for mild to moderate AD in more than 90 countries, for severe AD in about 30 countries, and for VaD in 12 countries. In Korea, the indication of Aricept is as follows:

[Indication] For the symptomatic treatment of Alzheimer's disease and symptomatic improvement of vascular dementia (with cerebrovascular disease).

7.1.1 Mechanism of Action

Donepezil is a selective and reversible inhibitor of AChE both in the periphery as well as in the central nervous system (CNS). It acts to increase the central cholinergic activity in the brain. Inhibitor of AChE activity prevents the breakdown of acetylcholine and results in increased acetylcholine concentration at the synaptic site. Biochemical studies have demonstrated that donepezil binds selectively to AChE, rather than butyrylcholinesterase, and reversibly inhibits AChE activity in the periphery as well as in the rat cerebral cortex, hippocampus, striatum, and hypothalamus. Donepezil binding to AChE has also been shown in human brain by positron emission tomography (PET) imaging.

7.1.2 Clinical Experience in VaD

Three large-scale clinical studies of VaD have been conducted to assess the efficacy and safety of donepezil in VaD by Eisai. These studies, E2020-A001-307, E2020-A001-308 and E2020-A001-319, were randomized, double-blind, placebo-controlled trials. A diagnosis of probable or possible VaD according to NINDS-AIREN criteria was required for enrollment (i.e., evidence of dementia and a probable or possible relationship between dementia and CVD). Patients with a prior diagnosis of AD and subsequent cognitive impairment due to stroke or CVD were excluded. In the first 2 studies, E2020-A001-307 and E2020-A001-308, patients were randomized to receive placebo, donepezil 5 mg/day or donepezil 10 mg/day (5 mg/day for first 28 days). Efficacy assessments included the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), the Mini-Mental State Examination (MMSE), and the Clinician's Interview-Based Impression of Change-plus version (CIBIC-plus).

In Study 307, a total of 603 patients were enrolled (199 placebo, 198 donepezil 5 mg/day, 206 donepezil 10 mg/day); 425 (70%) had probable VaD and 30% had possible VaD. Both donepezil-treated groups showed significant improvements in cognitive function compared with placebo for the ADAS-cog. The donepezil 5 mg/day group showed significant improvements in

global function compared with placebo on the CIBIC-plus. The patient population had a high incidence of CVD and cardiovascular disease. Donepezil was well tolerated in this population, with low withdrawal rates due to adverse events and a similar incidence of cardiovascular AEs across all treatments.

In Study 308, a total of 616 patients were enrolled (193 placebo, 208 donepezil 5 mg/day, 215 donepezil 10 mg/day); 468 (76%) had probable VaD and 24% had possible VaD. Both donepezil-treated groups showed significant improvements in cognitive function compared with placebo on the ADAS-cog and MMSE. Greater improvements on the CIBIC-plus were observed with both donepezil groups than with the placebo group. Donepezil was well tolerated in this population (of whom 90% had co-morbid cardiovascular disease), with low withdrawal rates due to adverse events (placebo, 8.8%; donepezil 5 mg, 10.1%; donepezil 10 mg, 16.3%).

In Study 319, patients were randomized to receive placebo or donepezil 5 mg/day. Efficacy assessments included the Vascular-Alzheimer's Disease Assessment Scale-Cognitive Subscale (V-ADAS-cog), the ADAS-cog, the MMSE, and the CIBIC-plus. A total of 974 patients were enrolled (326 placebo, 648 donepezil 5 mg/day). Donepezil group showed significant improvements in cognitive function compared with placebo on the V-ADAS-cog and ADAS-cog, however, donepezil group did not show significant improvements in global function compared with placebo on the CIBIC-plus. Donepezil was well tolerated in this population with low withdrawal rates due to adverse events (placebo, 5.5%; donepezil 5 mg, 11%)

7.1.3 Common Adverse Events

In Study 307, the most common adverse events were diarrhea (14.1%), infection (13.8%), accidental injury (12.9%), nausea (10.6%), and urinary tract infection (10.0%). Accidental injury, infection, and urinary tract infection occurred with similar frequency across the 3 treatment groups. Diarrhea and nausea occurred more frequently in the donepezil treatment groups than in the placebo group. Of these, a dose-related effect was observed only for nausea.

In Study 308, the four most commonly observed adverse events consisted of the following: infection (17.3% of patients in the 5 mg donepezil group, 14.0% of patients in the 10 mg donepezil group and 13.5% of those in the placebo group), diarrhea (11.5% of patients in the 5 mg donepezil group, 18.6% of patients in the 10 mg donepezil group and 10.4% of those in the placebo group), accidental injury (16.8% of patients in the 5 mg donepezil group, 12.6% of patients in the 10 mg donepezil group and 9.8% of those in the placebo group), and nausea (11.1% of patients in the 5 mg donepezil group, 16.7% of patients in the 10 mg donepezil group and 7.8% of those in the placebo group). Other adverse events that occurred significantly more frequently in the donepezil groups included abnormal dreams, insomnia and rhinitis.

In Study 319, the most common events in the donepezil group were diarrhea (11.7% versus 7.4% for placebo), infection (11.6% versus 11.0% for placebo), nausea (9.9% versus 4.3% for placebo), accidental injury (9.0% versus 10.1% for placebo), urinary tract infection (8.8% versus 10.1% for placebo), asthenia (8.2% versus 7.1% for placebo), headache (7.9% versus 6.4% for

placebo), and pain (7.6% versus 8.0% for placebo). The occurrence rates were statistically significantly higher in the donepezil group than the placebo group for the following events: diarrhea (11.7% versus 7.4%), nausea (9.9% versus 4.3%), abnormal dreams (3.4% versus 0.6%), hypertonia (3.2% versus 0.3%), and leg cramps (2.6% versus 0.6%). Most adverse events were mild to moderate.

In Study 307, the mortality rates were 2/198 (1.0%) on donepezil hydrochloride 5 mg, 5/206 (2.4%) on donepezil hydrochloride 10 mg and 7/199 (3.5%) on placebo. In Study 308, the mortality rates were 4/208 (1.9%) on donepezil hydrochloride 5 mg, 3/215 (1.4%) on donepezil hydrochloride 10 mg and 1/193 (0.5%) on placebo. In Study 319, the mortality rates were 11/648 (1.7%) on donepezil hydrochloride 5 mg and 0/326 (0%) on placebo. The total mortality rate for the three VaD studies in the donepezil hydrochloride group (1.7%) was numerically higher than in the placebo group (1.1%), however, this difference was not statistically significant. The majority of deaths in patients taking either donepezil hydrochloride or placebo appear to result from various vascular related causes, which could be expected in this elderly population with underlying vascular disease. An analysis of all serious non-fatal and fatal vascular events showed no difference in the rate of occurrence in the donepezil hydrochloride group relative to placebo.

7.2 STUDY RATIONALE

Three large-scale clinical studies of VaD have been conducted to assess the efficacy and safety of donepezil in VaD. In Study 307, both donepezil-treated groups showed significant improvements in cognitive function compared with placebo for the ADAS-cog. The donepezil 5 mg/day group showed significant improvements in global function compared with placebo on the CIBIC-plus. In study 308, both donepezil-treated groups showed significant improvements in cognitive function compared with placebo on the ADAS-cog. Greater improvements on the CIBIC-plus were observed with both donepezil groups than with the placebo group. In Study 319, the donepezil 5 mg/day group showed significant improvement in the cognitive function for the V-ADAS-cog and ADAS-cog. However, the donepezil 5 mg/day group did not show the significant result of the CIBIC-plus.

Donepezil has been used for vascular dementia (with cerebrovascular disease) in Korea since 2005. However, three pivotal studies lacked consistency in efficacy on global function measured by CIBIC-plus.

The objectives of this multi-center clinical trial in Korea are to confirm the efficacy of donepezil on cognitive and global function in patients with VaD.

8 STUDY OBJECTIVES

8.1 CO-PRIMARY OBJECTIVE

1) To confirm that donepezil hydrochloride (E2020) has superior efficacy compared with placebo in improving cognitive function, as measured by ADAS-cog, in patients with dementia associated with cerebrovascular disease (VaD).

2) To demonstrate that donepezil hydrochloride (E2020) has superior efficacy compared with placebo in improving global function, as measured by CIBIC-plus, in patients with VaD.

8.2 SECONDARY OBJECTIVE(S)

To evaluate the efficacy (as measured by MMSE and executive function test) and safety of E2020 compared with placebo, in patients with VaD.

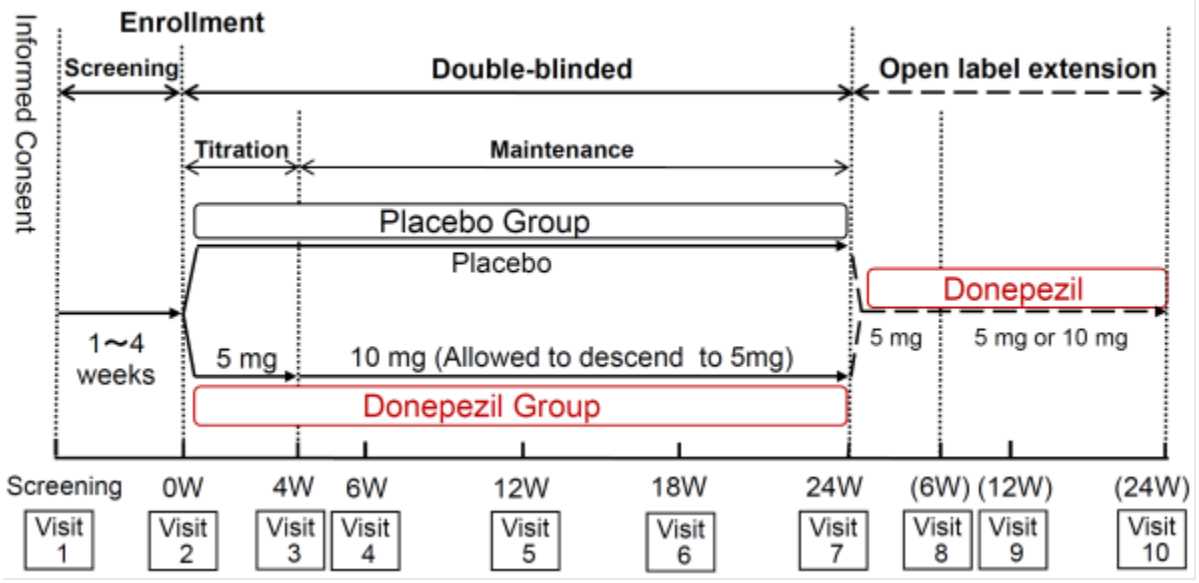
9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study with an open-label extension. The main part of the study consists of 2 phase; screening phase (SCR;1 to 4 weeks), and double-blind phase (DB;24 weeks, placebo-controlled). DB phase includes 2 periods; titration and maintenance. The duration of titration period is 4 weeks.

Prior to performing any procedures or evaluation, written informed consent will be obtained. Up to 4 weeks prior to randomization, prospective patients will be screened to confirm their diagnosis and suitability for study entry. Subjects who continue to meet all of the inclusion and none of the exclusion criteria will be randomly assigned to receive either donepezil or placebo.

Donepezil and placebo will be taken once daily in the evening for the duration of their participation in the study. 5 mg of donepezil will be administrated in the titration period and then the dose will be increased to 10 mg at Week 4 (Day 28-35) according to investigator's clinical judgment. During the maintenance period, dose reduction to 5 mg/day will be permitted only when 10 mg/day is intolerable due to adverse events. In this case, the dose cannot be escalated up to 10 mg/day again.



(Open-label Extension)
Subjects, who have completed the double-blind (DB) phase and want to continue the study participation, can be enrolled in the 24-week open-label extension phase. In this phase, treatment is initiated at 5 mg/day, and the dose is maintained until Week 6 (Day 28-42). After assessing clinical response during the period by examination, the dose can be increased to 10 mg/day. Dose reduction (from 10 mg/day to 5 mg/day) is permitted when the investigator judges it difficult to continue the 10 mg/day administration. It is possible to increase the dose to 10 mg/day again. Subjects will visit the study institution at Week 6, 12, and 24.

9.1.1 Screening (SCR) Phase

The SCR Phase will last for 1-4 weeks and will include a SCR period and a Baseline visit.

9.1.1.1 Screening Period

Screening will occur between 1 week and 4 week before the patients will be enrolled. The purpose of the SCR period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each patient, caregiver, and patient's legal guardian before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Results of the screening activities must be recorded on the appropriate case report form (CRF) to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.
Investigators should ensure that the patient and caregiver will be instructed that the patient is to discontinue use of all donepezil medication from previous prescriptions, so as to ensure that the patient does not consume any doses of donepezil other than or in addition to study.

9.1.1.2 Baseline visit

Investigators will reconfirm the inclusion/exclusion criteria and perform the assessments and evaluations to the subjects. Subjects whose screening assessments and evaluations are completed and reviewed by the principal investigator and who continue to meet all of the inclusion/exclusion criteria (Sections 9.3.1 and 9.3.2) will enter the DB phase. They will be randomly assigned in 1:1 ratio to receive either donepezil or placebo by Interactive Web Response System (IWRS).

9.1.2 Double-blind (DB) Phase

The duration of the DB phase will be 24 weeks and will include 2 periods: Titration and Maintenance. The duration of titration period is 4 weeks.

9.1.2.1 Titration Period

During the Titration period, subjects assigned to donepezil group will be started E2020 on 5 mg/day. On the other hand, subjects assigned to placebo group will be started placebo tablet

matched to 5 mg tablet. The duration of titration period is 4 weeks. The dose will be increased to 10 mg according to investigator's clinical judgment at Week 4 (Day 28-35).

9.1.2.2 Maintenance Period

During the Maintenance period, subjects will continue treatment with 10 mg of donepezil or placebo. Dose reduction to 5 mg/day will be permitted only when 10 mg/day is intolerable due to an occurrence of adverse events of which the causal relationship with the study drug is not ruled out. In this case, the dose cannot be escalated up to 10 mg/day again. The duration of maintenance period is 20 weeks. Subjects will visit the study institution at Week 6, 12, 18, and 24.

9.1.3 Open-label Extension (OLE) Phase

Before starting the OLE phase, subjects have to provide written informed consent to participate in OLE phase. Subjects, who have completed the DB phase, can be enrolled in the 24-week OLE phase. In this phase, treatment is initiated at 5 mg/day, and the dose is maintained until Week 6 (Day 28-42; for at least 4 weeks). After assessing clinical response at Week 6 visit, the dose can be increased to 10 mg/day. Dose reduction (from 10 mg/day to 5 mg/day) is permitted when the investigator judged it difficult to continue the 10 mg/day administration. It is possible to increase the dose to 10 mg/day again. Subjects will visit the study institution at Week 6, 12, and 24.

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING CHOICE OF CONTROL GROUPS

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

The double-blind, parallel-group design is considered to be appropriate for the comparison of efficacy and safety in patients receiving donepezil with that in patients receiving placebo. The intended sample size has been selected to achieve sufficient power for comparisons of efficacy.

9.3 SELECTION OF STUDY POPULATION

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive donepezil.

9.3.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible for inclusion in the study:

1. Male or female, age $\geq$ 40 years at the time of informed consent.

2. Possible or probable dementia associated with cerebrovascular disease as defined by NINDS-AIREN Criteria with dementia of greater than 3 months duration.
3. Radiological evidence of cerebrovascular disease.
4. Mini-Mental State Examination (MMSE) score is ≥ 10 and ≤ 24 at both Screening and Baseline.
5. Clinical Dementia Rating (CDR) ≥ 1.
6. Outpatients who are physically healthy, and ambulatory or ambulatory-aided (i.e., walker, cane or wheelchair).
7. Written informed consent (IC) is obtained from the patient (if possible) and from the patient's legal guardian prior to being exposed to any study-related procedures. Even if unable to provide written IC, the patient must assent verbally to participating in the study and the record should note this assent. The caregiver must separately provide IC for his/her own participation in the study.
8. Patients having caregivers who submit written consent to cooperate with this study, have regular contact with the patient (i.e., an average of ≥4 hours/day and ≥3 days/week), provide patients' information necessary for this study, ensure the regular administration of assigned donepezil, as well as all concomitant therapies, at the correct dose, and escort the patients on required visits to study institution.
   If, during the study, the designated caregiver relinquishes his/her responsibilities to another caregiver, the new caregiver must provide IC, and otherwise similarly qualify for inclusion in the study. If no replacement caregiver is available who meets the caregiver criteria, the subject must be discontinued from this study.
9. Patients who can visit study institution as required following with investigator's instruction.
10. Patients who have vision, hearing, speech, motor function and comprehension sufficient to be able to comply with testing procedures (glasses, contact lens, and hearing aid permissible).
11. Patients who meet prohibition/restriction of using concomitant medications before Screening.
12. Comorbid medical conditions are clinically stable prior to Baseline, unless otherwise specified. The following situations should be given particular attention;
    a. Patients with risk factors of hypertension and cardiac disease may be enrolled, provided that hypertension is well controlled by medication (supine diastolic blood pressure < 95 mmHg) and cardiac disease (*e.g. angina pectoris, congestive heart failure, or right bundle branch block*) is stable on appropriate medication for at least 12 weeks prior to Screening. Peripheral vascular disease must have been stable for 12 weeks prior to Screening. No elective surgical procedures should be planned during the course of the study (*e.g., vascular bypass procedures or coronary artery bypass surgery*).

b. Patients with diabetes mellitus or risk factors for diabetes mellitus may be enrolled, provided that the patient's disease is stable and that there have been no recent (within 12 weeks of Screening) hospitalizations for diabetic ketoacidosis, hyperosmolar coma, or hyperglycemia. Patients with non-insulin-dependent diabetes may b enrolled if controlled on diet or oral medications. All diabetic patients must have an HbA1c concentration of ≤ 10% and a random serum glucose concentration of ≤ 250 mg/dL at Screening.

c. Patients with risk factors of stroke may be enrolled, provided that the disease process has been stable or controlled on medication for greater than 12 weeks prior to Screening. Patients receiving anticoagulation with warfarin are eligible for inclusion in the study if the International Normalized Ratio (INR) for prothrombin time is within the therapeutic range for prophylaxis (1.4-3.0) and the dose of warfarin is stable. Patients with prosthetic heart valves, who require full anticoagulation, should have a stable (≥ 3 months) INR in the range of 2.5-3.5.

9.3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded:

1. Anti-dementia drug therapy (cholinesterase inhibitors or memantine) within 12 weeks prior to Screening.
2. Clinical and/or radiological evidence for other serious degenerative neurological disorders or neuropsychiatric disorders.
   e.g., Alzheimr's disease, Parkinson's disease, Huntinton's disease, Pick's disease, Creutzfeld-Jacob disease, dementia with Lewy Bodies, normal pressure hydrocephalus, olivopontocerebellar atrophy, multiple system atrophy, brain tumor, progressive supranuclear palsy, idiopathic seizure disorder, subdural hematoma, multiple sclerosis, active cerebral vasculitis, schizophrenia, and bipolar or unipolar depression
3. Known human immunodeficiency virus disease, neurosyphilis, or a history of significant head trauma followed by persistent neurological deficits or known structural brain abnormalities.
4. Hypothyroidism at Screening
   Patients may be enrolled, provided that they are on a stable dose of medication for at last 12 weeks prior to Screening, have normal thyroid stimulating hormone and free thyroxine at Screening, and are considered euthyroid.
5. Vitamin B12 or folate deficiency at Screening.
   Patients who are currently receiving B12 supplementation by oral or parenteral injection may be included, provided that dosing regimen has not changed for 12 weeks, plasma B12 levels are normal or above normal and there is documented evidence of continued cognitive deterioration after initiation of B12 treatment.

6. Evidence of a new TIA or stroke that occurs within 12 weeks prior to Screening, even if the symptoms are minor and do not require hospitalization, are excluded.

   These patients may subsequently become eligible for inclusion, if no new stroke or TIA is noted for 12 weeks (3 months) and all other criteria are net.
7. Supine diastolic blood pressure ≥ 95 mmHg at Screening or Baseline.
8. Complication of sick sinus syndrome, abnormal auricular and atrioventricular junction conductions (AV block, ≥ II ventricular block, etc.), or with a prolonged QT/QTc interval (> 450 ms) as demonstrated by a repeated ECG
9. A history of life-threatening arrhythmias (*e.g., unstable atrial flutter, unstable atrial fibrillation, ventricular tachycardia, ventricular fibrillation, or torsade de pointes*).
10. Evidence of clinically significant, severe, active, or unstable gastrointestinal, renal, hepatic, respiratory, hematological, endocrine, or cardiovascular system disease.
11. A history of malignant neoplasms (not including basal or squamous cell carcinoma of the skin) treated within 5 years prior to study entry, current evidence of malignant neoplasm, recurrent, or metastatic disease. Males with localized prostate cancer requiring no treatment would not be excluded.
12. A known or suspected history of drug or alcohol dependency or abuse within approximately the last 2 years.
13. Abnormal clinical laboratory values which are judged clinically significant by the investigator.
14. Hypersensitivity to donepezil or piperdine derivatives or any of the excipients.
15. Patients who cannot swallow or who have difficulty swallowing whole tablets, as tablets should not be broken or crushed.
16. Patients who will receive prohibited concomitant medication(s) or change dosing regimen of restricted concomitant medication(s) during this study.
17. Known plan for elective surgery that would require general anesthesia and administration of neuromuscular blocking agents, such as succinylcholine, to induce paralysis/muscle relaxation.

    Minor surgery, such as colonoscopy or cataract surgery, will be permitted as long as it does not require the use of these paralytic agents.
18. Pregnant women, lactating women, or women of child-bearing potential (< 1 year post menopausal) who don't agree to practice effective contraception (*e.g., abstinence, an intrauterine device, a double-barrier method such as condom + spermicide or condom + diaphragm with spermicide, a contraceptive implant, an oral contraceptive, or have a vasectomised partner*) throughout the entire study period and for 30 days after donepezil discontinuation, or who don't have a negative serum β-HCG test result or a negative urine pregnancy test result at Screening and Baseline.
    - All females will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea, in the appropriate age group and without other known or suspected cause) or have been sterilized

surgically (*i.e. bilateral tubal ligation, hysterectomy or bilateral oophorectomy, all with surgery at least one month before dosing*).

- All women who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and for 30 days after donepezil discontinuation.

19. Patients who have participated in another clinical study within 12 weeks before Screening.
20. Any condition that would make the patient or the caregiver, in the opinion of the investigator, unsuitable for the study.

9.3.3 Removal of Subjects from Therapy or Assessment

1) Scheduled Termination

The patient will be considered to have completed the DB phase after 24 weeks of double-blind treatment and completion of the Week 24 visit procedures. Patients who have completed the DB phase can be enrolled in the OLE phase. The patient will be considered to have completed the OLE phase after 24 weeks of open-label treatment and completion of the Week 24 visit procedures. Upon completion of DB phase or OLE phase, and after resolution of any AEs or laboratory abnormalities that may be present on the last study day, the patient will be considered to have completed the study.

2) Unscheduled Termination or Removal of Patients from the Study

In accordance with the Declaration of Helsinki, patients have the right to withdraw from the study at any time and for any reason. The principal investigator (PI) and/or the sponsor have the right to withdraw a patient from the study for any of the following reasons:

1. Adverse event (AE)
2. At the request of the patient, PI, or Sponsor, whether for administrative or other reasons
3. Protocol violation or unreliable, disruptive behavior
4. Patients could be considered for withdrawal at any time from the study for lack of efficacy or evidence of no therapeutic benefit.
5. Patients could be considered for withdrawal when the patients receive prohibited/restricted concomitant medication.

If a patient decides to discontinue participation, or is removed from the study prior to completion, the final discharge procedures should be conducted. Specific events leading to discontinuation and any related test results will be recorded and explained in the CRF.

If a patient decides to discontinue study medication for any reason, he/she will be instructed to immediately notify the PI. In such cases, an early termination visit must be scheduled as soon as possible, preferably within 1 to 3 days following discontinuation of study medication.

The date and time of the last drug dose and all observations collected up to the time of termination will be recorded in the source document and the corresponding CRF along with the reason for termination. Procedures at discharge will be conducted, if possible, as described under Scheduled Termination.

9.4 TREATMENTS

9.4.1 Treatments Administered

The following treatments will be administered to subjects in each study period. A tablet will be taken orally once daily basically in the evening.

(DB Phase)

Placebo group:

Titration: Placebo tablet matched to 5 mg tablet of donepezil
Maintenance: Placebo tablet matched to 10 mg tablet or 5 mg tablet of donepezil

Donepezil group:

Titration: 5 mg tablet
Maintenance: 10 mg or 5 mg tablet

During the Maintenance period, while patients taking 10 mg/day, dose reduction to 5 mg/day will be permitted only when the investigator judges it difficult to continue 10 mg/day administration due to an occurrence of adverse event of which the causal relationship with the donepezil is not ruled out. The dose cannot be escalated up to 10 mg/day again.

(Open-label Extension)

Until Week 6 (Day 28- 42): 5 mg tablet of donepezil
After Week 6: 10 mg or 5 mg tablet of donepezil

After Week 6, the dose can be increased to 10 mg/day. Dose reduction (from 10 mg/day to 5 mg/day) will be also permitted when the investigator judges it difficult to continue the 10 mg/day administration. It is possible to increase the dose to 10 mg/day again.

The study medication will be dispensed to patient at the Baseline, at Week 4, 6, 12 and 18 in DB phase. In OLE phase, the study medication will be dispensed to patient at OLE Week 0, 6, and 12. Patients should be instructed to take their study medication with approximately eight (8)

ounces or 225 ml of a non-alcoholic beverage (preferably water). Study medication must be administered whole. Tablets cannot be split, broken or crushed prior to administration.

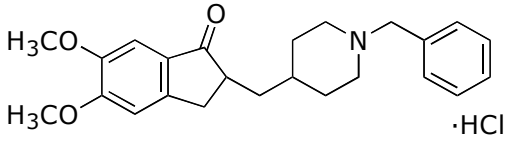
9.4.2 Identity of Investigational Product(s)

The donepezil 5 mg and 10 mg formulations and the corresponding matching placebo for each formulation will be supplied as tablets. They will be manufactured by Daewoong Co. LTD.
Description: 5 mg - white, round, film-coated tablet, 10 mg - yellow, round, film-coated tablet

The sponsor will provide the study drugs packaged in a double-blind configuration in labeled containers (bottles). Each subject's study drug will consist of either donepezil or the matching placebos. In OLE phase, the study drugs will be packed in open-labeled containers (bottles). The study drug will consist of donepezil only.
Packaging container: bottle packaging
materials for bottle: high-density polyethylene (HDPE), polypropylene (PP), polystyrene (PS)
materials for cap: PP, LDPE (low-density polyethylene), acrylonitrile butadiene styrene (ABS)

9.4.2.1 Chemical Name, Structural Formula of E2020

- Test drug code: E2020
- Generic name: Donepezil Hydrochloride
- Chemical name: (±)-2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxyindan-1-one monohydrochloride
- Molecular formula: $C_{24}H_{29}NO_3 \cdot HCl$
- Molecular weight: 415.96
- Structural formula:



9.4.2.2 Comparator Drug

Placebo tablet matched to 5 mg or 10 mg tablet

9.4.2.3 Labeling for Study Drug

The sponsor will provide study drug packed in labeled sheets to the pharmacist in investigational site. Labeling of study drug is in accordance with article 75 clause 6 of Enforcement Regulations of the Pharmaceutical Affairs Act in Korea and will include the following information.

1) Cautionary statement for 'Investigational drug'
2) Product code or generic name of active ingredient
3) Lot number and expiration date or retest date
4) Storage method
5) The name and address of the approved party for the clinical trial
6) Cautionary statement for 'It is not allowed to use for other purpose except clinical trial'

9.4.2.4 Storage Conditions

Donepezil will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the donepezil is maintained within an established room temperature range, 1°C to 30°C.

9.4.3 Method of Assigning Subjects to Treatment Groups

At the time of the Baseline visit, patients meeting the eligibility criteria will be randomly assigned (1:1) to either donepezil group or placebo group by IWRS system according to a computer-generated randomization code generated by an independent statistician.

The list of patient randomization codes will be generated using PROC PLAN in the SAS® procedures. A stratified block randomization approach will be used for the randomization with MMSE (≤ 19, 20 ≤) as stratum in each study site.

(Open-label extension)

This is an open-label extension phase. Subjects, who have completed the DB phase and have consented to continue participation of the study, can be enrolled in the 24-week open-label extension phase. All subjects who provide signed informed consent to participate in this phase will be assigned to receive active drug. There is no randomization in this phase.

9.4.4 Selection of Doses in the Study

Donepezil is currently approved for the treatment of dementia associated with Alzheimer's disease and for symptom improvement in vascular dementia at 5 mg/day and 10 mg/day in Korea. The dose can be escalated to 10 mg after assessing the clinical response of donepezil. Also, the maximum tolerance dose is 10 mg/day. Thus, for this study, placebo, 5 mg and 10 mg will be the doses studied.

9.4.5 Selection and Timing of Dose for Each Subject

After the baseline evaluations have been completed, subjects start taking study medication in the evening of the baseline. Study drugs will be taken orally once daily basically in the evening throughout the study.

9.4.6 Blinding

During the DB Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (e.g., Eisai Global Safety) until the time of unblinding, per standard operating procedure (SOP).

9.4.7 Prior and Concomitant Therapy

9.4.7.1 Prohibited and Restricted Concomitant Therapies and Drugs

1) Prohibited concomitant medication

12 weeks before the Screening to final day of the study

① Anti-dementia agents: Donepezil, rivastigmine, galantamine, memantine, except for the study drug

② Other investigational drugs

6 weeks before the Screening to final day of the study

③ Choline stimulants (cholinesterase inhibitor, choline agonists, except for topical agents)

3 weeks before the Screening to final day of the DB phase

④ Antiparkinsonian agents

⑤ Tricyclic antidepressants

⑥ Antipsychotics

⑦ Hypnotics (except for the short actin hypnotics defined as restricted concomitant drugs)

⑧ Nootropics (choline alfoscerate, acetyl-L-carnitine, oxiracetam et al.)

⑨ Gingko biloba

2) Restricted concomitant medications (The dose should be maintained)

3 weeks before the Screening to final day of DB phase

① Antidepressant (except for tricyclic antidepressants)

② Anxiolytics

③ Hypnotics (short acting hypnotics; zolpidem, brotizolam, lormetazepam, rilmazafone, zopiclone, ramelteon)

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Clinical research associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

At Week 4, 6, 12, 18 and 24 in DB phase and Week 6, 12, and 24 in OLE phase, the study medication from the previous treatment period will be returned to the investigator. The medication will be inventoried and the percent compliance calculated by dividing the number of doses removed from the sheets by the number of days of the treatment period. For example, if between weeks 6 and 12, the patient had a 42-day interval between clinic visit and 40 doses of medication have been removed and administered, the patient is 95% compliant (40/42 x 100= 95%). If compliance is less than 80% or greater than 120% at any visit, the reason(s) must be noted on the appropriate page of the CRF and in the source documents. If there are two consecutive visits where compliance is < 80% or > 120%, the patient will be discontinued from the study for non-compliance.

9.4.9 Drug Supplies and Accountability

The investigator and the study staff will be responsible for the accountability of study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to Good Clinical Practice (GCP) guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow study drugs to be used other than as directed by this protocol. Study drugs supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of study drugs, dispensing of study drugs supplies to the subject, collection and reconciliation of unused study drugs supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs supplies to the sponsor or (where applicable) destruction of reconciled study drugs supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (e.g., KFDA).

As applicable, all unused study drugs supplies and empty and partially empty containers from used study drugs are to be returned to the investigator by the subject and together with unused study drugs that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 STUDY ASSESSMENTS

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity.

9.5.1.2 Baseline Assessments

MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All pertinent medical and surgical history within 1 year must be noted on the appropriate CRF.

DIAGNOSIS

Patient will be diagnosed as possible or probable dementia associated with cerebrovascular disease according to NINDS-AIREN Criteria.

HACHINSKI ISCHEMIA SCALE

The Hachinski Ischemia Scale is a simple clinical tool widely used in the differentiation of Alzheimer's disease and ischemic vascular dementia (Swanwick et al., 1996). The scale consists of 13 criteria: abrupt onset, stepwise deterioration, fluctuating course, nocturnal confusion, preservation of personality, depression, somatic complaints, emotional incontinence, history of hypertension, history of strokes, associated arteriosclerosis, focal neurological symptoms, and focal neurological signs. The clinician marks all items that are present in the patient. Criteria are weighted individually and scored as either 1 (*no*) or 2 (*yes*)

NEUROLOGICAL EXAMINATION

A comprehensive neurological examination will be performed at the Screening Visit. The examination will include the evaluation of the cranial nerves (including visual fields), motor, sensory, brainstem, cerebellar and autonomic functions.

CRANIAL MRI OR CT

Cranial MRI or CT should be obtained as part of the Screening activities, if an MRI or CT was not obtained within the past 6 months. If obtained as part of Screening, a scan must be obtained at least 7 days prior to the Baseline visit.

CDR (CLINICAL DEMENTIA RATING)

The Clinical Dementia Rating (CDR) will be performed at the Screening Visit. The clinical Dementia Rating (CDR) is a global scale developed to clinically denote the presence of Dementia of the Alzheimer type (DAT) and stage its severity. The clinical protocol incorporates semi-structured interviews with the patient and informant to obtain information necessary to rate

the subject's cognitive performance in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Criterion validity for both the global CDR and scores on individual domains has been demonstrated, and the CDR also has been validated neuropathologically, particularly for the presence or absence of dementia.

9.5.1.3 Efficacy Assessments

Primary efficacy variable:

1) Cognitive function: Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog)

ADAS-cog will be assessed at Visit 2, 3, 5, 6, and 7 (Week 0, 4, 12, 18, and 24). Every ADAS-cog test for one subject should be administered by one rater throughout the study.

2) Global function: Clinicians Interview-Based Impression of Change-plus (CIBIC-plus)

CIBIC-plus will be assessed at Visit 2, 3, 5, and 7 (Week 0, 4, 12 and 24). CIBIS will be assessed at Visit 2 (Week 0). CIBIS and every CIBIC for one subject should be evaluated by one independent rater throughout the study. Clinical information about the subject from any source can be used for the CIBIS, but not at any other time for the CIBIC during the study. The rater will refer to the CIBIS to complete the CIBIC.

Secondary efficacy variables:

1) Mini-Mental Status Examination (MMSE) (Folstein et al., 1975)

The MMSE is a brief test for measuring the cognitive state of the patient. This 30-point test includes items evaluating orientation to time and place, recall of objects, attention, language, and conversational abilities. This test is conducted with the patient by a trained clinician. The MMSE will be assessed every clinic visits. Every test for one subject should be administered by one rater throughout the core study (Baseline and DB phase).

2) Executive function test (Trail making test)

Executive function test (Trail making test (K-TMT-e)) will be assessed at Visit 2, 5, and 7 (Week 0, 12, and 24). Every test for one subject should be administered by one rater throughout the study.

These will be assessed by trained investigators or psychometrists.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/Pharmacogenetic Assessments

Not applicable

9.5.1.5 Safety Assessments

ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. During clinical studies, adverse event information will be collected after signing of informed consent in order to collect study-associated events. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug(s) is 5 mg donepezil and corresponding matching placebo, as well as donepezil 10 mg and corresponding matching placebo.

The criteria for identifying AEs are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (e.g., ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (e.g., headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not.

A laboratory result should be considered by the investigator to be an AE if it:

- Results in the withdrawal of study drug
- Results in withholding of study drug pending some investigational outcome
- Results in an intervention, based on medical evaluation (e.g., potassium supplement for hypokalemia)
- Results in any out of range laboratory value that in the investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit. Serious AEs will be collected for 30 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the appropriate CRF.

It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

ASSESSING SEVERITY OF ADVERSE EVENTS

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Serious Adverse Events and Other Events of Interest [Section 9.5.1.5] for the definition of an SAE).

ASSESSING RELATIONSHIP TO STUDY TREATMENT

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

CLASSIFICATION OF CAUSALITY

Not Related	A causal relationship between the study treatment and the AE is not a reasonable possibility.
Related	A causal relationship between the study treatment and the AE is a reasonable possibility. The investigator must further qualify the degree of certainty as "possible" or "probable."

SERIOUS ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events of interest are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with events of interest are to be reported on the CRF whether or not they meet the criteria for SAEs.
The following hospitalizations are not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence associated with hospitalization.

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (e.g., battery replacement)that was in place before study entry

CLINICAL LABORATORY DETERMINATIONS

Blood and urine samples will be collected for Clinical Laboratory Determinations at the Screening visit and at all subsequent clinic visit except Visit 2, 3 (Week 0, 4) (DB phase: Visit 4, 5, 6, 7 and early discontinuation and OLE phase; Visit 8, 9, 10 and early discontinuation).
Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. Subjects should be in a seated or supine position during blood collection.

Table 1. Clinical Laboratory Tests

Category	Parameters
Hematology	hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), INR (only for patients taking warfarin)
Chemistry	
Electrolytes	chloride, potassium, sodium
Liver function tests	alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin
Renal function parameters	blood urea/blood urea nitrogen, creatinine
Other	albumin, calcium, cholesterol, creatine kinase, globulin, glucose, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid, HbA1c
Urinalysis	casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs
Others (only at Screening)	hepatitis B surface antigen, thyroid profile (TSH and free T4), vitamin B-12, folate
RBC = red blood cell, WBC = white blood cell, TSH = thyroid stimulating hormone	

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Adverse Events and Other Events of Interest [Section 9.5.1.5]) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the appropriate CRF.

For laboratory abnormalities meeting the criteria of SAEs (see Serious Adverse Events and Other Events of Interest [Sections 9.5.1.5]), the site must fax or email the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital signs (i.e., systolic and diastolic blood pressure (BP) [mmHg], pulse [beats per minute]), and weight [kg] will be obtained by a validated method at all clinic visits of DB and OLE phase (Table 2 and Table 3). BP will be measured by a qualified instrument in the supine position (only at Screening and Visit 2 (Week 0)) and in the sitting position (at all visits). Automated measurement is available. All BP measurements should be performed on the same arm, preferably by the same person. Weight will be recorded.

ELECTROCARDIOGRAMS

A 12-lead ECG will be performed at Screening and at the Visit 3, 4, 5, 6, 7 and early discontinuation of DB phase, and visit 8, 9 10 and early discontinuation of OLE phase. The ECG

will be a complete, standardized 12-lead recording. Electrocardiograms will be properly mounted and evaluated by the investigator or a qualified consultant.
An ECG abnormality may meet the criteria of an AE as described in this protocol (see Adverse Events and Other Events of Interest [Section 9.5.1.5]) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.
For ECG abnormalities meeting criteria of an SAE (see Serious Adverse Events and Other Events of Interest [Section 9.5.1.5]), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

PREGNANCY TEST

Pregnancy test will be performed at all visits only for female subjects of childbearing potential (pre-menopausal women or women who are amenorrhea for less than 12 months from the last menstrual cycle only). A serum β-hCG test will be performed at Screening, and urine test at all other visits.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2. Schedule of Procedures/Assessments in Study E2020-K082-418: <Core Study>

Phase	Screening		Double-Blind					
Period	Screening	Baseline	Titration	Maintenance				
Visit	1	2	3	4	5	6	7	Early Discontinuation
Duration (Weeks)		Week 0	Week 4	Week 6 [i)]	Week 12	Week 18	Week 24	
Duration (days)	-28 to -7	0	28-35	35-49	77-91	119-133	161-168	
Informed Consent [a)]	X							
Inclusion/Exclusion Criteria	X	X						
Demography/Medical History	X							
Diagnosis (NINDS-AIREN)	X							
Hachinski Ischemia Scale	X							
Neurological Examination	X							
Cranial MRI or CT [b)]	X							
CDR	X							
Prior and Concomitant Medications	X	X	X	X	X	X	X	X
Randomization		X						
Dispense Study Drug		X	X	X	X	X		
Study Drug Compliance			X	X	X	X	X	X
Return Unused Study Medication			X	X	X	X	X	X
Efficacy								
MMSE [c)]	X	X	X		X	X	X	X
ADAS-cog [c)]		X	X		X	X	X	X
Executive function test [c)]		X			X		X	X
CIBIC-plus								
CIBIS [d)]		X						
CIBIC [d)]			X		X		X	X
Safety								
Vital Signs [e)]	X	X	X	X	X	X	X	X
12-lead ECG	X		X	X	X	X	X	X
Clinical Laboratory Determinations [f)]	X			X	X	X	X	X
Pregnancy Test (females only) [g)]	X	X		X	X	X	X	X
Adverse Events [h)]	X	X	X	X	X	X	X	X

a) If the patient is unable to provide written informed consent, written consent must be obtained from the patient's representative and verbal assent must be obtained from the patient. The caregiver must separately provide IC for his/her own participation in the study.
b) To be obtained as part of the Screening activities, if an MRI or CT was not obtained within the past 6 months. If obtained as part of Screening, a scan must be obtained at least 7 days prior to the baseline visit.
c) Every test for one subject should administered by one rater throughout the core study (Baseline and DB phase).
d) CIBIS and every CIBIC for one subject should be evaluated by one rater throughout the study. Clinical information about the subject from any source can be used for the CIBIS, but not at any other time for the CIBIC during the study. The rater will refer to the CIBIS to complete the CIBIC.
e) Blood pressure, radial pulse, and Weight, all visits.
f) All clinical laboratory tests will include hematology, clinical chemistry and urinalysis. Additionally, at the Screening visit only, assessments of serum vitamin B12, folate levels, thyroid profile and hepatitis B and C titers will be obtained. INR only for patients taking warfarin.
g) To perform only for pre-menopausal women or women who are amenorrhea for less than 12 months from the last menstrual cycle. Serum at Screening, urine at other visits.
h) Adverse events will be collected from the time subject signs informed consent form through the last visit. Serious adverse events will be collected through the last visit and for 30 days after study termination.
i) There should be an interval of 1 week or longer between Week 4 (Visit 3) and Week 6 (Visit 4).

Table 3. Schedule of Procedures/Assessments in Study E2020-K082-418: <OLE phase>

Phase	Open-label extension				
Period	Titration	Maintenance (Flexible dose)			
Visit	7	8	9	10	Early Discontinuation
Duration (weeks of Core study)	Week 24				
Duration (weeks of OLE phase)	Week 0	Week 6 [o)]	Week 12	Week 24	
Duration (days of OLE phase)		28-42	77-91	161-175	
Informed Consent [j)]	X				
Concomitant Medications		X	X	X	X
Dispense Donepezil	X	X	X	X	
Donepezil Compliance		X	X	X	X
Return Unused Study Medication		X	X	X	X
Efficacy					
MMSE		X	X	X	X
Safety					
Vital Signs [k)]		X	X	X	X
12-lead ECG		X	X	X	X
Clinical Laboratory Determinations [l)]		X	X	X	X
Pregnancy Test (females only) [m)]		X	X	X	X
Adverse Events [n)]		X	X	X	X

j) Subjects who completed the DB phase can be enrolled in this phase. Written informed consent must be obtained again.

k) Blood pressure, radial pulse, and weight, all visits.

l) All clinical laboratory tests will include hematology, clinical chemistry and urinalysis. INR only for patients taking warfarin.

m) To perform only for pre-menopausal women or women who are amenorrhea for less than 12 months from the last menstrual cycle.

n) Adverse events will be collected from the time subject signs informed consent form through the last visit. Serious adverse events will be collected through the last visit and for 30 days after study termination.

o) The dose will be increased to 10 mg/day after confirmation of clinical response at Visit 8.

9.5.2.2 Description of Procedures/Assessments Schedule

SCREENING PHASE ASSESSMENT SCHEDULE

SCREENING PERIOD ASSESSMENTS

Screening Visit (Visit 1, Day -28 to Day -7)

Written informed consent is obtained from the patients (if possible) and from legal guardian. The caregiver should separately provide written informed consent for his/her own participation in the study. Once informed consent has been obtained, the following procedures and evaluations will be performed:

- Subject medical history; subject and caregiver demographic information
- Record prior and concomitant medication use over the past 12-week.
- Diagnosis (NINDS-AIREN): Hachinski Ischemia Scale, Neurological Examination, Cranial MRI or CT, CDR
- MMSE (Mini-Mental State Examination)
- Vital signs (systolic and diastolic BP in supine and sitting position, pulse), and weight
- 12-lead ECG
- Blood and urine samples for clinical laboratory assessments and pregnancy testing (serum, only females of childbearing potential)
- Any AEs to be collected from the time of consent
- Review of inclusion/exclusion criteria for subject and caregiver
- Schedule Baseline Visit 2

BASELINE ASSESSMENTS

Baseline Visit (Visit 2, Week 0)

The results of all screening assessments and evaluations must be completed and reviewed by the PI before the subject's arrival for the visit. Only those subjects who continue to meet all of the inclusion and none of the exclusion criteria are eligible to continue in the study. This is intended to minimize variability in subject and caregiver response. It is further recommended (whenever possible) that subjects be evaluated at approximately the same time of the day (e.g., morning or afternoon) at each subsequent visit.

The following procedures and evaluations will be performed:

- Record all prior and concomitant medication use.
- MMSE (Mini-Mental State Examination)
- Vital signs (systolic and diastolic BP in supine and sitting position, pulse), and weight
- Collect urine samples for pregnancy test (urine, only females of childbearing potential)
- Record any AEs
- Review of inclusion/exclusion criteria for subject and caregiver
- ADAS-cog, executive function test
- CIBIS

- Randomization (Randomly assigned as 1:1 ratio by IWRS system)
- Dispense study medication.
- Schedule Visit3

Caregiver's Responsibilities: Prior to leaving the study site, the caregiver will receive an appointment schedule for the next visit and study medication containing drug supply sufficient for the period prior to the next clinic visit. It is the caregiver's responsibility to help to ensure that the medication is stored safely in the home, to assist in patient compliance with taking their medication and making clinic visits and to provide the investigator with information for the evaluation of psychometric/neurological functions.

DOUBLE-BLIND PHASE ASSESSMENT SCHEDULE

TITRATION PERIOD ASSESSMENTS

Visits 3 (Week 4, Day 28-35)

The following procedures and evaluations will be performed:

- Record all concomitant medication use
- Collect unused study medication and record compliance
- MMSE
- ADAS-cog
- CIBIC
- Vital signs (sitting systolic and diastolic BP, pulse) and weight
- 12-Lead ECG
- Record any AEs
- Dispense study medication.
- Schedule Visit 4

MAINTENANCE PERIOD ASSESSMENTS

Visits 4 (Week6, Day 35-49)

The following procedures and evaluations will be performed:

- Record all concomitant medication use
- Collect unused study medication and record compliance
- Vital signs (sitting systolic and diastolic BP, pulse) and weight
- 12-Lead ECG
- Blood and urine samples for clinical laboratory determinations (including urine pregnancy test for females of childbearing potential)
- Record any AEs
- Dispense study medication.
- Schedule Visit 5

Visit 5 (Week12, Day 77-91)

The following procedures and evaluations will be performed:

- Record all concomitant medication use
- Collect unused study medication and record compliance
- MMSE
- ADAS-cog, executive function test
- CIBIC
- Vital signs (sitting systolic and diastolic BP, pulse) and weight
- 12-lead ECG
- Blood and urine samples for clinical laboratory determinations (including urine pregnancy test for all females of childbearing age)
- Record any AEs
- Dispense study medication.
- Schedule Visit 6

Visit 6 (Week 18, Day 119-133)

The following procedures and evaluations will be performed:

- Record all concomitant medication use
- Collect unused study medication and record compliance
- MMSE
- ADAS-cog
- Vital signs (sitting systolic and diastolic BP, pulse) and weight
- 12-lead ECG
- Blood and urine samples for clinical laboratory determinations (including urine pregnancy test for all females of childbearing age)
- Record any AEs
- Dispense study medication
- Schedule Visit 7

Visit 7 (Week 24, Day 161-168) or Early discontinuation

The following procedures and evaluations will be performed:

- Record all concomitant medication use
- Collect unused study medication and record compliance
- MMSE
- ADAS-cog, executive function test
- CIBIC
- Vital signs (sitting systolic and diastolic BP, pulse) and weight
- 12-lead ECG
- Blood and urine samples for clinical laboratory determinations (including urine pregnancy test for all females of childbearing age)

- Record any AEs

OPEN-LABEL EXTENSION PHASE ASSESSMENT SCHEDULE

BASELINE VISIT

Visit 7 (OLE Week 0, same as Week 24 of DB phase)

The following procedures and evaluations will be performed:

- Obtain written informed consent
- Dispense study medication.
- Schedule Visit 8 if the subjects will be enrolled in the open-label extension phase
-

TITRATION PERIOD ASSESSMENTS

Visit 8 (OLE Week 6, Day 28-42)

The following procedures and evaluations will be performed:

- Record all concomitant medication use
- Collect unused study medication and record compliance
- MMSE
- Vital signs (sitting systolic and diastolic BP, pulse) and weight
- 12-lead ECG
- Blood and urine samples for clinical laboratory determinations (including urine pregnancy test for all females of childbearing age)
- Record any AEs
- Dispense study medication.
- Schedule Visit 9

The dose can be increased to 10 mg/day after confirmation of clinical response at Visit 8 (Week 6).

MAINTENANCE (FLEXIBLE DOSE) PERIOD ASSESSMENTS

Visit 9 (OLE Week 12, Day 77-91)

The following procedures and evaluations will be performed:

- Record all concomitant medication use
- Collect unused study medication and record compliance
- MMSE
- Vital signs (sitting systolic and diastolic BP, pulse) and weight
- 12-lead ECG
- Blood and urine samples for clinical laboratory determinations (including urine pregnancy test for all females of childbearing age)
- Record any AEs
- Dispense study medication.

- Schedule Visit 10

Visit 10 (OLE Week 24, Day 161-175) and Early discontinuation

The following procedures and evaluations will be performed:

- Record all concomitant medication use
- Retrieve unused study medication and record compliance
- MMSE
- Vital signs (sitting systolic and diastolic BP, pulse) and weight
- 12-lead ECG
- Blood and urine samples for clinical laboratory determinations (including urine pregnancy test for all females of childbearing age)
- Record any AEs

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of dementia associated with cardiovascular disease.

The safety assessments to be performed in this study, including hematology analysis, blood chemistry test, urinalysis, radiologic studies and assessments of AEs, are standard evaluations to ensure subjects safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Other Events of Interest

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected through the last visit and for 30 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment should be reported to the sponsor regardless of the length of time that has passed since study completion.

Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 1 business day by emailing or faxing the completed SAE form.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues call: Designated CRO (C&R Research) contact number
For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.
Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.
Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment must be reported
If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.
A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).
Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.
A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Other Events of Interest

REPORTING OF ADVERSE EVENTS ASSOCIATED WITH STUDY DRUG OVERDOSE, MISUSE, ABUSE, OR MEDICATION ERROR

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the prescribed or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription

Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with an overdose should be captured on the Adverse Event CRF. Adverse events associated with overdose, misuse, abuse, or medication error should be reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 2 and Table 3).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or

other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded in the CRF.
Subjects who discontinue early from the study will be discontinued for one of these primary reasons: AE(s), lost to follow-up, subject choice, progression of disease, protocol violation, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate one or more of secondary reasons for discontinuation. Study disposition information will be collected on the appropriate CRF.

9.5.6 Abuse or Diversion of Study Drug
Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician
Not applicable.

9.6 DATA QUALITY ASSURANCE
This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection
Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.
Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management
All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (e.g., laboratory data), will be entered into a clinical system.

9.7 STATISTICAL METHODS
All statistical analyses will be performed by the sponsor or designee. Statistical analyses for DB phase will be performed after a snapshot of the database is obtained and released for unblinding.

Statistical analyses for OLE phase will be performed after the study is completed and the database is locked.

9.7.1 Statistical and Analytical Plans

The statistical analyses of core study data (DB phase) are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

CO-PRIMARY ENDPOINT(S)

1) Cognitive function: Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog)
   Assessment of cognitive function measured by ADAS-cog from baseline to Week 24.

2) Global function: Clinicians Interview-Based Impression of Change-plus (CIBIC-plus)
   Assessment of global function measured by CIBIC-plus at Week 24.

SECONDARY ENDPOINT(S)

1) Mini-Mental Status Examination (MMSE)
   Assessment of Mini-Mental Status Examination (MMSE) from baseline to Week 24 compared to placebo.
2) Executive function test (Trail making test (K-TMT-e))
   Assessment of executive function test from baseline to Week 24 compared to placebo.

EXPLORATORY ENDPOINT(S)

Not applicable

9.7.1.2 Definitions of Analysis Sets

The Safety Analysis Set (SAS) is the group of subjects who received at least one dose of study drug and had at least one postdose safety assessment.

The Full Analysis Set (FAS) is the group of randomized subjects who received at least one dose of study drug and had at least one postdose primary efficacy measurement.

The Per Protocol Set (PPS) is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding and will be specified in the Statistical Analysis Plan.

9.7.1.3 Subject Disposition

The disposition of all subjects will be summarized. Subject disposition tables will include the number (percent) of subjects who will:

- randomized into each treatment group;
- included in each analysis populations (Safety, FAS, PPS);
- discontinued from the study early, summarized by reason for discontinuation.
  The number of subjects screened and the number (percent) who fail screening will also be summarized.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for each analysis set will be summarized for each treatment group and total of treatment groups using descriptive statistics (e.g., mean, SD, median, minimum, maximum and frequency, proportion). Continuous demographic and baseline variables include age, weight etc. Categorical variables include sex, age group etc.

9.7.1.5 Prior and Concomitant Therapy

Prior medication is defined as any medication taken prior to the first dose of study drug. Concomitant medication is defined as any medication taken during the treatment period between the date of the first dose of study drug and the date of the last dose of study drug, inclusive.
Prior medications and concomitant medications will be summarized in number and percentages of subjects by Anatomical Therapeutic Chemical (ATC) Code by treatment group for all subjects.

9.7.1.6 Efficacy Analyses

The efficacy data observed from baseline to Week 24 will be used for analysis. All statistical tests will be conducted at the significance level of 5.0% (two-tailed).
The analysis will be conducted on the FAS and PPS, using the last observation carried forward (LOCF) method to impute missing data at Week 24, unless otherwise specified, and the observed cases (OC) populations at Week 24 and other time points.
The analysis of FAS is primary, and that of PPS is a sensitivity analysis of FAS.

CO-PRIMARY EFFICACY ANALYSIS

The co-primary efficacy variables are used as follows to determine whether donepezil has superior efficacy compared to placebo:

- For ADAS- cog change from baseline to Week 24, an analysis of covariance (ANCOVA) model with baseline as covariates and treatment as main effect will be used for testing main effect.
- For CIBIC-plus scores, least squares (LS) mean scores at Week 24 will be compared between groups to demonstrate numerical superiority of donepezil to placebo (the

difference is less than 0), using ANCOVA model with CIBIS-plus (covariate) and treatment group (main effect).

For the measurements of each visit and the change from baseline to each visit of both endpoints, descriptive statistics (median, mean, SD, minimum, maximum and number of patients with non-missing data for both variables; number and percentages of each score for CIBIC-plus) will be presented. Where appropriate, least square (LS) mean, between-treatment difference in least square (LS) means, 95% confidence intervals (CIs) for the difference and p value in each visit will also be presented.

SECONDARY EFFICACY ANALYSES

MMSE and executive function test score change from Baseline to Week 24 will be analyzed using a same ANCOVA model as is described for the ADAS-cog. Other statistical inference (estimating and testing) will also be analyzed in the same way with primary analysis.

EXPLORATORY EFFICACY ANALYSES

Not applicable

9.7.1.7 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

9.7.1.8 Safety Analyses

The evaluation of safety parameters will be conducted on the SAS. The incidence rates for AEs by body system, preferred term, severity, and relationship to study mediation will be calculated. Individual vital signs will be descriptively summarized by treatment group and total of treatment groups and visit. Changes from Baseline to each individual post- baseline visit and to the final visit will be calculated. For clinical laboratory parameters, changes from Baseline to each visit, will be summarized. Shift tables depicting shifts in or out of the normal range, from Baseline to the final study visit, will also be provided.

ECG data will be categorized at Baseline, and results for each subject at the end of treatment will be compared to those at Baseline. Data on other medications used by subjects during the study will be collected and summarized by therapeutic class and generic components.

EXTENT OF EXPOSURE

Study compliance and the extent of exposure to the study drug for the safety analysis set during the double-blind treatment period will be summarized descriptively.

ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 15 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Treatment-emergent AEs (TEAEs) will be summarized by treatment group. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (possibly related, probably related, and not related).

LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each post-baseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics(median, mean, SD, minimum, maximum and number of patients with non-missing data). Qualitative parameters listed in Section 9.5.1.5 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each post-baseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and relevant post-baseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

VITAL SIGNS

Descriptive statistics for vital signs parameters (i.e., systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], and weight (kg)) and changes from baseline will be presented by visit and treatment group.

ELECTROCARDIOGRAMS

For ECG Measurement, Changes from Baseline or Screening to the last visit in the 12-lead ECG during the double-blind phase will be calculated by the incidence of a new or worsening clinically significant finding (treatment emergent ECG measures and physical examination shift table).

OTHER SAFETY ANALYSES

Not applicable.

9.7.1.9 Other Analyses

Not planned

9.7.1.10 Extension Phase Analyses

DEFINITIONS OF ANALYSIS SETS IN EXTENSION PHASE

The Safety Analysis Set of OLE-phase (SAS-OLE) is the subjects who received at least one dose of study drug and had at least one post dose safety assessment after starting OLE Phase.

The Efficacy Analysis Set of OLE-phase (FAS-OLE) is the group of subjects who received at least one dose of study drug and had at least one post-dose MMSE measurement after starting Open-label Phase.

EFFICACY ANALYSIS

For the efficacy endpoint, MMSE, descriptive statistics (median, mean, SD, minimum, maximum and number of patients with non-missing data) of the measurement and the change from week0 of extension phase to each visit will be presented by visit and total.

SAFETY ANALYSIS

The same analysis method like the double-blind phase will be presented by total.

9.7.2 Determination of Sample Size

The primary endpoints are the change from baseline to Week 24 (LOCF) in ADAS-cog and the measurement at Week 24 (LOCF) of the CIBIC-plus.

The estimates of these endpoints were referred from the result of subgroup (MMSE less than 24) in pooled data of previous double blind studies (E2020-A001-307 and E2020-A001-308).

The mean difference and standard deviation of the change from baseline to final visit in ADAS-cog were estimated as -2.404±5.955, using pooled data of E2020 groups (5 mg+ 10 mg). When the significance level was set as 5.0% (two-tailed) and statistical power as 80.0%, the subject number needed to detect statistically significant difference by 2 sample t test was calculated to be 196 (98/arm).
On the other hand, the mean difference and the standard deviation of CIBIC-plus score at the final visit were estimated as -0.261 ± 1.162, when CIBIC-plus was regarded as continuous measurement [scored from 1 (marked improvement) to 7 (marked worsening) point]. The subject number needed to reduce the probability that donepezil is inferior to placebo in point estimate to 2.5% or less, was calculated to be 308 (154/arm)..
Therefore, the subjects number required to achieve primary objectives simultaneously became 308 (154/arm). In consideration of exclusion from the analysis set (approximately 5%), the sample size was defined as 324 (162/arm).

9.7.3 Interim Analysis

Not applicable

9.7.4 Other Statistical/Analytical Issues

Not applicable

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistician determines that the analysis plan requires revision after the study begins, the person in charge of analysis and the study director will examine the validity of the revision and its influence on the objectives of the study, and determine if the revision can be implemented. The details of the revision will be described in the SAP and CSR for the study.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 CHANGES TO THE PROTOCOL

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 ADHERENCE TO THE PROTOCOL

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5 and KGCP).

11.3 MONITORING PROCEDURES

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production

- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (e.g., sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (e.g., urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (e.g., questionnaires) that are completed directly by subjects and serve as their own source

11.4 RECORDING OF DATA

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.
This study will use electronic CRF system. The investigator must sign by electronic signature on each CRF.

11.5 IDENTIFICATION OF SOURCE DATA

ICH GCP guidelines specifically acknowledge that data may in some cases be recorded directly on CRFs. According to ICH guidance, if sections of the CRF are to be considered source documents, these sections or pages should be identified in the protocol before study inception.
All data to be recorded on the CRF must reflect the corresponding source documents. For the following item(s), the data recorded directly on the CRF are to be considered source data:

- (Using bullet format, add items to be recorded on the CRF that will be considered source data, e.g., reasons for discontinuation of study treatment, comments and other information on AEs [severity, relationship to study drug, outcome, etc.], reasons for dose modification, indication for prior/concomitant medication, sampling times for drug concentrations, sampling times for clinical laboratory tests.)

11.6 RETENTION OF RECORDS

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (e.g., ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. It is mandatory to keep the clinical related documents at least for 3 years from this clinical trial completion or termination.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 AUDITING PROCEDURES AND INSPECTION

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 HANDLING OF STUDY DRUG

All study drugs will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 PUBLICATION OF RESULTS

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to

the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.
The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 DISCLOSURE AND CONFIDENTIALITY

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.
All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 DISCONTINUATION OF STUDY

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).
The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 SUBJECT INSURANCE AND INDEMNITY

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

APPENDICES

APPENDIX I.

NINDS-AIREN CRITERIA FOR THE DIAGNOSIS OF VASCULAR DEMENTIA

PAGE 1 OF 4

Reference: Roman, G.C.; Tatemichi, T.K.; Erkinjuntti, T.; *et al*. Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 43: 250-260 (1993).

The diagnosis of dementia associated with cerebrovascular disease (VaD) can be easily made in patients with a clear history of strokes and cognitive impairment when there is an obvious temporal connection. However, the diagnosis can be difficult to establish if cerebrovascular disease alone is the cause for dementia or if it is merely a contributory or coincidental finding. To assist in determining causation, various criteria have been proposed to establish the diagnosis. The criteria for probable ischemic vascular dementia for research studies as determined by an international consortium (NINDS-AIREN) presented below.

NINDS-AIREN Criteria for Ischemic Vascular Dementia

Essential Requirements:

1) Dementia involving memory failure and other cognitive functions (not a circumscribed neurobehavioral deficit) interfering with function in daily living
2) Cerebrovascular disease as documented by a combination of history, examination and/or brain imaging.
3) Evidence that 1 and 2 are related; features that support causality include:
   Temporal relationship between stroke and dementia
   Abrupt or stepwise deterioration in mental function or a fluctuating course
   Specific brain imaging findings indicating damage to regions important for higher cerebral function.

APPENDIX I
NINDS-AIREN CRITERIA FOR THE DIAGNOSIS OF VASCULAR DEMENTIA
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Supportive Clinical Features

History of cerebrovascular risk factors (e.g., hypertension, diabetes mellitus, cardiac disease, hypercholesterolemia, smoking)
Early appearance of gait disturbance or frequent falls.
Early appearance of urinary incontinence not explained by urological disease
Frontal lobe or extrapyramidal features
Pseudobulbar features with or without emotional incontinence (pathological crying)

Diagnostic specificity for the NINDS-AIREN criteria have not been validated in large scale studies. The NINDS-AIREN criteria have a high specificity but low sensitivity for the diagnosis of probable vascular dementia. Physical impairment complicates evaluation of dementia and may introduce a bias against evaluation of agents which may potentially improve cognitive function.

Criteria for the Diagnosis of *Probable* Vascular Dementia:

1) Dementia:

Defined by a cognitive decline from a previously higher functioning and manifest by impairment of memory and two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control and praxis), preferably established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living *not due to the physical effects of stroke alone.*

Exclusion Criteria: disturbance of consciousness, delirium, psychosis, severe aphasia, major sensorimotor impairment precluding neuropsychological testing. Systemic disorders or other brain diseases (including AD) that in and of themselves could account for deficits in memory and cognition.

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NINDS-AIREN CRITERIA FOR THE DIAGNOSIS OF VASCULAR DEMENTIA
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2) Cerebrovascular Disease:

Defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without a history of stroke), and evidence for relevant cerebrovascular disease (CVD) by brain imaging (CT or MRI) including multiple large vessel infarcts or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain or anterior or posterior cerebral artery distribution), as well as *multiple basal ganglia and white matter lacune or extensive perivascular white matter lesions or combinations.*

3) A relationship between 1 and 2 above

Manifest or inferred by the presence of one or more of the following:

A) Onset of dementia within 3 months of a recognized stroke.
B) Abrupt deterioration in cognitive functions, or
C) Fluctuating stepwise progression of cognitive deficits.

Clinical features consistent with the diagnosis of probable vascular dementia include the following:

A) Early presence of a gait disturbance (small step gait or marche a petit pas, or magnetic apraxic-ataxic or parkinsonian gait);
B) History of unsteadiness and frequent unprovoked falls;
C) Early urinary frequency, urgency and other symptoms not explained by urologic disease;
D) Pseudobulbar palsy
E) Personality and mood changes, abulia, depression, emotional incontinence or other subcortical deficits including psychomotor retardation and abnormal executive function.

APPENDIX I
NINDS-AIREN CRITERIA FOR THE DIAGNOSIS OF VASCULAR DEMENTIA
PAGE 4 OF 4

Criteria for the Diagnosis of *Possible* Vascular Dementia:
Dementia as defined in section 1 above with focal neurologic signs in patients in whom brain imaging studies fail to confirm the presence of definite cerebrovascular disease as defined in Section 2 above; or the absence of a clear temporal relationship between dementia and stroke; or in patients with the subtle onset and variable course (plateau or improvement) of cognitive deficits and evidence for relevant cerebrovascular disease.

Criteria for the Diagnosis of *Definite* Vascular Dementia:
1) Clinical criteria for probable vascular dementia as described in section 1-3 above, and
2) Histopathologic evidence of cerebrovascular disease obtained from biopsy or autopsy
3) Absence of neurofibrillary tangles or neuritic plaques exceeding those expected for age
4) Absence of other clinical or pathologic disorders capable of producing dementia.

Criteria for the Diagnosis of Alzheimer's disease *with* Cerebrovascular disease:
1) Patients fulfill the clinical criteria for the diagnosis of Alzheimer's disease
2) Patients present clinical or brain imaging evidence for Cerebrovascular disease.

APPENDIX II.
CONCOMITANT MEDICATIONS

A. Concomitant Medications Not Allowed During the Study

The following medications are NOT ALLOWED as concomitant medications during the study. This list is not exhaustive and, therefore, the Investigator is asked to contact sponsor's Medical Monitor or CRO for clarification regarding the acceptability of other agents.

1) Prohibited concomitant medications

Anti-dementia drugs		
	donepezil(except for study drug)	galantamine
	rivastigmine	memantine
Choline stimulants (cholinesterase inhibitor, choline agonists, except for topical agents)		
	bethanechol	pilocarpine
	carbachol	pyridostigmine
	neostigmine	
Antiparkinsonian drugs		
	amantadine	benserazide/levodopa
	benztropine	biperiden
	bromocriptine	dihydroergocryptine
	Entacapone	levodopa/carbidopa
	pramipexole	procyclidine
	ropinirole	rotigotine
	selegiline	trihexyphenidyl
Tricyclic antidepressants		
	amitriptyline	amoxapine
	clomipramine	dothiepin
	imipramine	mirtazapine
	nortriptyline	quinupramine
Antipsychotics		
	amisulpride	nemonapride
	aripiprazole	olanzapine
	blonanserin	paliperidone palmitate
	bromperidol	perphenazine
	chlorpromazine	pimozide
	clozapine	quetiapine
	escitalopram oxalate	risperidone
	haloperidol	sulpiride
	levomepromazine	ziprasidone
	molindone	zotepine

Hypnotics		
	chloral	flurazepam
	chlordiazepoxide	midazolam
	dexmedetomidine	nimodipine
	diphenhydramine	phenobarbital
	doxylamine	Triazolam
	flunitrazepam	
Nootropics & Neurotonics		
	acetyl-L-carnitine	oxiracetam
	choline alfoscerate	piracetam
	citicoline	protirelin
	nimodipine	
Gingko biloba		

2) Restricted concomitant medications (The dose should be maintained)

Antidepressants		
	bupropion	moclobemide
	citalopram	paroxetine
	duloxetine	sertraline
	escitalopram	tianeptine
	fluoxetine	trazodone
	fluvoxamine	venlafaxine
	lithium	Hypericum
	mianserin	hyperici
	milnacipran	
Anxiolytics		
	alprazolam	ethyl loflazepate
	bromazepam	etizolam
	buspirone	hydroxyzine
	clobazam	lorazepam
	clorazepate dipotassium	mexazolam
	clotiazepam	tandospirone
	diazepam	tofisopam
Hypnotics (only short acting)		
	zolpidem	brotizolam
	lormetazepam	rilmazafone
	zopiclone	ramelteon

APPENDIX III.
SPONSOR'S GRADING FOR LABORATORY VALUES

The table below is an example of the Sponsor's Grading Laboratory Values based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010). The study team should assess whether the Sponsor's Grading for Laboratory Values is appropriate for individual studies. If this appendix is used, it is the study team's responsibility to ensure that the current version of the Sponsor's Grading Laboratory Values is placed in the appendix.

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	< LLN – 10.0 g/dL < LLN – 100 g/L < LLN – 6.2 mmol/L	< 10.0 – 8.0 g/dL < 100 – 80 g/L < 6.2 – 4.9 mmol/L	< 8.0 g/dL < 80 g/L < 4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	< LLN – 3.0 x 10^9/L < LLN – 3000/mm^3	< 3.0 – 2.0 x 10^9/L < 3000 – 2000/mm^3	< 2.0 – 1.0 x 10^9/L < 2000 – 1000/mm^3	< 1.0 x 10^9/L < 1000/mm^3
Lymphocytes	< LLN – 800/mm^3 < LLN – 0.8 x 10^9/L	< 800 – 500/mm^3 < 0.8 – 0.5 x 10^9/L	< 500 – 200/mm^3 < 0.5 – 0.2 x 10^9/L	< 200/mm^3 < 0.2 x 10^9/L
Neutrophils	< LLN – 1.5 x 10^9/L < LLN – 1500/mm^3	< 1.5 – 1.0 x 10^9/L < 1500 – 1000/mm^3	< 1.0 – 0.5 x 10^9/L < 1000 – 500/mm^3	< 0.5 x 10^9/L < 500/mm^3
Platelets	< LLN – 75.0 x 10^9/L < LLN – 75,000/mm^3	< 75.0 – 50.0 x 10^9/L < 75,000 – 50,000/mm^3	< 50.0 – 25.0 x 10^9/L < 50,000 – 25,000/mm^3	< 25.0 x 10^9/L < 25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	< LLN – 3 g/dL < LLN – 30 g/L	< 3 – 2 g/dL < 30 – 20 g/L	< 2 g/dL < 20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
ALT	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
AST	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Bicarbonate, serum-low	< LLN – 16 mmol/L	< 16 – 11 mmol/L	<11 – 8 mmol/L	< 8 mmol/L
Bilirubin (hyperbilirubinemia)	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN
Calcium, serum-low (hypocalcemia)	< LLN – 8.0 mg/dL < LLN – 2.0 mmol/L	< 8.0 – 7.0 mg/dL < 2.0 – 1.75 mmol/L	< 7.0 – 6.0 mg/dL < 1.75 – 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Calcium, serum-high (hypercalcemia)	> ULN – 11.5 mg/dL > ULN – 2.9 mmol/L	> 11.5 – 12.5 mg/dL > 2.9 – 3.1 mmol/L	> 12.5 – 13.5 mg/dL > 3.1 – 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	> ULN – 300 mg/dL > ULN – 7.75 mmol/L	> 300 – 400 mg/dL > 7.75 – 10.34 mmol/L	> 400 – 500 mg/dL > 10.34 – 12.92 mmol/L	> 500 mg/dL > 12.92 mmol/L
Creatinine	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN
GGT (γ-Glutamyl transpeptidase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: > ULN – 160 mg/dL > ULN – 8.9 mmol/L	Fasting glucose value: > 160 – 250 mg/dL > 8.9 – 13.9 mmol/L	> 250 – 500 mg/dL; > 13.9 – 27.8 mmol/L; hospitalization indicated	> 500 mg/dL; > 27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	< LLN – 55 mg/dL < LLN – 3.0 mmol/L	< 55 – 40 mg/dL < 3.0 – 2.2 mmol/L	< 40 – 30 mg/dL < 2.2 – 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	< LLN – 2.5 mg/dL < LLN – 0.8 mmol/L	< 2.5 – 2.0 mg/dL < 0.8 – 0.6 mmol/L	< 2.0 – 1.0 mg/dL < 0.6 – 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L hospitalization indicated	> 7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	< LLN – 3.0 mmol/L	< LLN – 3.0 mmol/L; symptomatic; intervention indicated	< 3.0 – 2.5 mmol/L hospitalization indicated	< 2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L hospitalization indicated	> 160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	< LLN – 130 mmol/L	N/A	< 130 – 120 mmol/L	< 120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	> 300 – 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 – 1000 mg/dL >5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L life-threatening consequences

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uric acid, serum-high (hyperuricemia)	> ULN – 10 mg/dL ≤ 0.59 mmol/L without physiologic consequences	N/A	> ULN – 10 mg/dL ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dL > 0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2020-K082-418

Study Protocol Title: *A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Donepezil Hydrochloride (E2020) in Patients with Dementia Associated with Cerebrovascular Disease*

Investigational Product Name: E2020 donepezil HCl (Aricept®)

SIGNATURE
Sponsor:

PPD

PPD

Date

Eisai Co., Ltd.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number: E2020-K082-418

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Investigational Product Name: E2020 donepezil HCl (Aricept®)

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

Protocol Amendment Comparison Table: from v2.1 (5 Apr 2013) to v2.2 (6 July 2017)

No	Page No	Content	Detail Content	Before (V2.1, 5 Apr 2013)	After (V2.2, 6 July 2017)	Remark
1	1 page	1. Title	Approval Date	V2.1, 5 Apr 2013	V2.2, 6 July 2017	Version update
2	3 page	2. Clinical Protocol Synopsis	Study Period and Phase of Development	From June 2013 to December 2017, Phase 4	From June 2013 to January 2019, Phase 4	Study period Extension (Extension of due date for CSR submission was approved by MFDS)