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:	**20 Sep 2018 / v2.0**
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_____ Chairman	_____ Signature	20 Sep 2018 Date
Jim Rock_____ VP of Global Development	_____ Signature	20 Sep 2018 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 September 20, 2018 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 NC.

_____
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 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 – 70 subjects • Group B: AR1001 30 mg – 70 subjects • Group C: Placebo – 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 (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 (Mini-mental status examination) from baseline at Week 26 • Changes of CDR-SOB (Clinical Dementia Rating-Sum of Boxes) 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 with mild to moderate dementia (stage 4 – 5) according to the NIA-AA (National Institute of Aging and Alzheimer's Associations) criteria at the screening. 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 screening with findings consistent with the diagnosis of dementia due to Alzheimer's disease 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 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 with myocardial infarction, unstable angina, New York Heart Association (NYHA) class III or IV heart failure or stroke within the last 12 months. 6. Subjects with uncontrolled hypertension (systolic blood pressure >160mm Hg or diastolic blood pressure > 95mm Hg). 7. Subjects who have clinically significant renal (creatinine > 1.5x ULN) or hepatic impairment (AST or ALT > 2.5x ULN or total bilirubin > 1.5x ULN). 8. Subjects who have history of cancer or malignant tumor within 5 years prior to screening with the exception of basal or squamous cell carcinoma of the skin or

Name of Sponsor/Company:	AriBio Co., Ltd.
Name of Investigational Product:	AR1001
Protocol Number	AR1001-ADP2-US01
Indication	Alzheimer's Disease (AD)
	cervical dysplasia and in situ Grade 1 cervical cancer fully treated at least 2 years prior to screening. 9. Subjects who have history of untreated thyroid disorder or a seizure disorder. 10. Subjects who are being treated, or likely to require treatment during the study, with any medications prohibited by the study protocol. 11. 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. 12. 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. 13. 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. 14. 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. 15. Subjects who currently take an alpha-1 blocker (e.g., tamsulosin). 16. Subjects who currently take any other phosphodiesterase type 5 (PDE-5) inhibitors. 17. Subjects with current use of nitrate agents. 18. 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. 19. 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. 20. Subjects, in the opinion of the Investigator, who are unsuitable to participate in the study.
Statistical Analysis	The preliminary efficacy variable, score change of ADAS-Cog from baseline at Week 26 will be analyzed using Analysis of Covariance (ANCOVA) with factors of treatment, analysis center, treatment-by-analysis center interaction, and Baseline as a covariate. The secondary efficacy variables include the percentage of subjects who show improvement along with several change scores from baseline. The change scores will be analyzed using ANOVA or Kruskal-Wallis tests, as appropriate. Safety variables will be summarized descriptively, by treatment group and visit.

SCHEDULE OF ASSESSMENTS

Procedure	Screen		Treatment				Follow-Up	Early Termination
	V1	V2	V3	V4	PC	V5	V6	
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
Pregnancy test [3]	V			V		V		V
Electrocardiogram	V		V			V		V
ADAS-Cog		V	V	V		V		V
ADCS-CGIC		V	V	V		V		V
MMSE	V	V		V		V		V
CDR-SOB		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 test is 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
CDR-SOB	Clinical Dementia Rating-Sum of Boxes
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 [1]. 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 [2, 3] and extensive inflammation [4]. 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 [5]. 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) [6]. 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 [7, 8]. 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 tadalfil, 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 (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 (Mini-mental status examination) from baseline at Week 26
- Changes of CDR-SOB (Clinical Dementia Rating-Sum of Boxes) 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 at Visits 2, 3, 4 and 5 or Early Termination
- ADCS-CGIC at Visits 2, 3, 4 and 5 or Early Termination
- MMSE at Visits 2, 4 and 5 or Early Termination
- CDR-Box at Visits 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 (Alzheimer's Disease Assessment Scale-cognitive subscale), ADCS-CGIC (Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change), MMSE (Mini-mental status examination), CDR-SOB (Clinical Dementia Rating-Sum of Box), 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 20 investigational centers in the United States may be utilized so that a total of approximately 210 subjects will be randomized.

4.2 Selection of Study Population

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

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) 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 with mild to moderate dementia (stage 4 – 5) according to the NIA-AA (National Institute of Aging and Alzheimer's Associations) criteria at the screening.

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 screening with findings consistent with the diagnosis of dementia due to Alzheimer's disease 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 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 with myocardial infarction, unstable angina, New York Heart Association (NYHA) class III or IV heart failure or stroke within the last 12 months.

6) Subjects with uncontrolled hypertension (systolic blood pressure >160mm Hg or diastolic blood pressure > 95mm Hg).

7) Subjects who have clinically significant renal (creatinine > 1.5x ULN) or hepatic impairment (AST or ALT > 2.5x ULN or total bilirubin > 1.5x ULN).

8) Subjects who have history of cancer or malignant tumor within 5 years prior to screening with the exception of basal or squamous cell carcinoma of the skin or cervical dysplasia and in situ Grade 1 cervical cancer fully treated at least 2 years prior to screening.

9) Subjects who have history of untreated thyroid disorder or a seizure disorder.

10) Subjects who are being treated, or likely to require treatment during the study, with any medications prohibited by the study protocol.

11) 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.

12) 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.

13) 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.

14) 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.
15) Subjects who currently take an alpha-1 blocker (e.g., tamsulosin).

16) Subjects who currently take any other phosphodiesterase type 5 (PDE-5) inhibitors.
17) Subjects with current use of nitrate agents.

18) 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.
19) 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.

20) 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

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 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 2 tablets per day (1 tablet from each bottle) for 26 weeks.

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 at dried place under 15°C - 25°C. 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.

A code-break envelope for each subject including the randomization code information will be retained by each site and can be opened, revealing the randomization information, for emergency purposes only. Investigator should note that the occurrence of a SAE should not routinely precipitate immediate unblinding. An attempt to contact the sponsor must be made prior to 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 concomitant treatment(s) becomes necessary, 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):

- 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 diary. The returned diaries will be reviewed to determine the subject compliance. If a subject miss 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 within 1 week before Visit 2 unless otherwise indicated:

- Record demographic data (i.e., date of birth, race and height).
- Record medical and medication history.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Measure 12-lead ECG.
- Collect blood and urine samples for hematology, serum chemistry, pregnancy test (only for women of childbearing potential) and urinalysis.
- Complete MMSE assessment.

6.2 Treatment Period

6.2.1 Visit 2: Baseline (Week 0)

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

- Complete the following questionnaires: ADAS-Cog (see Appendix 2), MMSE (see Appendix 3), CDR-SOB (see Appendix 4). NPI (see Appendix 5), GDS (see Appendix 6), ADCS-CGIC (see Appendix 7), C-SSRS (see Appendix 8), and QOL-AD (see Appendix 9).
- 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 questionnaires: ADAS-Cog (see Appendix 2), ADCS-CGIC (see Appendix 7), and C-SSRS (see Appendix 8).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.

- Perform a complete physical examination.
- Measure 12-lead ECG.
- 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, and urinalysis.
- Dispense 2 kits of study drugs and subject diary.

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 questionnaires: ADAS-Cog (see Appendix 2), MMSE (see Appendix 3), CDR-SOB (see Appendix 4). NPI (see Appendix 5), GDS (see Appendix 6), ADCS-CGIC (see Appendix 7) and C-SSRS (see Appendix 8).
- 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.
- 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.
- Dispense 3 kits of study drugs and subject diary.

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:

- Record any 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 questionnaires: ADAS-Cog (see Appendix 2), MMSE (see Appendix 3), CDR-SOB (see Appendix 4). NPI (see Appendix 5), GDS (see Appendix 6), ADCS-CGIC (see Appendix 7), C-SSRS (see Appendix 8), and QOL-AD (see Appendix 9).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- 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.

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.
- Record any 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 (see Appendix 2), MMSE (see Appendix 3), CDR-SOB (see Appendix 4). NPI (see Appendix 5), GDS (see Appendix 6), ADCS-CGIC (see Appendix 7), C-SSRS (see Appendix 8), and QOL-AD (see Appendix 9).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- 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 either verifiable against source documents or have been directly entered into the eCRF, in which case the entry in the eCRF will be considered as the source data. 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 and subject initials will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated 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 list to enable subjects' records to be identified.

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 will be analyzed with an ANCOVA with factors of treatment, analysis center, treatment by analysis center interaction, and the Baseline ADAS-Cog 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 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 score will be analyzed with an ANCOVA with factors of treatment, analysis center, treatment by analysis center interaction, and the Baseline ADAS-Cog 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, CDR-SOB, NPI, GDS, ADCS-CGIC, and QOL-AD will be compared between groups using ANOVA or Kruskal-Wallis tests, as appropriate. If the change is approximately normally distributed, 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, MMSE, CDR-Box, NPI, GDS, and ADCS-CGIC and at Visit 5 or Early Termination for QOL-AD will be compared between groups using 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 has an overall standard deviation of 3.1 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, 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 (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are 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) OR

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 7.1) observed by the investigator or reported by subjects after the first dose of 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 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 to this question with either Yes or No.

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. For this reporting process, subject assessments must be made 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. REFERENCES

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12. APPENDICES

Appendix 1. Laboratory Parameters

Appendix 2. ADAS-Cog (Alzheimer's Disease Assessment Scale-cognitive subscale)

Appendix 3. MMSE (Mini-mental status examination)

Appendix 4. CDR-SOB (Clinical Dementia Rating-Sum of Box)

Appendix 5. NPI (Neuropsychiatric Inventory)

Appendix 6. GDS (Geriatric Depression Scale)

Appendix 7. ADCS-CGIC (Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change)

Appendix 8. C-SSRS (Columbia Suicide Severity Rating Scale)

Appendix 9. QOL-AD (Quality of Life in Alzheimer's Disease)

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	Blood
Monocytes (absolute)	Sodium	Leukocyte esterase
Eosinophils (absolute)	Potassium	WBC
Basophils (absolute)	Chloride	RBC
Platelets	Bicarbonate	Epithelial cell
PT-INR	Calcium	Bacteria
	HCG *	Hyaline casts
	B12**	
	TSH**	
	HIV **	
	HBV**	
	HCV**	
	RPR**	

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

** Visit 1 only

Appendix 2. ADAS-Cog (Alzheimer's Disease Assessment Scale-cognitive subscale)

Study	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AR1001 to Treat Patients with Mild to Moderate Alzheimer's Disease		Protocol
AR1001P2 AR1001			AR1001-ADP2-US01
	Date of Assessment DD-MMM-YYYY	**Time of Assessment (24-hour clock)**	**Assessor's Initials**
		:	
Visit Number		**Subject Number**	**Subject Initials**

Alzheimer's Disease Assessment Scale – Cognitive Behavior (ADAS-Cog)

ADAS Initial Conversation Notes

Instructions:

For Specific instructions for all tasks, refer to the Administration Manual. The first several minutes are spent in open-ended conversation in order to assess various aspects of expressive and receptive speech. Then the remaining cognitive tests are administered. Language abilities are evaluated throughout the interview and on specific tests. Questions eliciting "yes" and "no" answers assess comprehension on a very basic level. Other questions should require specific information and well-developed communication skills.

Engage the subject in a short conversation about neutral topics (for example: weather, the subject's trip to the clinic, or what the subject had for breakfast). This conversation will help to put the subject at ease before the testing begins and will give the examiner an opportunity to observe how well the subject can use and understand language. There are three clinical ratings of language ability on the cognitive part of the ADAS. Use this page to record your interview notes. Documentation should be evident on this form to support rating of Spoken Language Ability, Word Finding Difficulty and Comprehension. Any rating of impairment should be supported by notes documented on this page.

Possible Topics	Weather	Breakfast	Clinic trip	Other
1) Comprehension				
2) Word Finding				
3) Spoken Language				

Testing Comments: _____

_____

_____

1. Commands

This task is designed to assess receptive speech. The subject is asked to carry out five separate commands with 1 to 5 steps per command. Each command should be read once. If the subject does not respond or looks confused, or asks for a repetition, the examiner should give the entire command one more time. Then go on to the next command. All commands should be given to every subject. *Examiner should check a response (yes/no) for every command.*

To begin testing, say: **"Now I am going to ask you to do a few things. First..."**

	Command performed correctly?	
Command	**Yes**	**No**
a. "Make a ***fist***." (say "***Relax it***" if needed upon completion).		
b. "Point to the ***ceiling***, and then to the ***floor***."		
Line up a pencil, watch and card (left to right from subject's point of view) on the table.		
c. "Put the ***pencil on top of the card*** and then ***put it back***."		
d. "Put the ***watch on the other side of the pencil*** and ***turn over the card***."		
e. "Tap ***each shoulder twice*** with ***two fingers***, keeping your ***eyes shut***."		

If task not administered, please specify reason (check one):

☐ Not done (for reasons other than physical/cognitive impairment)
☐ Subject refused
☐ Subject unable for physical reasons
☐ Subject unable for cognitive reasons **(if selected, circle "5" on the scoring table below)**

Scoring: (circle one)

0	= all commands correct
1	= 1 command incorrect
2	= 2 commands incorrect
3	= 3 commands incorrect
4	= 4 commands incorrect
5	= 5 commands incorrect

2. Constructional Praxis

This test assesses the subject's ability to copy 4 geometric forms. The forms should be presented one at a time. If the subject looks confused or dissatisfied with the drawing, or asks to try again, the subject should be allowed **a second attempt** for each shape. If a second attempt is made, ask the subject to indicate which one is better, and score only that attempt. *Examiner should check a response (yes/no) for every form.*

To begin testing, say: **"On this piece of paper is a shape. Try to draw another one that looks just like this, somewhere on the page."**

Figure	Figure drawn correctly? Yes	No
a. **Circle** A closed curved figure. Small gaps do not count as errors. Size is not critical.		
b. **Two overlapping rectangles** Figure must be four-sided, and overlap must be similar to presented form. Changes in size are not scored.		
c. **Diamond (Rhombus)** Figure must be four-sided, oriented so that the points are at the top and bottom, and the sides approximately equal in length (e.g., longest side is not > 1.5 times the length of the shortest side).		
d. **Cube** The figure is 3-demensional, with front face in the correct orientation, internal lines drawn correctly between corners. Opposite sides of faces should be approximately parallel.		
e. No figures drawn; scribbles; parts of forms; words instead of form		

If task not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons **(if selected, circle "5" on the scoring table below)**

Scoring: (circle one)

0	= all 4 drawings correct
1	= 1 form drawn incorrectly
2	= 2 forms drawn incorrectly
3	= 3 forms drawn incorrectly
4	= 4 forms drawn incorrectly
5	= no figures drawn; scribbles; parts of forms; words instead of forms

3. Word-recall (Word List 1)

To begin testing, say: **"I am going to show you some words printed on these white cards. Please read each word out loud and try to remember it, because later I will ask you to try to remember all of the words I have shown you. Ready, read the word and try to remember it."**

Present each word to the subject and ask him/her to say it aloud. After all 10 words have been presented, say: **"Good, now tell me all the words you can remember that were on that list."** Prompt with **"Any others?"** as necessary. For trials 2 and 3 say: **"Now I am going to show you that same list again. Read each word out loud and try to remember it."** *Examiner should check a response (yes/no) for every word.*

	Word recalled correctly?	
Trial 1	**Yes**	**No**
BUTTER		
ARM		
SHORE		
LETTER		
QUEEN		
CABIN		
POLE		
TICKET		
GRASS		
ENGINE		

Total Not Recalled ☐

	Word recalled correctly?	
Trial 2	**Yes**	**No**
POLE		
LETTER		
BUTTER		
QUEEN		
ARM		
SHORE		
GRASS		
CABIN		
TICKET		
ENGINE		

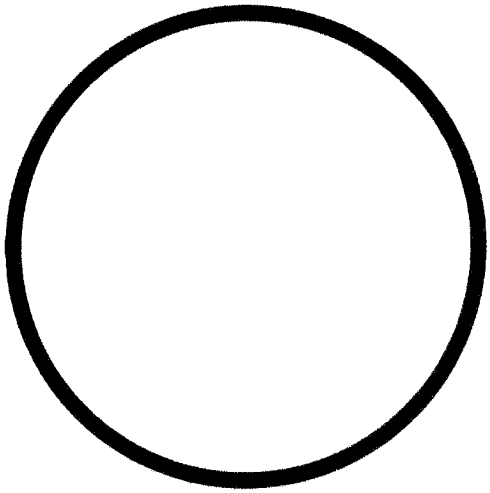
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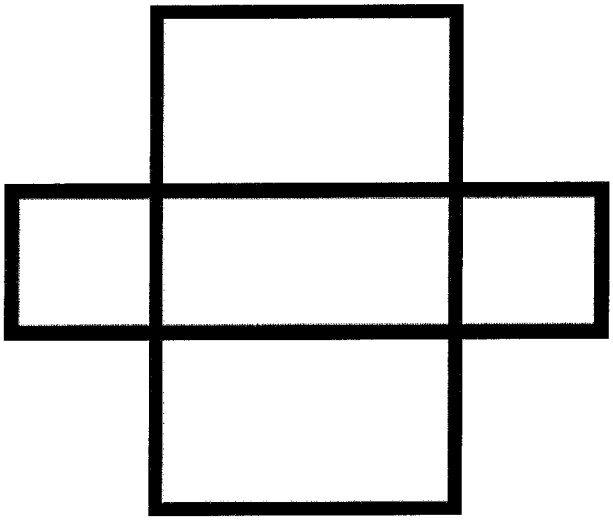
	Word recalled correctly?	
Trial 3	**Yes**	**No**
SHORE		
LETTER		
ARM		
CABIN		
POLE		
TICKET		
ENGINE		
GRASS		
BUTTER		
QUEEN		

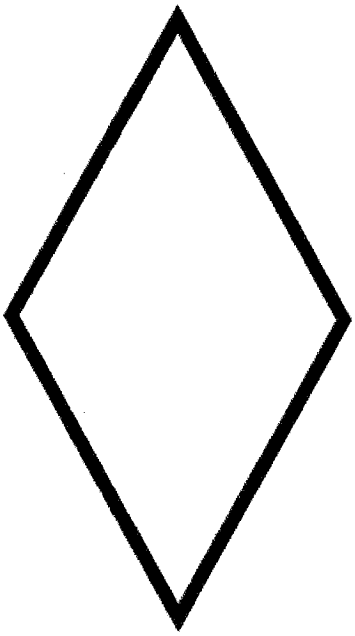
Total Not Recalled ☐

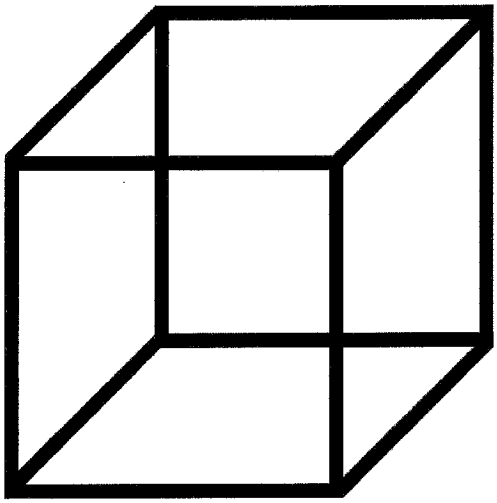
If any trial not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons **(if selected, enter a score of "10" in eCRF)**









4. Naming Objects/Fingers

For this task, the subject is asked to name 12 randomly presented real objects. Objects should be presented in random order. Give the subject instructions similar to the following: **"Now I am going to show you some objects. I want you to tell me what their names are. What is this called?"** (present object). If the subject responds with the object's function say: **"Yes, that's what it does, but what is its name?"** If the subject does not respond, the examiner should give the semantic cue for that item (provided below). If the subject still does not respond or makes an error, proceed to the next object. *Examiner should check a response (yes/no) for every object/finger.*

		Response correct?	
Item	**Acceptable Clue**	**Yes**	**No**
Flower	grows in garden		
Bed	used for sleeping		
Whistle	makes a sound when you blow on it		
Pencil	used for writing		
Rattle	a baby's toy		
Mask	hides your face		
Scissors	cuts paper		
Comb	used on hair		
Wallet	holds your money		
Harmonica	a musical instrument		
Stethoscope	doctor uses it to listen to your heart		
Tongs	picks up food		

The subject is also asked to name the fingers on his/her dominant hand. Say: **"Please place your right (or left) hand on the table. Now I am going to point to a part of your hand and I want you to tell me what it's called. What is this?"** If a query is necessary say: **"What is another name for this finger?"**

	Response correct?	
Fingers	**Yes**	**No**
Thumb		
Index/Pointer/Forefinger		
Middle		
Ring		
Pinky/Little/Baby		

If task not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons **(if selected, circle "5" on the scoring table below)**

Scoring: (circle one)

0	= 0-2 items (objects and fingers) named incorrectly
1	= 3-5 items (objects and fingers) named incorrectly
2	= 6-8 items (objects and fingers) named incorrectly
3	= 9-11 items (objects and fingers) named incorrectly
4	= 12-14 items (objects and fingers) named incorrectly
5	= 15-17 items (objects and fingers) named incorrectly

5. Ideational Praxis

This task is designed to determine whether the subject can perform a familiar but complex sequence of actions. There are 5 components to this task. Place a blank long envelope, an 8 ½ x 11" sheet of paper and a pencil in front of the subject.

Read the following instruction to the subject exactly as written:
"I want you to pretend you have written yourself a letter. Take this piece of paper, fold it so that it will fit into the envelope, and then put it into the envelope. Then seal the envelope, address the envelope to yourself, and show me where the stamp goes."

If the subject forgets part of the task, or is having difficulty, the tester should repeat the instruction for the component of the task where the subject is having difficulty. After the first complete instruction, only one additional reminder should be given for each component. *Examiner should check a response (yes/no) for every component.*

	Action correct?	
Component	**Yes**	**No**
a. Folds paper		
b. Put paper in envelope		
c. Seal envelope		
d. Address envelope		
e. Indicate where stamp goes		

If task not administered, please specify reason (check one):

☐ Not done (for reasons other than physical/cognitive impairment)
☐ Subject refused
☐ Subject unable for physical reasons
☐ Subject unable for cognitive reasons **(if selected, circle "5" on the scoring table below)**

Scoring: (circle one)

0	= all components performed correctly
1	= failure to perform 1 component
2	= failure to perform 2 components
3	= failure to perform 3 components
4	= failure to perform 4 components
5	= failure to perform 5 components

6. Orientation

This task is designed to determine how well oriented the subject is with regard to time and place. Ask the subject for each of these pieces of information **one at a time**. One restatement of each question is allowed (e.g. if subject confuses day and date.) Questions must not be restated based on an incorrect response but only if the subject does not understand the initial question or asks for a repetition. *Examiner should check a response (yes/no) for every question.*

Question	Response correct? Yes	No
Full name: (must be exact)		
Month: (must be exact)		
Date: (± 1 day)		
Year: (must be exact)		
Day of the week: (must be exact)		
Season: (within 1 week of upcoming season or within 2 weeks of previous season)		
Place: (Partial names are acceptable, but generic terms are not) Say: **"Where are we now?"** or **"What is the name of this place?"**		
Time: (± 1 hour) Say: **"Without looking at your watch, tell me approximately what time it is."**		

If task not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons **(if selected, circle "8" on the scoring table below)**

Scoring: (circle one)

0	= all responses correct
1	= 1 response incorrect
2	= 2 responses incorrect
3	= 3 responses incorrect
4	= 4 responses incorrect
5	= 5 responses incorrect
6	= 6 responses incorrect
7	= 7 responses incorrect
8	= 8 responses incorrect

7. Word Recognition (Word List 1)

In the learning portion of this test, the subject is given one trial to learn a list of 12 words. Say: **"I am going to show you some words printed on these white cards. I want you to read each word out loud and try to remember it."**

In the recognition portion of this test, the examiner should say: **"Now I'm going to show you another set of words. Some of the words were on the list I just showed you and others are new. For each word I want you to tell me whether it is one of the words I just showed you."**

The examiner shows that first word and says either **"Is this one of the words I showed you before, yes or no?"**, or **"Did I show you this word before?"** The same instruction is given before the second test word. For the remaining test words the examiner should say **"How about this one?"**

Check the **subject's response** to each word **Yes** or **No**. If the subject needs to be reminded of the task during the exam, the examiner should repeat the question and place a check in the reminder column.

***R = Reminder given**

If task not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reason
- ☐ Subject unable for cognitive reasons **(Enter Max Score or "12")**

Check Subject Response

Word	Yes	No	*R
NURSE			
MAGAZINE			
WIZARD			
VAN			
LEOPARD			
SALE			
SEA			
TRAIN			
COIN			
SHIP			
INSTITUTION			
MAP			
AXE			
BOARD			
CARROT			
MILK			
VOLUME			
FOREST			
ANCHOR			
GEM			
CAT			
FUND			
EDGE			
CAKE			

Total Not Recalled (Max Score=12) ☐ ***Reminder Given**

8. Remembering Test Instructions

This item evaluates the subject's ability to remember the requirements of the **Word Recognition task**. The number of reminders given on the Word Recognition task are counted to rate this item. If the Word Recognition task was not completed or not attempted, then this item must not be scored.

Each instance of memory failure for the test instructions after the first two items is scored.

Scoring: (circle one)

0	**None**	=	subject never needs extra reminders of instructions
1	**Very mild**	=	forgets once
2	**Mild**	=	must be reminded 2 times
3	**Moderate**	=	must be reminded 3 or 4 times
4	**Moderately severe**	=	must be reminded 5 or 6 times
5	**Severe**	=	must be reminded 7 or more times

9. Comprehension

This item evaluates the subject's ability to understand speech. To rate this item consider how well the subject was able to understand the examiner's speech during the opening discussion and during the test session.
Do not count performance on Commands subtest when rating this item.

Scoring: (circle one)

0	**None**	=	subject understands
1	**Very mild**	=	one or two instance of misunderstanding
2	**Mild**	=	3-5 instances of misunderstanding
3	**Moderate**	=	requires several repetitions and rephrasing
4	**Moderately severe**	=	subject only occasionally responds correctly; i.e. yes/no questions
5	**Severe**	=	subject rarely responds to questions appropriately, not due to poverty of speech

10. Word Finding Difficulty

To rate this item, the examiner must determine whether the subject has difficulty in finding the desired word in spontaneous speech during the interview and test session. **Do not count performance on Naming Objects and Fingers subtest when rating this item.** Documentation should be evident on page 1 to support any rating above zero.

Scoring: (circle one)

0	**None**	=	no evidence of word finding difficulty in spontaneous speech
1	**Very mild**	=	1 or 2 instances, not clinically significant
2	**Mild**	=	noticeable circumlocution or synonym substitution
3	**Moderate**	=	loss of words without compensation on occasion
4	**Moderately severe**	=	frequent loss of words without compensation
5	**Severe**	=	nearly total loss of contest of words; speech sounds empty; 1-2 word utterances

11. Spoken Language Ability

This item is a global rating of the quality of speech, *i.e.*, clarity, difficulty in making oneself understood. In rating this item the examiner should consider all of the speech produced by the subject in the initial interview and the test session. Documentation should be evident on Page 1 to support any rating above zero. (Refer to the procedures manual for guidelines)

Scoring: (circle one)

0	**None**	=	no instances where it is difficult to understand the subject
1	**Very mild**	=	one instance of lack of understandability
2	**Mild**	=	subject has difficulty less than 25 % of the time
3	**Moderate**	=	subject has difficulty 25-50% of the time
4	**Moderately severe**	=	subject has difficulty more than 50% of the time
5	**Severe**	=	one or two word utterance; fluent, but empty speech; mute

12. Delayed Word Recall

Say to the subject, **"Now I want you to try to remember the words that I showed you earlier on printed cards. Can you tell me any of those words?"** Allow a maximum of two minutes for recall.

Check *each* word correctly recalled. Total equals words ***not correctly*** recalled.

Word	Word recalled correctly? Yes	No
BLOOD		
CAMP		
COTTON		
FIRE		
HALL		
LAD		
PLANT		
RIVER		
STEAM		
TOY		

Total Not Recalled ☐

If any trial not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive).
- ☐ Subject refused.
- ☐ Subject unable for physical reasons.
- ☐ Subject unable for cognitive reasons. (If selected, enter a score of "10" in eCRF)

13. Executive Function (Maze)

Present the practice maze in the correct orientation in front of the participant. Indicate where to begin and where to exit the maze. Say to the subject, **"I want you to find the route from the start to the exit of this maze. Put your pencil here (point to the start) at the start. Here (point to the exit) is the exit of the maze. Try not to run into dead ends or cross solid lines. Please keep your pencil on the paper at all times."** If the participant lift his or her pencil, remind him or her to keep the pencil on the page.

Once the participant has completed the Mandatory Practice Maze, proceed to the Scored Maze.

Check *each* word correctly recalled. Total equals words ***not correctly*** recalled.

a. Number of errors (range = 0-2) ☐

b. Time at completion or second error (maximum = 240 seconds total) ☐☐☐

If task not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons (If selected, enter a score of "5" in eCRF)

Scoring: (circle one)

0	= 0-30 seconds at completion or second error
1	= 31-60 seconds at completion or second error
2	= 61-90 seconds at completion or second error
3	= 91-120 seconds at completion or second error
4	= 121 - 239 seconds at completion or second error
5	= 240 seconds at completion or second error

14. Number Cancellation

Place the **practice** form face up in front of the participant. Say the following instructions word-for-word:
"On the top of this page are two numbers. In this row of numbers you will find these numbers mixed in with other numbers. I'd like you to begin here" (point to the beginning of the line) and cross off each number that matches either of the two numbers at the top of the page. Please work as quickly as you can."
Correct any errors and re-explain as necessary to ensure understanding of the task. Discontinue the example after 30 seconds or when the participant finishes the line, whichever is first.

Place the **test** form face up in front of the participant. Say the following instructions word-for-word:
"On the top of this page are two numbers. Throughout this page you will find these numbers mixed in with other numbers. I'd like you to begin here" (point to the beginning of the line) and going across off each number that matches either of the two numbers at the top of the page. Please work as quickly as you can."

If the participant stops at the end of a line, before the last line, and there is still time left, ask him or her to "keep going." Discontinue the task after 45 seconds or when the participant finishes the last line, whichever is first.

a. Number of targets hit (range = 0-49) ☐☐

b. Number of errors ☐☐

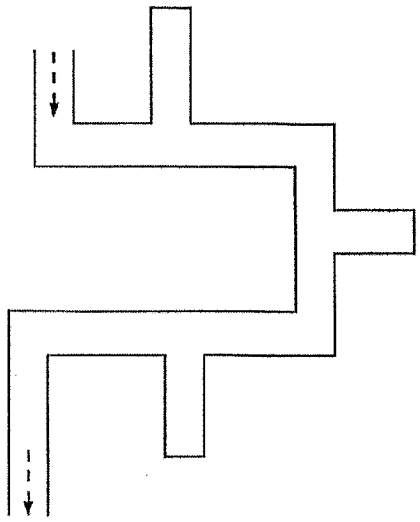
c. Number of times reminded of task ☐☐

If task not administered, please specify reason (check one):
- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons

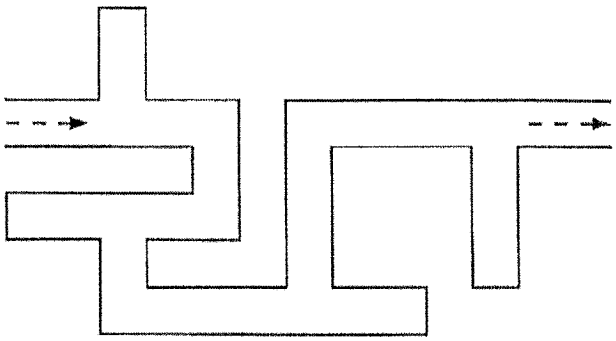
Scoring: (circle one)

0	= >/= 30 total score
1	= 24-29 total score
2	= 18-23 total score
3	= 12-17 total score
4	= 6-11 total score
5	= 0-5 total score

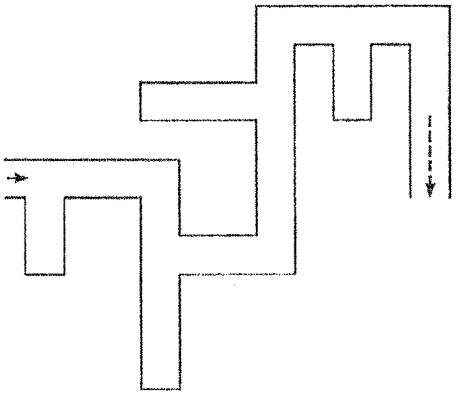
(Example)



(Test 1)



(Test 2)



(Example)

"6" and "1"

1 2 2 4 5 9 5 6 6 9 1 9 6 7 8 3 2 4 3 7 2 1 4 2 2 1 2 6 6 3

Example for use with versions A, B, and C

(Test)

"2" and "8"

6 2 6 7 2 3 1 3 8 5 5 5 8 1 7 9 1 7 2 7 4 5 7 6 1 3 9 6 2 1

9 4 6 9 5 7 1 8 9 5 6 5 4 2 7 1 5 2 7 9 1 7 1 1 1 4 2 8 5 8

1 9 7 9 7 1 6 7 8 6 5 5 7 2 9 6 5 9 5 4 7 3 2 4 5 6 1 4 3 4

4 6 8 4 1 4 1 7 2 4 7 1 7 6 7 5 4 9 8 7 5 6 2 1 6 9 3 1 4 8

7 8 6 7 1 7 1 3 4 3 9 8 6 5 1 8 3 4 2 6 9 9 6 1 6 4 3 9 3 4

4 9 3 8 7 2 5 4 4 8 7 6 4 1 4 7 2 6 8 7 5 6 3 2 6 4 4 6 8 4

4 8 3 4 7 5 4 4 7 9 7 3 6 8 6 5 4 7 4 3 4 9 2 5 3 5 4 7 3 5

4 9 3 3 8 1 8 4 2 6 5 6 6 1 7 2 4 2 9 7 9 7 6 1 5 1 4 1 9 8

A

Appendix 3. MMSE (Mini-mental status examination)

Study	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AR1001 to Treat Patients with Mild to Moderate Alzheimer's Disease		Protocol
AR1001P2 AR1001			AR1001-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

Mini-Mental State Examination (MMSE)

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Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct. Begin by asking the following two questions:

Do you have any trouble with your memory? **May I ask you some questions about your memory?**

ORIENTATION TO TIME		RESPONSE	SCORE (circle one)	
What is the...	**year?**	_____	0	1
	season?	_____	0	1
	month of the year?	_____	0	1
	day of the week?	_____	0	1
	date?	_____	0	1

ORIENTATION TO PLACE*

Where are you now? What is the...

state (province)**?**	_____	0	1
county (or city/town)**?**	_____	0	1
city/town (or part of city/ neighborhood)**?**	_____	0	1
building (name of type)**?**	_____	0	1
floor of the building (room number or address)**?**	_____	0	1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are...APPLE [*pause*], **PENNY** [*pause*], **TABLE** [*pause*]. **Now repeat those words back to me.**
[*Repeat up to 5 times, but score only the first trial.*]

APPLE	_____	0	1
PENNY	_____	0	1
TABLE	_____	0	1

Now keep those words in mind. I am going to ask you to say them again in a few minutes.
*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION [*Serial* 7s]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]	_____	0	1
If needed, say: ***Keep going.***	[86]	_____	0	1
If needed, say: ***Keep going.***	[79]	_____	0	1
If needed, say: ***Keep going.***	[72]	_____	0	1
If needed, say: ***Keep going.***	[65]	_____	0	1

*Alternative item (WORLD backward) should only be administered if the examinee refuses to perform the Serial 7s task

Substitute and score this item only if the examinee refuses to perform the Serial 7s task.
Spell WORLD forward, then backward.
Correct forward spelling if misspelled,
But score only the backward spelling.

(D = 1)	(L = 1)	(R = 1)	(O = 1)	(W = 1)	(0 to 5)
_____	_____	_____	_____	_____	_____

RECALL	RESPONSE	SCORE (circle one)
What were those three words I asked you to remember? [*Do not offer any hints.*]		
APPLE	_____	0 1
PENNY	_____	0 1
TABLE	_____	0 1

NAMING*

What is this? [*Point to a pencil or pen.*]	_____	0 1
What is this? [*Point to a watch.*]	_____	0 1

*Alternative common objects (e.g., eyeglasses, chair, keys) may be substituted and noted.

REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that.

[*Repeat up to 5 times, but score only the first trial.*]

NO IFS, ANDS, OR BUTS.	_____	0 1

Detach the next page along the lengthwise perforation, and then tear it in half along the horizontal perforation. Use the upper half of the page (blank) for the Comprehension, Writing, and Drawing items that follow. Use the lower half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") and Drawing (intersecting pentagons) items.

COMPREHENSION

Listen carefully because I am going to ask you to do something.

Take this paper in your right hand [*pause*]**, *fold it in half*** [pause]**, and put it on the floor (*or* table).**

TAKE IN RIGHT HAND	_____	0 1
FOLD IN HALF	_____	0 1
PUT ON FLOOR (*or* TABLE)	_____	0 1

READING

Please read this and do what it says. [*Show examinee the words on the stimulus form.*]

CLOSE YOUR EYES	_____	0 1

WRITING

Please write a sentence. [*If examinee does not respond, say:* ***Write about the weather.***] 0 1

Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

DRAWING

Please copy this design. [*Display the intersecting pentagons on the stimulus form.*]

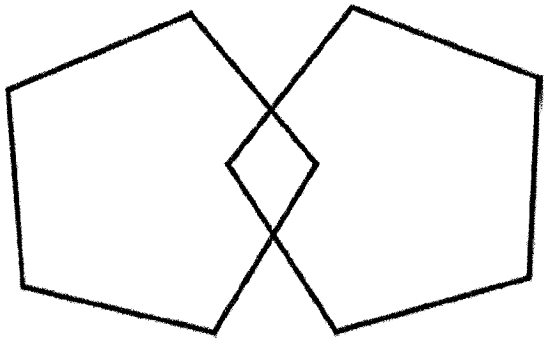
Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure. 0 1

Assessment of level of consciousness.

Alert/ Responsive	Drowsy	Stuporous	Comatose/ Unresponsive

Total Score = _____ (30 points max.)
(sum all item scores.)

CLOSE YOUR EYES



Appendix 4. CDR-SOB (Clinical Dementia Rating-Sum of Box)

Study	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AR1001 to Treat Patients with Mild to Moderate Alzheimer's Disease		Protocol
AR1001P2 AR1001			AR1001-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

Clinical Dementia Rating Worksheet

This is a semi-structured interview. Please ask all of these questions. Ask any additional questions necessary to determine the subject's CDR. Please note information from the additional questions.

Memory Questions for Informant:

1. Does he/she have a problem with his/her memory or thinking? ☐Yes ☐No
1a. If yes, is this a consistent problem (as opposed to inconsistent)? ☐Yes ☐No
2. Can he/she recall recent events? ☐ Usually ☐ Sometimes ☐ Rarely
3. Can he/she remember a short list of items (shopping)? ☐ Usually ☐ Sometimes ☐ Rarely
4. Has there been some decline in memory during the past year? ☐Yes ☐No
5. Is his/her memory impaired to such a degree that it would have interfered with his/her activities of daily life a few years ago (or pre-retirement activities)? (collateral sources opinion) ☐Yes ☐No
6. Does he/she completely forget a major event (e.g., trip, party, family wedding) within a few weeks of the event? ☐ Usually ☐ Sometimes ☐ Rarely
7. Does he/she forget pertinent details of the major event? ☐ Usually ☐ Sometimes ☐ Rarely
8. Does he/she completely forget important information of the distant past (e.g., birthdate, wedding date, place of employment)? ☐ Usually ☐ Sometimes ☐ Rarely
9. Tell me about some recent event in his/her life that he/she should remember. (For later testing, obtain details such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).
   Within 1 week : _____
   _____
   Within 1 month: _____
   _____
10. When was he/she born? _____
11. Where was he/she born? _____
12. What was the last school he/she attended? _____
    Name _____
    Place _____
    Grade _____
13. What was his/her main occupation/job (or spouse's job if subject was not employed)? _____
14. What was his/her last major job (or spouse's job if subject was not employed?) _____
15. When did he/she (or spouse) retire and why? _____

Clinical Dementia Rating Worksheet

Orientation Questions for Informant:

How often does he/she know of the exact:

1. Date of the Month?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

2. Month?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

3. Year?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

4. Day of the Week?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

5. Does he/she have difficulty with time relationships (when events happened in relation to each other)?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Can he/she find his/her way about familiar streets?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

7. How often does he/she know how to get from one place to another outside his/her neighborhood?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

8. How often can he/she find his/her way about indoors?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

Clinical Dementia Rating Worksheet

Judgment and Problem Solving Questions for Informant:

1. In general, if you had to rate his/her abilities to solve problems at the present time, would you consider them:

☐ As good as they have ever been
☐ Good, but not as good as before
☐ Fair
☐ Poor
☐ No ability at all

2. Rate his/her ability to cope with small sums of money (e.g., make change, leave a small tip):

☐ No loss
☐ Some loss
☐ Severe loss

3. Rate his/her ability to handle complicated financial or business transaction (e.g., balance check-book, pay bills):

☐ No loss
☐ Some loss
☐ Severe loss

4. Can he/she handle a household emergency (e.g., plumbing leak, small fire)?

☐ As well as before
☐ Worse than before because of trouble thinking
☐ Worse than before, another reason (why) _____

_____

_____

5. Can he/she understand situations or explanations?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Does he/she behave* appropriately [i.e., in his/her usual (premorbid) manner] in social situations and interactions with other people?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

*This item rates behavior, not appearance.

Clinical Dementia Rating Worksheet

Community Affairs Questions for Informant:
Occupational

1. Is the subject still working? ☐ Yes ☐ No ☐ N/A
   If not applicable, proceed to item 4
   If yes, proceed to item3
   If no, proceed to item 2
2. Did memory or thinking problem contribute to the subject's decision to retire? ☐ Yes ☐ No ☐ D/K
   (Question 4 is next)
3. Does the subject have significant difficulty in his/her job because of problems with memory or thinking?
   ☐ Rarely or Never ☐ Sometimes ☐ Usually ☐ Don't Know

Social

4. Did he/she ever drive a car? ☐ Yes ☐ No
   Does the subject drive a car now? ☐ Yes ☐ No
   If no, is this because of memory or thinking problems? ☐ Yes ☐ No
5. If he/she is still driving, are there problems or risks because of poor thinking? ☐ Yes ☐ No
*6. Is he/she able to independently shop for needs?
   ☐ Rarely or Never (Needs to be accompanied on any shopping trip) ☐ Sometimes (Shops for limited number of items: buys duplicate items or forgets needed items) ☐ Usually ☐ Don't Know
7. Is he/she able to independently carry out activities outside the home?
   ☐ Rarely or Never (Generally unable to perform activities without help) ☐ Sometimes (Limited and/or routine, e.g., superficial participation in church or meetings: trips to beauty parlor) ☐ Usually (Meaningful participation in activities, e.g., voting) ☐ Don't Know
8. Is he/she taken to social functions outside a family home? ☐ Yes ☐ No
   If no, why not? _____
9. Would a casual observer of the subject's behavior think the subject was ill? ☐ Yes ☐ No
10. If in nursing home, does he/she participate well in social functions (thinking)? ☐ Yes ☐ No

IMPORTANT:
Is there enough information available to rate the subject's level of impairment in community affairs?
If not, please probe further.

Community Affairs: Such as going to church, visiting with friends or family, political activities, professional organizations such as bar association, other professional groups social clubs, service organization, educational programs.

***Please add notes if needed to clarify subject's level of functioning in this area.**

Home and Hobbies Questions for Informant:

1a. What changes have occurred in his/her abilities to perform household chores? _____

_____

_____

1b. What can he/she still do well? _____

_____

2a. What changes have occurred in his/her abilities to perform hobbies? _____

_____

2b. What can he/she still do well? _____

_____

3. If in nursing home, what can he/she no longer do well (H and H)?

_____

Everyday Activities (Blessed):

4. Ability to perform household tasks

No Loss		Severe Loss
0	0.5	1

Please describe: _____

_____

_____

5. Is he/she able to perform household chores at the level of:
(Pick one. Informant does not need to be asked directly).

☐ No meaningful function.
(Performs simple activities, such as making a bed, only with much supervision)

☐ Functions in limited activities only.
(With some supervision, washes dishes with acceptable cleanliness; sets table)

☐ Functions independently in some activities.
(Operates appliances, such as a vacuum cleaner; prepares simple meals)

☐ Functions in usual activities but not at usual level.

☐ Normal function in usual activities.

IMPORTANT:
Is there enough information available to rate the subject's level of impairment in HOME & HOBBIES?
If not, please probe further.

Homemaking Tasks: Such as cooking, laundry, cleaning, grocery shopping, taking out garbage, yard work, simple care maintenance, and basic home repair.

Hobbies: Sewing, painting, handicrafts, reading entertaining photography, gardening, going to theater or symphony, woodworking, participation in sports.

Clinical Dementia Rating Worksheet

Personal Care Questions for Informant:

*What is your estimate of his/her mental ability in the following areas:

		Unaided	Occasionally misplaced buttons, etc.	Wrong sequence commonly forgotten items	Unable to dress
A.	Dressing (Blessed)	0	1	2	3

		Unaided	Needs prompting	Sometimes needs help	Always or nearly always needs help
B.	Washing, grooming	0	1	2	3

		Cleanly: proper utensils	Messily: spoon	Simple solids	Has to be fed completely
C.	Eating habits	0	1	2	3

		Normal complete control	Occasionally wets bed	Frequently wets bed	Doubly incontinent
D.	Sphincter control (Blessed)	0	1	2	3

*A box-score of 1 can be considered if the subject's personal care is impaired from a previous level, even if they do not receive prompting.

Clinical Dementia Rating Worksheet

Memory Questions for Subject:

1. Do you have problems with memory or thinking? ☐ Yes ☐ No
2. A few moments ago your (spouse, etc.) told me a few recent experiences you had. Will you tell me something about those? (Prompt for details, if needed such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

Within 1 week

1.0 – Largely correct _____
0.5 _____
0.0 – Largely incorrect _____

Within 1 month

1.0 – Largely correct _____
0.5 _____
0.0 – Largely incorrect _____

3. I will give you a name and address to remember for a few minutes. Repeat this name and address after me: (Repeat until the phrase is correctly repeated or to a maximum of three trials).

Elements	1	2	3	4	5
	John	Brown,	42	Market Street,	Chicago
	John	Brown,	42	Market Street,	Chicago
	John	Brown,	42	Market Street,	Chicago

(Underline elements repeated correctly in each trial).

4. When were you born? _____
5. Where were you born? _____
6. What was the last school you attended?
   Name _____
   Place _____ Grade _____
7. What was your main occupation job (or spouse if not employed)? _____
8. What was your last major job (or spouse if not employed)? _____
9. When did you (or spouse) retire and why? _____
10. Repeat the name and address I asked you to remember:

Elements	1	2	3	4	5
	John	Brown,	42	Market Street,	Chicago

(Underline elements repeated correctly).

Clinical Dementia Rating Worksheet

Orientation Question for Subject:

Record the subject's answer verbatim for each question

1. What is the date today? ☐ Correct ☐ Incorrect

   _____

2. What day of the week is it? ☐ Correct ☐ Incorrect

   _____

3. What is the month? ☐ Correct ☐ Incorrect

   _____

4. What is the year? ☐ Correct ☐ Incorrect

   _____

5. What is the name of this place? ☐ Correct ☐ Incorrect

   _____

6. What town or city are we in? ☐ Correct ☐ Incorrect

   _____

7. What time is it? ☐ Correct ☐ Incorrect

   _____

8. Does the subject know who the informant is (in your judgment)? ☐ Correct ☐ Incorrect

   _____

Clinical Dementia Rating Worksheet

Judgment and Problem Solving Question for Subject:

Instructions: If initial response by subject does not merit a grade 0, press the matter to identify the subject's best understanding of the problem. Circle nearest response.

Similarities:

Example: "How are a pencil and pen alike? (writing instruments)

How are these things alike?" Subject's Response

1. turnip . . . . . cauliflower _____
   (0 = vegetables)
   (1 = edible food, living things, can be cooked, etc.)
   (2 = answers not pertinent; differences; buy them)
2. desk . . . . . bookcase _____
   (0 = furniture, office furniture; both hold books)
   (1 = wooden, legs)
   (2 = not pertinent, differences)

Differences:

Example: "What is the difference between sugar and vinegar? (sweet vs. sour)

What is the difference between these things?"

3. lie . . . . . mistake _____
   (0 = one deliberate, one unintentional)
   (1 = one bad the other good – or explains only one)
   (2 = anything else, similarities)
4. river . . . . . canal _____
   (0 = natural – artificial)
   (2 = anything else)

Calculations:

5. How many nickels in a dollar? ☐ Correct ☐ Incorrect
6. How many quarters in $6.75? ☐ Correct ☐ Incorrect
7. Subtract 3 from 20 and keep subtracting 3 from each new number all the way down. ☐ Correct ☐ Incorrect

Judgment:

8. Upon arriving in a strange city, how would you locate a friend that you wished to see?
   (0 = try the telephone book, go to the courthouse for a directory; call a mutual friend)
   (1 = call the police, call operator (usually will not give address)
   (2 = no clear response)
9. Subject's assessment of disability and station in life and understanding of why he/she is present at the examination (may have covered, but rate here):

   ☐ Good Insight ☐ Partial Insight ☐ Little Insight

Clinical Dementia Rating (CDR)

CLINICAL DEMENTIA RATING (CDR)	0	0.5	1	2	3

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragment remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

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Clinical Dementia Rating

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

Categories	Score
Memory	
Orientation	
Judgement & Problem Solving	
Community Affairs	
Home & Hobbies	
Personal Care	
CDR Sum of Boxes Score	

Appendix 5. NPI (Neuropsychiatric Inventory)

Study	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AR1001 to Treat Patients with Mild to Moderate Alzheimer's Disease		Protocol
AR1001P2 AR1001			AR1001-ADP2-US01
	Date of Assessment DD-MMM-YYYY	**Time of Assessment (24-hour clock)**	**Assessor's Initials**
		:	
Visit Number		**Subject Number**	**Subject Initials**

Neuropsychiatric Inventory (NPI)

Comprehensive Assessment of Psychopathology in Patients with Dementia

by Jeffrey L. Cummings, MD

A. Delusions **(NA)**

Does the patient have beliefs that you know are not true (for example, insisting that people are trying to harm him/her or steal from him/her)? Has he/she said that family members are not who they say they are or that the house is not their home? I'm not asking about mere suspiciousness; I am interested if the patient is convinced that these things are happening to him/her.

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient believe that he/she is in danger – that others are planning to hurt him/her? _____
2. Does the patient believe that others are stealing from him/her? _____
3. Does the patient believe that his/her spouse is having an affair? _____
4. Does the patient believe that unwelcome guests are living in his/her house? _____
5. Does the patient believe that his/her spouse or others are not who they claim to be? _____
6. Does the patient believe that his/her house is not his/her home? _____
7. Does the patient believe that family members plan to abandon him/her? _____
8. Does the patient believe that television or magazine figures are actually present in the home? [Does he/she try to talk or interact with them?] _____
9. Does the patient believe any other unusual things that I haven't asked about? _____

If the screening question is confirmed, determine the frequency and severity of the delusions.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – delusions present but seem harmless and produce little distress in the patient.
2. Moderate -delusions are distressing and disruptive.
3. Marked – delusions are very disruptive and are a major source of behavioral disruption. [If PRN medications are prescribed, their use signals that the delusions are of marked severity.]

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

B. Hallucinations **(NA)**

Does the patient have hallucinations such as seeing false visions or hearing imaginary voices? Does he/she seem to see, hear or experience things that are not present? By this question we do not mean just mistaken belief such as stating that someone who has died is still alive; rather we are asking if the patient actually has abnormal experiences of sounds or visions.

No (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient describe hearing voices or act as if he/she hears voices? _____
2. Does the patient talk to people who are not there? _____
3. Does the patient describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights, etc.)? _____
4. Does the patient report smelling odors not smelled by others? _____
5. Does the patient describe feeling things on his/her skin or otherwise appear to be feeling things crawling or touching him/her? _____
6. Does the patient describe tastes that are without any known cause? _____
7. Does the patient describe any other unusual sensory experiences? _____

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – hallucinations are present but harmless and cause little distress for the patient.
2. Moderate – hallucinations are distressing and are disruptive to the patient.
3. Marked – hallucinations are very disruptive and are a major source of behavioral disturbance. PRN medications may be required to control them.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

C. **Agitation/Aggression** (NA)

Does the patient have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient get upset with those trying to care for him/her or resist activities such as bathing or changing clothes? _____
2. Is the patient stubborn, having to have things his/her way? _____
3. Is the patient uncooperative, resistive to help from others? _____
4. Does the patient have any other behaviors that make him hard to handle? _____
5. Does the patient shout or curse angrily? _____
6. Does the patient slam doors, kick furniture, throw things? _____
7. Does the patient attempt to hurt or hit others? _____
8. Does the patient have any other aggressive or agitated behaviors? _____

If the screening question is confirmed, determine the frequency and severity of the agitation.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week
3. Frequently – several times per week but less than daily.
4. Very frequently – once or more per day.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – behavior is disruptive but can be managed with redirection or reassurance.
2. Moderate – behaviors are disruptive and difficult to redirect or control.
3. Marked – agitation is very disruptive and a major source of difficulty; there may be a threat of personal harm. Medications are often required.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. moderately
4. Severely
5. Very severely or extremely

D. Depression/Dysphoria **(NA)**

Does the patient seem sad or depressed? Does he/she say that he/she feels sad or depressed?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient have periods of tearfulness or sobbing that seem to indicate sadness? _____
2. Does the patient say or act as if he/she is sad or in low spirits? _____
3. Does the patient put him/herself down or say that he/she feels like a failure? _____
4. Does the patient say that he/she is a bad person or deserves to be punished? _____
5. Does the patient seem very discouraged or say that he/she has no future? _____
6. Does the patient say he/she is a burden to the family or that the family would be better off without him/her? _____
7. Does the patient express a wish for death or talk about killing him/herself? _____
8. Does the patient show any other signs of depression or sadness? _____

If the screening question is confirmed, determine the frequency and severity of the depression.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – essentially continuously present.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – depression is distressing but usually responds to redirection or reassurance.
2. Moderate – depression is distressing, depressive symptoms are spontaneously voiced by the patient and difficult to alleviate.
3. Marked – depression is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

E. Anxiety (NA)

Is the patient very nervous, worried, or frightened for no apparent reason? Does he/she seem very tense or fidgety? Is the patient afraid to be apart from you?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient say that he/she is worried about planned events? _____
2. Does the patient have periods of feeling shaky, unable to relax, or feeling excessively tense? _____
3. Does the patient have periods of [or complain of] shortness of breath, gasping, or sighing for no apparent reason other than nervousness? _____
4. Does the patient complain of butterflies in his/her stomach, or of racing or pounding of the heart in association with nervousness? [Symptoms not explained by ill health] _____
5. Does the patient avoid certain places or situations that make him/her more nervous such as riding in the car, meeting with friends, or being in crowds? _____
6. Does the patient become nervous and upset when separated from you [or his/her caregiver]? [Does he/she cling to you to keep from being separated?] _____
7. Does the patient show any other signs of anxiety? _____

If the screening question is confirmed, determine the frequency and severity of the anxiety.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – anxiety is distressing but usually responds to redirection or reassurance.
2. Moderate – anxiety is distressing, anxiety symptoms are spontaneously voiced by the patient and difficult to alleviate.
3. Marked – anxiety is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

F. Elation/Euphoria (NA)

Does the patient seem too cheerful or too happy for no reason? I don't mean the normal happiness that comes from seeing friends, receiving presents, or spending time with family members. I am asking if the patient has a persistent and abnormally good mood or finds humor where others do not.

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient appear to feel too good or to be too happy, different from his/her usual self? _____
2. Does the patient find humor and laugh at things that others do not find funny? _____
3. Does the patient seem to have a childish sense of humor with a tendency to giggle or laugh inappropriately (such as when something unfortunate happens to others)? _____
4. Does the patient tell jokes or make remarks that have little humor for others but seem funny to him/her? _____
5. Does he/she play childish pranks such as pinching or playing "keep away" for the fun of it? _____
6. Does the patient "talk big" or claim to have more abilities or wealth than is true? _____
7. Does the patient show any other signs of feeling too good or being too happy? _____

If the screening question is confirmed, determine the frequency and severity of the elation/euphoria.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – essentially continuously present.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – elation is notable to friends and family but is not disruptive.
2. Moderate – elation is notably abnormal.
3. Marked – elation is very pronounced; patient is euphoric and finds nearly everything to be humorous.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

G. Apathy/Indifference **(NA)**

Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or does he/she lack motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the patient apathetic or indifferent?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient seem less spontaneous and less active than usual? _____
2. Is the patient less likely to initiate a conversation? _____
3. Is the patient less affectionate or lacking in emotions when compared to his/her usual self? _____
4. Does the patient contribute less to household chores? _____
5. Does the patient seem less interested in the activities and plans of others? _____
6. Has the patient lost interest in friends and family members? _____
7. Is the patient less enthusiastic about his/her usual interests? _____
8. Does the patient show any other signs that he/she doesn't care about doing new things? _____

If the screening question is confirmed, determine the frequency and severity of the apathy/indifference.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – nearly always present.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – apathy is notable but produces little interference with daily routines; only mildly different from patient's usual behavior; patient responds to suggestions to engage in activities.
2. Moderate – apathy is very evident; may be overcome by the caregiver with coaxing and encouragement; responds spontaneously only to powerful events such as visits from close relatives or family members.
3. Marked – apathy is very evident and usually fails to respond to any encouragement or external events.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

H. Disinhibition **(NA)**

Does the patient seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient act impulsively without appearing to consider the consequences? _____
2. Does the patient talk to total strangers as if he/she knew them? _____
3. Does the patient say things to people that are insensitive or hurt their feelings? _____
4. Does the patient say crude things or make sexual remarks that he/she would not usually have said? _____
5. Does the patient talk openly about very personal or private matters not usually discussed in public? _____
6. Does the patient take liberties or touch or hug others in way that is out of character for him/her? _____
7. Does the patient show any other signs of loss of control of his/her impulses? _____

If the screening question is confirmed, determine the frequency and severity of the disinhibition.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than one per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – essentially continuously present.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – disinhibition is notable but usually responds to redirection and guidance.
2. Moderate – disinhibition is very evident and difficult to overcome by the caregiver.
3. Marked – disinhibition usually fails to respond to any intervention by the caregiver, and is a source of embarrassment or social distress.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

I. Irritability/Lability **(NA)**

Does the patient get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if the patient has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self.

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient have a bad temper, flying "off the handle" easily over little things? _____
2. Does the patient rapidly change moods from one to another, being fine one minute and angry the next? _____
3. Does the patient have sudden flashes of anger? _____
4. Is the patient impatient, having trouble coping with delay or waiting for planned activities? _____
5. Is the patient cranky and irritable? _____
6. Is the patient argumentative and difficult to get along with? _____
7. Does the patient show any other signs of irritability? _____

If the screening question is confirmed, determine the frequency and severity of the irritability/lability.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than one per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – essentially continuously present.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – irritability or lability is notable but usually responds to redirection and reassurance.
2. Moderate – irritability and lability are very evident and difficult to overcome by the caregiver.
3. Marked – irritability and lability are very evident, they usually fail to respond to any intervention by the caregiver, and they are a major source of distress.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

J. **Aberrant Motor Behavior** (NA)

Does the patient pace, do things over and over such as opening closets or drawers, or repeatedly pick at things or wind string or threads?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient pace around the house without apparent purpose? _____
2. Does the patient rummage around opening and unpacking drawers or closets? _____
3. Does the patient repeatedly put on and take off clothing? _____
4. Does the patient have repetitive activities or "habits" that he/she performs over and over? _____
5. Does the patient engage in repetitive activities such as handling buttons, picking wrapping string, etc? _____
6. Does the patient fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot? _____
7. Does the patient do any other activities over and over? _____

If the screening question is confirmed, determine the frequency and severity of the aberrant motor activity:

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – essentially continuously present.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – abnormal motor activity is notable but produces little interference with daily routines.
2. Moderate – abnormal motor activity is very evident; can be overcome by the caregiver.
3. Marked – abnormal motor activity is very evident, usually fails to respond to any intervention by the caregiver, and is a major source of distress.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

K. Sleep (NA)

Does the patient have difficulty sleeping (do not count as present if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient have difficulty falling asleep? _____
2. Does the patient get up during the night (do not count if the patient gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? _____
3. Does the patient wander, pace, or get involved in inappropriate activities at night? _____
4. Does the patient awaken you during the night? _____
5. Does the patient awaken at night, dress, and plan to go out thinking that it is morning and time to start the day? _____
6. Does the patient awaken too early in the morning (earlier than was his/her habit)? _____
7. Does the patient sleep excessively during the day? _____
8. Does the patient have any other nighttime behaviors that bother you that we haven't talked about? _____

If the screening question is confirmed, determine the frequency and severity of the nighttime behavior disturbance.

Frequency: Now I want to find out how often these things [define using the description of behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day (every night)

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – nighttime behaviors occur but they are not particularly disruptive.
2. Moderate – nighttime behaviors occur and disturb the patient and the sleep of the caregiver; more than one type of nighttime behavior may be present.
3. Marked – nighttime behaviors occur; several types of nighttime behavior may be present; the patient is very distressed during the night and the caregiver's sleep is markedly disturbed.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

L. Appetite and eating disorders **(NA)**

Has he/she had any change in appetite, weight, or eating habits (count as NA if the patient is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Has he/she had a loss of appetite? _____
2. Has he/she had an increase in appetite? _____
3. Has he/she had a loss of weight? _____
4. Has he/she gained weight? _____
5. Has he/she had a change in eating behavior such as putting too much food in his/her mouth at once? _____
6. Has he/she had a change in the kind of food he/she likes such as eating too many sweets or other specific types of food? _____
7. Has he/she developed eating behaviors such as eating exactly the same types of food each day or eating the food in exactly the same order? _____
8. Have there been any other changes in appetite or eating that I haven't asked about?

If the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day or continuously

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – changes in appetite or eating are present but have not led to changes in weight and are not disturbing
2. Moderate – changes in appetite or eating are present and cause minor fluctuations in weight.
3. Marked – obvious changes in appetite or eating are present and cause fluctuations in weight, are embarrassing, or otherwise disturb the patient.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

Appendix 6. GDS (Geriatric Depression Scale)

Study	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AR1001 to Treat Patients with Mild to Moderate Alzheimer's Disease		Protocol
AR1001P2 AR1001	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

Geriatric Depression Scale (GDS) (Short Form)

Instructions read to the Subject: Choose the best answer for how you felt over the past week.

Evaluation		Yes	No
1	Are you basically satisfied with your life?	☐ 0	☐ 1
2	Have you dropped many of your activities and interests?	☐ 1	☐ 0
3	Do you feel that your life is empty?	☐ 1	☐ 0
4	Do you often get bored?	☐ 1	☐ 0
5	Are you in good spirits most of the time?	☐ 0	☐ 1
6	Are you afraid that something bad is going to happen to you?	☐ 1	☐ 0
7	Do you feel happy most of the time?	☐ 0	☐ 1
8	Do you often feel helpless?	☐ 1	☐ 0
9	Do you prefer to stay at home, rather than going out and doing new things?	☐ 1	☐ 0
10	Do you feel you have more problems with memory than most?	☐ 1	☐ 0
11	Do you think it is wonderful to be alive now?	☐ 0	☐ 1
12	Do you feel pretty worthless the way you are now?	☐ 1	☐ 0
13	Do you feel full of energy?	☐ 0	☐ 1
14	Do you feel that your situation is hopeless?	☐ 1	☐ 0
15	Do you think that most people are better off than you are?	☐ 1	☐ 0
		Total GDS Score:	

Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clin Gerontol.* 1986 June; 5(1/2): 165-173.

Appendix 7. ADCS-CGIC (Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change)

Study	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AR1001 to Treat Patients with Mild to Moderate Alzheimer's Disease		Protocol
AR1001P2 AR1001			AR1001-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

Clinical Impression of Change from Baseline:

- ☐ Marked improvement
- ☐ Moderate improvement
- ☐ Minimal improvement
- ☐ No change
- ☐ Minimal worsening
- ☐ Moderate worsening
- ☐ Marked worsening

Comments:

CLINICAL GLOBAL IMPRESSION OF CHANGE (CGIC)

Instructions to Rater

The ADCS–CGIC consists of three parts:

- Part I – **Baseline evaluation** (includes information from both patient and caregiver)
- Part II – **Worksheets for 2, 6, and 12 Month** evaluations (includes information from both patient and caregiver)
- Part III – **Clinician's Impression of Change** (completed at 2, 6, and 12 Month Visits from Part II worksheets)

The overall intent of the ADCS version of the CGIC is to provide a means to reliably assess global change from baseline in a clinical trial. It provides a semi-structured format to allow clinicians to gather necessary clinical information from both the patient and caregiver, in order to make a global impression of clinical change.

Part I is used to record baseline information to serve as a reference for future ratings.

Part II is a set of worksheets designed to assist the clinician in gathering information necessary to assess change from baseline.

Part III is a Clinician's Impression of Change case report form. The purpose of this form is for clinicians to rate their impression of change from baseline on a seven-item, Likert-type scale.

Method of Administration

Part I – Baseline Evaluation. At baseline, the clinician interviews the patient and caregiver, recording onto Part I notes about baseline status for later reference. At baseline only, clinical information about the patient from the Screening Visit, medical history, physical exam, and neurological exam may be used.

Parts I and II share a similar format for recording relevant clinical information. The column headed "Area" identifies various areas that a clinician might consider while evaluating a patient for potential clinical change. The "Probes" column provides sample items that a clinician might

find useful in assessing an area, and are intended only as guides for collecting relevant information. The last column provides space for notes. There are separate spaces for notes taken from the caregiver and patient interviews.

There is no specified amount of time to complete the baseline form.

Parts II and III – Follow-up Visits. Parts II and III are administered at the 2, 6, and 12 Month Visits. For this study, there is no requirement regarding the order in which the patient and caregiver interviews are conducted.

After completing the Part II worksheets, the clinician records his/her clinical impression of change on a seven-item, Likert-type scale (from marked improvement to marked worsening) on the Part III Clinician's Impression of Change case report form. A CGIC is a rating of change from baseline, and not of severity. The clinician may refer only to his/her own baseline information compiled in Part I when making the assessment of change.

The clinician alone, must make decisions about change without consulting other staff. At the beginning of the interview, the clinician should caution the interviewee to refrain from mentioning any side effects she may be experiencing.

WORKSHEETS

Clinical Global Impression of Change

NOTE TO CGIC RATER

At baseline only, clinical information about the patient from the Screening Visit, medical history, physical exam, and neurologic exam may be used. Information may be obtained from the patient, caregiver, and staff members.

BASELINE VISIT

Brief Instructions: See instruction sheet. Use this form to record baseline information for assessing change at a later date. Refer to the cover page for instructions on obtaining relevant information. A brief clinical assessment of mental state should be made. No particular format or order is suggested for the interview.

Area	Probes	Notes
Relevant history	• recent relevant clinical events, illnesses?	Patient
		Caregiver
Observation/ Evaluation	• appearance	Patient
		Caregiver
MENTAL/COGNITIVE STATE [Structured exam, if used: _____]		
Arousal/ Alertness/ Attention/ Concentration	• confusion/clarity • excitement/reactivity • state of consciousness	Patient
		Caregiver

Area	Probes	Notes
Orientation	• time • place • person	Patient
		Caregiver
Memory	• registration • recall • long term/remote • recall for past events	Patient
		Caregiver
Language/ Speech	• fluency/ expressive language receptive language • comprehension • paraphasia/word finding • naming, amount • repetition • follows directions	Patient
		Caregiver
Praxis	• constructional ability • ideational praxis • ideomotor/imitation	Patient
		Caregiver

Area	Probes	Notes
Judgment/ Problem solving/ Insight	• patient's behavior in situations requiring judgment	Patient
		Caregiver
BEHAVIOR		
Thought content	• organization • appropriateness	Patient
		Caregiver
Hallucinations/ Delusions/ Illusions	• auditory/visual • misperceptions • systematized/developed	Patient
		Caregiver
Behavior/Mood	• affect/lability • unusual/bizarre • uninhibited/sexually inappropriate • motivation/energy • wandering/getting lost • agitation/aggression • hostility • depression-related • anxiety-related • appropriateness • cooperativeness • demanding/dependent	Patient
		Caregiver

Area	Probes	Notes
Sleep/Appetite	• sleep disorder • insomnia (type?) • nocturnal activity • hyper-, hyposomnia • appetite/weight change	Patient
		Caregiver
Neurological/ Psychomotor activity	• overall motor activity • posture/gait • movement disorder • unusual motor behavior • daily patterns • pacing	Patient
		Caregiver
FUNCTIONING		
Basic and complex (instrumental) functional ability	• mobility • hygiene/grooming • dressing • self-feeding • shopping • household chores/ hobbies • finances • driving	Patient
		Caregiver
Social function	• participation in: social interactions community activities • independence • helplessness	Patient
		Caregiver

Notes, comments, summary statement:

Information from other sources:

The following sources of information were used in completing this form:

____ Interview/examination of patient

____ Interview of caregiver. Describe relationship to patient:_____

____ Information on neuropsychological test performance

____ General information derived from a staff conference about the patient

____ Other:_____

WORKSHEETS

Clinical Global Impression of Change

NOTE TO CGIC RATER

Please caution both the caregiver and patient to refrain from discussing which treatment condition they are receiving. Refer only to the Baseline Visit CGIC worksheets when making CGIC rating.

CIRCLE VISIT: 4W 13W 26W

Brief Instructions: See instruction sheet. Use this form to record information for making a CGIC rating after interviewing both caregiver and patient. You may refer only to the Baseline Evaluation form. A brief clinical assessment of mental state should be made. No particular format or order is suggested for the interview.

Area	Probes	Notes
Relevant history	• clinical events since baseline: changes? illnesses?	Patient
		Caregiver
Observation/ Evaluation	• appearance	Patient
		Caregiver
MENTAL/COGNITIVE STATE (Structured exam, if used: _____)		
Arousal/ Alertness/ Attention/ Concentration	• confusion/clarity • excitement/reactivity • state of consciousness	Patient
		Caregiver

Area	Probes	Notes
Orientation	• time • place • person • time relationships • travel • find his/her way • recognizes self/others/ objects • reacts appropriately	Patient
		Caregiver
Memory	• registration • recall • long term/remote • recall for past events	Patient
		Caregiver
Language/ Speech	• fluency/ expressive language receptive language • comprehension • paraphasia/word finding • naming, amount • repetition • follows directions	Patient
		Caregiver
Praxis	• constructional ability • ideational praxis • ideomotor/imitation	Patient
		Caregiver

Area	Probes	Notes
Judgment/ Problem solving/ Insight	• patient's behavior in situations requiring judgment	Patient
		Caregiver
BEHAVIOR		
Thought content	• organization • appropriateness • hostile expression	Patient
		Caregiver
Hallucinations/ Delusions/ Illusions	• auditory/visual • misperceptions • systematized/developed	Patient
		Caregiver
Behavior/Mood	• affect/lability • unusual/bizarre • uninhibited/sexually inappropriate • motivation/energy • wandering/getting lost • agitation/aggression • hostility • depression-related • anxiety-related • appropriateness • cooperativeness • demanding/dependent	Patient
		Caregiver

Area	Probes	Notes
Sleep/Appetite	• sleep disorder • insomnia (type?) • nocturnal activity • hyper-, hyposomnia • appetite/weight change	Patient
		Caregiver
Neurological/ Psychomotor activity	• overall motor activity • posture/gait • movement disorder • unusual motor behavior • daily patterns • pacing	Patient
		Caregiver
FUNCTIONING		
Basic and complex (instrumental) functional ability	• mobility • hygiene/grooming • dressing • self-feeding • shopping • household chores/ hobbies • finances • driving	Patient
		Caregiver
Social function	• participation in: social interactions community activities • independence • helplessness	Patient
		Caregiver

Notes, comments, summary statement:

Information from other sources:

Appendix 8. C-SSRS (Columbia-Suicide Severity Rating Scale)

Study	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AR1001 to Treat Patients with Mild to Moderate Alzheimer's Disease		Protocol
AR1001P2 AR1001			AR1001-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

COLUMBIA-SUICIDE SEVERITY RATING SCALE

(C-SSRS)

Baseline/Screening Version

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J.J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp.103 – 130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION				
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**		**Past 2 Months**	
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it"* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐

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Intensity of Ideation		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - **Most severe Ideation:** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past 2 Months - **Most severe Ideation:** _____ (Type # (1-5)) _____ (*Description of Ideation*)	Most Severe (Lifetime)	Most severe (Past 2 Months)
Frequency **How many times have you had these thoughts?** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	_____	_____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting – few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	_____	_____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	_____	_____
Deterrents ***Are there things – anyone or anything (e.g., family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	_____	_____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equality to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling.) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	_____	_____

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SUICIDAL BEHAVIOR *(Check All that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 6 Months**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury result, this is considered an attempt. Inferring Intent: Event if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you _____ as a way to end your life?*** ***Did you want to die (even a little) when you _____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from _____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?***(Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

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Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second- degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	Enter Code _____	Enter Code _____	Enter Code _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	Enter Code _____	Enter Code _____	Enter Code _____

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Study	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AR1001 to Treat Patients with Mild to Moderate Alzheimer's Disease		Protocol
AR1001P2 AR1001			AR1001-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

COLUMBIA-SUICIDE SEVERITY RATING SCALE

(C-SSRS)

Since Last Visit

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J.J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp.103 – 130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask question 3,4, and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it"* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

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Intensity of Ideation	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. **Most severe Ideation:** _____ *Type # (1-5)* _____ *Description of Ideation*	Most Severe
Frequency **How many times have you had these thoughts?** (1)Less than once a week (2)Once a week (3)2-5 times in week (4)Daily or almost daily (5)Many times each day	_____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting – few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	_____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	_____
Deterrents ***Are there things – anyone or anything (e.g., family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	_____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equality to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling.) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	_____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury result, this is considered an attempt. Inferring Intent: Event if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you _____ as a way to end your life?*** ***Did you want to die (even a little) when you _____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from _____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐

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Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second- degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	Enter Code _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	Enter Code _____

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Appendix 9. QOL-AD (Quality of Life in Alzheimer's Disease)

Study	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AR1001 to Treat Patients with Mild to Moderate Alzheimer's Disease		Protocol
AR1001P2 AR1001	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
	☐☐-☐☐☐-☐☐☐☐	☐☐:☐☐	☐☐☐
Visit Number		Subject Number	Subject Initials
		☐☐☐☐☐☐	☐☐☐

UWMC/ADPR/QOL
Aging and Dementia: Quality of Life in AD

Quality of Life: AD

(Family Version)

Score (for clinician's use only)

ID Number ☐☐☐☐☐☐

Assessment Number ☐☐

Interview Date ☐☐ ☐☐ ☐☐ (Month Day Year)

Instructions: Please rate your relative's current situation, as you see it. Circle your responses.

1. Physical health	Poor	Fair	Good	Excellent	
2 Energy	Poor	Fair	Good	Excellent	
3. Mood	Poor	Fair	Good	Excellent	
4. Living situation	Poor	Fair	Good	Excellent	
5. Memory	Poor	Fair	Good	Excellent	
6. Family	Poor	Fair	Good	Excellent	
7. Marriage	Poor	Fair	Good	Excellent	
8. Friends	Poor	Fair	Good	Excellent	
9. Self as a whole	Poor	Fair	Good	Excellent	
10. Ability to do chores around the house	Poor	Fair	Good	Excellent	
11. Ability to do things for fun	Poor	Fair	Good	Excellent	
12. Money	Poor	Fair	Good	Excellent	
13. Life as a whole	Poor	Fair	Good	Excellent	

Comments:

_____

_____

Total

UWMC/ADPR/QOL *Aging and Dementia: Quality of Life in AD* **Quality of Life: AD** (Participant Version)					Score (for clinician's use only)
ID Number ☐☐☐☐☐☐	Assessment Number ☐☐		Interview Date ☐☐ ☐☐ ☐☐ Month Day Year		
Instructions: Interviewer administer according to standard instructions. Circle your responses.					
1. Physical health	Poor	Fair	Good	Excellent	
2 Energy	Poor	Fair	Good	Excellent	
3. Mood	Poor	Fair	Good	Excellent	
4. Living situation	Poor	Fair	Good	Excellent	
5. Memory	Poor	Fair	Good	Excellent	
6. Family	Poor	Fair	Good	Excellent	
7. Marriage	Poor	Fair	Good	Excellent	
8. Friends	Poor	Fair	Good	Excellent	
9. Self as a whole	Poor	Fair	Good	Excellent	
10. Ability to do chores around the house	Poor	Fair	Good	Excellent	
11. Ability to do things for fun	Poor	Fair	Good	Excellent	
12. Money	Poor	Fair	Good	Excellent	
13. Life as a whole	Poor	Fair	Good	Excellent	
Comments: _____ _____					Total

Score Summary Sheet

Informant's score of subject's QOL ☐ (maximum 52)

Subject's own QOL rating ☐ (maximum 52)