Clinical Study Protocol

Protocol Title:	**A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Efficacy and Safety of 26-Week Treatment of AR1001 in Patients with Mild to Moderate Alzheimer's Disease**
Protocol Number:	**AR1001-ADP2-US01**
Date of Protocol/Version:	**18 Apr 2019 / v4.0**
Drug Product:	**AR1001**
IND No.:	**133281**
Study Phase:	**2**
Sponsor:	**AriBio Co., Ltd.** **F5 Pangyo Seven Venture Valley 2 Building #1** **17 Pangyo-ro 228-gil** **Seongnam-si, Gyeonggi-do 13487** **Republic of Korea** **Tel: +82-70-7462-9490** **Fax: +82-70-7462-9485** **E-mail: fredkim@aribiousa.com**

Confidentiality Statement

This confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from Sponsor.

Sponsor Signature Page

Protocol Number: AR1001-ADP2-US01

The signatures of the representatives below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations stated in the protocol, including all statements as to confidentiality. It is also agreed that the study will not be initiated without the approval of an appropriate Institutional Review Board or Ethics Review Committee.

Approved by the Following:

Sponsor Internal Personnel (AriBio Co., Ltd.)

Matthew Choung		19 Apr 2019
Chairman	Signature	Date
Jim Rock		19 APR 2019
SVP of Global Clinical Operations	Signature	Date

Protocol Signature Page

I have carefully read the attached protocol entitled "A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Efficacy and Safety of 26-Week Treatment of AR1001 in Patients with Mild to Moderate Alzheimer's Disease" dated April 18, 2019 and agree to its terms including principles of disclosure and confidentiality.

I agree to obtain the approval for this protocol from the Institutional Review Board prior to initiation of the study.

I also agree to comply with the International Conference of Harmonization (ICH) Tripartite Guidelines on good Clinical Practice, and applicable regulations/guidelines set forth in the Code of Federal Regulations (CFR), Title 21, Parts 11, 50, 54, 56, and 312.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of AriBio Co., Ltd.

_____
Signature

_____ _____
Name of Principal Investigator Date (DD/MMM/YYYY)

PROTOCOL SYNOPSIS

Name of Sponsor/Company:	AriBio Co., Ltd.
Name of Investigational Product:	AR1001
Protocol Number	AR1001-ADP2-US01
Indication	Alzheimer's Disease (AD)
Protocol Title	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Efficacy and Safety of 26-Week Treatment of AR1001 in Patients with Mild to Moderate Alzheimer's Disease
Phase	2
Planned Number of Subjects	Total approximately 210 subjects (3 groups)
Objectives	The objectives of this trial are: • To evaluate the efficacy of AR1001 when administered to adults with Alzheimer's Disease • To evaluate the safety of AR1001 when administered to adults with Alzheimer's Disease
Study Design	This is a double-blind, randomized, placebo-controlled, parallel-group comparison study to evaluate the efficacy and safety of AR1001 for the treatment of subjects with mild to moderate Alzheimer's Disease. This study consists of 3 phases: • Screening phase (2 weeks) • Treatment phase (26 weeks) • Follow-up phase (2 weeks) Following a 2-week screening period, subjects who meet all inclusion and exclusion criteria will be randomly assigned into one of the following treatment arms: • Group A: AR1001 10 mg – approximately 70 subjects • Group B: AR1001 30 mg – approximately 70 subjects • Group C: Placebo – approximately 70 subjects The assigned dose will be orally administered to subjects once a day for 26 consecutive weeks. After randomization at Visit 2 (Week 0), randomized subjects will visit their respective trial site at Weeks 4, 13, 26 and 28 (Visits 3, 4, 5 and 6).
Drug Administration	Study drug (AR1001 10mg, 30mg or placebo) will be orally administered once daily for 26 weeks.
Study Visits	Visit 1 (Week -2) – Screening Visit 2 (Week 0) – Baseline Visit 3 (Week 4) Visit 4 (Week 13) Phone Call (Week 20) Visit 5 (Week 26) – End of Treatment Visit 6 (Week 28) – Safety follow-up
Study Hypothesis	AR1001 treatment group has improvement on neurological/neurocognitive assessment from baseline at Week 26 compared to the placebo group.
Clinical Endpoints	The **primary endpoint** to determine the efficacy of AR1001 is the following: • Change of ADAS-Cog 13 (Alzheimer's Disease Assessment Scale-cognitive subscale) from baseline at Week 26 • Changes of ADCS-CGIC (Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change) from baseline at Week 26

Name of Sponsor/Company:	AriBio Co., Ltd.
Name of Investigational Product:	AR1001
Protocol Number	AR1001-ADP2-US01
Indication	Alzheimer's Disease (AD)
	The **secondary endpoints** to determine the efficacy and safety of AR1001 are: • Change of MMSE-2 (Mini-mental status examination) from baseline at Week 26 • Changes of NPI (Neuropsychiatric Inventory) from baseline at Week 26 • Changes of GDS (Geriatric Depression Scale) from baseline at Week 26 • Changes of C-SSRS (Columbia Suicide Severity Rating Scale) from baseline at Week 26 • Changes of QOL-AD (Quality of Life in Alzheimer's Disease) from baseline at Week 26 • Number of subjects with treatment related adverse events as assessed by analysis of adverse events including symptoms, and abnormal findings on physical examination, vital signs, ECG, and standard laboratory examination results
Inclusion/ Exclusion Criteria	**Inclusion Criteria** 1. Male or female subjects aged 55-80 years at the time of signing the Informed Consent Form. 2. Subjects (or subject's legally acceptable representative) and caregiver(s) who can sign an Informed Consent to participate in the study. Same caregiver(s) must assist the subject throughout the entire duration of the study. 3. Subjects who have a diagnosis of probable Alzheimer's disease according to the NIA-AA (National Institute of Aging and Alzheimer's Associations, 2011) criteria with mild to moderate dementia (stage 4 – 5, Appendix 3) at screening [1]. 4. Subjects who have mild-to-moderate cognitive impairment with MMSE Score of 16-26 at the screening. 5. Subjects who have an MRI (either 1.5T or 3T) or CT scan performed after onset of symptoms and prior to randomization with findings consistent with the diagnosis of dementia due to Alzheimer's disease and without any other clinically significant comorbid pathologies. 6. Subjects who have one (or more) identified adult study partner(s) who, in the opinion of the investigator, has sufficient contact with and knowledge about the subject as to be able to report knowledgably about the subject's safety, compliance and adherence, cognition, function, and behavior. **Exclusion Criteria** 1. Subjects who are female who are pregnant, nursing, or of childbearing potential and not practicing effective contraception. 2. Subjects who have signs of delirium. 3. Subjects who have had a cortical stroke within the preceding 2 years. 4. Subjects who have any diagnosis of dementia other than that related to Alzheimer's Disease, including concomitant vascular dementia. 5. Subjects who have a PET scan performed after onset of symptoms with negative amyloid results. 6. Subjects with a history of myocardial infarction, unstable angina, New York Heart Association (NYHA) class III or IV heart failure or stroke within the last 12 months. 7. Subjects with uncontrolled hypertension (systolic blood pressure >160mm Hg or diastolic blood pressure > 95mm Hg) or hypotension (systolic blood pressure <90mm Hg or diastolic blood pressure <50mm Hg). 8. Subjects who have clinically significant renal impairment (creatinine > 1.5x ULN) or hepatic impairment (AST or ALT > 2.5x ULN or total bilirubin > 1.5x ULN). 9. Subjects who have history of cancer or malignant tumor within 5 years prior to screening with the exception of:

Name of Sponsor/Company: AriBio Co., Ltd.	
Name of Investigational Product: AR1001	
Protocol Number	AR1001-ADP2-US01
Indication	Alzheimer's Disease (AD)
	a. Basal or squamous cell carcinoma of the skin or cervical dysplasia which has been adequately treated. b. In situ Grade 1 cervical cancer, fully treated at least 2 years prior to screening and without recurrence. c. Prostate cancer, confined to the prostate gland, which has been adequately treated (surgery and/or radiation) with normal or low and stable PSA levels for 2 years prior to screening. 10. Subjects who have history of untreated thyroid disorder or a seizure disorder. 11. Subjects who are being treated, or likely to require treatment during the study, with any medications prohibited by the study protocol (Appendix 2). 12. Subjects who have participated in any investigational drug or device trial within the previous 30 days or five half-lives of the investigational drug at screening, whichever one is longer. 13. Subjects who have any other clinically significant abnormal result in laboratory tests such as abnormally low B12 or high TSH levels, as determined by the Investigator. 14. Subjects with any current psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessments, or affect the subject's ability to complete the study. 15. Subjects whose treatment with FDA-approved AD medication (donepezil, galantamine, memantine, rivastigmine or their combinations) has not been stable for at least 3 months prior to screening. Treatment and dosing should remain stable, with no changes throughout the trial. 16. Subjects who currently take an alpha-1 blocker (Appendix 2). 17. Subjects who currently take any other phosphodiesterase type 5 (PDE-5) inhibitors (Appendix 2). 18. Subjects with current use of nitrate agents (Appendix 2). 19. Subjects who are currently receiving (or unable to stop use for at least 21 days [3 weeks] prior to receiving the first dose of the AR1001 and throughout the study) prescription or non-prescription medications or other products known to be moderate or potent inhibitors/inducers of CYP3A4 (Appendix 2). 20. Subjects who have had any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the first administration of the AR1001 and throughout the study. 21. Subjects, in the opinion of the Investigator, who are unsuitable to participate in the study.
Statistical Analysis	For the primary analysis, the change in the ADAS-Cog 13 and ADCS-CGIC score from baseline to 26 weeks will be summarized as the mean (±SD) change among patients with complete data at both baseline and 26 weeks. To establish the cognitive and functionality of the treatment effect, the change in the ADAS-Cog and ADCS-CGIC score from baseline to 26 weeks in the AR1001 10 mg and 30 mg groups will be compared with the change in the placebo group by statistical analysis, and the results will be expressed as the difference (plus 95% confidence interval), with adjustment for the baseline value. Changes in secondary outcomes will be summarized and compared in a similar fashion.

SCHEDULE OF ASSESSMENTS

Procedure	Screen	Treatment					Follow-Up	Early Termination
	V1	V2 (+5)	V3 (±5)	V4 (±5)	PC (±5)	V5 (±5)	V6 (+7)	
Tested Group	-W2	W0	W4	W13	W20	W26	W28	
Informed Consent[1]	V							
Inclusion/Exclusion Criteria	V	V						
Demographic information	V							
Medical/medication history	V	V						
Physical examination		V	V	V		V	V	V
Vital signs and weight	V	V	V	V		V	V	V
Hematology, serum chemistry, and urinalysis [2]	V		V	V		V		V
Plasma sample collection for biomarker study	V			V		V		
Pregnancy test [3]	V			V		V		V
Electrocardiogram	V		V			V		V
ADAS-Cog 13		V	V	V		V		V
ADCS-CGIC		V	V	V		V		V
MMSE-2	V	V		V		V		V
NPI		V		V		V		V
GDS		V		V		V		V
C-SSRS		V	V	V		V		V
QOL-AD		V				V		V
Drug Distribution and/or Return		V	V	V		V		V
Subject Diary Distribution and/or Return		V	V	V		V		V
Concomitant medications		V	V	V	V	V	V	V
Adverse events		V	V	V	V	V	V	V
Medication compliance			V	V	V	V		

[1] Informed Consent Form should be signed prior to any clinical trial related activities.

[2] See Appendix 1 for the complete list of laboratory tests.

[3] Serum pregnancy tests are performed for all females of childbearing potential.

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GLOSSARY AND ABBREVIATIONS

Aβ	Amyloid beta
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-cognitive subscale
ADCS-CGIC	Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
ANCOVA	Analysis of Covariance
ANOVA	Analysis of variance
APP	Amyloid Precursor Protein
AST (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
BUN	Blood Urea Nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
CBF	Cerebral blood flow
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CNS	central nervous system
CT	Computed Tomography
CYP3A4	Cytochrome P450 3A4
ECG	Electrocardiography
eCRF	Electronic Case Report Form
EDC	Electronic data capture
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDPE	High-Density Polyethylene
HIV	Human Immunodeficiency Virus
ICH	International Conference of Harmonization
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MMSE	Mini-mental status examination
MRI	Magnetic Resonance Imaging
NIA-AA	National Institute on Aging-Alzheimer's Association
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke; Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
NYHA	New York Heart Association

PDE5	Phosphodiesterase 5
PE	Physical Examination
PP	Per Protocol
PT-INR	Prothrombin Time - International Normalized Ratio
QOL-AD	Quality of Life in Alzheimer's Disease
RBC	Red Blood Cell Count
RPR	Rapid Plasma Reagin
SAE	Serious Adverse Event
SD	Standard Deviation
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell Count
WMH	White Matter Hyperintensity

1. PURPOSE OF STUDY

The purpose of this study is to evaluate the efficacy and safety of AR1001 in patients with mild to moderate Alzheimer's disease.

2. INTRODUCTION

Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder in the United States affecting approximately 5.4 million Americans [2]. AD is characterized by progressive loss in memory and as well as a decline in the ability to learn that is associated with neuronal death. Well known hallmarks of AD are neuritic plaques and neurofibrillary tangles [3], [4] and extensive inflammation [5]. Currently, no treatment has been developed to fully cure or prevent the progression of dementia that is associated with AD.

In addition to neuritic plaques and neurofibrillary tangles, oxidative stress, mitochondrial dysfunction, hormone dysregulation, inflammation, mitotic dysfunction, calcium imbalance, and genetic risk factors are all involved in the AD processes [6]. Alzheimer's disease is now recognized as multifactorial, and it strongly demands more effective treatments.

In the past decade, research interests in phosphodiesterase type 5 (PDE5) inhibition have expanded to vascular targets, such as in cardiac disease, well beyond their current therapeutic indication for erectile dysfunction (ED) [7]. PDE5 inhibitors, such as sildenafil, vardenafil, and tadalafil, have demonstrated cardioprotective effects, improved cerebral blood flow (CBF), neurogenesis, angiogenesis and synaptogenesis following an experimental stroke [8], [9]. According to the Alzheimer's Drug Discovery Foundation, the widely used PDE5 inhibitor drug class may represent the next new treatment approach for dementia caused by Alzheimer's disease.

AR1001 is a novel pyrrolo-pyrimidinone compound that demonstrates potent, reversible, and selective PDE5 inhibition. Similar to sildenafil, vardenafil, and tadalafil, AR1001 was first developed for treatment of ED in South Korea. AR1001 is now being developed as a treatment for AD and shows great potential with favorable attributes for a central nervous system (CNS) drug (i.e., high specificity and potency, as well as good pharmacokinetic, bioavailability, CNS penetration, and ensured safety).

The clinical study of AR1001 aims to evaluate the efficacy and safety of AR1001 as a potential treatment for AD. Based on the preclinical results, AR1001 could be an effective treatment option with a mechanism of action that has not been explored for AD indication.

3. STUDY ENDPOINTS

3.1 Study Endpoints

Primary endpoints used to determine the efficacy of AR1001 is the following:

- Change of ADAS-Cog 13 (Alzheimer's Disease Assessment Scale-cognitive subscale) from baseline at Week 26
- Change of ADCS-CGIC (Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change) from baseline at Week 26

Secondary endpoints used to determine the efficacy and safety of AR1001 are the following:

- Change of MMSE-2 (Mini-mental status examination) from baseline at Week 26
- Changes of NPI (Neuropsychiatric Inventory) from baseline at Week 26
- Changes of GDS (Geriatric Depression Scale) from baseline at Week 26
- Changes of C-SSRS (Columbia Suicide Severity Rating Scale) from baseline at Week 26
- Changes of QOL-AD (Quality of Life in Alzheimer's Disease) from baseline at Week 26
- Number of subjects with treatment related adverse events as assessed by analysis of adverse events including symptoms and abnormal findings on physical examination, vital signs, ECG, and standard laboratory examination results

3.2 Efficacy Variables

- ADAS-Cog 13 at Visits 2, 3, 4 and 5 or Early Termination
- ADCS-CGIC at Visits 2, 3, 4 and 5 or Early Termination
- MMSE-2 at Visits 1, 2, 4 and 5 or Early Termination
- NPI at Visits 2, 4 and 5 or Early Termination
- GDS at Visits 2, 4 and 5 or Early Termination
- QOL-AD at Visits 2 and 5 or Early Termination

The rating scales used in this study are ADAS-Cog 13 (Alzheimer's Disease Assessment Scale-cognitive subscale), ADCS-CGIC (Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change), MMSE-2 (Mini-mental status examination), NPI (Neuropsychiatric Inventory), GDS (Geriatric Depression Scale), and QOL-AD (Quality of Life in Alzheimer's Disease). All questionnaires that are subject-administered should be completed by the subjects alone or along with caregiver at the beginning of each visit to minimize the influences from other procedures to be performed at that visit. A short explanation should be given to each subject about the purpose and the necessity of these questionnaires.

3.3 Safety Variables

- Hematology, blood chemistry and urinalysis at Visits 1, 3, 4, and 5 or Early Termination. See Section Appendix 1 for a complete list of laboratory tests to be done.
- ECG evaluation at Visits 1, 3 and 5 or Early Termination
- Complete physical examination at Visits 2, 3, 4 and 5 or Early Termination
- Vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight will be measured at all visits.

- C-SSRS at Visit 2, 3, 4, and 5 or Early Termination
- Data regarding AEs and concomitant medications will be collected at all visits

4. INVESTIGATIONAL PLAN

4.1 Study Design

This is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AR1001 for the treatment of Alzheimer's Disease. Up to 25 investigational centers may be utilized to randomize approximately 210 subjects.

4.2 Selection of Study Population

The study population will be males or females, aged 55-80, who have diagnosis of probable Alzheimer's disease according to the NIA-AA (National Institute of Aging and Alzheimer's Associations, 2011) criteria with mild to moderate dementia (stage 4 – 5, Appendix 3) and 16-26 MMSE score [1].

4.2.1 Inclusion Criteria

1. Male or female subjects aged 55-80 years at the time of signing the Informed Consent form.
2. Subjects or subject's legally acceptable representative (LAR) and caregiver(s) who can sign an Informed Consent to participate in the study. Same caregiver(s) must assist the subject throughout the entire duration of the study. A LAR is an individual or a legal body authorized under applicable law to consent, on behalf of a prospective participant, to the individuals' participation in the clinical trial.
3. Subjects who have a diagnosis of probable Alzheimer's disease according to the NIA-AA (National Institute of Aging and Alzheimer's Associations, 2011) criteria with mild to moderate dementia (stage 4 – 5, Appendix 3) at screening [1].
4. Subjects who have mild-to-moderate cognitive impairment with MMSE Score of 16-26 at the screening.
5. Subjects who have an MRI (either 1.5T or 3T) or CT scan performed after onset of symptoms and prior to randomization with findings consistent with the diagnosis of dementia due to Alzheimer's disease and without any other clinically significant comorbid pathologies.
6. Subjects who have one (or more) identified adult study partner(s) who, in the opinion of the investigator, has sufficient contact with and knowledge about the subject as to be able to report knowledgably about the subject's safety, compliance and adherence, cognition, function, and behavior.

4.2.2 Exclusion Criteria

1. Subjects who are female who are pregnant, nursing, or of childbearing potential and not practicing effective contraception.
2. Subjects who have signs of delirium.
3. Subjects who have had a cortical stroke within the preceding 2 years.
4. Subjects who have any diagnosis of dementia other than that related to Alzheimer's Disease, including concomitant vascular dementia.
5. Subjects who have a PET scan performed after onset of symptoms with negative amyloid results.
6. Subjects with a history of myocardial infarction, unstable angina, New York Heart Association (NYHA) class III or IV heart failure or stroke within the last 12 months.

7. Subjects with uncontrolled hypertension (systolic blood pressure >160mm Hg or diastolic blood pressure > 95mm Hg) or hypotension (systolic blood pressure <90mm Hg or diastolic blood pressure <50mm Hg).
8. Subjects who have clinically significant renal impairment (creatinine > 1.5x ULN) or hepatic impairment (AST or ALT > 2.5x ULN or total bilirubin > 1.5x ULN).
9. Subjects who have history of cancer or malignant tumor within 5 years prior to screening with the exception of:
    a. Basal or squamous cell carcinoma of the skin or cervical dysplasia which has been adequately treated.
    b. In situ Grade 1 cervical cancer, fully treated at least 2 years prior to screening and without recurrence.
    c. Prostate cancer, confined to the prostate gland, which has been adequately treated (surgery and/or radiation) with normal PSA levels for 2 years prior to screening.
10. Subjects who have history of untreated thyroid disorder or a seizure disorder.
11. Subjects who are being treated, or likely to require treatment during the study, with any medications prohibited by the study protocol (Appendix 2).
12. Subjects who have participated in any investigational drug or device trial within the previous 30 days or five half-lives of the investigational drug at screening, whichever one is longer.
13. Subjects who have any other clinically significant abnormal result in laboratory tests such as abnormally low B12 or high TSH levels, as determined by the Investigator.
14. Subjects with any current psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessments, or affect the subject's ability to complete the study.
15. Subjects whose treatment with FDA-approved AD medication (donepezil, galantamine, memantine, rivastigmine or their combinations) has not been stable for at least 3 months prior to screening. Treatment and dosing should remain stable, with no changes throughout the trial.
16. Subjects who currently take an alpha-1 blocker (Appendix 2).
17. Subjects who currently take any other phosphodiesterase type 5 (PDE-5) inhibitors (Appendix 2).
18. Subjects with current use of nitrate agents (Appendix 2).
19. Subjects who are currently receiving (or unable to stop use for at least 21 days [3 weeks] prior to receiving the first dose of the AR1001 and throughout the study) prescription or non-prescription medications or other products known to be moderate or potent inhibitors/inducers of CYP3A4 (Appendix 2).
20. Subjects who have had any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the first administration of the AR1001 and throughout the study.
21. Subjects, in the opinion of the Investigator, who are unsuitable to participate in the study.

4.3 Removal of Subjects from Study

Subjects may be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being
- At the specific request of the sponsor

Also, subjects must be withdrawn for the following reasons:

- A significant violation of the protocol, as determined by the sponsor or the investigator
- Highly significant abnormalities in the laboratory results (Highly significant abnormalities generally follow lab related exclusion criteria, but a PI can determine the high significance on any abnormalities for the safety of subject)
- Use of any other investigational drugs
- Subjects enrolled in the current trial but taking any prohibited medication/therapy stated in the inclusion/exclusion criteria
- Subject enrolled in the current trial but pregnant or becomes pregnant

If a subject prematurely withdraws from the study, the subject must return to the clinical site for the early termination visit. In all cases, the reason for withdrawal must be recorded in the electronic Case Report Form (eCRF) and in the subject's medical records.

Contact will be maintained with subjects who are removed due to an adverse event (AE) until it has been resolved or stabilized, and the information will be documented in the eCRF and in the subject's medical records.

4.4 Premature Termination of Study / Closure of Center

The sponsor has the right to terminate this study, and the investigator/sponsor has the right to close a clinical site, at any time, although this should occur only after consultation between involved parties; the IRB must be informed in any case. Should the clinical site be closed prematurely, all study materials (equipment, study medication, etc.) must be returned to the sponsor.

This study will discontinue due to medical or administrative reasons such as:

- Serious adverse events probably related to study drug administration so that the use of study drug may no longer be justifiable
- 2 or more deaths are attributed to the study drug during any point in the trial
- Significant change of benefit-risk ratio for the subjects
- Sponsor discontinues the investigation of AR1001 for the treatment of Alzheimer's Disease or determines that the doses being studied are no longer justifiable

Possible reasons for closing of a clinical site include the following:

- The investigator feels that the number or severity of related adverse events is excessive
- A change of technical, administrative, or personal circumstances occurs, and the conduct of the study no longer meets ICH-GCP guidelines
- In case of evident, significant non-compliance to protocol or poor data quality

5. Treatment

5.1 Treatment to be Administered

At Visit 2 (Week 0), a subject, who is qualified for this study, will be randomized to one of three study groups; 10 or 30 mg of AR1001 or placebo control. The randomized subjects will receive kits containing 2 bottles and take 1 tablet from each bottle each day for 26 weeks. The investigational product should be taken in the morning in a fasted state, at least 30 minutes before eating.

5.2 Identity of Investigational Product

34 tablets of 10 or 20 mg AR1001 or placebo are packed in one 40cc HDPE bottle and 2 bottles are packed in one kit box based on the randomization plan. The study drugs need to be stored in a dried place at 15℃ - 25℃. All manufacturing and packaging activities will be performed according to cGMP guidelines.

5.3 End of Study

The efficacy results will be analyzed when the last subject completes Visit 5 (Week 26) and this study is finished when the last subject completes Visit 6 (Week 28 follow-up).

5.4 Selection of Dose in Study

The dose of AR1001 was chosen on the basis of results of preclinical efficacy and safety studies. The detailed results are documented in the Investigator's Brochure.

5.5 Choice of Control/Comparator

This study uses an inert placebo tablet as a negative control. The purpose of this is to reduce all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic or toxicological action of the study medication.

5.6 Randomization and Blinding

As this is a double-blinded study, blinding of the drug contents from the subjects, investigators, and other study personnel at each clinical site is necessary.

After the eligibility is confirmed, a subject will be assigned with one randomization code using the electronic data capture (EDC) system on Visit 2 (Week 0). A randomization code is assigned into one of three groups.

In the event of an emergency where the unblinding of a patient is necessary for his or her safety, subjects can be unblinded using the IWRS as determined by the investigator. Investigator should note that the occurrence of a SAE should not routinely precipitate immediate unblinding. The investigator must attempt to contact the sponsor prior to any unblinding. If unblinding occurs, the subject must be early terminated; a written explanation must be prepared immediately.

5.7 Prior and Concomitant Treatments

If the use of any additional concomitant treatment(s) becomes necessary after screening, the treatment(s) must be recorded in the eCRF, including the name of the drug or treatment, dose, route of administration, date and time of the treatment, and indication. In the event that concomitant medication is administered, the principal investigator or qualified sub-investigator must assess the subject's eligibility of continuing the participation in the study.

The following medications/therapies are not allowed to be taken/used by subjects enrolled in this study during the trial (up to Week 28, a final follow-up visit), unless discusses and approved by the sponsor:

- Any investigational drug
- Any PDE 5 inhibitors
- Any therapy that may affect Alzheimer's disease, in the judgment of the investigator
- Immunosuppressant
- Cytotoxic drug
- Corticosteroids or similar steroidal anti-inflammatory medication (e.g., Prednisone) on a regular basis (exceptions allowed include; regular use of steroidal nasal sprays, topical steroids, and estrogen-replacement therapy)
- Moderate or potent inhibitors/inducers of CYP3A4.
- Any alpha-1 blockers
- Any nitrate agents

5.8 Treatment Compliance

All subjects will return on Visits 3, 4, and 5 (Weeks 4, 13 and 26) or at Early Termination with all used/unused study medication and the completed diary. The returned diaries will be reviewed to determine the subject compliance. If a subject misses 30% or more out of total doses, the subject may be dropped from the study after consultation with the sponsor.

6. STUDY PROCEDURES

6.1 Screening Period

A signed and dated Institutional Review Board (IRB) approved informed consent must be obtained before any study-specific procedures are performed. Once written informed consent has been obtained, the subject will be screened to determine eligibility and document adherence to the preliminary inclusion/exclusion criteria.

6.1.1 Visit 1: Screening (Week -2)

The following screening assessments/procedures must be performed, and the results documented prior to Visit 2 unless otherwise indicated:

- Record demographic data (i.e., date of birth, race and height).
- Record medical and medication history including any available data on biomarker assessment via CSF or PET imaging.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Obtain, review, and measure 12-lead ECG including heart rate, PR interval, QRS duration, and QT interval. The investigator should assess and document whether the ECG is "normal," "abnormal but clinically not significant," or "abnormal and clinically significant."
- Collect blood and urine samples for hematology, serum chemistry, pregnancy test (only for women of childbearing potential) and urinalysis.
- Collect plasma samples for future biomarker studies (if consented by the subject).
- Complete MMSE assessment.
- CT or MRI scan may be ordered during screening with sponsor approval.

6.2 Treatment Period

6.2.1 Visit 2: Baseline (Week 0)

Visit 2 will occur up to 2 weeks (+ 5 days) after Visit 1. During this visit, the following assessments/procedures should be performed:

- Complete the following assessments: ADAS-Cog 13, ADCS-CGIC, MMSE-2, NPI, GDS, C-SSRS, and QOL-AD. The assessments should be given in the same order and, preferably, on the same day. If necessary, the assessments may be split over a few days as long as all the assessments fall within the visit window.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Record any changes in concomitant medications.
- Record any adverse events, if applicable.
- Dispense 1 kit of study drugs and subject diary.
- Instruct the dosing and recording methods to the subject and help the subject take the first dose and write the record on the subject diary at the study center.

6.2.2 Visit 3 (Week 4)

Visit 3 will occur at Week 4 (± 5 days) from the first dosing date. During this visit, the following assessments/procedures should be performed:

- Complete the following assessments: ADAS-Cog 13, ADCS-CGIC, and C-SSRS. The assessments should be given in the same order and, preferably, on the same day. If necessary, the assessments may be split over a few days as long as all the assessments fall within the visit window.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Obtain, review, and measure 12-lead ECG including heart rate, PR interval, QRS duration, and QT interval. The investigator should assess and document whether the ECG is "normal," "abnormal but clinically not significant," or "abnormal and clinically significant."
- Review the returned kits and subject diary with the subject and check for drug accountability.
- Record any changes in concomitant medications.
- Review and update prior adverse events and record any new adverse events, if applicable.
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis.
- Dispense 2 kits of study drugs, per IWRS, and subject diary. The subject should take the dose in the clinic if it has not already been taken, and a new drug diary should be started.

6.2.3 Visit 4 (Week 13)

Visit 4 will occur at Week 13 (± 5 days) from the first dosing date. During this visit, the following assessments/procedures should be performed:

- Complete the following assessments: ADAS-Cog 13, ADCS-CGIC, MMSE-2, NPI, GDS, and C-SSRS. The assessments should be given in the same order and, preferably, on the same day. If necessary, the assessments may be split over a few days as long as all the assessments fall within the visit window.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Review the returned kits and subject diary with the subject and check for drug accountability.
- Record any changes in concomitant medications.
- Review and update prior adverse events and record any new adverse events, if applicable.
- Collect blood and urine samples for hematology, serum chemistry, pregnancy test (only for women of childbearing potential) and urinalysis.
- Collect plasma samples for future biomarker studies (if consented by the subject).
- Dispense 3 kits of study drugs, per IWRS, and subject diary. The subject should take the dose in the clinic if it has not already been taken, and a new drug diary should be started.

6.2.4 Phone Call Follow-Up (Week 20)

A phone call follow-up will occur at Week 20 (± 5 days) from the first dosing date. During the phone call, the following assessments/procedures should be performed:

- Review and update prior adverse events and record any new adverse events, if applicable.
- Record any changes in concomitant medications.
- Check study medication compliance.

6.2.5 Visit 5 (Week 26)

Visit 5 will occur at Week 26 (± 5 days) from the first dosing date. During this visit, the following assessments/procedures should be performed:

- Complete the following assessments: ADAS-Cog 13, ADCS-CGIC, MMSE-2, NPI, GDS, C-SSRS, and QOL-AD. The assessments should be given in the same order and, preferably, on the same day. If necessary, the assessments may be split over a few days as long as all the assessments fall within the visit window.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Obtain, review, and measure 12-lead ECG including heart rate, PR interval, QRS duration, and QT interval. The investigator should assess and document whether the ECG is "normal," "abnormal but clinically not significant," or "abnormal and clinically significant."
- Review the returned kits and subject diary with the subject and check for drug accountability.
- Record any changes in concomitant medications.
- Review and update prior adverse events and record any new adverse events, if applicable.
- Collect blood and urine samples for hematology, serum chemistry, pregnancy test (only for women of childbearing potential) and urinalysis.
- Collect plasma samples for future biomarker studies (if consented by the subject).

6.3 Safety Follow-up: Visit 6 (Week 28)

The follow-up visit, Visit 6, will occur approximately 2 weeks (+ 7 days) from the last dosing. During this visit, the following assessments/procedures should be performed:

- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any changes in concomitant medications.
  Review and update prior adverse events and record any new adverse events, if applicable.

6.4 Early Termination Visit

If a subject will drop-out the study before Visit 5 (Week 26), the clinical site will try to schedule an early termination visit. During this visit, the following assessments and procedures should be performed:

- Complete the following questionnaires: ADAS-Cog 13, ADCS-CGIC, MMSE-2, NPI, GDS, C-SSRS, and QOL-AD. The assessments should be given in the same order and, preferably, on the same day. If necessary, the assessments may be split over a few days as long as all the assessments fall within the visit window.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Obtain, review, and measure 12-lead ECG including heart rate, PR interval, QRS duration, and QT interval. The investigator should assess and document whether the ECG is "normal," "abnormal but clinically not significant," or "abnormal and clinically significant."
- Review the returned kits and subject diary with the subject.
- Record any changes in concomitant medications.
- Record any adverse events, if applicable.
- Collect blood and urine samples for hematology, serum chemistry, pregnancy test (only for women of childbearing potential) and urinalysis.

- Schedule a safety follow-up visit after 2 weeks (± 7 days) from the last dosing unless the early termination visit occurs after 2 weeks from the last dosing.

6.5 Data Quality

Monitoring and auditing procedures defined/agreed by the sponsor will be followed in compliance with current GCP guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP guideline, and other regulatory aspects. This will include on-site review of the eCRF for completeness and clarity, consistency with source documents, and clarification of administrative matters.

6.6 Documentation

Entries made in the eCRF must be verifiable against source documents. The source data parameter to be verified and the identification of the source document must be documented. The study file and all source data should be retained/archived until notification by the sponsor for change of archive site or destruction.

7. ETHICAL AND LEGAL ASPECTS

7.1 Institutional Review Board (IRB)

Documented approval from the IRB will be obtained for all participating trial center(s)/clinic(s) prior to study start, according to GCP and applicable laws and regulations. When necessary, an extension, amendment, or renewal of the IRB approval must be obtained and also forwarded to the sponsor. The IRB must supply to the sponsor, upon request, a list of the IRB members involved in the vote and a statement to confirm that the IRB is organized and operates according to GCP and applicable laws and regulations.

7.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local laws and regulations. This may include an inspection by the sponsor representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/sponsor representatives and must allow direct access to source documents to the Regulatory Authority/sponsor representatives.

Modifications to the study protocol will be implemented by the investigator only after sponsor's approval. However, the investigator may implement a deviation form, or change of the protocol to eliminate any immediate hazard(s) to the trial subjects without prior IRB/sponsor approval. The implemented deviation or change, the reasons for it and, if appropriate, the proposed amendment should be submitted to the IRB/sponsor as soon as possible. Any deviations from the protocol must be fully explained and documented by the investigator.

7.3 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/notifications, where required, will be in place and fully documented prior to the study's start.

7.4 Subject Information Consent

A core information and Informed Consent Form will be provided. Prior to the beginning of the study, the investigator must have the IRB written approval of the Informed Consent Form and any other written information that will be provided to the subjects. The written approval of the IRB with the approved Informed Consent Form must be in the study files.

Written informed consent must be obtained before any study specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files.

7.5 Insurance

All subjects participating in the study will have insurance coverage by the sponsor, which is in line with applicable laws and/or regulations.

7.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be redacted before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the sponsor, IRB, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

Even if the results of the study are published, the subject's identity will remain confidential. The investigator will maintain a subject identification list to enable subjects' records to be identified. This list will remain only in the investigator's study files.

8. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

8.1 Statistical and Analytical Plans

8.1.1 Analytical Populations

8.1.1.1 Intent-to-Treat Population

An intent-to-treat (ITT) population will include subjects who taken at least one dose and have post-dose efficacy measurements. This population will be evaluated for all efficacy variables.

8.1.1.2 Per-Protocol Population

All subjects valid for ITT who complete Visit 5 (Week 26) will be 'valid per protocol' (also called 'valid for efficacy'). Additional criteria may be added prior to unblinding the study database. As with the ITT population, this per-protocol (PP) cohort will also be evaluated for all efficacy variables.

8.1.1.3 Safety Population

A safety population will include subjects who received at least one dose and have post-dose safety measurements. This population will be evaluated for all safety variables.

8.1.2 Treatment Group Comparability

Demographic variables, medical history, treatment duration, and efficacy variables at baseline will be summarized by treatment group for the subjects valid for potential safety analysis. Because, in theory, the goal of randomization is to balance out the subject characteristics, statistical tests are not planned for these variables.

8.1.3 Pooling of Data for Analysis

The clinical study will be conducted under a common protocol for each investigational center with the intention of pooling the data for analysis. The consistency of treatment response will be investigated across the analysis centers subsequent to combining the data. Statistical tests will be conducted to identify if there are extreme analysis centers that could affect the interpretation of common statistical and clinical conclusions. A center by treatment interaction will be included in the primary variable analysis to test for parallel treatment effect at an alpha level of 0.05. The change from Baseline ADAS-Cog 13 and ADCS-CGIC will be analyzed with factors of treatment, analysis center, treatment by analysis center interaction, and the Baseline ADAS-Cog 13 and ADCS-CGIC result as a covariate. Further analysis will follow if the interaction p-value is less than 0.05. Otherwise, the conclusions from the pooled data will be considered to be free of the impact of extreme analysis centers.

8.1.4 Significance Level

The primary efficacy hypothesis test will be performed using a 5% significance level. For the secondary efficacy endpoints, hypothesis tests will be performed individually at the 5% significance level. All hypothesis tests will be performed with two-sided alternative hypotheses. No adjustments on the significance level for multiple comparisons are planned, as this is a phase 2 study.

8.1.5 Primary Efficacy Analyses

The primary efficacy variable is the change from Baseline on the ADAS-Cog 13 and ADCS-CGIC score at Week 26. The primary efficacy variable will be summarized with means, standard deviations, medians and ranges, overall and by group. The change from Baseline ADAS-Cog 13 and ADCS-CGIC score will be analyzed with factors of treatment, analysis center, treatment by analysis center interaction, and the Baseline ADAS-Cog 13 and ADCS-CGIC score as a covariate.

If p-value is less than 0.05, then AR1001 will be considered effective for the treatment of Alzheimer's Disease.

8.1.6 Secondary Efficacy Analyses

The secondary efficacy analyses are described below. The endpoints will be summarized with means, standard deviations, medians and ranges for continuous variables and with counts and percentages for categorical variables.

Change from baseline at Week 26 in MMSE-2, NPI, GDS, ADCS-CGIC, and QOL-AD will be compared between groups using ANCOVA, ANOVA or Kruskal-Wallis tests, as appropriate. If the change is approximately normally distributed, ANCOVA or ANOVA will be used. If the change is markedly non-normally distributed, Kruskal-Wallis test will be used.

If p-value is less than 0.05, and the result is in the desired direction of effectiveness, then AR1001 will be considered effective for the treatment of Alzheimer's Disease.

8.1.7 Exploratory Efficacy Analyses

Change from baseline scores at Visits 3, 4, and 5 or Early Termination for ADAS-Cog 13, ADCS-CGIC, MMSE, NPI, and GDS and at Visit 5 or Early Termination for QOL-AD will be compared between groups using ANCOVA, ANOVA, or Kruskal-Wallis tests, as appropriate. The changes will be summarized with means, standard deviations, medians and ranges.

8.1.8 Safety Analyses

AE rates will be summarized by treatment group and overall, and will be broken down by severity, seriousness and relation to study drug. Change of C-SSRS, physical examinations, vital signs, ECG and standard laboratory results will be summarized with means, standard deviations, medians and ranges for continuous variables and with counts and percentages for categorical variables. Statistical tests are not planned for safety variables.

8.1.9 Missing Data

No adjustments for missing data and no imputation methods are planned for this phase 2 study.

8.2 Determination of Sample Size

Assuming that change of ADAS-Cog 13 has an overall standard deviation of 6.7 points, with alpha=0.025, and power=90%, a two-point difference in the group means can be detected as statistically significant with a sample size of 56 per group for a total sample size of n=168. Considering a 20% drop-out rate, approximately 210 subjects will be enrolled into the study.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definitions

9.1.1 Adverse Events

An adverse event is defined in the 21 CFR 312.32(a) as "Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose. Worsening of a pre-existing medical condition (e.g., diabetes, migraine headaches, and gout) after the drug administration should be considered an adverse event if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from baseline values. Abnormal laboratory findings without clinical significance ("Not Clinically Significant" or "NCS," based on the investigator's judgment) should not be recorded as adverse events, unless otherwise considered "Clinically Significant" or "CS" in the opinion of the investigator; however, laboratory value changes requiring therapy or adjustment in prior therapy should be considered adverse events.

Adverse events will be reviewed continuously throughout the study.

9.1.2 Serious Adverse Events

A serious adverse event (SAE) is any AE or suspected adverse reaction that in the view of either the investigator or Sponsor, results in any of the following outcomes:

- Death
- A life-threatening AE: it is defined as an AE or suspected adverse reaction that in the view of the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function.
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of outcomes listed in the above definition

Life threatening: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as 'serious', UNLESS at least one of the following exceptions is met:

- the admission results in a hospital stay of less than 24 hours OR
- the admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study)

However, it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a SAE dependent on clinical judgment.

Disability means a substantial disruption of a person's ability to conduct normal life functions.

Important medical event: Important medical events that may not result in death, be life-threatening, or require hospitalization but may be considered serious when they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition, based upon appropriate medical judgment. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse."

9.2 Reporting Procedures for All Adverse Events

The investigator is responsible for ensuring that all adverse events, (as defined in Section 9.1) observed by the investigator or reported by subjects after the first dose for each subject are properly captured in the subject's medical records and reported on the eCRF.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with subject identification, relationship to investigational product, start and stop dates, severity, action taken, and outcome.

9.2.1 Relationship of Adverse Event to Study Drug

The following adverse event attributes must be assigned by the investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to study drug and action taken. The investigator may be asked to provide redacted follow-up information, discharge summaries, and extracts from medical records or eCRFs.

If applicable, the relationship of the adverse event to the study drug will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the study drug?" The investigator should respond using the following scale:

- Not Related – No evidence of any causal relationship with the investigational drug

- Unlikely Related – Little evidence to suggest a causal relationship or another reasonable explanation for the event
- Possibly Related – Some evidence suggests a causal relationship, but there may be other factors that contributed to the event
- Probably Related – Evidence to suggest a causal relationship, and influence of other factors is unlikely
- Definitely Related – Strong evidence to suggest a causal relationship, and no other factors contributed to the event

9.2.2 Adverse Event Severity

The severity of adverse events should be graded as follows:

- Mild – Usually transient in nature and generally not interfering with normal activities
- Moderate – Sufficiently discomforting to interfere with normal activities
- Severe – Prevents normal activities

Medically significant adverse events considered related to the study drug by the investigator or Sponsor will be followed until resolved or considered stable.

It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

9.3 Serious Adverse Event Reporting Procedures

Serious Adverse Events, including laboratory test abnormalities fulfilling the definition of serious, after the first dose, and during follow-up period must immediately (within 24 hours of the investigator's awareness) be reported to the person/parties as detailed in the study file. A Serious Adverse Event form must also be completed within 1 day of the investigator's awareness and forwarded to the designated person/parties as detailed in the study file. Each Serious Adverse Event must be followed up until resolution or stabilization by submission of updated reports to the designated person/parties.

Reporting of SAEs begins from the first administration of the study drug through within 2 weeks after the last dose of study drug. Events assessed by the Investigator as related to study drug (or having an unknown relationship at the time of reporting) should be reported within 24 hours regardless of the number of days since the last dose.

For all deaths, available autopsy reports and relevant medical reports should be faxed to Sponsor or their designee. Assessment of deaths must be reported within 2 weeks after administration of the last dose of study drug. Deaths assessed by the Investigator as related to study drug (or having an unknown relationship at the time of reporting) should be reported within 24 hours regardless of the number of days since the last dose.

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be included in the initial or follow-up Serious Adverse Event Report Form as well as the End of Study Case Report Form. When required, and according to local law and regulations, serious adverse events must be reported to the institutional review board and Regulatory Authorities.

10. USE OF DATA AND PUBLICATION

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, while free to utilize data derived from the study for scientific purposes, must discuss any publication with the sponsor prior to release and obtain written consent of the sponsor on the intended publication. The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the sponsor thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly, and approval will not be withheld unreasonably. In case of a difference of opinion between the sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution that satisfies both parties.

The investigator is encouraged to participate in the evaluation of the data for scientific purposes but is expected to work with the sponsor in the development of any scientific presentation or publication. Since the sponsor authors will be included, it is expected that all co-authors of the manuscripts will have an opportunity for feedback in the content and conclusions. The technical and editorial resources of the sponsor will be available to assist in the development of abstracts, presentations, and publications regarding this study and it is expected that drafts will be sent to the sponsor with adequate time for input and revisions prior to submission.

11. APPENDICES

Appendix 1. Laboratory Parameters

Blood and urine samples for complete laboratory evaluation (hematology, serum chemistry, and urinalysis) at Visits 1, 3, 4 and 5 or Early Termination.

HEMATOLOGY	CHEMISTRY	URINALYSIS
Hemoglobin	Total bilirubin	Color
Hematocrit	Alkaline phosphatase	Appearance
RBC	ALT (SGPT)	Specific gravity
WBC	AST (SGOT)	pH
MCV	Blood urea nitrogen (BUN)	Protein
MCH	Creatinine	Glucose
MCHC	Glucose	Ketones
Neutrophils (absolute)	Albumin	Bilirubin
Lymphocytes (absolute)	Total protein	Urobilinogen
Monocytes (absolute)	Sodium	Blood
Eosinophils (absolute)	Potassium	Leukocyte esterase
Basophils (absolute)	Chloride	Nitrite
Platelets	Bicarbonate	
PT-INR	Calcium	Manual differential testing: may
aPTT	HCG *	be performed if indicated by
	B12**	automated testing.
	TSH**	
	HIV **	Reflex microscopic analysis: may
	HBV**	be performed if positive protein,
	HCV**	leukocyte esterase, blood or
	RPR**	nitrite results are obtained.

* HCG (pregnancy test) only for all females of childbearing potential at Visits 1, 4, and 5 or Early Termination

** Visit 1 only

Appendix 2. Prohibited Medications

AR1001-ADP2-US01

List below are examples of the most commonly used medications that may be prohibited on this protocol *List is not all inclusive; please review patients' medications

Use of the following medications during this trial may not be allowed:

Alpha 1 Blockers:
alfuzosin
doxazosin
prazosin
silodosin
tamsulosin
terazosin

PDE-5 inhibitors:
avanafil
sildenafil
tadalafil
vardenafil

Nitrate medications:
nitroglycerin containing medications
(such as: sublingual tablets, aerosols, pump sprays, ointments, infusions, patches, and capsules)

CYP3A4 inhibitors/inducers:

amiodarone	ethinyl estradiol	miconazole	progesterone
cannabinoids	ethosuximide	nafcillin	quinidine
carbamazepine	fluconazole	nefazodone	quinine
clarithromycin	fluvoxamine	nelfinavir	quinupristine and
clotrimazole	gestodene	nevirapine	dalfopristin
cyclosporine	glucocorticoids	norfloxacin	rifabutin
danazol	grapefruit juice	norfluoxetine	rifampin
delavirdine	griseofulvin	oxcarbazepine	ritonavir
dexamethasone	indinavir	oxiconazole	saquinavir
diethyldithiocarbamate	isoniazid	phenobarbital	St John's wort
diltiazem	ketoconazole	phenylbutazone	troglitazone
erythromycin	mibefradil	phenytoin	troglitazone
		primidone	troleandomycin

*Please contact the CRA or medical monitor, with any questions after discussing with the investigator.

Appendix 3. The Global Deterioration Scale for Assessment of Primary Degenerative Dementia [10]

Level	Clinical Characteristics
1 **No cognitive decline**	No subjective complaints of memory deficit. No memory deficit evident on clinical interview.
2 Very mild cognitive decline **(Age Associated Memory Impairment)**	Subjective complaints of memory deficit, most frequently in following areas: (a) forgetting where one has placed familiar objects; (b) forgetting names one formerly knew well. No objective evidence of memory deficit on clinical interview. No objective deficits in employment or social situations. Appropriate concern with respect to symptomatology.
3 Mild cognitive decline **(Mild Cognitive Impairment)**	Earliest clear-cut deficits. Manifestations in more than one of the following areas: (a) patient may have gotten lost when traveling to an unfamiliar location; (b) co- workers become aware of patient's relatively poor performance; (c) word and name finding deficit becomes evident to intimates; (d) patient may read a passage or a book and retain relatively little material; (e) patient may demonstrate decreased facility in remembering names upon introduction to new people; (f) patient may have lost or misplaced an object of value; (g) concentration deficit may be evident on clinical testing. Objective evidence of memory deficit obtained only with an intensive interview. Decreased performance in demanding employment and social settings. Denial begins to become manifest in patient. Mild to moderate anxiety accompanies symptoms.
4 Moderate cognitive decline **(Mild Dementia)**	Clear-cut deficit on careful clinical interview. Deficit manifest in following areas: (a) decreased knowledge of current and recent events; (b) may exhibit some deficit in memory of one's personal history; (c) concentration deficit elicited on serial subtractions; (d) decreased ability to travel, handle finances, etc. Frequently no deficit in following areas: (a) orientation to time and place; (b) recognition of familiar persons and faces; (c) ability to travel to familiar locations. Inability to perform complex tasks. Denial is dominant defense mechanism. Flattening of affect and withdrawal from challenging situations frequently occur.
5 Moderately severe cognitive decline **(Moderate Dementia)**	Patient can no longer survive without some assistance. Patient is unable during interview to recall a major relevant aspect of their current lives, e.g., an address or telephone number of many years, the names of close family members (such as grandchildren), the name of the high school or college from which they graduated. Frequently some disorientation to time (date, day of week, season, etc.) or to place. An educated person may have difficulty counting back from 40 by 4s or from 20 by 2s. Persons at this stage retain knowledge of many major facts regarding themselves and others. They invariably know their own names and generally know their spouses' and children's names. They require no assistance with toileting and eating but may have some difficulty choosing the proper clothing to wear.
6 Severe cognitive decline **(Moderately Severe Dementia)**	May occasionally forget the name of the spouse upon whom they are entirely dependent for survival. Will be largely unaware of all recent events and experiences in their lives. Retain some knowledge of their past lives but this is very sketchy. Generally unaware of their surroundings, the year, the season, etc. May have difficulty counting from 10, both backward and, sometimes, forward. Will require some assistance with activities of daily living, e.g., may become incontinent, will require travel assistance but occasionally will be able to travel to familiar locations. Diurnal rhythm frequently disturbed. Almost

	always recall their own name. Frequently continue to be able to distinguish familiar from unfamiliar persons in their environment. Personality and emotional changes occur. These are quite variable and include: (a) delusional behavior, e.g., patients may accuse their spouse of being an impostor, may talk to imaginary figures in the environment, or to their own reflection in the mirror; (b) obsessive symptoms, e.g., person may continually repeat simple cleaning activities; (c) anxiety symptoms, agitation, and even previously nonexistent violent behavior may occur; (d) cognitive abulia, i.e., loss of willpower because an individual cannot carry a thought long enough to determine a purposeful course of action.
7 Very severe cognitive decline **(Severe Dementia)**	All verbal abilities are lost over the course of this stage. Frequently there is no speech at all -only unintelligible utterances and rare emergence of seemingly forgotten words and phrases. Incontinent of urine, requires assistance toileting and feeding. Basic psychomotor skills, e.g., ability to walk, are lost with the progression of this stage. The brain appears to no longer be able to tell the body what to do. Generalized rigidity and developmental neurologic reflexes are frequently present.

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