Clinical Study Protocol

Title: A Phase 2A Multicenter, Randomized, Double-Blind, Parallel Group, 26-Week, Placebo-Controlled Study of 50 mg and 100 mg of SUVN-502 in Subjects with Moderate Alzheimer's Disease Currently Treated with Donepezil Hydrochloride and Memantine Hydrochloride

Protocol Number: CTP2S1502HT6

NCT02580305

Date: 02 March 2016

A PHASE 2A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, 26-WEEK, PLACEBO-CONTROLLED STUDY OF 50 MG AND 100 MG OF SUVN-502 IN SUBJECTS WITH MODERATE ALZHEIMER'S DISEASE CURRENTLY TREATED WITH DONEPEZIL HYDROCHLORIDE AND MEMANTINE HYDROCHLORIDE

Sponsor:	Suven Life Sciences Ltd Serene Chambers Road – 5 Avenue – 7 Banjara Hills Hyderabad, 500034 India
[redacted]	[redacted]
[redacted]	[redacted]
Sponsor Protocol No.:	CTP2S1502HT6
IND No.:	[redacted]
EudraCT No.:	Not applicable
Study Drug Name:	SUVN-502
Development Phase:	2A
Date of Protocol:	02 March 2016, Version 2
Date of Previous Protocol:	16 July 2015, Version 1

The study will be conducted according to the protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki [1], and with other applicable regulatory requirements.

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A Phase 2A Multicenter, Randomized, Double-Blind, Parallel Group, 26-Week, Placebo-Controlled Study of 50 mg and 100 mg of SUVN-502 in Subjects with Moderate Alzheimer's Disease Currently Treated with Donepezil Hydrochloride and Memantine Hydrochloride

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the guidelines on Good Clinical Practice.

[redacted]

11-March-2016

Date

11 March 2016.

Date

Declaration of the Global Coordinating Investigator

Title: A Phase 2A Multicenter, Randomized, Double-Blind, Parallel Group, 26-Week, Placebo-Controlled Study of 50 mg and 100 mg of SUVN-502 in Subjects with Moderate Alzheimer's Disease Currently Treated with Donepezil Hydrochloride and Memantine Hydrochloride

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the guidelines on Good Clinical Practice.

Global Coordinating Investigator

[redacted]

3-10-2016

Date

Declaration of the Investigator

Title: A Phase 2A Multicenter, Randomized, Double-Blind, Parallel Group, 26-Week, Placebo-Controlled Study of 50 mg and 100 mg of SUVN-502 in Subjects with Moderate Alzheimer's Disease Currently Treated with Donepezil Hydrochloride and Memantine Hydrochloride

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, electronic Case Report Form (eCRF), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

PROTOCOL SYNOPSIS

Title	A Phase 2A Multicenter, Randomized, Double-Blind, Parallel Group, 26-Week, Placebo-Controlled Study of 50 mg and 100 mg of SUVN-502 in Subjects with Moderate Alzheimer's Disease Currently Treated with Donepezil Hydrochloride and Memantine Hydrochloride
Sponsor Study No.	CTP2S1502HT6
Phase	2A
Sponsor	Suven Life Sciences Ltd [redacted] [redacted]
Study Center(s)	Approximately 90 study centers located in the United States of America (USA)
Objective(s)	The primary objective of the study is to evaluate the efficacy of a serotonin receptor subtype 6 (5-HT_6) antagonist, SUVN-502, at daily doses of 50 mg or 100 mg compared to placebo, as adjunct treatment in subjects with moderate Alzheimer's disease (Mini-Mental State Examination [MMSE] score of 12 to 20) currently treated with the acetylcholinesterase inhibitor, donepezil hydrochloride (HCl), and the N-methyl-D-aspartic acid (NMDA) antagonist, memantine HCl. Efficacy will be assessed by the 11-item Alzheimer's Disease Assessment Scale for Cognitive Behavior (ADAS-Cog) after 26 weeks of treatment. Secondary objectives are: • To further evaluate the efficacy of these treatments using the following scales: - Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) - MMSE - Alzheimer's Disease Co-operative Study Activity of Daily Living (ADCS-ADL) - Neuropsychiatric Inventory (NPI) 12 item - Cornell Scale for Depression and Dementia (C-SDD) • To evaluate the safety and therapeutic tolerability of these treatments using adverse events (AEs), laboratory evaluations, blood pressure, electrocardiograms (ECGs), physical and neurological examination, and the Columbia Suicide Severity Rating Scale (C-SSRS) • To evaluate the pharmacokinetics of SUVN-502 administered in combination with donepezil HCl and memantine HCl • To explore the relationship between the efficacy of SUVN-502 and apolipoprotein E (APO-E) genotype, as well as analyze subjects more likely to have Alzheimer's disease
Design	This is a phase 2A, proof-of-concept, 26-week, double-blind, multicenter, randomized, parallel group, placebo-controlled study to compare the efficacy and safety of treatment with SUVN-502 (50 mg or 100 mg once daily [qd]) to placebo treatment in subjects with moderate Alzheimer's disease (MMSE score of 12 to 20) receiving donepezil HCl (10 mg qd) and either memantine HCl (10 mg twice daily [bid]) or Namenda XR® (28 mg memantine HCl extended-release qd) or the combination therapy, Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd. The study consists of a 2 to 4-week screening period, followed by a 26-week double-blind treatment period and a 4-week single-blind placebo washout period.

Treatment	Eligible subjects will receive double-blind oral administration of one of three treatments: SUVN-502 (50 mg qd), SUVN-502 (100 mg qd), or placebo (qd) in a 1:1:1 ratio. Throughout the study, all subjects will also continue to receive donepezil HCl (10 mg qd) and memantine HCl (10 mg bid) or Namenda XR® (28 mg memantine HCl extended-release qd) or the combination therapy, Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd. Subjects will be treated with SUVN-502 or placebo for a total of 26 weeks followed by a 4-week single-blind placebo washout period. During the washout period, all subjects will receive placebo in addition to donepezil HCl and memantine HCl. SUVN-502 will be supplied as identically appearing tablets that contain either 50 mg or 100 mg of SUVN-502. Placebo tablets matching SUVN-502 tablets will also be supplied. Generic formulations of donepezil HCl (10 mg) and memantine HCl (10 mg) will be provided by the Sponsor and dispensed to the subjects from baseline. Subjects treated with Namenda XR® or Namzaric™ should continue to take their own medication as prescribed by their prescribing physician.
Number of Subjects	A total of 537 subjects will be enrolled and randomized into one of three treatment groups: SUVN-502 50 mg, SUVN-502 100 mg, or placebo (179 subjects per group).
Population	The study population will include male or female subjects, 50 to 85 years of age, with moderate dementia due to probable Alzheimer's disease based on the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, diagnosed at least 1 year prior to the study and receiving stable doses for at least 3 months of donepezil HCl (10 mg qd) and either memantine HCl (10 mg bid) or Namenda XR® (28 mg memantine HCl extended-release qd) or the combination therapy, Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd.
Criteria for Evaluation of Efficacy	The primary efficacy variable will be the ADAS-Cog. Secondary efficacy variables will include the following: • CDR-SB • MMSE • ADCS-ADL • NPI • C-SDD
Criteria for Evaluation of Safety	Safety evaluations will include the reporting of AEs throughout the study and blood pressure measurement, ECG, physical and neurological examination, and assessments of suicidality using the C-SSRS at each visit. Blood and urine samples for laboratory evaluations will be collected at screening, baseline and Weeks 4 (liver function tests only) 13, 26 and 30. An independent Data and Safety Monitoring Board (DSMB) will be assembled to periodically review and evaluate accumulated study data for subject safety, study conduct and progress and, if appropriate, efficacy. The DSMB will be responsible for making recommendations concerning continuation, modification, or termination of the study, based on their independent evaluation of study related safety data. The DSMB role and activities are described in detail in the DSMB charter. The DSMB will consist of a chairperson and at least 2 additional members including 1 statistician.

Other Criteria	At baseline, a blood sample will be drawn for APO-E genotype testing. Plasma samples will be analyzed for levels of SUVN-502 and its primary metabolite (M1 of SUVN-502), at steady state (Week 4 of treatment) and at the end of study (Week 26) to gather information on population pharmacokinetics. Plasma samples will be analyzed for levels of donepezil and memantine at screening, at Week 4 of treatment and at the end of study (Week 26) to determine compliance with study medication.
Statistical Methods	A total of 537 subjects will be randomized into one of three treatment groups, SUVN-502 (50 mg), SUVN-502 (100 mg) or placebo (179 subjects per group). With a sample size of 537 subjects, there is at least 80% power to detect a 2-point drug-placebo difference on the ADAS-Cog with a standard deviation of 6, a two-sided 5% significance level and a drop-out rate of ≤20%. Efficacy analyses will be performed on the modified Intent to Treat (ITT) population and the Evaluable Population (EP). The modified ITT population is defined as all randomized subjects who receive at least one dose of study medication and have one post-baseline evaluation of the primary efficacy variable. The EP is defined as all randomized subjects who complete 26 weeks of treatment, are compliant with taking study medication (≥80%), and have no significant protocol deviation. Safety analyses will be performed on the Safety Population (SP), defined as all randomized subjects who receive at least one dose of study medication. Pharmacokinetic (PK) analyses will be performed on the SP. Statistical analysis of the primary endpoint will be performed using mixed model repeated measures (MMRM) without imputation of missing data. The MMRM model will include fixed categorical effects for treatment, pooled site, week, and treatment-by-week interaction, as well as a continuous covariate of baseline score and baseline score-by-week interaction. An unstructured covariance matrix will be used to model the variation of the repeated measures within patient. The primary efficacy analysis will compare the effect of each dose of SUVN-502 (50 mg and 100 mg), separately, to the effect of placebo, for the change from baseline to week 26 of the ADAS-Cog score using the modified ITT population and the above mentioned MMRM model. No adjustment for multiplicity will be made. Secondary efficacy analyses include the comparison of the effect of SUVN-502 (50 mg and 100 mg) to the effect of placebo using the same MMRM approach as described above for the following measures: • ADAS-Cog at Weeks 4 and 13 • CDR-SB at Weeks 4, 13 and 26 • MMSE at Weeks 4, 13 and 26 • ADCS-ADL at Weeks 4, 13 and 26 • NPI at Weeks 4, 13 and 26 • C-SDD at Weeks, 4, 13 and 26 Sensitivity analyses for the primary and secondary variables using last observation carried forward (LOCF) and using the EP analysis set will be conducted. Exploratory analyses of the primary and secondary efficacy criteria will be conducted based on APO-E4 carrier status.

Schedule of Procedures

Study period	Screening	Baseline	Treatment Period		End of Treatment	Follow-up
Time	**Days -28 to -14[a]**	**Day 1[a]**	**Week 4 Day 28±2**	**Week 13 Day 91±2**	**Week 26 Day 182±3 or early withdrawal**	**Week 30 Day 210±2**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**
Procedures						
Informed Consent	X					
Inclusion / Exclusion Criteria	X	X				
Demographics, Medical History	X	X				
Prior and Concomitant Medications	X	X	X	X	X	X
MRI or CT Scan (if Necessary)	X					
Blood Sample for APO-E Genotype Testing		X				
Study Treatment Dispensation [b]		X	X	X	X	
MMSE and ADAS-Cog	X	X	X	X	X	
Modified Hachinski Ischemic Scale	X					
CDR-SB, ADCS-ADL, and NPI		X	X	X	X	
C-SDD	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X
Review of AEs	X	X	X	X	X	X
Laboratory Tests	X [c]	X	X [d]	X	X [c]	X
Blood Pressure Measurements	X	X	X	X	X	X
ECG	X	X	X [e]	X [e]	X [e]	X
Physical and Neurological Examination	X	X	X	X	X	X
Plasma Levels of SUVN-502 and M1 of SUVN-502			X [f]		X [f]	
Plasma Levels of Donepezil and Memantine	X		X [f]		X [f]	

Schedule of Procedures (Continued)

ADAS-Cog=Alzheimer's Disease Assessment Scale; ADCS-ADL=Alzheimer's Disease Cooperative Study Activity of Daily Living; AE=adverse event; APO-E=Apolipoprotein E; CDR-SB=Clinical Dementia Rating Scale – Sum of Boxes; C-SDD=Cornell Scale of Depression and Dementia; C-SSRS=Columbia Suicide Severity Rating Scale; CT=Computed Tomography; ECG=Electrocardiogram; MHIS = Modified Hachinski Ischemic Scale; MMSE= Mini-Mental State Evaluation; MRI=Magnetic Resonance Imaging; NPI=Neuropsychiatric Inventory.

***Note:** It is strongly recommended that one rater is assigned for each subject for each of the following assessment scales so that one rater scores a subject's assessment for the entire study: MMSE, ADAS-Cog, CDR-SB, ADCS-ADL, NPI, C-SDD, and C-SSRS.*

a. *For Screening and Baseline Visits, the following assessments, included in study entry criteria, should be performed first in order to limit the number of assessments performed for subjects who do not meet the study entry criteria: MMSE, the MHIS, C-SDD, C-SSRS, ECG, pregnancy test (for women of child bearing potential), and laboratory tests.*
b. *On the day of the study visits, subjects will be instructed not to take their treatment at home, as treatment will be dispensed at the study center.*
c. *A urine pregnancy test will be done at screening and Week 26 visit for women of childbearing potential. A positive urine test will be confirmed by a serum pregnancy test.*
d. *At Week 4, laboratory tests will only include liver function tests.*
e. *3 hours after study treatment administration, i.e. the approximate time of maximum concentration of SUVN-502.*
f. *Plasma samples for PK assessments will be collected before study drugs are administered to the subjects.*

LIST OF STUDY PERSONNEL

Sponsor

[redacted]

Suven Life Sciences Ltd
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Avenue – 7
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TABLE OF CONTENTS

Tables in Text

Figures in Text

List of Appendices

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5-HT_6	Serotonin receptor subtype 6
ADAS-Cog	Alzheimer's Disease Assessment Scale for Cognitive Behavior
ADCS-ADL	Alzheimer's Disease Cooperative Study Activity of Daily Living
AE	Adverse event
ALT	Alanine aminotransferase
APO-E	Apolipoprotein E
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical [Classification System]
BID, bid	Twice daily
cAMP	Cyclic adenosine monophosphate
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating Scale – Sum of Boxes
CRE-Luc	Cyclic adenosine monophosphate (cAMP) response element-luciferase
C-SDD	Cornell Scale of Depression and Dementia
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computed tomography
CYP3A4	Cytochrome P450 3A4
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transpeptidase
HbA1c	Hemoglobin A1c or glycated hemoglobin
HCl	Hydrochloride
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IR	Immediate release

IRB	Institutional Review Board
ITT	Intent-to-treat; intention-to-treat
IVRS	Interactive Voice Response System
Kb	Dissociation constant
Ki	Inhibition constant
LD_{50}	Median lethal dose
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MHIS	Modified Hachinski Ischemic Scale
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association
NMDA	N-methyl-D-aspartic acid
NOAEL	No observed adverse effect level
NPI	Neuropsychiatric Inventory
PK	Pharmacokinetic
PT	Preferred term
QD, qd	Once daily
QTcF	Fridericia's formula corrected QT interval
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
USA	United States of America

1 INTRODUCTION

1.1 Background

SUVN-502 is proposed as a novel, highly selective and orally active antagonist at a non-peripheral central nervous system serotonin receptor, the serotonin receptor subtype 6 (5-HT_6), intended for the treatment of cognitive disorders associated with Alzheimer's disease.

1.1.1 Alzheimer's Disease

Alzheimer's disease is a progressive and fatal neurodegenerative disorder manifested by cognitive and memory deterioration in addition to progressive impairment of activities of daily living. Currently available treatments, including acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and non-competitive N-methyl-D-aspartic acid (NMDA) receptor blockers (memantine) are seen as minimally effective, with only minor symptomatic improvements for a limited duration, and they do not slow the progression of the disease.

1.1.2 Summary of Findings from Non-Clinical Studies

1.1.2.1 Pharmacology

SUVN-502 and its metabolite "M1 of SUVN-502" selectively bind to 5-HT_6 receptors with inhibition constant (Ki) values of 2.16 and 1.28 nM respectively, when tested by the *in vitro* radio-ligand binding technique on human recombinant 5-HT_6 receptors. SUVN-502 and its metabolite, M1 of SUVN 502, exhibited antagonist-like properties in CRE-Luc (cyclic adenosine monophosphate [cAMP] response element-luciferase) based reporter gene assay on human recombinant 5-HT_6 receptor, with dissociation constant [redacted] which is in agreement with values determined by radio-ligand binding assay (2.16 and 1.28 nM respectively) and showing no detectable agonist activity.

SUVN-502 has shown selectivity of [redacted] over a hundred target sites including neurotransmitter related receptors, enzymes, peptides, growth factors/hormones, ion channels, steroids, immunological factors, second messengers, and prostaglandins.

SUVN-502 was found to be active in the novel object recognition task (episodic memory), in time-induced memory disruption as well as in scopolamine-induced memory disruption. SUVN-502 was found to enhance cognition in the Morris water maze (spatial memory) in both adult and aged rats. SUVN-502 was found to reverse the scopolamine-induced amnesia in both models. Thus, SUVN-502 acts via the cholinergic pathway. In the passive avoidance box (emotional memory), there was a reversal in the time-induced memory disruption. SUVN-502 potentiated the pro-cognitive effect of donepezil hydrochloride (HCl), and combined donepezil HCl and memantine HCl treatment. SUVN-502 was found to be safe in the central nervous system, cardiovascular system, respiratory, gastrointestinal and renal safety pharmacological studies at the tested doses.

In vivo rat brain microdialysis performed in the ventral hippocampus established that single oral administration of SUVN-502 significantly increased extracellular acetylcholine levels demonstrating cognition-enhancement properties are likely to be mediated by enhancements of cholinergic function. Oral administration of SUVN-502 produced significant increases in extracellular levels of glutamate in the frontal cortex of rats. Dysfunction in the glutamatergic function has been suggested to be causal in the cognitive and memory dysfunction in psychiatric patients. Additionally, SUVN-502 potentiated the procognitive effects and acetylcholine increase produced by the combination of donepezil HCl and memantine HCl. These studies provide further support for the potential therapeutic utility of SUVN-502 in cognition deficient disorders.

[redacted]

1.1.2.3 Toxicology

[redacted]

1.1.3 Summary of Findings from Previous Clinical Studies

Two phase 1 clinical studies enrolled 122 healthy subjects, including 104 who received SUVN-502 at single oral doses of 5 to 200 mg or daily oral doses of 50 to 130 mg during 7 to 14 days:

- In the First-in-Human study, SUVN-502 was tested at single doses up to 200 mg/day and repeated doses up to 130 mg/day for 7 days; the drug was well tolerated. This study was conducted using a capsule formulation.
- The second phase 1 study used the immediate release (IR) tablet formulation. SUVN-502 was well tolerated at both 50 mg and 100 mg administered as a single dose in healthy elderly male, young adult male or female subjects or as repeated daily doses in healthy elderly male subjects. No safety concerns or notable differences between age, gender, and food groups were reported based on safety laboratory, vital signs, electrocardiograms (ECGs), and physical examination assessments. No safety concerns or notable differences between SUVN-502 50 mg, SUVN-502 100 mg, or active-treated cohorts and placebo were reported based on safety laboratory, vital signs, ECG, physical examination, and C-SSRS assessments.
  After a single oral dose of 100 mg, there was no significant effect of gender and food on the pharmacokinetics of SUVN-502 and M1 of SUVN-502.
  Following repeated daily doses of SUVN-502, steady state was reached for SUVN-502 on Day 4 and Day 2 for the 50 mg and 100 mg dose groups, respectively. For metabolite M1 of SUVN-502, steady state was reached on Day 6 and Day 4 for the 50 mg and 100 mg dose groups, respectively. After daily doses of SUVN-502 50 mg, SUVN-502 exposure was approximately 1.5 to 1.6-fold higher on Day 14 compared to Day 1, while metabolite M1 of SUVN-502 exposure was approximately 2.1 to 2.5-fold higher on Day 14 compared to Day 1. After daily doses of SUVN-502 100 mg, SUVN-502 exposure was comparable between Day 14 and Day 1, while metabolite M1 of SUVN-502 exposure was approximately 1.6 to 1.8-fold higher on Day 14 compared to Day 1. On Day 14, median time to maximum concentration (t_{max}) of SUVN-502 was 2.00 and 2.98 hours after daily doses of 50 mg and 100 mg respectively. Mean half-life was comparable between the two doses at 13.7 and 12.5 hours, respectively. Median t_{max} of metabolite M1 of SUVN-502 and absorption lag time were similar between the two doses at 3.0 hours and 0 hours, respectively.

1.2 Rationale

[redacted]

1.3 Risk-Benefit Assessment

Animal toxicology data support the safety of the two dosage levels of SUVN-502, 50 mg and 100 mg to be used in this study and data from a Phase I single and multiple dose studies suggest SUVN-502 should be relatively safe and well tolerated in subjects with moderate Alzheimer's disease currently receiving both donepezil HCl and memantine HCl.

The clinical efficacy of SUVN-502 has not yet been tested in subjects with Alzheimer's disease. However, nonclinical data suggest that SUVN-502 may improve the cognitive status of subjects with Alzheimer's disease treated with donepezil HCl and memantine HCl.

The utility of SUVN-502 in Alzheimer's disease is supported by the clinical study of another 5-HT_6 antagonist, idalopirdine (Wilkinson et al, 2014) [2]. The study enrolled 278 subjects with moderate Alzheimer's disease receiving donepezil HCl (10 mg once

daily [qd]) and showed a statistically significant improvement in the change from baseline to Week 24 in the 11-Item Alzheimer's Disease Assessment Scale for Cognitive Behavior (ADAS-Cog) score in subjects treated with idalopirdine in comparison to the placebo group. During the study, 25 subjects (7 taking placebo and 18 taking idalopirdine) discontinued treatment because of adverse events (AEs), the difference between groups being mainly due to asymptomatic transient increases in transaminase concentrations in some idalopirdine-treated subjects. The most common AEs were increased gamma-glutamyltransferase (GGT, 10% of subjects in the idalopirdine group versus 2% in the placebo group), diarrhea (4% versus 7%), urinary tract infection (2% versus 7%), fall (2% versus 6%), increased alanine aminotransferase (6% versus 0%), and benign prostatic hyperplasia (5% versus 0%). Serious AEs (SAEs) were reported by 10% of subjects in both treatment groups. One death occurred in each treatment group, neither regarded as being related to treatment.

Overall, considering the potential efficacy of SUVN-502 on the cognitive and functional symptoms of Alzheimer's disease and limited safety concerns identified from the nonclinical studies and phase 1 clinical studies in healthy volunteers, the benefit-risk ratio of subjects enrolled in the study is considered to be reasonable.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of a 5-HT_6 antagonist, SUVN-502 at daily doses of 50 mg or 100 mg compared to placebo, as adjunct treatment in subjects with moderate Alzheimer's disease (Mini-Mental State Examination [MMSE] score of 12 to 20) currently treated with the acetylcholinesterase inhibitor, donepezil HCl, and the NMDA antagonist, memantine HCl. Efficacy will be assessed by the ADAS-Cog after 26 weeks of treatment.

2.2 Secondary Objective(s)

Secondary objectives of the study are:

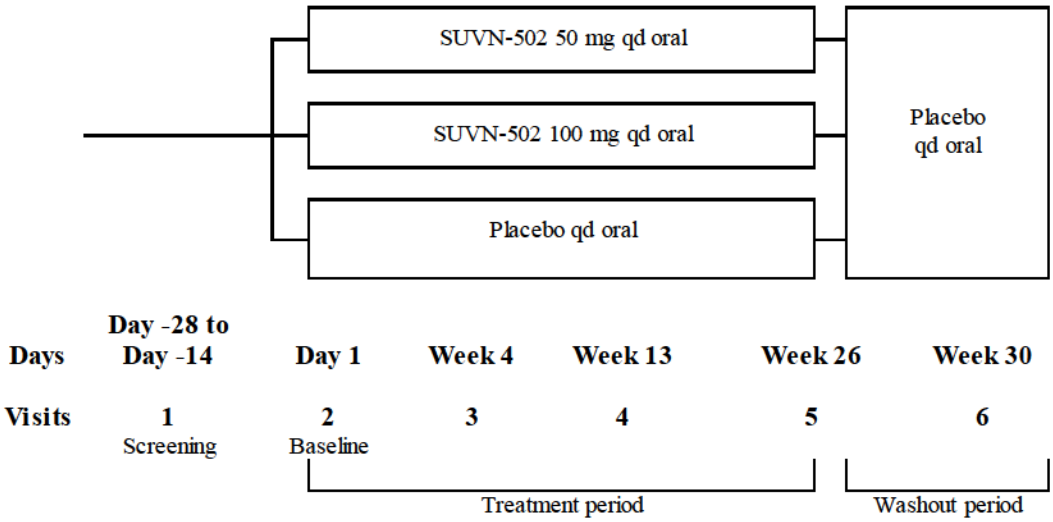
- To further evaluate the efficacy of these treatments using the following scales:
  - Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB)
  - MMSE
  - Alzheimer's Disease Co-operative Study Activity of Daily Living (ADCS-ADL)
  - Neuropsychiatric Inventory (NPI) 12 item
  - Cornell Scale for Depression and Dementia (C-SDD)
- To evaluate the safety and therapeutic tolerability of these treatments using AEs, laboratory evaluations, blood pressure, ECGs, physical and neurological examination, and the Columbia Suicide Severity Rating Scale (C-SSRS)
- To evaluate the pharmacokinetics of SUVN-502 administered in combination with donepezil HCl and memantine HCl
- To explore the relationship between the efficacy of SUVN-502 and apolipoprotein E (APO-E) genotype, as well as analyze subjects more likely to have Alzheimer's disease

3 OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Overview

This is a phase 2A, proof-of-concept, 26-week, double-blind, multicenter, randomized, parallel group, placebo-controlled study to compare the efficacy and safety of treatment with SUVN-502 (50 mg or 100 mg qd) to placebo treatment in subjects with moderate Alzheimer's disease receiving donepezil HCl (10 mg qd) and either memantine HCl (10 mg twice daily [bid]) or Namenda XR® (28 mg memantine HCl extended-release qd) or the combination therapy, Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd.

The study consists of a 2 to 4-week screening period, followed by a 26-week double-blind treatment period and a 4-week single-blind placebo washout period (Figure 1).



qd: once daily

Figure 1: Study Design

At the screening visit, subjects and their caregiver or appropriate legal representative will sign the informed consent form prior to any procedures. The inclusion and exclusion criteria will be reviewed including demographics, medical history and prior and concomitant treatment, NINCDS-ADRDA criteria, MMSE, Modified Hachinski Ischemic Scale (MHIS), and C-SSRS. If no magnetic resonance imaging (MRI) or computed tomography (CT) scan was performed within the past 12 months, a MRI or CT scan will be performed at screening to confirm that findings are consistent with the diagnosis of dementia due to Alzheimer's disease without any other clinically significant comorbid pathologies. Subjects will undergo physical and neurological examination, blood pressure assessment, electrocardiogram (ECG). Urine and blood samples will be collected for laboratory evaluations (including pregnancy test for women of childbearing potential) and plasma levels of donepezil and memantine. The ADAS-Cog and C-SDD scores will also be obtained.

The baseline visit will occur 14 to 28 days after screening. Inclusion and exclusion criteria will be reviewed to confirm eligibility of the subject. Subjects will be evaluated

for AEs and undergo physical and neurological examination, blood pressure assessment, and ECG. Urine and blood samples will be collected for laboratory evaluations and APO-E genotype testing. Baseline scores will be assessed for the MMSE, ADAS-Cog, CDR-SB, ADCS-ADL, NPI, C-SDD and C-SSRS.

Following confirmation of eligibility, subjects will be randomized in a 1:1:1 ratio to one of the following three treatment groups:

- SUVN-502 (50 mg)
- SUVN-502 (100 mg)
- Placebo

Blinded SUVN-502/placebo treatment and generic formulations of donepezil HCl 10 mg and memantine HCl 10 mg will be dispensed to the subjects for treatment until the next visit.

During the 26-week treatment period, subjects and caregivers will have study visits at Weeks 4, 13, and 26. At each of these visits, subjects will be evaluated for AEs and undergo physical and neurological examination, blood pressure assessment, and ECG. The MMSE, ADAS-Cog, CDR-SB, ADCS-ADL, NPI, C-SDD and C-SSRS scores will be assessed. Urine and blood samples for laboratory evaluations will be collected at Weeks 4 (liver function tests only), 13 and 26. For women of childbearing potential, a pregnancy test will be performed at Week 26. Blood samples for plasma levels of SUVN-502, its metabolite (M1 of SUVN-502), donepezil and memantine will be collected at Weeks 4 and 26.

Subjects who complete the 26-week treatment period, will undergo a 4-week single-blind placebo washout period. At Week 30, subjects will attend a follow-up visit to the study center. During this visit, subjects will be evaluated for AEs and undergo physical and neurological examination, blood pressure assessment, ECG, laboratory evaluations. The C-SDD and C-SSRS scores will be assessed.

Subjects who discontinue treatment prematurely (see Section 4.3) should attend a final visit similar to Week 26 visit and, if subjects agree, the subjects will return 4 weeks later for a follow-up visit similar to Week 30 visit.

During the course of the study, an independent Data and Safety Monitoring Board (DSMB) will be assembled to periodically review and evaluate accumulated study data for subject safety, study conduct and progress. The DSMB will have the responsibility to make recommendations concerning continuation, modification, or termination of the study.

The approximate blood volume to be collected during the study is 135.5 mL, with a maximum of 26 mL per visit.

3.2 Criteria for Evaluation of the Study

3.2.1 Primary Efficacy Criterion

The primary criterion for the evaluation of efficacy will be the change from baseline to Week 26 in ADAS-Cog score.

3.2.2 Secondary Efficacy Criteria

The change from baseline in the ADAS-Cog score will also be assessed at Weeks 4 and 13.

Secondary efficacy criteria will also include the change from baseline of the following variables:

- CDR-SB at Weeks 4, 13 and 26
- MMSE at Weeks 4, 13 and 26
- ADCS-ADL at Weeks 4, 13 and 26
- NPI at Weeks 4, 13 and 26
- C-SDD at Weeks 4, 13 and 26

3.2.3 Safety Criteria

Safety evaluations will include the reporting of AEs throughout the study, blood pressure measurement, ECGs, physical and neurological examination, and assessment of suicidality using the C-SSRS at each visit.

Blood and urine samples for laboratory evaluations will be collected at screening, baseline and Weeks 4 (liver function tests only), 13, 26 and 30.

3.2.4 Other Criteria

At baseline, a blood sample will be drawn for APO-E genotype testing.

Plasma samples will be analyzed for levels of SUVN-502 and M1 of SUVN-502, at steady state (Week 4 of treatment) and at the end of study (Week 26 of treatment) to gather information on population pharmacokinetics.

Plasma samples will be analyzed for levels of donepezil and memantine at screening, at Week 4 of treatment and at the end of study to determine compliance with study medication.

3.3 Justification of the Study Design

This study is designed to test the hypothesis that 50 mg and 100 mg of SUVN-502 improves the cognitive status of Alzheimer's disease subjects who are currently receiving donepezil HCl and memantine HCl, compared to placebo.

Animal toxicology data support the safety of the two dosage levels of SUVN-502, 50 mg and 100 mg to be used in this study and data from a phase 1 single and multiple dose studies suggest SUVN-502 should be relatively safe and well tolerated in subjects with moderate Alzheimer's disease currently receiving donepezil HCl and memantine HCl.

The design of this study follows the recommendations of the Food and Drug Administration (FDA [3]) and the European Medicine Agency (EMA [4]) for studies of small molecule symptomatic drugs in Alzheimer's disease. The study is double-blind, placebo-controlled and follows an add-on design to the standard-of-care. Efficacy assessments include cognitive, functional and global evaluations using well-recognized scales.

4 STUDY POPULATION

The study population will consist of subjects with moderate Alzheimer's disease (MMSE 12-20). Subjects and caregivers must meet all the inclusion criteria and none of the exclusion criteria.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be enrolled into the study:

1. Male or female subjects, aged between 50 and 85 years inclusive at screening.
2. Has a diagnosis of probable Alzheimer's disease based on the NINCDS-ADRDA criteria at least 1 year prior to the screening visit.
3. Has a score between 12 and 20 inclusive on the MMSE at the screening and baseline visits.
4. Has a MRI or CT scan performed within 12 months prior to screening with findings consistent with the diagnosis of dementia due to Alzheimer's disease without any other clinically significant comorbid pathologies.
5. Has a MHIS score of 4 or less.
6. Must be receiving treatment with stable doses of donepezil HCl (10 mg qd), either as 10 mg donepezil HCl only or part of the combination therapy, Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd for at least 3 months prior to screening visit. Subjects are likely to be maintained on this 10 mg daily dose of donepezil HCl or Namzaric™ for the entire duration of the study.
7. Must be receiving treatment with stable doses of memantine HCl (10 mg bid) or Namenda XR® (28 mg memantine HCl extended-release qd) or as part of the combination therapy, Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd for at least 3 months prior to the screening visit. Subjects are likely to be maintained on their current dose of memantine HCl or Namenda XR® or Namzaric™ for the duration of the study.
8. Availability of a person (caregiver) who in the investigator's judgment has frequent and sufficient contact with the subject, such that this person is qualified, willing and able to provide accurate information regarding the subject's cognitive and functional abilities and will accompany the subject to study visits. The caregiver should have face to face contact with the subject for a minimum of approximately 12 hours per week spread over 3 to 5 days during the week (for example: 3 hours per day for 4 days a week, or 4 hours per day for 3 days a week).
9. Must be living in the community or an assisted living facility. No subjects currently residing in a nursing home or anticipated to move into a nursing home during the study will be allowed entry into the study.
10. Must be ambulatory or ambulatory aided (use of cane or walker).
11. Must have vision and hearing (corrected) sufficient to comply with the testing procedures.

12. Both subject and caregiver must be able to read and understand English or Spanish and have appropriate literacy skills to ensure compliance with the testing and study visit procedures.
13. Is not pregnant or planning to become pregnant during the study. Women of childbearing potential must have a negative pregnancy test at screening and must be using oral or injectable contraception (non-childbearing potential is defined as post-menopausal for at least 1 year or surgical sterilization or hysterectomy at least 3 months before study start).
14. Subject (or subject's legally acceptable representative) and caregiver must sign an Informed Consent to participate in the study.

4.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be allowed to be randomized into the study:

1. Has a diagnosis of dementia due to other causes, including vascular disease, Parkinson's disease, Lewy Body disease, AIDS, Creutzfeldt-Jakob disease, fronto-temporal dementia, Huntington's disease, major head trauma, primary or secondary cerebral neoplasia, or other non-Alzheimer disorders. Subjects with major strokes (large cortical/subcortical or in brain areas related to cognition), based on medical history, physical exam or MRI, are excluded.
2. Has a diagnosis of schizophrenia, bipolar disorder or current major depressive disorder (MDD) or subjects whose C-SDD scores are suggestive of probable depression (typically scores ≥12). Subjects with history of MDD who are currently treated and controlled on medication for at least 6 months may be enrolled. Subjects taking low doses of antipsychotics for the treatment of sleep disturbances or for agitation or aggression, for which the dose has been stable for at least 1 month and not anticipated to change during the course of the study, can be enrolled.
3. Is taking cholinesterase inhibitors other than donepezil HCl, including rivastigmine and galantamine. Subjects currently taking 5 mg of donepezil HCl, or taking 23 mg daily doses of donepezil HCl or subjects taking 10 mg daily dose of donepezil HCl for whom the physician contemplates increasing the dose to 23 mg during the conduct of the study, will not be enrolled.
4. Is taking doses of memantine HCl other than 10 mg bid or Namenda XR® (28 mg memantine HCl extended-release qd) or Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd.
5. Has uncontrolled cardiac disease or hypertension. This includes subjects with history of myocardial infarction within 6 months of screening visit; congestive heart failure; history of unstable angina within 6 months of screening visit; and clinically significant ECG at screening visit and subjects whose hypertension has not been controlled on medication for at least 3 months prior to screening.
6. Has a history or current evidence of long QT syndrome, Fridericia's formula corrected QT (QTcF) interval ≥ 470 ms (for male subjects) or ≥ 480 ms (for female

subjects), or torsades de pointes, as determined by an ECG read by a central ECG vendor.

7. Has bradycardia (<50 bpm) or tachycardia (>100 bpm) on the ECG at screening.
8. Has uncontrolled Type-1 or Type-2 diabetes (glycated hemoglobin [HbA1c] above 6.5%). A Subject with HbA1c levels up to 7.5% can be enrolled if the investigator believes the subject's diabetes is under control.
9. Has cancer or a malignant tumor, or has been treated for an active malignancy within the past 5 years. Subjects with stable untreated prostate cancer, localized squamous cell cancer or basal cell cancer will be allowed.
10. Has untreated thyroid disorder. Subjects who are considered euthyroid on medication with normal free thyroxine (T4) will be allowed.
11. Has a history of seizure disorder.
12. Has clinically significant renal or hepatic impairment.
13. Has any clinically significant abnormal laboratory values. Subjects with liver function tests (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) greater than twice the upper limit of normal will be excluded.
14. Is treated or likely to require treatment during the study, with any medications prohibited by the study protocol.
15. Has abnormal vitamin B-12 levels that are lower than normal limits and remains low on repeat testing. Subjects taking vitamin B-12 supplements who are within normal limits or above at screening or within normal limits or above at repeat testing will be allowed.
16. Has participated in a previous clinical study within 26 weeks of the screening visit, or has been previously treated with the investigational product, SUVN-502.
17. Subject (or caregiver) is deemed otherwise ineligible for participation in this study in the investigator's judgment.
18. Is at imminent risk of self-harm, based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the Investigators. Subjects must be excluded if they report suicidal ideation with intent, with or without a plan or method (e.g. positive response to Items 4 or 5 in assessment of suicidal ideation on the C-SSRS) in the past 2 months, or suicidal behavior in the past 6 months.

4.3 Subject Withdrawal and Replacement

Subjects and caregivers may withdraw from the entire study including follow-up at any time without penalty and for any reason without prejudice to his or her future medical care.

Subjects must be withdrawn from **study drug** under the following circumstances:

- Pregnancy (see Section 6.2.1.7)
- Elevated ALT, AST, or total bilirubin (see Section 6.2.2)
- Suicidal ideation or behavior (see Section 6.2.6.1)

- Treatment with prohibited concomitant medications is required (see Section 5.7.2)
- Treatment with donepezil HCl cannot be maintained at the dose of 10 mg qd or as part of the combination therapy of Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd.
- Treatment with memantine HCl cannot be maintained at either 10 mg bid of memantine HCl or 28 mg memantine HCl extended-release qd of Namenda XR® or as part of the combination therapy of Namzaric™ (28 mg memantine HCl extended-release /10 mg donepezil HCl) qd
- Subject's noncompliance to study treatment (see Section 5.6)
- A medical condition or personal circumstance which, in the opinion of the Investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the study or does not allow the subject to adhere to the requirements of the protocol

Subjects may be required to withdraw from study drug, according to the Investigator's judgment, for the following reasons:

- AE(s)
- Any reason at the discretion of the Investigator

In all cases, the reason(s) for withdrawal, and the primary reason, must be recorded on the electronic Case Report Form (eCRF). If a subject is prematurely withdrawn from the study drug for any reason, the Investigator must make every effort to perform the evaluations described for the Week 26 visit and a follow-up visit 4 weeks later.

If a subject withdraws consent and still agrees to undergo a final examination, this will be documented on the eCRF and the Investigator's copy of the informed consent form (ICF), which will be countersigned and dated by the subject.

A subject may also be withdrawn from study drug by the Sponsor, Regulatory Authorities, or Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs).

Subjects will also be withdrawn if the entire study is terminated prematurely as described in Section 9.11.

Withdrawn subjects will not be replaced. If the caregiver withdraws consent, the investigator should consult with the Sponsor/Medical Monitor regarding potential replacement of the caregiver.

4.4 Planned Sample Size and Number of Study Centers

It is planned to recruit 537 subjects at approximately 90 centers in the United States of America (USA) for this study. See Section 8.9 for a discussion of sample size.

4.5 Subject Identification and Randomization

4.5.1 Subject Identification

After informed consent is obtained, each subject will receive a unique screening number. Enrolled subjects who drop out of the study before randomization will retain their screening number. The screening number for each subject will be a 6-digit identification

number such that all patients from a center are given consecutive identification number in successive order of inclusion. The first 3 digits of the screening number will be the designated investigator center number and the last 3 digits will be assigned at the investigator center (e.g., the third patient at center 5 would be given the number 005003).

4.5.2 Randomization Scheme

Eligible subjects will be randomized to receive one of the three treatments: SUVN-502 50 mg, SUVN-502 100 mg, or placebo in a 1:1:1 ratio, using permuted blocked randomization.

4.5.3 Allocation/Randomization of Subjects to Treatment

Randomization of subject to treatment will occur at baseline (Visit 2) after all screening procedures have been performed and eligibility for the study confirmed. Each randomized subject will receive a unique randomization number. Randomized subjects who terminate their study participation for any reason, regardless of whether study drug was taken or not, will retain their randomization number.

For the randomization of subjects, the Investigator will use an Interactive Voice Response System (IVRS). Details can be found in the study file. IVRS will assign subjects in a double-blind manner to a treatment group based on the pre-defined randomization list.

5 STUDY DRUG

5.1 Identity

5.1.1 Investigational Treatment: SUVN-502 and Matching Placebo

From Day 1 to the end of Week 26, eligible subjects will receive double-blind oral administration of one of following three treatments:

- SUVN-502 50 mg
- SUVN-502 100 mg
- placebo

During the single-blind placebo washout period (Weeks 27 to 30), all subjects will receive placebo.

[redacted]

5.1.2 Other Study Drugs

In addition to the investigational drug, all subjects will also continue to receive daily administrations of the following treatments throughout the study (including the single-blind placebo washout period):

- donepezil HCl 10 mg qd

  AND
- memantine HCl 10 mg bid or Namenda XR® (28 mg memantine HCl extended-release) qd

  OR
- Namzaric™ (28 mg memantine HCl extended-release /10 mg donepezil HCl) qd.

5.2 Administration

5.2.1 Investigational Treatment: SUVN-502 and Matching Placebo

Each tablet of SUVN-502 50 mg, SUVN-502 100 mg and matching placebo will contain the daily dose to be administered to the subjects.

Treatment will start after the baseline visit where subjects and caregivers will be provided with the number of tablets needed until the next visit.

On days with no scheduled study visits, subjects will take one tablet per day in the morning, with a glass of water (with or without food).

On the day of the study visits, subjects will be instructed not to take their treatment at home, as treatment will be dispensed at the study center.

5.2.2 Other Study Drugs

Donepezil HCl (10 mg qd), memantine HCl (10 mg bid) and Namenda XR® (28 mg memantine HCl extended-release qd) or Namzaric™ (28 mg memantine HCl extended-release/10 mg donepezil HCl) qd should be administered at stable doses throughout the study at the same time every day, as directed by their prescribing physician.

Generic formulations of donepezil HCl (10 mg) and memantine HCl (10 mg) will be provided by the Sponsor and dispensed to the subjects from baseline.

Subjects treated with Namenda XR® or Namzaric™ will continue to take their own medication as directed by their prescribing physician.

Any cessation of these medications, if recommended by the personal physician, must be reported immediately to the Investigator and the Sponsor/Medical Monitor for consultation.

Subjects requiring dose modifications for donepezil HCl or memantine HCl will be withdrawn.

On the day of the study visits, subjects should not take their treatment at home, as treatment will be dispensed at the study center.

5.3 Packaging, Labeling and Storage

5.3.1 Investigational Treatment: SUVN-502 and Matching Placebo

SUVN-502 will be supplied as identically appearing tablets that contain either 50 mg or 100 mg of SUVN-502. Placebo tablets matching SUVN-502 tablets will also be supplied.

SUVN-502 50 mg, SUVN-502 100 mg and matching placebo will be provided in bottles containing 35 tablets. The study drugs will be packaged by the Sponsor according to all local legal requirements. Study drug will be labeled in accordance with applicable regulatory requirements.

All supplies must be stored in accordance with the manufacturer's instructions or in accordance with USP Controlled Room Temperature (20–25°C [68–77°F] with excursions permitted between 15 and 30°C [59 – 86°F]). Until dispensed to the subjects, the study drug will be stored in a securely locked area, accessible to authorized personnel only.

5.3.2 Other Study Drugs

Generic formulations of donepezil HCl (10 mg) and memantine HCl (10 mg) will be provided by the Sponsor in their commercially available packaging with the label 'for clinical trial use only'.

5.4 Blinding and Breaking the Blind

The study will be performed in a double-blind manner. SUVN-502 will be supplied as identically appearing tablets that contain either 50 mg or 100 mg of SUVN-502. Placebo tablets matching SUVN-502 tablets will also be supplied. Tablets will be similar in color, smell, taste, and appearance, thereby enabling double-blind conditions.

The study blind should not be broken except in a medical emergency (where knowledge of the study drug received would affect the treatment of the emergency) or regulatory requirement.

The blind must only be broken following discussion on a case-by-case basis, at the discretion of the Sponsor/Medical Monitor.

If the blind is broken, the date, time, and reason must be recorded in the subject's eCRF, and any associated AE report.

The Investigator should notify the Sponsor/Medical Monitor prior to contacting IVRS. All calls resulting in an unblinding event will be recorded and reported by the IVRS to the CRO Medical Monitor and the Sponsor.

The DSMB will have access to the randomization code, and the code for a particular subject may be disclosed after appropriate discussion with the Sponsor.

If an Investigator, site personnel performing assessments, or subject, is unblinded, the subject must be listed as major protocol deviation. However, the subject will not be withdrawn from study treatment.

Serious unexpected suspected adverse reactions (SUSARs), which are subject to expedited reporting, should be unblinded before submission to the Regulatory Authorities

The overall randomization code will be broken only for reporting the final results of the study. This will occur once all final clinical data have been entered onto the database, all data queries have been resolved, the assignment of subjects to the analysis sets has been completed, the SAP has been finalized and the database has been locked.

5.5 Drug Accountability

The Investigator is responsible for maintaining accurate study drug accountability records throughout the study.

Each dispensing of study drug will be documented in the eCRF.

The Investigator is responsible for returning all unused or partially used study drug to the Sponsor or Sponsor's designee and must verify that all unused or partially used drug supplies have been returned by the subject and that no remaining supplies are in the Investigator's possession.

5.6 Compliance

Note that the caregiver is responsible for holding, dispensing, and returning study drugs and for overseeing all medications.

As part of the routine recording of the amount of study medication (including SUVN-502 or placebo tablets, donepezil HCl, and memantine HCl if provided by the Sponsor) taken by each subject, the caregiver will return study medication at each clinic visit, including

empty bottles (beginning at Visit 3) and the number of tablets remaining in the study packaging will be counted and recorded. These results will be used to calculate subject compliance. Instances where the subject took more or less study medication than prescribed will be recorded on the eCRF.

To monitor for potential for misuse, the site will document significant discrepancies in drug returns where the caregiver returns less study medication than expected but denies taking extra study medication (e.g., lost or missing medication equivalent to more than one tablet per week).

In addition to routine surveillance of subject study medication compliance, subjects/caregivers will be given study drugs "calendar sleeves" which affix to the exterior of study medication bottles to help subjects remember when to take study medication. These sleeves will also help subject/caregiver to remember when the subject missed a dose. These sleeves will be provided to the site and the site will slide them onto the bottles. The site will then instruct the caregiver on how to make them subject-specific (i.e., document on the "calendar sleeve" the date to start taking study medication, bottle number).

When the subject/caregiver returns to the clinical site, the site will perform a tablet count and also review the "calendar sleeve" to verify tablet count and any possible missed or extra doses taken. If there is a discrepancy between the bottle and the "calendar sleeve" subject/caregiver verbal account will be the final decision for which to document in the eCRF. Discrepancies should be documented in the site's source documents and the reasoning for what was ultimately recorded in the eCRF.

For subjects who discontinue study medication early but remain in the study, site personnel should ensure the subject returns all study medication at the early termination visit. Subjects and caregivers will also be reminded to continue background therapy for Alzheimer's disease (donepezil HCl and memantine HCl).

Administration of study drugs will be witnessed by the Investigator and/or study staff at each visit. All other study treatments should be administered by the subject at home (with assistance from the caregiver, as needed).

Compliance with donepezil HCl and memantine HCl treatment will also be assessed by measuring drug levels in plasma samples collected at screening, Week 4 and Week 26.

Subjects showing less than 80% compliance to any study treatment (including SUVN-502 or placebo tablets, donepezil HCl, and memantine HCl if provided by the Sponsor) for two consecutive visits will be withdrawn from the study.

5.7 Previous and Concomitant Medications

5.7.1 Permitted Concomitant Medications

Any medication the subject takes other than the study drug, including herbal and other non-traditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At Screening, subjects will be asked what medications they have taken during the last 3 months. At each subsequent study visit, subjects will be asked what concomitant medications they are currently taking.

5.7.2 Prohibited Concomitant Medications

Strong inhibitors of CYP3A4, including protease inhibitors (atazanavir, indinavir, ritonavir, saquinavir, nelfinavir), azole antifungals (ketoconazole, itraconazole, fluconazole), macrolide antibiotics (erythromycin, clarithromycin, telithromycin), calcium channel blockers (verapamil and diltiazem) and grapefruit juice are prohibited during the study.

Strong inducers of CYP3A4, including rifampicin, phenytoin, phenobarbital, carbamazepine, dexamethasone and St. John's Wort (herbal supplement) are prohibited during the study.

Subjects requiring treatment with prohibited concomitant medications should be withdrawn from the study.

6 VARIABLES AND METHODS OF ASSESSMENT

6.1 Efficacy Variables

It is strongly recommended that one rater is assigned for each subject for each of the efficacy assessment scales described below, so that one rater scores a subject's assessment for the entire study. For example, the rater assigned to perform the MMSE would rate that scale for all visits for that subject.

6.1.1 Primary Efficacy Variable

The primary efficacy variable for the study is the ADAS-Cog.

The ADAS-Cog is a brief measure of cognition, including word recall, commands, constructional praxis, naming objects and fingers, ideational praxis, orientation, word recognition, remembering test instructions, spoken language ability, word-finding difficulty, and comprehension of spoken language.

The ADAS-Cog will be administered to the subject and scored by a qualified, trained rater at screening, baseline and at Weeks 4, 13 and 26 as indicated in the Schedule of Procedures (Table 3).

Further details regarding the assessment are provided in Appendix 1.

6.1.2 Secondary Efficacy Variables

6.1.2.1 Clinical Dementia Rating Scale – Sum of Boxes

The Washington University Clinical Dementia Rating Scale (CDR) is a global assessment of cognition and function rated in 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care, which is used to assess the severity of dementia.

Each domain is rated on a 5-point scale of functioning as follows:

- 0: no impairment
- 0.5: questionable impairment
- 1: mild impairment
- 2: moderate impairment
- 3: severe impairment

Personal care is scored on a 4-point scale without a 0.5 rating available.

The CDR will be administered through semi-structured interviews to the subjects and caregivers by a qualified, trained rater at baseline and Weeks 4, 13 and 26 as indicated in the Schedule of Procedures (Table 3). The CDR-SB score will be obtained by summing each of the domain box scores (i.e., sum of boxes), with scores ranging from 0 to 18.

Further details regarding the assessment are provided in Appendix 2.

6.1.2.2 Mini-Mental State Examination

The MMSE is a brief cognitive screening measure and assesses orientation to time and place, immediate and delayed recall of words, attention and calculation, language (naming, comprehension and repetition), and spatial ability (copying a figure). The

MMSE will be administered to the subject and scored by a qualified, trained rater at screening, baseline and Weeks 4, 13 and 26 as indicated in the Schedule of Procedures (Table 3).

Further details regarding the assessment are provided in Appendix 3.

6.1.2.3 Alzheimer's Disease Co-operative Study Activity of Daily Living (ADCS-ADL)

The ADCS-ADL is a validated scale for measuring functional abilities in activities of daily living in subjects with Alzheimer's disease. It measures 6 basic and 17 instrumental activities of daily living and was specifically developed as a sensitive tool to track changes in functional performance in Alzheimer's disease over time. The basic activities include self-care tasks such as eating, walking, toileting, bathing, grooming, and dressing. The instrumental activities are more complex skills that are required to successfully live independently and include shopping, keeping appointments, traveling outside of home, making a meal or snack, reading, and writing. It will be administered to the subject's caregiver and scored by a qualified, trained rater at baseline and Weeks 4, 13 and 26 as indicated in the Schedule of Procedures (Table 3).

Further details regarding the assessment are provided in Appendix 4.

6.1.2.4 Neuropsychiatric Inventory

The NPI is an interview-based tool for assessing behavioral domains common in dementia (hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior, sleep and night-time behavior change, appetite and eating change) in terms of frequency, severity and distress.

The NPI will be administered to the subject's caregiver and scored by a qualified, trained rater at baseline and Weeks 4, 13 and 26 as indicated in the Schedule of Procedures (Table 3).

Further details regarding the assessment are provided in Appendix 5.

6.1.2.5 Cornell Scale for Depression and Dementia

The C-SDD was specifically developed to assess signs and symptoms of major depression in demented subjects.

The scale contains nineteen questions, each of which can be given a score ranging from 0 (absent) to 2 (severe) and is divided into five sub-scales:

- mood-related signs: anxiety, sadness, a minimal reaction to pleasant events and irritability
- behavioral disturbance: agitation, psychomotor retardation, multiple physical complaints and loss of interest
- physical signs: loss of appetite, weight loss and lack of energy
- cyclic functions: diurnal variation in mood, difficulty falling asleep, multiple awakening during the night and early morning awakening
- ideational disturbance: suicidal tendencies, low self-esteem, pessimism and mood-congruent delusions

The C-SDD will be administered through semi-structured interviews to the subjects and caregivers by a qualified trained rater at screening, baseline and Weeks 4, 13, 26 and 30 as indicated in the Schedule of Procedures (Table 3).

Further details regarding the assessment are provided in Appendix 6.

6.2 Safety Variables

6.2.1 Adverse Events

6.2.1.1 Collection of Adverse Events

It is the responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questionings e.g., "How have you felt since I last saw you?"

6.2.1.2 Definitions

An AE is any untoward medical-occurrence that occurs in a subject or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

All AEs, including intercurrent illnesses, occurring during the study will be documented in the eCRF. Concomitant illnesses, which existed before entry into the study, will not be considered AEs unless they worsen during the treatment period. All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, reported by subject), must be documented.

Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study drug has been administered.

6.2.1.3 Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the following categories:

- Seriousness
- Intensity
- Causality

6.2.1.3.1 Seriousness

A SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
  This means that the subject is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

6.2.1.3.2 Intensity

The intensity of each AE must be assessed by the Investigator using one of the following categories, and recorded in the eCRF:

- Mild: An AE that does not interfere with usual activities;
- Moderate: An AE that may cause some interference with usual activities;
- Severe: An AE that prevents usual activities and is usually incapacitating.

6.2.1.3.3 Causality

The Investigator will assess the causality/relationship between the study drug and the AE and record that assessment in the eCRF. Causality will be shown as a 'probably related', 'possibly related', 'unlikely related', 'not related' or 'not assessable'.

The most likely cause of an SAE (e.g., disease under treatment, concomitant disease, concomitant medication, other) will be indicated on the eCRF with details of the concomitant disease or medication or other cause.

The causal relationship of the AE to study drug will be described in terms of:

- Probable: the AE:
  - Follows a reasonable temporal sequence from administration of the study drug.
  - Could not be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administrated to the subject.
  - Disappears or decreases on cessation or reduction in dose of the study drug.
  - Follows a known pattern of response to the study drug.
  - Reappears or worsens upon rechallenge.
- Possible: the AE:
  - Follows a reasonable temporal sequence from administration of the study drug.
  - Could be reasonable explained by the subject's clinical state, environmental or toxic factors or other therapies administrated to the subject.
  - Follows a known pattern of response to the study drug.
- Unlikely: the AE
  - Does not follow a reasonable temporal sequence from administration of the study drug.

- Could be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administrated to the subject.
- Does not follow a known pattern of response to the study drug.
- Does not reappear or worsen upon rechallenge.

- Not related:
  - The AE does not meet the above criteria.
  - There is sufficient information that the etiology of the AE is not related to the study drug.
- Not assessable/unclassifiable:
  - The AE cannot be judged because of insufficient or contradictory information, which cannot be supplemented or verified.

The study conduct relatedness for SAEs will also be assessed and documented.

6.2.1.4 Recording Adverse Events

The period for adverse event reporting will extend from signing of informed consent until 14 days after the last study treatment administration (including placebo during the single-blind placebo washout period). Adverse events occurring after the end of the study should be reported to the Sponsor or Sponsor's designee by the Investigator if the Investigator considers there is a causal relationship with the study drug.

All AEs, regardless of the relationship to study drug, will be recorded in the eCRF. All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to study drug, action taken with the study drug, outcome, and whether the event is classified as serious.

6.2.1.5 Reporting Serious Adverse Events

The Investigator must report any SAEs to the [redacted] Clinical Studies Safety Center within 24 hours of becoming aware of the event.

When calling to report an SAE, state that you are reporting an SAE and give the Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.

The Investigator and the Sponsor (or Sponsor's designee) will review each SAE report and the Sponsor/[redacted] will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Sponsor (or Sponsor's designee) will evaluate the expectedness according to the reference document (Investigator Brochure or Summary of Product Characteristics). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

All SAEs will be recorded from signing of informed consent until 14 days after the last study treatment administration (including placebo during the single-blind placebo washout period). Serious AEs occurring after the end of the study and coming to the attention of the Investigator must be reported only if they are considered (in the opinion of the Investigator) causally-related to the investigational drug.

[redacted]

1. Telephone the Medical Monitor to inform her that you are faxing a SAE form. If the Medical Monitor is not available or you are calling after business hours (8:30 am to 5:30 pm Eastern time, Monday to Friday), leave a message in her voice mailbox.
2. Provide the Medical Monitor with the Principal Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.
3. Fax the SAE form and any supporting documentation to the Medical Monitor within 24 hours of becoming aware of the event.
4. After business hours, the Medical Monitor may be reached through [redacted] 24-hour answering service [redacted] Give the answering service the protocol number, the study drug name, and the Sponsoring pharmaceutical company.

6.2.1.6 Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

6.2.1.7 Pregnancy

The Sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the study drug.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

All pregnancies must be reported by the Investigator to the Sponsor/Medical Monitor on the initial pregnancy report form within 30 days after becoming aware of the pregnancy. The Investigator must follow up and document the course and the outcome of all pregnancies even if the subject was discontinued from the study or if the study has finished.

All outcomes of pregnancy must be reported by the Investigator to Sponsor/Medical Monitor on the pregnancy outcome report form within 30 days after he or she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy (including SAEs occurring after last administration of study drug) must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth,

neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

6.2.2 Laboratory Variables

Laboratory assessments will be performed by a central laboratory, as identified in the List of Study Personnel. For safety reasons, laboratory assessments may also be performed locally in case of an emergency.

Blood samples should be taken using standard venipuncture techniques. Further instructions are available in the Manual for laboratory evaluations.

The following laboratory variables will be determined at screening, baseline and Weeks 4 (liver function tests only), 13, 26 and 30 as indicated in the Schedule of Procedures (Table 3):

Table 2: Laboratory Assessments

Hematology:	erythrocytes hemoglobin hematocrit MCV MCH neutrophils eosinophils basophils lymphocytes monocytes platelets leukocytes	Endocrinology:	free T4 pregnancy test [a]
Clinical chemistry:	sodium potassium chloride calcium phosphorus glucose creatinine urea uric acid total bilirubin [b] direct bilirubin [b] indirect bilirubin [b] alkaline phosphatase [b] AST [b] ALT [b] GGT [b] albumin [b] total protein [b] triglycerides cholesterol calculated creatinine clearance vitamin B12 HbA1c	Urinalysis (macroscopy): Microscopy will be done if macroscopy is abnormal	appearance bilirubin color glucose ketone leukocytes nitrite occult blood protein reaction pH reducing substance specific gravity

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyl transpeptidase; HbA1c=glycated hemoglobin; MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin; T4=thyroxine.

a. At screening and Week 26 for women of childbearing potential, a urine pregnancy test will be performed. Positive result will be confirmed by a serum pregnancy test

b. At Week 4, only liver function tests will be performed.

All clinical laboratory test results outside of the reference range will be interpreted by the investigator using the following categories:

- Abnormal but not a clinically significant worsening

- Abnormal and a clinically significant worsening.

A laboratory test result that has significantly worsened (according to medical judgment) compared to the baseline result will be recorded on the eCRF as an AE.

Subjects with elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin, meeting any one of the following criteria should be withdrawn from the study as described in Section 4.3:

- ALT or AST ≥ 8x ULN;
- ALT or AST ≥ 5x ULN for more than 2 weeks;
- ALT or AST ≥ 3x ULN and total bilirubin ≥ 2x ULN at the same visit;
- ALT or AST ≥ 3x ULN with the appearance of symptoms indicating hepatitis (e.g., worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia).

6.2.3 Vital Signs

The following vital signs will be assessed at screening, baseline and Weeks 4, 13, 26 and 30 as indicated in the Schedule of Procedures (Table 3):

- Blood pressure (systolic and diastolic; mmHg)

Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to the assessment of blood pressure. The correct size of the blood pressure cuff and the correct positioning on the subjects' arm is essential to increase the accuracy of blood pressure measurements.

6.2.4 Electrocardiograms

Standard 12-lead ECGs will be performed at screening, baseline and Weeks 4, 13, 26 and 30 as indicated in the Schedule of Procedures (Table 3). For Weeks 4, 13 and 26, ECGs will be performed approximately 3 hours post study drug administration, the approximate time of maximum concentration of SUVN-502.

The ECGs will be performed according to the instructions in a separate ECG instruction manual provided by the central ECG vendor and reviewed by a central reviewer.

The ECG parameters (including heart rate and PR, RR, QRS, and QT intervals) will be assessed by central review using a central ECG vendor.

6.2.5 Physical and Neurological Examinations

Physical and neurological examinations, including weight, will be performed at screening, baseline and Weeks 4, 13, 26 and 30 as indicated in the Schedule of Procedures (Table 3).

A complete physical examination will be performed by the Principal Investigator. The following body systems should be included in the physical exam:

- Head, ear, nose, and throat
- Eyes
- Neck
- Cardiovascular system

- Respiratory system
- Abdomen
- Skin
- Extremities
- Neurological system
- Chest
- Musculoskeletal system

Examination of the breast, rectum, and urogenital system are at the PI's discretion (i.e., if clinically indicated). If a physical or neurological abnormality is noted post-treatment, the PI will indicate whether or not the result is clinically significant and if it constitutes an AE.

A general neurological exam will be performed by the Principal Investigator, as described in Appendix 7.

6.2.6 Additional Safety Assessments

6.2.6.1 Columbia Suicide Severity Rating Scale

Suicidal ideation and behavior will be prospectively assessed during the study using the C-SSRS. The C-SSRS (screening and since last visit versions) will be administered by a qualified trained rater at screening, baseline and Weeks 4, 13, 26, and 30, as indicated in the Schedule of Procedures (Table 3), as well as at unscheduled visits as clinically indicated. Site staff should review the contents of the C-SSRS for completeness and then transcribe the data to the eCRF.

Subjects who, at any time during this study, report an AE of suicidal ideation or behavior, either between visits or during visit interviews, must be assessed by trained raters and reviewed by an MD or a clinician PhD. Subjects who report suicidal ideation with intent, with or without a plan or method (i.e., a positive response to Items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior must be evaluated that day by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker or nurse practitioner. Only subjects whose suicidal ideation is passive, who expressly deny any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the course of the study may continue in the study; others must be discontinued from study participation and receive appropriate clinical follow-up care to ensure their safety.

All reports of suicidal ideation or behavior must be reported as an AE. Sites should indicate which health care professionals are to be responsible for acute care on-site and specify referral center(s) to be used for further evaluation.

Further details regarding the assessment are provided in Appendix 8. Additional detailed information concerning administration, scoring and recording will also be provided by the Rater Training Vendor.

6.3 Demographics and Baseline Characteristics

Demographics and Baseline Characteristics consist of those variables that are assessed only at screening/baseline.

6.3.1 Subject Demography

Subject demography consists of:

- Age at screening
- Height
- Race
- Sex

6.3.2 Disease History

For disease history the following will be documented:

- Date of first diagnosis
- Date of first treatment
- Date of additional treatment

6.3.3 Medical History

For the documentation of the medical history, any previous and concomitant diseases before screening will be documented.

The medical history will be obtained by interviewing the subject or by inspecting his/her medical records.

For coding of medical history, see Section 9.4.

6.3.4 Previous and Concomitant Medications

Previous and concomitant medication will be documented as described in Section 5.7.

6.4 Other Assessments

6.4.1 Screening Assessments

6.4.1.1 MRI and CT scan

Subjects who did not have an MRI or CT scan within the past 12 months will have a 1.5 Tesla or 3.0 Tesla MRI scan or a CT scan as part of screening. If an MRI or CT scan is required, the subject should be scheduled for a Screening MRI only after the Principal Investigator or trained designee has verified that the subject has met all of the inclusion and none of the exclusion criteria.

6.4.1.2 Modified Hachinski Ischemic Scale (MHIS)

The MHIS, a tool to identify the possibility of a vascular etiology for the subject's dementia, will be completed by a qualified, trained rater at the screening visit, as described in Appendix 9.

6.4.1.3 National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association Criteria for Probable Alzheimer's Disease

The NINCDS-ADRDA criteria for probable Alzheimer's disease will be reviewed at screening, as described in Appendix 10.

6.4.2 Apolipoprotein E Genotype Testing

At baseline, a blood sample will be drawn for APO-E genotype testing. Subjects (or caregiver) will be provided the results of the test at the conclusion of the study, upon request.

To obtain sufficient DNA for APO-E genotyping, a single blood sample of 4 mL will be drawn into the appropriate tube (see the Laboratory Manual for sample acquisition, shipping and labeling instructions).

6.4.3 Pharmacokinetics

Plasma samples will be analyzed for levels of SUVN-502 and M1 of SUVN-502 at steady state (Week 4 of treatment) and at Week 26 to gather information on population pharmacokinetics. Plasma samples will be analyzed for levels of donepezil and memantine at screening, Week 4 and at Week 26 to determine compliance with these study treatments.

At Weeks 4 and 26, plasma samples will be collected before study drugs are administered to the subjects. It is recommended, on the day prior to and/or day of visits where pharmacokinetic (PK) sampling is performed, that the date, time and frequency (qd or bid) of SUVN-502, donepezil HCl and memantine HCl administration be noted by the subject or the caregiver to determine the timing of last dose administered. This information will be reviewed during each study visit and entered into the eCRF.

Venous blood samples (approximately 6 mL) will be collected in Li-Heparin vacutainer, and centrifuged within 30 minutes of collection, for 10 min, at 3000 RPM at +4°C to obtain plasma samples. If a refrigerated centrifuge is not available at the site, samples can be centrifuged at ambient temperature. The blood sample should be kept on crushed ice until centrifuged. The plasma should be divided into 4 tubes:

- One tube will be used for plasma levels of SUVN-502 and M1 of SUVN-502.
- One tube will be used for plasma levels of donepezil and memantine.
- The remaining two tubes will serve as backup samples and should be shipped separately from the primary samples.

At screening, only 2 tubes are required for plasma levels of donepezil and memantine (1 primary sample and 1 backup sample).

All PK samples should be stored at -70°C.

On the day of sample collection, the primary samples should be shipped on dry ice to the bioanalytical lab.

If the study center has a -70°C freezer, backup samples should be stored at -70°C and shipped monthly on dry ice to the bioanalytical lab. If the study center does not have a -70°C freezer, backup samples should be stored at -20°C and shipped on dry ice to the bioanalytical lab, one day after the sample collection.

7 STUDY CONDUCT

7.1 Schedule of Procedures

Table 3: Schedule of Procedures

Study period	Screening	Baseline	Treatment Period		End of Treatment	Follow-up
Time	**Days -28 to -14[a]**	**Day 1[a]**	**Week 4 Day 28±2**	**Week 13 Day 91±2**	**Week 26 Day 182±3 or early withdrawal**	**Week 30 Day 210±2**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**
Procedures						
Informed Consent	X					
Inclusion / Exclusion Criteria	X	X				
Demographics, Medical History	X	X				
Prior and Concomitant Medications	X	X	X	X	X	X
MRI or CT Scan (if Necessary)	X					
Blood Sample for APO-E Genotype Testing		X				
Study Treatment Dispensation [b]		X	X	X	X	
MMSE and ADAS-Cog	X	X	X	X	X	
Modified Hachinski Ischemic Scale	X					
CDR-SB, ADCS-ADL, and NPI		X	X	X	X	
C-SDD	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X
Review of AEs	X	X	X	X	X	X
Laboratory Tests	X [c]	X	X [d]	X	X [c]	X
Blood Pressure Measurements	X	X	X	X	X	X
ECG	X	X	X [e]	X [e]	X [e]	X
Physical and Neurological Examination	X	X	X	X	X	X
Plasma Levels of SUVN-502 and M1 of SUVN-502			X [f]		X [f]	
Plasma Levels of Donepezil and Memantine	X		X [f]		X [f]	

Table 3: Schedule of Procedures (Continued)

ADAS-Cog=Alzheimer's Disease Assessment Scale; ADCS-ADL=Alzheimer's Disease Cooperative Study Activity of Daily Living; AE=adverse event; APO-E=Apolipoprotein E; CDR-SB=Clinical Dementia Rating Scale – Sum of Boxes; C-SDD=Cornell Scale of Depression and Dementia; C-SSRS=Columbia Suicide Severity Rating Scale; CT=Computed Tomography; ECG=Electrocardiogram; MHIS = Modified Hachinski Ischemic Scale; MMSE= Mini-Mental State Evaluation; MRI=Magnetic Resonance Imaging; NPI=Neuropsychiatric Inventory.

Note: *It is strongly recommended that one rater is assigned for each subject for each of the following assessment scales so that one rater scores a subject's assessment for the entire study: MMSE, ADAS-Cog, CDR-SB, ADCS-ADL, NPI, C-SDD, and C-SSRS.*

a. *For Screening and Baseline Visits, the following assessments, included in study entry criteria, should be performed first in order to limit the number of assessments performed for subjects who do not meet the study entry criteria: MMSE, the MHIS, C-SDD, C-SSRS, ECG, pregnancy test (for women of child bearing potential), and laboratory tests.*
b. *On the day of the study visits, subjects will be instructed not to take their treatment at home, as treatment will be dispensed at the study center.*
c. *A urine pregnancy test will be done at screening and Week 26 visit for women of childbearing potential. A positive urine test will be confirmed by a serum pregnancy test.*
d. *At Week 4, laboratory tests will only include liver function tests.*
e. *3 hours after study treatment administration, i.e. the approximate time of maximum concentration of SUVN-502.*
f. *Plasma samples for PK assessments will be collected before study drugs are administered to the subjects.*

7.2 Procedures by Visit

Visits should occur within ±2 days (except where noted) of the scheduled visit. All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 pm).

For Screening and Baseline Visits, the following assessments, included in study entry criteria, should be performed first in order to limit the number of assessments performed for subjects who do not meet the study entry criteria: MMSE, MHIS, C-SDD, C-SSRS, ECG, pregnancy test (for women of child bearing potential), and laboratory tests. It is strongly recommended that one rater is assigned for each subject for each of the following assessment scales so that one rater scores a subject's assessment for the entire study: MMSE, ADAS-Cog, CDR-SB, ADCS-ADL, NPI, C-SDD, and C-SSRS.

7.2.1 Screening (Visit 1, Day -28 to -14)

The screening visit (visit 1) will take place 14 to 28 days before the baseline visit. The following procedures will be performed:

- Obtain written informed consent;
- Inclusion/exclusion criteria review including
  - Demographics
  - NINCDS-ADRDA criteria
  - MMSE
  - C-SDD
  - MHIS
  - MRI or CT scan if not performed with the past 12 months
  - Medical history
  - Prior and concomitant treatment review
  - C-SSRS (screening version)
- AE review
- Physical and neurological examinations
- Blood pressure measurement
- ECG
- Blood and urine samples for clinical laboratory tests, including pregnancy test for women of childbearing potential
- Plasma sample for measurement of donepezil and memantine levels.
- ADAS-Cog

7.2.2 Baseline Visit (Visit 2, Day 1)

The following procedures will be performed at the baseline visit on Day 1 of the study:

- Inclusion/exclusion criteria review
- Medical history
- AE review
- Concomitant medications review

- Physical and neurological examinations
- Blood pressure measurement
- MMSE
- ADAS-Cog
- CDR-SB, ADCS-ADL, NPI and C-SDD
- C-SSRS (since last visit version)
- ECG
- Blood and urine samples for clinical laboratory tests
- Blood sample for APO-E genotype testing
- Study drug dispensation

7.2.3 Week 4 Visit (Visit 3, Day 28)

The following procedures will be performed at Week 4 (Day 28±2 days) of the study:

- AE review
- Concomitant medications review
- Plasma sample for measurement of SUVN-502, M1 of SUVN-502, donepezil and memantine levels
- Blood sample for liver function tests
- Study drug compliance check and dispensation
- Physical and neurological examinations
- Blood pressure measurement
- MMSE
- ADAS-Cog
- CDR-SB, ADCS-ADL, NPI and C-SDD
- C-SSRS (since last visit version)
- ECG 3 hours post-treatment

7.2.4 Week 13 Visit (Visit 4, Day 91)

The following procedures will be performed at Week 13 (Day 91±2 days) of the study:

- AE review
- Concomitant medications review
- Study drug compliance check and dispensation
- Physical and neurological examinations
- Blood pressure measurement
- Blood and urine samples for clinical laboratory tests
- MMSE
- ADAS-Cog
- CDR-SB, ADCS-ADL, NPI and C-SDD
- C-SSRS (since last visit version)

- ECG 3 hours post-treatment

7.2.5 Week 26 Visit (Visit 5, Day 182)

The following procedures will be performed at Week 26 (Day 182±3 days) of the study:

- AE review
- Concomitant medications review
- Plasma sample for measurement of SUVN-502, M1 of SUVN-502, donepezil and memantine levels
- Study drug compliance check and dispensation
- Blood and urine samples for clinical laboratory tests, including pregnancy test for women of childbearing potential
- Physical and neurological examinations
- Blood pressure measurement
- MMSE
- ADAS-Cog
- CDR-SB, ADCS-ADL, NPI and C-SDD
- C-SSRS (since last visit version)
- ECG 3 hours post-treatment

7.2.6 Week 30 Visit (Visit 6, Day 210)

The following procedures will be performed at Week 30 (Day 210 ±2 days) of the study:

- AE review
- Concomitant medications review
- Physical and neurological examinations
- Blood pressure measurement
- Blood and urine samples for clinical laboratory tests
- C-SDD
- C-SSRS (since last visit version)
- Study drug compliance check
- ECG

7.2.7 Early Termination and Follow-Up Visits

Subjects who discontinue early from the study should, if possible, have an Early Termination visit. This visit should take place as soon as possible after the subject stops taking study drug. The observations and procedures scheduled for Visit 5 (Week 26) should be performed at the Early Termination visit. If the subject agrees, he/she should return for a follow-up visit 4 weeks later. The observations and procedures scheduled for Visit 6 should be performed at the Follow-up visit.

8 STATISTICAL METHODS

The statistical considerations summarized in this section outline the plan for data analysis of this study.

Before unblinding, a separate statistical analysis plan (SAP) will be finalized, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described and justified in the final integrated clinical study report.

8.1 Study Subjects

8.1.1 Disposition of Subjects

The number and percentage of subjects entering and completing each phase of the study will be presented, stratified by treatment.

A subject who completes all visits up to Week 30, will be considered to have completed the study. For evaluation of efficacy, a completed subject is defined as any subject who completes all visits up to Week 26.

The disposition of subjects will also include information on the number and percentage of subjects who:

- Completed study drug and follow-up.
- Completed study drug but not follow-up.
- Withdrew from study drug but completed follow-up.
- Withdrew from study drug and from follow-up.

8.1.2 Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as "minor" or "major" in cooperation with the Sponsor. Major deviations from the protocol will lead to the exclusion of a subject from the Evaluable Population (EP). Deviations will be defined prior to unblinding.

8.1.3 Analysis Sets

Modified intent to treat (ITT) population:	All randomized subjects who receive at least one dose of study medication and have one post-baseline evaluation of the primary efficacy variable.
Evaluable Population (EP):	All randomized subjects who complete 26 weeks of treatment, are compliant with taking study medication (≥80%), and have no significant protocol deviations.
Safety Population (SP):	All randomized subjects who receive at least one dose of study medication.

Efficacy analyses will be performed on the modified ITT population and the Evaluable EP. The primary efficacy analysis will be based on the modified ITT population and a secondary analysis will also be performed based upon the EP, to assess the sensitivity of

the analysis to the choice of analysis set. All other secondary efficacy analyses will also be performed on the modified ITT population and the EP.

Safety analyses will be performed on the SP. Patients will be assigned to the treatment group based on the actual treatment received.

Demographic and baseline characteristics will be evaluated for the modified ITT population. If one or more subjects received incorrect study drug, these summaries will also be presented for the safety set.

8.2 General Considerations

All statistical tests will be two-sided and will be performed at the 5% level of significance, unless otherwise stated.

Continuous data will be summarized by treatment group using descriptive statistics (number, mean, median, standard deviation [SD], minimum, and maximum). Categorical data will be summarized by treatment group using frequency tables (frequencies and percent).

Analysis and data conventions:

Definition of baseline

The baseline assessment will be the latest, valid pre-dose assessment available.

Unscheduled assessments

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than one laboratory value is available for a given visit, the first valid observation will be used in summaries and all observations will be presented in listings. It is noted that invalid laboratory data may not be used (from hemolyzed samples, mishandled samples, quantity not sufficient, or other conditions that would render values invalid).

Missing data conventions

In general, data will not be imputed, unless stated otherwise. Imputation details will be in the SAP.

Pooling

Pooled sites will be used in the efficacy analyses. Sites with fewer than 5 subjects in any treatment group will be pooled together. Starting with the smallest site, pooling will be carried out with the next smallest site until the criteria for at least 5 subjects per treatment group have been met. If the pooled site is larger than 1.5x the largest site, pooling will be modified to create more than one pooled site. Details of the pooling will be documented prior to breaking the blind.

Outliers

Any outliers that are detected during the blind review of the data will be investigated. If necessary, queries will be issued to the Investigator, to either correct or confirm the outlier.

8.3 Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographic data, medical history, concomitant disease, and concomitant medication will be summarized using descriptive statistics, overall and stratified by treatment.

8.4 Treatment Compliance

Treatment Compliance is calculated as:

$$\frac{\text{Number of compliant days}}{\text{Expected number of compliant days}} \times 100\%$$

Number of compliant days is the number of days on which double-blind treatment was taken.

Expected number of compliant days is the number of days that double-blind treatment is scheduled based on the subject's duration of participation in the study, excluding the follow-up phase.

Treatment compliance will be summarized using descriptive statistics, stratified by treatment.

8.5 Efficacy Analyses

8.5.1 Primary Efficacy Analysis

8.5.1.1 Hypotheses to be Tested

The primary hypotheses will compare each dose of SUVN-502 with placebo. The null and alternative hypotheses to be tested are as follows:

$$Ho: \hat{\mu}_{SUVN-502\ 50\ mg} = \hat{\mu}_{Placebo}$$
$$Ha: \hat{\mu}_{SUVN-502\ 50\ mg} \neq \hat{\mu}_{Placebo}$$

and

$$Ho: \hat{\mu}_{SUVN-502\ 100\ mg} = \hat{\mu}_{Placebo}$$
$$Ha: \hat{\mu}_{SUVN-502\ 100\ mg} \neq \hat{\mu}_{Placebo}$$

where $\hat{\mu}$ is the mean change from baseline at week 26 for the ADAS-Cog score.

8.5.1.2 Statistical Methods

Change from baseline in ADAS-Cog score will be analyzed using a mixed effects model for repeated measures (MMRM) based on mITT population. The model will include fixed categorical factors for treatment, pooled site, week, and treatment-by-week interaction, as well as a continuous covariate of baseline score and the baseline score-by-week interaction. An unstructured covariance matrix will be used to model the variation within subject for the repeated measures. Missing data will be maintained as missing. The Least Square (LS) means of each treatment group, and the differences between each

SUVN-502 dose group (50 mg and 100 mg) and placebo will be reported for Weeks 4, 13 and 26, along with the corresponding 95% confidence intervals and p-values.

Sensitivity analyses to assess the impact of missing data will be conducted. These analyses will utilize the same methods as described previously. One analysis will use the EP analysis set and another will use the mITT population but will impute missing data using LOCF. If warranted, additional analyses may be investigated.

8.5.1.3 Subgroup Analyses

Exploratory subgroup analyses will be done according to the APO-E4 carrier status. The same MMRM model will be used with the addition of the following fixed categorical factors; APO-E4 carrier status and treatment-by-APO-E4 carrier status interaction.

8.5.2 Secondary Efficacy Analyses

Change from baseline in the secondary variables will be analyzed and reported in a similar manner as the primary efficacy variable, which will include:

- CDR-SB
- MMSE
- ADCS-ADL
- NPI
- C-SDD

8.6 Safety Analyses

8.6.1 Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of subjects reporting TEAEs, treatment emergent SAEs including deaths, TEAEs considered related to study drug and TEAEs leading to discontinuation from study drug will be tabulated by treatment, System Organ Class (SOC) and preferred term (PT).

The TEAEs by maximum severity and relationship will also be tabulated by treatment, SOC and PT.

A by-subject AE data listing (including TEAEs) will be provided.

8.6.2 Laboratory Assessments

Descriptive statistics by treatment will be provided for the observed values and changes from baseline at each scheduled visit with laboratory assessment.

A shift table (abnormal low, normal, abnormal high) will be provided for selected laboratory tests.

A by-subject laboratory assessments data listing will be provided.

8.6.3 Vital Signs

Descriptive statistics by treatment will be provided for the observed values and changes from baseline at each scheduled visit with vital signs assessment.

A by-subject vital signs data listing will be provided.

8.6.4 Electrocardiograms

A by-subject data listing of ECG parameters and findings will be provided.

Electrocardiogram parameters will be summarized by visit using appropriate descriptive statistics.

8.6.5 Physical and Neurological Examinations

A by-subject physical and neurological examinations data listing will be provided.

Results of the physical and neurological exams will be summarized by visit using appropriate descriptive statistics.

8.6.6 Additional Safety Assessments

A by-subject C-SSRS data listing will be provided.

Change from baseline in C-SSRS scores will be summarized by visit and differences between each SUVN-502 dose group (50 mg and 100 mg) and placebo will be reported for Weeks 4, 13 and 26.

8.7 Pharmacokinetics Analyses

Concentration data will be summarized for SUVN-502 and M1 of SUVN-502 for each treatment group, by visit, using descriptive statistics.

Concentration data for donepezil and memantine will be summarized for each treatment group, by visit, using descriptive statistics. These summaries will be based on the SP.

8.8 Interim Analyses

No interim analysis is planned for this study.

8.9 Determination of Sample Size

A total of 537 subjects will be randomized into one of three treatment groups, SUVN-502 (50 mg), SUVN-502 (100 mg) or placebo (179 subjects per group). With a sample size of 537 subjects, there is at least 80% power to detect a 2-point drug-placebo difference on the ADAS-Cog with a standard deviation of 6, assuming a two-sided 5% significance level and a drop-out rate of 20% or less.

9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1 Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation. Investigators, whose sites are well known to the Sponsor and Sponsor's designee and meet specific criteria, can be qualified by telephone interview.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the eCRF for this study must be consistent with the subjects' source documentation (i.e., medical records).

9.1.1 Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manger will raise a query in the electronic data capture (EDC) application. The appropriate staff at the study site will answer queries sent to the investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

9.2 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the eCRFs. All source documents from which eCRF entries are derived should be placed in the subject's medical records. Measurements for which source documents are usually available include laboratory assessments, ECG recordings, MRI and CT scans.

Data that will be entered directly into the eCRF (i.e., for which there is no prior written or electronic record of data, such as Quality of Life assessments) are considered to be source data.

The original eCRF entries for each subject may be checked against source documents at the study site during monitoring visits by the [redacted] site monitor.

Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in a training manual and eCRF entry guidelines. In addition, site personnel will receive training on the eCRF.

9.2.1 Data Collection

The Investigators (and appropriately authorized staff) will be given access to an online web−based EDC) system which is 21 CFR Part 11 compliant. This system is specifically designed for the collection of the clinical data in electronic format. Access and right to the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each subject included in the study and should reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or immediately after the subject's visit or assessment. The investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the eCRF.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on−line directly by the Investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the investigator will be required to electronically sign off the clinical data.

Data about all study drugs dispensed to the subject and any dosage changes will be tracked on the eCRF.

9.3 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, Regulatory Authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures [redacted] and the Sponsor of the necessary support at all times.

9.4 Data Processing

All data will be entered by site personnel into the eCRF (as detailed in Section 9.2.1).

The data-review and data-handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/correction sheets for unresolved queries will be sent to the study monitors for resolution with the Investigator. The database will be updated on the basis of signed corrections.

Previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Reference List (DRL), which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

Previous and concomitant diseases as well as AEs will be coded with MedDRA.

The versions of the coding dictionaries will be provided in the Clinical Study Report.

9.5 Archiving Study Records

According to International Conference on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

9.6 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the Good Clinical Practice guidelines of the ICH, and of the Declaration of Helsinki (1996). The study also will be carried out in keeping with local legal requirements.

9.7 Informed Consent

Before each subject is admitted to the study, informed consent will be obtained from the subject (or his/her legally authorized representative) and from the caregiver according to the regulatory and legal requirements of the participating country. This consent form must be dated and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

9.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). Following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted.

Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.9 Data and Safety Monitoring Board

A DSMB will be assembled to periodically review and evaluate accumulated study data for subject safety, study conduct and progress. The DSMB will have the responsibility to make recommendations concerning continuation, modification, or termination of the study based on their independent evaluation of all study related safety data. The DSMB role and activities are described in detail in the DSMB charter. The DSMB will consist of a chairperson and at least 2 additional members, including 1 statistician.

9.10 Duration of the Study

For an individual subject, the maximum duration of the study for each subject will be up to 34 weeks (including up to 4 weeks for screening, up to 26 weeks of treatment and up to 4 weeks follow-up).

9.11 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- Failure to enroll subjects at an acceptable rate.
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.
- A recommendation from the DSMB to terminate the study.

If the study is terminated prematurely, all withdrawn subjects should attend a final visit with the same procedures as the Week 26 visit.

9.12 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be identified on eCRF and other documents submitted to [redacted] by their subject number, initials and/or birth date, not by name. Documents not to be submitted to [redacted] that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

9.13 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties – Regulatory Authorities, Investigators, and IRB/IECs, as required.

A significant safety issue is one that has a significant impact on the course of the clinical study or program (including the potential for suspension of the development program or amendments to protocols) or warrants immediate update of informed consent.

10 REFERENCE LIST

1. World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

2. Wilkinson D., Windfeld K, Colding-Jørgensen E. 2014. Safety and efficacy of idalopirdine, a 5-HT6 receptor antagonist, in patients with moderate Alzheimer's disease (LADDER): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 13: 1092–99

3. The Food and Drug Administration Guidance for Industry: Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease. Draft Guidance. February 2013.

4. Committee for Medicinal Products for Human Use [CHMP] Guideline on Medicinal Products for the Treatment of Alzheimer's Disease and Other Dementias. July 2008, CPMP/EWP/553/95 Rev. 1

11 APPENDICES

APPENDIX 1:
ALZHEIMER'S DISEASE ASSESSMENT SCALE - COGNITIVE BEHAVIOR (ADAS-Cog)

Used with permission from the NIA Alzheimer's Disease Cooperative Study [redacted]

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. WORD RECALL TASK (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.*

Trial 1	**Word recalled correctly?**	
	Yes	**No**
Butter		
Arm		
Shore		
Letter		
Queen		
Cabin		
Pole		
Ticket		
Grass		
Engine		
Total Not Recalled		

Trial 2	**Word recalled correctly?**	
	Yes	**No**
Pole		
Letter		
Butter		
Queen		
Arm		
Shore		
Grass		
Cabin		
Ticket		
Engine		
Total Not Recalled		

Trial 3	**Word recalled correctly?**	
	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)**

2. 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	Command performed correctly?	
	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

3. 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** Figures 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-dimensional, 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

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.*

Item	Acceptable Clue	Response correct?	
		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?"**

Fingers	Response correct?	
	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 8½" × 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.*

Component	Action correct?	
	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 TASK (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 the 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.

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 **(Enter maximum score of "12")**

Word	Check Subject Response		
	Yes	**No**	***R**
Nurse			
Magazine			
Wizard			
Van			
Leopard			
Sale			
Sea			
Train			
Coin			
Ship			
Institution			
Map			
Axe			
Board			
Carrot			
Milk			
Volume			
Forrest			
Anchor			
Gem			
Cat			
Fund			
Edge			
Cake			
Total Not Recalled: (Maximum 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**	= 1 or 2 instances 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 content 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

APPENDIX 2:
CLINICAL DEMENTIA RATING SCALE

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 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?
   ☐ Yes ☐ No
3. Can he/she remember a short list of items (shopping)?
   ☐ Yes ☐ No
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 source's opinion)
   ☐ Yes ☐ No
6. Does he/she completely forget a major event (e.g. a trip, a party, a family wedding) within a few weeks of the event?
   ☐ Yes ☐ No
7. Does he/she forget pertinent details about the major event?
   ☐ Yes ☐ No
8. Does he/she completely forget important information of the distant past (e.g. date of birth, wedding date, place of employment)?
   ☐ Yes ☐ No
9. Tell me about some recent event in his/her life 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 patient 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 patient was not employed)?
14. What was his/her major job (or spouse's job if patient was not employed)?
15. When did he/she (or spouse) retire and why?

ORIENTATION QUESTIONS FOR INFORMANT:

How often does he/she know 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 around 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 around indoors?
   □ Usually □ Sometimes □ Rarely □ Don't Know

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. calculate change, leave a small tip):
   - □ No loss
   - □ Some loss
   - □ Severe loss
3. Rate his/her ability to handle complicated financial or business transactions (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

COMMUNITY AFFAIRS QUESTIONS FOR INFORMANT

Occupational ☐ Yes ☐ No ☐ N/A

1. Is the patient still working?
   ☐ If not applicable, proceed to item 4
   ☐ If yes, proceed to item 3
   ☐ If no, proceed to item 2
2. Did memory or thinking problems contribute to the patient's decision to retire? (Question 4 is next)
   ☐ Yes
   ☐ No
   ☐ Don't know
3. Does the patient have significant difficulty in his/her job because of problems with memory or thinking?
   ☐ Rarely or Never
   ☐ Sometimes
   ☐ Usually
   ☐ Don't Know
4. Did he/she ever drive a car?
   ☐ Yes ☐ No
   Does the patient 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)
   ☐ Sometime (Shops for limited number of items: buys duplicate items or forgets needed items)
   ☐ Usually
   ☐ Don't Know
7. Is he/she able to carry out activities independently 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 salons)

- ☐ Usually (Meaningful participation in activities e.g. voting)
- ☐ Don't Know

8. Is he/she taken to social functions outside the family home?
   ☐ Yes ☐ No
   If no, why not _____
9. Would a casual observer of the patient's behavior think the patient was ill?
   ☐ Yes ☐ No
10. If in a 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 friends or family, political activities, professional organizations such as bar association, other professional groups, social clubs, service organizations, educational programs.

HOME AND HOBBIES QUESTIONS FOR INFORMANT

*Please add notes if needed to clarify patient'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 tasks? _____
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 a nursing home, what can he/she no longer do well (Home and Hobbies)? _____

Everyday Activities (The Dementia Scale of Blessed):

4. Ability to perform household tasks
   - ☐ 0 (No Loss)
   - ☐ 0.5
   - ☐ 1 (Severe Loss)

   Please describe _____
5. Is he/she able to perform household tasks at the level of:
   (Pick one. The 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, washed 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 patient's level of impairment in HOME & HOBBIES?

If not, please probe further.

Household Tasks: such as cooking, laundry, cleaning, grocery shopping, taking out garbage, front and backyard work, simple care maintenance and basic home repair.

Hobbies: Sewing, painting, handicrafts, reading, entertaining, photography gardening, going to theatre or concert, woodworking, participating in sports

PERSONAL CARE QUESTIONS FOR INFORMANT:

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

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

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

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

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

---

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

MEMORY QUESTIONS FOR PATIENT

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 patient 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 attempts)

Elements	1	2	3	4	5
	John	Brown	42	Market	St Sydney
	John	Brown	42	Market	St Sydney
	John	Brown	42	Market	St Sydney

(Underline elements repeated correctly in each attempt)

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's if not employed)?
8. What was your last major job (or spouse's if not employed)?
9. When did you (or your 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	St Sydney

(Underline elements repeated correctly.)

ORIENTATION QUESTIONS FOR PATIENT:

Record the patient'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 patient know who the informant is (in your judgment)? _____ ☐ Correct ☐ Incorrect

JUDGEMENT AND PROBLEM SOLVING QUESTIONS FOR THE PATIENT:

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

SIMILARITIES:

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

"How are these things alike?" Patient's Response

1. turnip.....cauliflower
   (0 = vegetables)
   (1 = edible foods, 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?" Patient's Response

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 five cent pieces in a dollar?
   □ Correct □ Incorrect
6. How many 20 cent pieces in $5.40?
   □ Correct □ Incorrect
7. Subtract 3 from 20 and keep subtracting 3 from each new number all the way down.
   □ Correct □ Incorrect

JUDGEMENT:

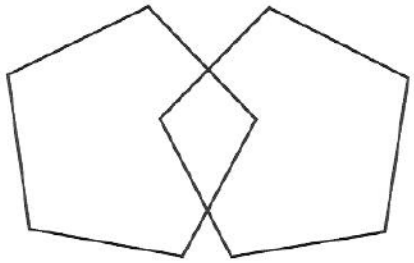
8. Upon arriving in a strange city, how would you locate a friend that you wished to see?
   (0 = try the telephone book, city directory, go to the courthouse for a directory; call a mutual friend)
   (1 = call the police, call the operator (usually will not give address)
   (2 = no clear response)
9. Patient'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)	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 fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented to place of 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 and handles business and financial affairs well; judgment good in relation to past performances	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 the family home independent function	Appears too ill to be taken to functions outside the family home
Home & Hobbies	Life at home, hobbies and intellectual interests well maintained	Life at home, hobbies and intellectual interest slightly impaired	Mild but definite impairment of function at home more difficult tasks abandoned; more complicated hobbies and interests abandoned	Only simple tasks preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Full 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.

APPENDIX 3:
MINI-MENTAL STATE EXAMINATION

Maximum Score	Patient's Score	Questions
5		"What is the (year) (season) (date) (day) (month)?"
5		"Where are we: (country) (city) (part of city) (number of flat/house) (name of street)?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The rater repeats them until patient learns all of them if possible. Number of trials: __
5		"I would like you to count backward from 100 by sevens" (93, 86, 79, 72, 65, …). Stop after 5 answers.
3		"Earlier I told you the name of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands or buts' "
3		"Take the paper in your right hand, fold it in half and put it on the floor" (The rater gives the patient a piece of blank paper.)
1		"Please read this and do what it says:" (Written instruction is "Close your eyes".)
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The rater gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

APPENDIX 4:
ALZHEIMER'S DISEASE CO-OPERATIVE STUDY ACTIVITY OF DAILY LIVING

NOTES:

(1) {P} refers to the participant and should be replaced by the participant's name or relationship to the study partner each time an ADL question is asked of the study partner.

(2) This ADL inventory must be given in the format of an interview of the study partner, either directly or by telephone. The form should NOT be given to a study partner to complete on his/her own.

READ THE FOLLOWING INSTRUCTIONS TO THE STUDY PARTNER:

I am going to ask you about a number of daily activities that {P} may have performed during the past 4 weeks. Please tell me about {P}'s actual performance, not about what he/she could have done if an opportunity had arisen. For each activity that {P} attempted, I'm going to ask you to choose one out of a number of descriptions that best fits his/her most usual performance.

For some activities, I'll ask about whether {P} performed independently, or with supervision or help. Let me explain how we are defining these words:

- **Independently** means that {P} completed the activity without being helped. We still consider it independent if {P} was reminded or prompted to get started, or received a little prompting while performing the activity.
- **With supervision** means that {P} required verbal reminders and instructions while doing the activity.
- **With help** means that {P} was given some degree of physical assistance by another person to perform the activity.

INSTRUCTIONS FOR THE RATER:

If the study partner states that {P} had no opportunity to perform the task during the past four weeks (e.g., {P} did not have access to a telephone, therefore could not possibly make phone calls), the response should be recorded as 'no.'

If either the study partner's answer or the questionnaire is unclear, please make notes on the case report form detailing the problem.

For questions regarding specific ADL items, please refer to the ADL Response Card.

Instructions: For each question, use the subject's name where {P} appears.

Before beginning, read the questionnaire guidelines to the informant.

1. Regarding **eating**, which best describes {P} usual performance during the past 4 weeks?
   - 3 ☐ ate without physical help, and used a knife
   - 2 ☐ used a fork or spoon, but not a knife, to eat
   - 1 ☐ used fingers to eat
   - 0 ☐ usually or always was fed by someone else
2. Regarding **walking** (or getting around in a wheelchair), in the past 4 weeks, which best describes his/her **optimal performance**:
   - 3 ☐ mobile outside of home without physical help
   - 2 ☐ mobile across a room without physical help
   - 1 ☐ transferred from bed to chair without help
   - 0 ☐ required physical help to walk or transfer
3. Regarding bowel and bladder function **at the toilet**, which best describes his/her **usual** performance in the past 4 weeks:
   - 3 ☐ did everything necessary without supervision or physical help
   - 2 ☐ needed supervision, but no physical help
   - 1 ☐ needed physical help, and was usually continent
   - 0 ☐ needed physical help, and was usually incontinent
4. Regarding **bathing**, in the past 4 weeks, which best describes his/her **usual performance**:
   - 3 ☐ bathed without reminding or physical help
   - 2 ☐ no physical help, but needed supervision/reminders to bathe completely
   - 1 ☐ needed minor physical help (e.g., with washing hair) to bathe completely
   - 0 ☐ needed to be bathed completely
5. Regarding **grooming**, in the past 4 weeks, which best describes his/her **optimal performance**:
   - 3 ☐ cleaned and cut fingernails without physical help
   - 2 ☐ brushed or combed hair without physical help
   - 1 ☐ kept face and hands clean without physical help
   - 0 ☐ needed help for grooming of hair, face, hands, and fingernails

6a. Regarding **dressing**, in the past 4 weeks, which best describes his/her **usual performance** when **selecting his/her first set of clothes** for the day:
   - 3 ☐ without supervision or help
   - 2 ☐ with supervision
   - 1 ☐ with physical help
   - 0 ☐ did not select his/her clothes for the day
   - 0 ☐ don't know

6b. Regarding **physically getting dressed**, which best describes his/her **usual performance** in the past 4 weeks:

4 ☐ dressed completely without supervision or physical help
3 ☐ dressed completely with supervision, but without help
2 ☐ needed physical help only for buttons, clasps, or shoelaces
1 ☐ dressed without help if clothes needed no fastening or buttoning
0 ☐ always needed help, regardless of the type of clothing
0 ☐ don't know

7. Regarding **telephone usage** in the past 4 weeks, which best describes his/her **highest level of performance**:

5 ☐ made calls after looking up numbers in white or yellow pages, or by dialing directory assistance
4 ☐ made calls only to well-known numbers, without referring to a directory or list
3 ☐ made calls only to well-known numbers, by using a directory, list, or pre-programmed numbers
2 ☐ answered the phone; did not make calls
1 ☐ did not answer the phone, but spoke when put on the line
0 ☐ did not use the phone
0 ☐ don't know

8. During the past 4 weeks, did {P} watch **television**?

☐ yes
☐ no
☐ don't know

If yes, ask all questions:

a. Did {P} usually select or ask for different programs or his/her favorite show?

1 ☐ yes
0 ☐ no
0 ☐ don't know

b. Did {P} usually talk about the content of a program while watching it?

1 ☐ yes
0 ☐ no
0 ☐ don't know

c. Did {P} talk about the content of a program within a day (24 hours) after watching it?

1 ☐ yes
0 ☐ no
0 ☐ don't know

9. During the past 4 weeks, did {P} ever appear to pay attention to **conversation or small talk** for at least 5 minutes, which best describes his/her **usual degree of participation**:

   Note: {P} did not need to initiate the conversation.

   3 ☐ usually said things that were related to the topic

   2 ☐ usually said things that were not related to the topic

   1 ☐ rarely or never spoke

   0 ☐ did not participate in conversations or small talk

   0 ☐ don't know

10. During the past 4 weeks, which best describes how {P} **usually cleared dishes from the table** after a meal or snack:

   3 ☐ without supervision or help

   2 ☐ with supervision

   1 ☐ with physical help

   0 ☐ did not clear dishes

   0 ☐ don't know

11. During the past 4 weeks, which best describes how {P} **usually managed to find his/her personal belongings** at home:

   3 ☐ without supervision or help

   2 ☐ with supervision

   1 ☐ with physical help

   0 ☐ did not find personal belongings

   0 ☐ don't know

12. During the past 4 weeks, which best describes {P}'s **highest level of performance** when **obtaining a hot or cold beverage** for him/herself:

   3 ☐ made a hot beverage, usually without physical help

   2 ☐ made a hot beverage, usually if someone else heated the water

   1 ☐ obtained a cold beverage, usually without physical help

   0 ☐ did not obtain a beverage for him/herself

   0 ☐ don't know

13. During the past 4 weeks, which best describes {P}'s **highest level of performance** when **making him/herself a meal or snack** at home:

   4 ☐ cooked or microwaved food, with little or no help

   3 ☐ cooked or microwaved food, with extensive help

   2 ☐ mixed or combined food items for a meal or snack, without cooking or microwaving (e.g., made a sandwich}

   1 ☐ obtained food on his/her own, without mixing or cooking it

   0 ☐ did not make him/herself a meal or snack

   0 ☐ don't know

14. During the past 4 weeks, which best describes how {P} **usually disposed of garbage or litter** in the appropriate place or container at home:

3 ☐ without supervision or help

2 ☐ with supervision

1 ☐ with physical help

0 ☐ did not dispose of garbage or litter in an appropriate place or container

0 ☐ don't know

15. During the past 4 weeks, which best describes {P}'s **optimal performance** when **getting around (or traveling) outside of his/her home**:

4 ☐ alone, went at least 1 mile away from home

3 ☐ alone, but remained within 1 mile of home

2 ☐ only when accompanied and supervised, regardless of the trip

1 ☐ only with physical help, regardless of the trip

0 ☐ did not get around (or travel) outside of his/her home

0 ☐ don't know

16a. On **shopping trips** during the past 4 weeks, which best describes how {P} **usually selected items**:

3 ☐ without supervision or physical help

2 ☐ with some supervision or physical help

1 ☐ not at all, or selected mainly random or inappropriate items

0 ☐ did not go shopping

0 ☐ don't know

16b. On **shopping trips** during the past 4 weeks, did {P} **usually pay for items without supervision or physical help**?

1 ☐ yes

0 ☐ no

0 ☐ did not go shopping

0 ☐ don't know

17. During the past 4 weeks, when keeping appointments or meetings with other people such as relatives, a doctor, the hairdresser, etc., which best describes {P}'s **awareness of the appointment or meeting ahead of time**:

3 ☐ usually remembered, may have needed written reminders e.g. notes, a diary, or calendar

2 ☐ only remembered the appointment after verbal reminders on the day

1 ☐ usually did not remember, in spite of verbal reminders on the day

0 ☐ did not keep any appointments or meetings

0 ☐ don't know

18. During the past 4 weeks, was {P} **ever left on his/her own**?

Note: *Being taken to day care or having a sitter at home does not constitute being left alone.*

☐ yes

☐ no

☐ don't know

☐ not applicable – {P} is institutionalized

If yes, ask all questions:

a. Was {P} left away from home, for 15 minutes or longer, during the day?

1 ☐ yes

0 ☐ no

0 ☐ don't know

b. Was {P] left at home, for an hour or longer, during the day?

1 ☐ yes

0 ☐ no

0 ☐ don't know

c. Was {P] left at home, for less than 1 hour, during the day?

1 ☐ yes

0 ☐ no

0 ☐ don't know

19. During the past 4 weeks, did {P} **talk about current events**?

Note: *This means events or incidents that occurred during the past month.*

☐ yes

☐ no

☐ don't know

If yes, ask all questions:

a. Did {P} talk about events that: he/she heard or read about or saw on TV but did not take part in?

1 ☐ yes

0 ☐ no

0 ☐ don't know

b. Did {P} talk about events that: he/she took part in outside home involving family, friends, or neighbors?

1 ☐ yes

0 ☐ no

0 ☐ don't know

c Did {P} talk about events that: occurred at home that he/she took part in or watched?

1 ☐yes
0 ☐no
0 ☐don't know

20a. Did {P} **usually talk about details of what he/she read while or shortly (less than 1 hour) after reading**?

1 ☐yes
0 ☐no
0 ☐don't know

20b. Did {P} **usually talk about what he/she read 1 hour or longer after reading**?

1 ☐yes
0 ☐no
0 ☐don't know

21. During the past 4 weeks, which best describes the **most complicated things that {P} wrote down**:

3 ☐ letters or long notes that other people understood
2 ☐ short notes or messages that other people understood
1 ☐ his/her signature or name
0 ☐ did not write things down
0 ☐ don't know

22. During the past 4 weeks, which best describes how {P} **usually performed** his/her **most common pastime, hobby, or game**:

Note: *Walking does not count as a pastime/hobby for this scale. Examples include card or board games (including bridge, chess, checkers), bingo, crosswords, art, musical instrument, knitting, sewing, reading, gardening, golf, tennis, workshop, fishing.*

3 ☐ without supervision or help
2 ☐ with supervision
1 ☐ with physical help
0 ☐ did not perform any pastimes, hobbies, or games
0 ☐ don't know

If {P} performed hobbies/pastimes, were they performed only at day care?

☐ yes
☐ no

23. Regarding the use of a **household appliance to do chores** during the past 4 weeks, which best describes how {P} **usually used the most common appliances**:

Note: *This does not include a TV. Examples include washer, dryer, vacuum, dishwasher, toaster, toaster oven, range, microwave, food processor.*

4 ☐ without help, operating more than on-off controls if needed

3 ☐ without help, but operated only on/off controls

2 ☐ with supervision, but no physical help

1 ☐ with physical help

0 ☐ did not use a household appliance to do chores

0 ☐ don't know

Total Score (0-78): ___

Number of "Don't Know" Responses: ___

APPENDIX 5:
NEUROPSYCHIATRIC INVENTORY 12-ITEM

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.

☐ Yes (If yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question)
☐ NA

1. Does the patient believe that he/she is in danger - that others are planning to hurt him/her?
   ☐ Yes ☐No
2. Does the patient believe that others are stealing from him/her?
   ☐ Yes ☐No
3. Does the patient believe that his/her spouse is having an affair?
   ☐ Yes ☐No
4. Does the patient believe that unwelcome guests are living in his/her house?
   ☐ Yes ☐No
5. Does the patient believe that his/her spouse or others are not who they claim to be?
   ☐ Yes ☐No
6. Does the patient believe that his/her house is not his/her home?
   ☐ Yes ☐No
7. Does the patient believe that family members plan to abandon him/her?
   ☐ Yes ☐No
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?)
   ☐ Yes ☐No
9. Does the patient believe any other unusual things that I haven't asked about?
   ☐ Yes ☐No

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

Frequency:

☐ 1. Rarely– less than once per week
☐ 2. Sometimes– about once per week
☐ 3. Often– several times per week but less than every day
☐ 4. Very often– once or more per day

Severity:

☐ 1. Mild– delusions present but seem harmless and produce little distress in the patient.
☐ 2.Moderate – delusions are distressing and disruptive.
☐ 3. Severe– 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 (almost no change in work routine)
☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

B. HALLUCINATIONS (NA)

Does the patient have hallucinations such as seeing false visions or hearing false voices? Does he/she seem to see, hear or experience things that are not present? By this question we do not mean just mistaken beliefs 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.

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question)
☐ N/A

1. Does the patient describe hearing voices or act as if he/she hears voices?
   ☐ Yes ☐No
2. Does the patient talk to people who are not there?
   ☐ Yes ☐No
3. Does he/she describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights, etc.)?
   ☐ Yes ☐No
4. Does he/she report smelling odors not smelled by others?
   ☐ Yes ☐No
5. Does he/she describe feeling things on his/her skin or otherwise appear to be feeling things crawling or touching him/her?
   ☐ Yes ☐No
6. Does he/she describe tastes that are without any known cause?
   ☐ Yes ☐No
7. Does he/she describe any other unusual sensory experiences?
   ☐ Yes ☐No

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

Frequency:

☐ 1. Rarely– less than once per week.
☐ 2. Sometimes– about once per week.
☐ 3. Often– several times per week but less than every day.
☐ 4. Very often– once or more per day.

Severity:

☐ 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. Severe– 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 (almost no change in work routine)
☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

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?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question)
☐ N/A

1. Does the patient get upset with those trying to care for him/her or resist activities such as bathing or changing clothes?
   ☐ Yes ☐No
2. Is the patient stubborn, having to have things his/her way?
   ☐ Yes ☐No
3. Is the patient uncooperative, resistive to help from others?
   ☐ Yes ☐No
4. Does the patient have any other behaviors that make him/her hard to handle?
   ☐ Yes ☐No
5. Does the patient shout or curse angrily?
   ☐ Yes ☐No
6. Does the patient slam doors, kick furniture, throw things?
   ☐ Yes ☐No
7. Does the patient attempt to hurt or hit others?
   ☐ Yes ☐No
8. Does the patient have any other aggressive or agitated behaviors?
   ☐ Yes ☐No

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

Frequency:

☐ 1. Rarely– less than once per week.
☐ 2. Sometimes – about once per week.
☐ 3. Often– several times per week but less than every day.
☐ 4. Very often– once or more per day.

Severity:

☐ 1. Mild– agitation is disruptive but can be managed with redirection or reassurance.

☐ 2. Moderate– agitation is disruptive and difficult to redirect or control.

☐ 3. Severe– 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 (almost no change in work routine)

☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)

☐ 3. Moderately (disrupts work routine, requires time rebudgeting)

☐ 4.Severely (disruptive, upsetting to staff and other residents, major time infringement)

☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

D. DEPRESSION/DYSPHORIA (NA)

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

☐ Yes (if yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

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

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

Frequency:

☐ 1. Rarely– less than once per week.

☐ 2. Sometimes– about once per week.

☐ 3. Often– several times per week but less than every day.

☐ 4.Very often – essentially continuously present.

Severity:

☐ 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. Severe– 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 (almost no change in work routine)

☐2. Mildly (almost no change in work routine but little time rebudgeting required)

☐ 3. Moderately (disrupts work routine, requires time rebudgeting)

☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)

☐ 5. VerySeverely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

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?

☐ Yes (if yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

1. Does the patient say that he/she is worried about planned events?
   ☐ Yes ☐No
2. Does the patient have periods of feeling shaky, unable to relax, or feeling excessively tense?
   ☐ Yes ☐No
3. Does the patient have periods of [or complain of] shortness of breath, gasping, or sighing for no apparent reason other than nervousness?
   ☐ Yes ☐No
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)
   ☐ Yes ☐No
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?
   ☐ Yes ☐No
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?)
   ☐ Yes ☐No
7. Does the patient show any other signs of anxiety?
   ☐ Yes ☐No

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

Frequency:

☐ 1. Rarely– less than once per week.

☐ 2.Sometimes – about once per week.

☐ 3. Often– several times per week but less than every day.

☐ 4. Very often– once or more per day.

Severity:

☐ 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. Severe– 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 (almost no change in work routine)

☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)

☐ 3. Moderately (disrupts work routine, requires time rebudgeting)

☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)

☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

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.

☐ Yes (if yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

1. Does the patient appear to feel too good or to be too happy, different from his/her usual self?
   ☐ Yes ☐No
2. Does the patient find humor and laugh at things that others do not find funny?
   ☐ Yes ☐No
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)?
   ☐ Yes ☐No
4. Does the patient tell jokes or make remarks that are not funny to others but seem funny to him/her?
   ☐ Yes ☐No
5. Does he/she play childish pranks such as pinching or playing "keep away" for the fun of it?
   ☐ Yes☐ No
6. Does the patient "talk big" or claim to have more abilities or wealth than is true?
   ☐ Yes ☐No
7. Does the patient show any other signs of feeling too good or being too happy?
   ☐ Yes ☐No

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

Frequency:

☐ 1. Rarely– less than once per week.

☐ 2. Sometimes– about once per week.

☐ 3. Often– several times per week but less than every day.

☐ 4. Very often– essentially continuously present.

Severity:

☐ 1. Mild– elation is notable to friends and family but is not disruptive.

☐ 2. Moderate– elation is notably abnormal.

☐ 3. Severe– 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 (almost no change in work routine)

☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)

☐ 3. Moderately (disrupts work routine, requires timerebudgeting)

☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)

☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

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?

☐ Yes (if yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

1. Does the patient seem less spontaneous and less active than usual?
   ☐ Yes☐ No
2. Is the patient less likely to initiate a conversation?
   ☐ Yes ☐No
3. Is the patient less affectionate or lacking in emotions when compared to his/her usual self?
   ☐ Yes ☐No
4. Does the patient contribute less to household chores?
   ☐ Yes ☐No
5. Does the patient seem less interested in the activities and plans of others?
   ☐ Yes ☐No
6. Has the patient lost interest in friends and family members?
   ☐ Yes ☐No
7. Is the patient less enthusiastic about his/her usual interests? ☐
   Yes ☐ No

8. Does the patient show any other signs that he/she doesn't care about doing new things?
☐ Yes ☐No

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

Frequency:

☐ 1. Rarely– less than once per week.

☐2. Sometimes – about once per week.

☐ 3. Often– several times per week but less than every day.

☐ 4. Very often– nearly always present.

Severity:

☐ 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. Severe– 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 (almost no change in work routine)

☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)

☐ 3. Moderately (disrupts work routine, requires time rebudgeting)

☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)

☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

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?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question)
☐ N/A

1. Does the patient act impulsively without appearing to consider the consequences?
☐ Yes ☐No
2. Does the patient talk to total strangers as if he/she knew them?
☐ Yes ☐No
3. Does the patient say things to people that are insensitive or hurt their feelings?
☐ Yes ☐No
4. Does the patient say crude things or make sexual remarks that he/she would not usually have said?
☐ Yes ☐No

5. Does the patient talk openly about very personal or private matters not usually discussed in public?
☐ Yes ☐No
6. Does the patient take liberties or touch or hug others in way that is out of character for him/her?
☐ Yes ☐No
7. Does the patient show any other signs of loss of control of his/her impulses?
☐ Yes ☐No

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

Frequency:

☐ 1. Rarely– less than once per week.
☐ 2. Sometimes– about once per week.
☐ 3. Often– several times per week but less than every day.
☐ 4. Very often– essentially continuously present.

Severity:

☐ 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. Severe– 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 (almost no change in work routine)
☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severelyor Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

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.

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question)
☐ N/A

1. Does the patient have a bad temper, "flying off the handle" easily over little things?
☐ Yes ☐No
2. Does the patient rapidly change moods from one to another, being fine one minute and angry the next?
☐ Yes ☐No
3. Does the patient have sudden flashes of anger?
☐ Yes ☐No

4. Is the patient impatient, having trouble coping with delays or waiting for planned activities?
☐ Yes☐ No
5. Is the patient cranky and irritable?
☐ Yes ☐No
6. Is the patient argumentative and difficult to get along with?
☐ Yes ☐No
7. Does the patient show any other signs of irritability?
☐ Yes ☐No

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

Frequency:

☐ 1. Rarely– less than once per week.
☐ 2. Sometimes– about once per week.
☐ 3. Often– several times per week but less than every day.
☐ 4.Very often – essentially continuously present.

Severity:

☐ 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. Severe– 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 (almost no change in work routine)
☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

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?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question)
☐ N/A

1. Does the patient pace around the house without apparent purpose?
☐ Yes ☐No
2. Does the patient rummage around opening and unpacking drawers or closets?
☐ Yes ☐No
3. Does the patient repeatedly put on and take off clothing?
☐ Yes ☐No

4. Does the patient have repetitive activities or "habits" that he/she performs over and over?
☐ Yes ☐No
5. Does the patient engage in repetitive activities such as handling buttons, picking, wrapping string, etc.?
☐ Yes ☐No
6. Does the patient fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot?
☐ Yes ☐No
7. Does the patient do any other activities over and over?
☐ Yes ☐No

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

Frequency:

☐ 1. Rarely– less than once per week.
☐ 2. Sometimes– about once per week.
☐ 3. Often– several times per week but less than every day.
☐ 4. Very often– essentially continuously present.

Severity:

☐ 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. Severe– 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 (almost no change in work routine)
☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

K. SLEEP AND NIGHTTIME BEHAVIOR DISORDERS (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?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question)
☐ N/A

1. Does the patient have difficulty falling asleep?
   ☐ Yes ☐No
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)?
   ☐ Yes ☐No
3. Does the patient wander, pace, or get involved in inappropriate activities at night?
   ☐ Yes ☐No
4. Does the patient awaken you during the night?
   ☐ Yes ☐No
5. Does the patient wake up at night, dress, and plan to go out, thinking that it is morning and time to start the day?
   ☐ Yes ☐No
6. Does the patient awaken too early in the morning (earlier than was his/her habit)?
   ☐ Yes ☐No
7. Does the patient sleep excessively during the day?
   ☐ Yes ☐No
8. Does the patient have any other nighttime behaviors that bother you that we haven't talked about?
   ☐ Yes ☐No

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

Frequency:

☐ 1. Rarely– less than once per week.

☐ 2. Sometimes– about once per week.

☐ 3. Often– several times per week but less than every day.

☐ 4. Very often– once or more per day (every night).

Severity:

☐ 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. Severe– 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 (almost no change in work routine)

☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)

☐ 3. Moderately (disrupts work routine, requires time rebudgeting)

☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)

☐ 5. Very Severelyor Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

L. APPETITE AND EATING CHANGES (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?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question)
☐ N/A

1. Has he/she had a loss of appetite?
   ☐ Yes ☐No
2. Has he/she had an increase in appetite?
   ☐ Yes ☐No
3. Has he/she had a loss of weight?
   ☐ Yes ☐No
4. Has he/she gained weight?
   ☐ Yes ☐No
5. Has he/she had a change in eating behavior such as putting too much food in his/her mouth at once?
   ☐ Yes ☐No
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?
   ☐ Yes ☐No
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?
   ☐ Yes ☐No
8. Have there been any other changes in appetite or eating that I haven't asked about?
   ☐ Yes ☐No

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

Frequency:

☐ 1. Rarely– less than once per week.
☐ 2. Sometimes– about once per week.
☐ 3. Often– several times per week but less than every day.
☐ 4. Very often– once or more per day or continuously.

Severity:

☐ 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.Severe – 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 (almost no change in work routine)
☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)

☐ 3. Moderately (disrupts work routine, requires time rebudgeting)

☐ 4.Severely (disruptive, upsetting to staff and other residents, major time infringement)

☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

APPENDIX 6:
CORNELL SCALE FOR DEPRESSION AND DEMENTIA

Ratings should be based on symptoms and signs occurring during the week before interview. No score should be given if symptoms result from physical disability or illness.

INSTRUCTIONS

1. The same rater should conduct the interview each time to assure consistency in the response.
2. The assessment should be based on the patient's normal weekly routine.
3. If uncertain of answers, questioning other caregivers may further define the answer.
4. Answer all questions by placing a check in the column under the appropriately numbered answer. (a=unable to evaluate, 0=absent, 1=mild to intermittent, 2=severe).
5. Add the total score for all numbers checked for each question.
6. Place the total score in the "SCORE" box and record any subjective observation notes in the "Notes/Current Medications" section.
7. Scores totaling 12 points or more indicate probable depression.

SCORING SYSTEM

9999=Unable to evaluate; 0=Absent; 1=Mild to Intermittent; 2=Severe.

Score greater than 12=Probable Depression

A. MOOD-RELATED SIGNS					
1.	Anxiety; anxious expression, rumination, worrying	9999	0	1	2
2.	Sadness; sad expression, sad voice, tearfulness	9999	0	1	2
3.	Lack of reaction to pleasant events	9999	0	1	2
4.	Irritability; annoyed, short tempered	9999	0	1	2
B. BEHAVIORAL DISTURBANCE					
5.	Agitation; restlessness, hand wringing, hair pulling	9999	0	1	2
6.	Retardation; slow movements, slow speech, slow reactions	9999	0	1	2
7.	Multiple physical complaints (score 0 if gastrointestinal symptoms only)	9999	0	1	2
8.	Loss of interest; less involved in usual activities (score 0 only if change occurred acutely, i.e., in less than one month)	9999	0	1	2
C. PHYSICAL SIGNS					
9.	Appetite loss; eating less than usual	9999	0	1	2
10.	Weight loss (score 2 if greater than 5 pounds in one month)	9999	0	1	2
11.	Lack of energy; fatigues easily, unable to sustain activities	9999	0	1	2
D. CYCLIC FUNCTIONS					
12.	Diurnal variation of mood; symptoms worse in the morning	9999	0	1	2
13.	Difficulty falling asleep; later than usual for this individual	9999	0	1	2

14. Multiple awakenings during sleep	9999	0	1	2
15. Early morning awakening; earlier than usual for this individual	9999	0	1	2
E. IDEATIONAL DISTURBANCE				
16. Suicidal; feels life is not worth living	9999	0	1	2
17. Poor self-esteem; self-blame, self-depreciation, feelings of failure	9999	0	1	2
18. Pessimism; anticipation of the worst	9999	0	1	2
19. Mood congruent delusions; delusions of poverty, illness or loss	9999	0	1	2

APPENDIX 7:
GENERAL NEUROLOGICAL EXAM

The General Neurological Examination will be performed at the timepoints specified in the protocol flow chart.

Note to the Investigator: If, at any time, abnormalities are observed in the General Neurological Exam, the Investigator should do additional examinations as needed based on his or her medical judgment.

The General Neurological Examination includes all of the modules listed below and is intended to be a general screening examination and sufficient for this trial and subject population.

(Module 1-Mental Status Examination is not included because the content is covered in other assessments in the study.)

MODULE 2 – CRANIAL NERVE ASSESSMENT

A. II – Visual Fields and acuity

B. II, III – Pupil Size and Reactivity

C. III, IV, VI – Extraocular Movements (range of motion, smooth pursuit, saccades, nystagmus)

   1. Observe for nystagmus during eye movements, increased nystagmus at the end of gaze or other oculomotor changes (mild nystagmus at extremes of gaze is normal).

      Note direction of nystagmus

D. V – Facial Sensation, Jaw Strength

E. VII – Muscles of Facial Expression (wrinkle brow, squeeze eyes shut, smile)

F. VIII – Auditory Acuity (assessed using a bed-side screening test e.g. by rubbing fingers on each side of subject's head or by whispering numbers)

G. IX – Gag reflex

H. X – Swallow

I. XI – Shoulder shrug

J. Tongue Protrusion (midline)

Score: left and right (except for G, H, J)

Grade: NORMAL or IMPAIRED and describe abnormality

MODULE 3 - MOTOR SYSTEM

A. Muscle Tone

   1. Ask the volunteer to relax.
   2. Flex and extend the volunteer's elbows and knees (bilaterally).
   3. There is a small, continuous resistance to passive movement.
   4. Observe for involuntary movements (e.g., tremor, tics, fasciculations). Observe for resistance to passive movement; observe for decreased (flaccid) or increased (rigid/spastic) tone.

   Score: left and right

   Grade: NORMAL, INCREASED or DECREASED

B. Muscle Strength

1. Ask the subject to stand up from sitting without using hands

   Grade: NORMAL, IMPAIRED and describe abnormality

2. Test proximal limb strength by having the volunteer flex and extend the knees and elbows against your resistance.

   Test bilaterally, and compare one side to the other.

   Score: left and right

   Grade: 5/5: normal; 4/5: movement against resistance impaired; 3/5: movement against gravity but not against resistance; 2/5: visible movement but not against gravity; 1/5: visible contraction; 0/5: no visible activity

3. Test distal limb strength by having the volunteer conduct dorsiflexion and plantar flexion of the volunteer's feet; finger abduction and handgrip strength against your resistance.

   Test bilaterally, and compare one side to the other.

   Score: left and right

   Grade: 5/5: normal; 4/5: movement against resistance impaired; 3/5: movement against gravity but not against resistance; 2/5: visible movement but not against gravity; 1/5: visible contraction; 0/5: no visible activity

C. Pronator Drift

1. Ask the volunteer to hold both arms straight forward with, palms up and eyes closed for ~10-15 seconds as tolerated; watch for how well the arm position is maintained.

2. Instruct the volunteer to keep both arms still while you tap them briskly downward. The volunteer should normally be able to maintain extension and supination. Inability to maintain extension and supination (and drift into pronation) indicates an upper motor neuron deficit.

   Score: left and right

   Grade: NORMAL or IMPAIRED and describe abnormality

MODULE 4 - REFLEXES

A. Biceps

B. Knee

Note: Other deep tendon reflexes may be tested at PI's discretion (e.g. elbow, wrist or Achilles tendon)

Score: left and right

Grade: NORMAL, INCREASED, DECREASED or ABSENT

C. Babinski

Score: left and right

Grade: NORMAL or ABNORMAL

MODULE 5 - COORDINATION AND GAIT

A. Rapid, Rhythmic Alternating Movements

1. Testing each hand separately, ask the volunteer to tap the distal thumb with the tip of each finger, in sequence, as fast as possible.

   Score: left and right

Grade: NORMAL or IMPAIRED

Reminder: If the rapid alternate movements are disturbed, the subject will be asked to strike his hand on the thigh, raise the hand, turn it over and then strike the back of the hand down on the same place. (This test is impaired in cerebellar disease, extra pyramidal disease and upper MN weakness.)

B. Point-to-Point Movements

1. Ask the volunteer to touch your index finger and their nose alternately several times.

   Move your finger about as the volunteer performs this task.

   Score: left and right

   Grade: NORMAL or IMPAIRED

   Reminder: If the point-to-point testing is disturbed, the subject will be asked to place one heel on the opposite knee and then run it down the shin to the big toe. Repeat this for both sides. (Impaired tests indicate cerebellar disease.)

C. Romberg

1. Ask the volunteer to stand with both feet together and eyes closed for 20 to 30 seconds without support.
2. Be prepared to catch the volunteer if they are unstable.

   Grade: NORMAL or IMPAIRED

D. Gait

1. Ask the volunteer to walk across the room, turn and come back (assess posture, balance, swinging of arms and movement of the legs).

   Grade: NORMAL or IMPAIRED and describe abnormality
2. Ask the volunteer to walk heel-to-toe in a straight line (tandem gait).

   Grade: NORMAL or IMPAIRED and describe abnormality

MODULE 6 - SENSORY

A. Pin prick: safety pin touched lightly to skin of forearms and legs, bilaterally.

B. Position sense: perception of thumb and toe movement, bilaterally.

Score: left and right

Grade: NORMAL OR IMPAIRED and describe abnormality (for each A to F)

APPENDIX 8:
COLUMBIA SUICIDE SEVERITY RATING SCALE

SCREENING (14 January 2009)

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.	**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** □
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** □
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) Equally 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	____
SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)	**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 results, this is considered an attempt. Inferring Intent: Even 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 _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**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 interrupted _____
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 aborted _____
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** □
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 _____

SINCE LAST VISIT (14 January 2009)

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.	**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** □
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). For prior to study entry, 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 (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	____
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) Equally 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	____
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 results, this is considered an attempt. Inferring Intent: Even 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 interrupted _____

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 aborted _____
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** □ □
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 _____

APPENDIX 9:
MODIFIED HACHINSKI ISCHEMIC SCALE

Record the presence or absence of the clinical features listed below and add the point values assigned to each feature. Summation of points produces a score.

	Present	Absent
a. Abrupt onset of dementia e.g. reported rapid onset with acknowledgment that gradual changes may have also occurred	☐ 2	☐ 0
b. Stepwise deterioration of dementia e.g. cognitive decline, aside from onset, noted to occur over days to weeks and followed by plateaus	☐ 1	☐ 0
c. Somatic complaints e.g. headache, tinnitus, chest pain, malaise	☐ 1	☐ 0
d. Emotional incontinence e.g. episodes of uncontrollable crying or laughter in response to minimal provocation, or beyond that which would be considered appropriate to a given situation	☐ 1	☐ 0
e. History or presence of hypertension e.g. history of blood pressure of > 150/95 confirmed upon repeated measures, or requiring diet modification or treatment	☐ 1	☐ 0
f. History of strokes e.g. hemiparesis, aphasia	☐ 2	☐ 0
g. Focal neurological symptoms e.g. transient monocular blindness, unilateral weakness or sensory loss; diplopia lasting hours; seizures	☐ 2	☐ 0
h. Focal neurological signs (on examination) e.g. asymmetric rigidity or deep tendon reflexes, extensor plantar response, nystagmus	☐ 2	☐ 0
TOTAL SCORE		

References:

Hachinski VC, Iliff LD, Zilhka E, Du Boulay GH, McAllister VL, Marshall J, Russell RW, Symon L. "Cerebral blood flow in dementia." Arch Neurol. 1975;32:632-7.

Molsa PK, Paljarvi L, Rinne JO, Rinne UK, Sako E. "Validity of clinical diagnosis in dementia: a prospective clinicopathological study." J Neurol Neurosurg Psychiatry. 1985;48:1085-90.

APPENDIX 10:
NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISEASES AND STROKE/ALZHEIMER'S DISEASE AND RELATED DISORDERS ASSOCIATION CRITERIA FOR PROBABLE ALZHEIMER'S DISEASE

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

- dementia established by clinical examination and documented by the Mini –Mental Test; Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- deficits in two or more areas of cognition;
- progressive worsening of memory and other cognitive functions;
- no disturbance of consciousness;
- onset between ages 40 and 90, most often after age 65; and
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer‘s disease is supported by:

- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perceptions (agnosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if confirmed neuropathologically; and
- laboratory results of:
  - normal lumbar puncture as evaluated by standard techniques,
  - normal pattern or non-specific changes in EEG, such as increased slow wave activity, and
- evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer‘s disease, after exclusion of causes of dementia other than Alzheimer‘s disease, include:

- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;
- other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- seizures in advanced disease; and
- CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

- sudden, apoplectic onset;
- focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
- seizures or gait disturbances at the onset or very early in the course of the illness.

Reference:

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984 Jul;34(7):939-44.

APPENDIX 11:
SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1 (VERSION 2)

Protocol Title:

A PHASE 2A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, 26-WEEK, PLACEBO-CONTROLLED STUDY OF 50 MG AND 100 MG OF SUVN-502 IN SUBJECTS WITH MODERATE ALZHEIMER'S DISEASE CURRENTLY TREATED WITH DONEPEZIL HYDROCHLORIDE AND MEMANTINE HYDROCHLORIDE

This appendix summarizes the changes made to the Protocol Version 1.0 issued 16 July 2015 in Version 2.0 issued 02 March 2016.

The integrated protocol version 2.0 has been updated to allow the use of Namzaric™ as combination Alzheimer's treatment, as well as including changes to the exclusion criteria (#8 & #15), and the follow-up visit schedule for subjects who discontinue prematurely. Other minor changes have been incorporated for consistency providing clarification in sections within the protocol. The details are summarized below:

Change 1: Allowance for Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) once daily and clarification of drug ingredients in Namenda XR®

Sections of protocol affected:

- Synopsis, Design
- Synopsis, Treatment
- Synopsis, Population
- 3.1 Overview
- 4.1 Inclusion Criteria
- 4.2 Exclusion Criteria
- 4.3 Subject Withdrawal and Replacement
- 5.1.2 Other Study Drugs
- 5.2.2 Other Study Drugs

Synopsis, Design (1st paragraph) and Section 3.1 (1st paragraph):

Added text:

This is a phase 2A, proof-of-concept,……and either memantine HCl (10 mg twice daily [bid]) or Namenda XR® (28 mg **memantine HCl extended-release** qd) **or**

the combination therapy, Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd.

Synopsis, Treatment (2nd paragraph):

Added text:

Throughout the study, all subjects…… or Namenda XR® (28 mg **memantine HCl extended-release** qd) **or the combination therapy, Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd.**

Synopsis, Treatment (5th or last paragraph, 2nd sentence):

Added text:

Generic formulations……subjects from baseline. Subjects treated with Namenda XR® **or Namzaric™** should continue to take their own medication as prescribed by their prescribing physician.

Synopsis, Population:

Added text:

The study population will……or Namenda XR® (28 mg **memantine HCl extended-release** qd) **or the combination therapy, Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd**.

Section 4.1 Inclusion Criteria (Inclusion Criteria #6 and *#7):*

Added text:

6. Must be receiving treatment with stable doses of donepezil HCl (10 mg qd), **either as 10 mg donepezil HCl only or part of the combination therapy, Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd** for at least 3 months prior to screening visit. Subjects are likely to be maintained on this 10 mg daily dose of donepezil HCl **or Namzaric™** for the entire duration of the study.
7. Must be receiving treatment with stable doses of memantine HCl (10 mg bid) or Namenda XR® (28 mg **memantine HCl extended-release** qd) **or as part of the combination therapy, Namzaric™ (28 mg memantine HCl extended-release / 10 mg donepezil HCl) qd** for at least 3 months prior to the screening visit, in addition to donepezil HCl treatment. Subjects are likely to be maintained on their current dose of memantine HCl or Namenda XR® **or Namzaric™** for the duration of the study.

Section 4.2 Exclusion Criteria (Exclusion Criteria #4):

Added text:

4. Is taking doses of memantine HCl other than 10 mg bid or Namenda XR® **(**28 mg **memantine HCl extended-release** qd**) or Namzaric™ (28 mg memantine HCl extended-release /10 mg donepezil HCl) qd**.

Section 4.3 Subject Withdrawal and Replacement (2nd paragraph, 6th bullet):

Added text:

- Treatment with memantine HCl cannot be maintained at either 10 mg bid of memantine HCl or 28 mg of memantine HCl qd of Namenda XR® **or as part of the combination therapy of Namzaric™ (28 mg memantine HCl extended-release /10 mg donepezil HCl) qd**

Section 5.1.2 Other Study Drugs (2nd bullet):

Added text:

- memantine HCl 10 mg bid or Namenda XR® (28 mg **memantine HCl extended-release)** qd **or Namzaric™ (28 mg memantine HCl extended-release /10 mg donepezil HCl) qd**.

Section 5.2.2 Other Study Drugs ((1st paragraph and 3rd paragraph):

Added text:

Donepezil HCl (10 mg qd), memantine HCl (10 mg bid) and Namenda XR® (28 mg **memantine HCl extended-release qd) or Namzaric™ (28 mg memantine HCl extended-release /10 mg donepezil HCl) qd** should be administered……prescribing physician.

Generic formulations of donepezil HCl (10 mg)……..the subjects from baseline.

Subjects treated with Namenda XR® **or Namazaric™** will continue to take their own medication as directed by their prescribing physician.

Rationale for change: A new combination therapy containing 28 mg memantine HCl extended-release and 10 mg donepezil HCl (Namazaric™) qd is now available and prescribed. This combination formulation is similar to concomitant medication already allowed in this study and does not pose any issues for potential subjects who want to participate in this study. This change allows subjects who are taking Namazaric™ to participate and continue this medication during the study.

Change 2: Exclusion criteria for subjects whose C-SDD scores suggest probable depression

Section of protocol affected:

- 4.2 Exclusion Criteria

Section 4.2 Exclusion Criteria (Exclusion Criteria #2, 1st sentence):

Added text:

2. Has a diagnosis of schizophrenia, bipolar disorder or current major depressive disorder (MDD) **or subjects whose C-SDD scores are suggestive of probable depression [typically scores ≥12]**.

Rationale for change: The addition of the C-SDD scores to the exclusion criteria was made to provide an additional assessment tool to be used by investigators to determine if a potential subject is currently depressed and should be excluded from this study.

Change 3: Definition of controlled diabetes for subjects whose HbA1c levels are above 6.5% at Screening for exclusion purposes

Section of protocol affected:

- 4.2 Exclusion Criteria

Section 4.2 Exclusion Criteria (Exclusion Criteria #8):

Previous text:

8. Has uncontrolled Type-1 or Type-2 diabetes (glycated hemoglobin [HbA1c] above 6.5%). Subject~~s whose~~ diabetes is ~~controlled with medication and diet will~~ be ~~allowed, provided their HbA1c is within the normal range~~.

Revised text:

8. Has uncontrolled Type-1 or Type-2 diabetes (glycated hemoglobin [HbA1c] above 6.5%). **A** subject **with HBA1c levels up to 7.5% can be enrolled if the investigator believes the** subject**'s** diabetes is **under control**.

Rationale for change: Many older subjects with Type 2 diabetes do not achieve HbA1c levels that are within normal limits once their diabetes is considered under control or stabilized with medication. This change in the exclusion criteria reflects this clinical observation and allows the investigator to include subjects whose diabetes they consider under control or stabilized, but only for subjects who have HbA1c values ≤7.5%.

Change 4: Clarification in exclusion criteria for subjects with low Vitamin B-12 levels

Section of protocol affected:

- 4.2 Exclusion Criteria

Section 4.2 Exclusion Criteria (Exclusion Criteria #15):

Previous text:

15. Has abnormal vitamin B-12 levels. Subjects taking vitamin B-12 supplements who are within normal limits at screening will be allowed.

Added text:

15. Has abnormal vitamin B-12 levels **that are lower than normal limits and remains low on repeat testing**. Subjects taking vitamin B-12 supplements who are within normal limits **or above** at screening **or within normal limits or above at repeat testing** will be allowed.

Rationale for change: This change was made to clarify that a subject with a vitamin B-12 value lower than the normal limit could be allowed if repeat testing results indicated that the vitamin B-12 levels were within the normal limits. Also allows subjects who have higher vitamin B-12 levels than normal limits to participate in this study.

Change 5: Single-blind medication not required for subjects who terminate the study early

Section of protocol affected:

- 7.2.7 Early Termination and Follow-up Visits

Section 7.2.7 Early Termination and Follow-up Visits (4th sentence):

Previous Text:

If the subject agrees, he/she should ~~complete the wash-out period and~~ a follow-up visit 4 weeks later.

Revised text:

If the subject agrees, he/she should **return for** a follow-up visit 4 weeks later.

Rationale for change: Subjects who terminate the study prior to the single-blind placebo washout period are not expected to take additional medication as scheduled during the washout period, but should complete the Week 26 (Visit 5) assessments in the Early Termination Visit and encouraged to return 4 weeks later to complete the assessments in the Follow-up Visit.

Change 6: Revised text with Modified Hachinski Ischemic Scale (MHIS) and replaced Appendix 9 with MHIS

Sections of protocol affected:

- 3.1 Overview
- 4.1 Inclusion Criteria
- 6.4.1.2 Modified Hachinski Ischemic Scale
- 7.2.1 Screening (Visit1, Day -28 to -14)
- Appendix 9

Section 3.1 Overview (3rd paragraph, 2nd sentence); Section 4.1 Inclusion Criteria (Inclusion Criteria #5); Section 6.4.1.2 Modified Hachinski Ischemic Scale (heading title and 1st sentence); and *Section 7.2.1 Screening (Visit1, Day -28 to -14):*

Previous text:

~~Hachinski Ischemic Score~~

Revised text:

Modified Hachinski Ischemic Scale or the abbreviation: **MHIS**

Appendix 9 Modified Hachinski Ischemic Scale (heading title)

Previous title:

APPENDIX 9
HACHINSKI ISCHEMIC ~~SCORE~~

Revised title:

APPENDIX 9
MODIFIED HACHINSKI ISCHEMIC SCALE

Appendix 9 Modified Hachinski Ischemic Scale(assessment)

Previous text:

~~Feature~~	~~Score~~	~~Feature~~	~~Score~~
~~Abrupt onset~~	~~2~~	~~Emotional incontinence~~	~~1~~
~~Stepwise deterioration~~	~~1~~	~~History of hypertension~~	~~1~~
~~Fluctuating course~~	~~2~~	~~History of strokes~~	~~2~~
~~Nocturnal confusion~~	~~1~~	~~Evidence of associated atherosclerosis~~	~~1~~
~~Relative preservation of personality~~	~~1~~	~~Focal neurological symptoms~~	~~2~~
~~Depression~~	~~1~~	~~Focal neurological signs~~	~~2~~
~~Somatic complaints~~	~~1~~		

~~**TOTAL SCORE:**~~

Revised text:

See Appendix 9.

Rationale for change: The Modified Hachinski Ischemic Scale was used instead of the standard Hachinski Ischemic Scale.

Change 7: Clarification of which assessments in the Table 3 Schedule of Procedures should be performed first in order to be more efficient in eliminating subjects who do not meet the study entry criteria at Screening and Baseline and the assignment of one rater for each subject for specific assessments

Section of protocol affected:

- 6.1 Efficacy Variables
- Synopsis, Schedule of Procedures
- 7.1 Schedule of Procedures
- 7.2 Procedures by Visit

Section 6.1 Efficacy Variables:

Added text:

It is strongly recommended that one rater is assigned for each subject for each of the efficacy assessment scales described below, so that one rater scores a subject's assessment for the entire study. For example, the rater assigned to perform the MMSE would rate that scale for all visits for that subject.

Synopsis, Schedule of Procedures and *Section 7.1 Schedule of Procedures (Table 3 Schedule of Procedures):*

Previous table:

Table 3: Schedule of Procedures

Study period	Screening	Baseline	Treatment Period		End of Treatment	Follow-up
Time	**Days -28 to -14**	**Day 1**	**Week 4 Day 28±2**	**Week 13 Day 91±2**	**Week 26 Day 182±3 or early withdrawal**	**Week 30 Day 210±2**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**
Procedures						
Informed Consent	X					
Inclusion / Exclusion Criteria	X	X				
Demographics, Medical History	X	X				
Prior and Concomitant Medications	X	X	X	X	X	X
MRI or CT Scan (if Necessary)	X					
Blood Sample for APO-E Genotype Testing		X				
Study Treatment Dispensation ~~[a]~~		X	X	X	X	
MMSE and ADAS-Cog	X	X	X	X	X	
CDR-SB, ADCS-ADL, and NPI		X	X	X	X	
C-SDD	X	X	X	X	X	X
Review of AEs	X	X	X	X	X	X
Laboratory Tests	X [b]	X	X [c]	X	X [b]	X
Blood Pressure Measurements	X	X	X	X	X	X
ECG	X	X	X [d]	X [d]	X [d]	X
Physical and Neurological Examination	X	X	X	X	X	X
~~C-SSRS~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Plasma Levels of SUVN-502 and M1 of SUVN-502			X [e]		X [e]	
Plasma Levels of Donepezil and Memantine	X		X [e]		X [e]	

(continued)

Table 3: Schedule of Procedures (Continued)

ADAS-Cog=Alzheimer's Disease Assessment Scale; ADCS-ADL=Alzheimer's Disease Cooperative Study Activity of Daily Living; AE=adverse event; APO-E=Apolipoprotein E; CDR-SB=Clinical Dementia Rating Scale – Sum of Boxes; C-SDD=Cornell Scale of Depression and Dementia; C-SSRS=Columbia Suicide Severity Rating Scale; CT=Computed Tomography; ECG=Electrocardiogram; MMSE= Mini-Mental State Evaluation; MRI=Magnetic Resonance Imaging; NPI=Neuropsychiatric Inventory.

a. *On the day of the study visits, subjects will be instructed not to take their treatment at home, as treatment will be dispensed at the study center.*
b. *A urine pregnancy test will be done at screening and Week 26 visit for women of childbearing potential. A positive urine test will be confirmed by a serum pregnancy test.*
c. *At Week 4, laboratory tests will only include liver function tests.*
d. *3 hours after study treatment administration, i.e. the approximate time of maximum concentration of SUVN-502.*
e. *Plasma samples for PK assessments will be collected before study drugs are administered to the subjects.*

Revised table:

Table 3: Schedule of Procedures

Study period	Screening	Baseline	Treatment Period		End of Treatment	Follow-up
Time	**Days -28 to -14[a]**	**Day 1[a]**	**Week 4 Day 28±2**	**Week 13 Day 91±2**	**Week 26 Day 182±3 or early withdrawal**	**Week 30 Day 210±2**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**
Procedures						
Informed Consent	X					
Inclusion / Exclusion Criteria	X	X				
Demographics, Medical History	X	X				
Prior and Concomitant Medications	X	X	X	X	X	X
MRI or CT Scan (if Necessary)	X					
Blood Sample for APO-E Genotype Testing		X				
Study Treatment Dispensation [b]		X	X	X	X	
MMSE and ADAS-Cog	X	X	X	X	X	
Modified Hachinski Ischemic Scale	**X**					
CDR-SB, ADCS-ADL, and NPI		X	X	X	X	
C-SDD	X	X	X	X	X	X
C-SSRS	**X**	**X**	**X**	**X**	**X**	**X**
Review of AEs	X	X	X	X	X	X
Laboratory Tests	X [c]	X	X [d]	X	X [c]	X
Blood Pressure Measurements	X	X	X	X	X	X
ECG	X	X	X [e]	X [e]	X [e]	X
Physical and Neurological Examination	X	X	X	X	X	X
Plasma Levels of SUVN-502 and M1 of SUVN-502			X [f]		X [f]	
Plasma Levels of Donepezil and Memantine	X		X [f]		X [f]	

(continued)

Table 3: Schedule of Procedures (Continued)

ADAS-Cog=Alzheimer's Disease Assessment Scale; ADCS-ADL=Alzheimer's Disease Cooperative Study Activity of Daily Living; AE=adverse event; APO-E=Apolipoprotein E; CDR-SB=Clinical Dementia Rating Scale – Sum of Boxes; C-SDD=Cornell Scale of Depression and Dementia; C-SSRS=Columbia Suicide Severity Rating Scale; CT=Computed Tomography; ECG=Electrocardiogram; MHIS = Modified Hachinski Ischemic Scale; MMSE= Mini-Mental State Evaluation; MRI=Magnetic Resonance Imaging; NPI=Neuropsychiatric Inventory.

Note: It is strongly recommended that one rater is assigned for each subject for each of the following assessment scales so that one rater scores a subject's assessment for the entire study: MMSE, ADAS-Cog, CDR-SB, ADCS-ADL, NPI, C-SDD, and C-SSRS.

a. ***For Screening and Baseline Visits, the following assessments, included in study entry criteria, should be performed first in order to exclude subjects and not waste time assessing subjects who do not meet the study entry criteria: MMSE, the MHIS, C-SDD, C-SSRS, ECG, pregnancy test (for women of child bearing potential), and laboratory tests.***
b. *On the day of the study visits, subjects will be instructed not to take their treatment at home, as treatment will be dispensed at the study center.*
c. *A urine pregnancy test will be done at screening and Week 26 visit for women of childbearing potential. A positive urine test will be confirmed by a serum pregnancy test.*
d. *At Week 4, laboratory tests will only include liver function tests.*
e. *3 hours after study treatment administration, i.e. the approximate time of maximum concentration of SUVN-502.*
f. *Plasma samples for PK assessments will be collected before study drugs are administered to the subjects.*

Section 7.2 Procedures by Visit (2nd paragraph)

For Screening and Baseline Visits, the following assessments, included in study entry criteria, should be performed first in order to limit the number of assessments performed for subjects who do not meet the study entry criteria: MMSE, MHIS, C-SDD, C-SSRS, ECG, pregnancy test (for women of child bearing potential), and laboratory tests. It is strongly recommended that one rater is assigned for each subject for each of the following assessment scales so that one rater scores a subject's assessment for the entire study: MMSE, ADAS-Cog, CDR-SB, ADCS-ADL, NPI, C-SDD, and C-SSRS.

Rationale for changes: The changes were made to clarify which assessments in the Schedule of Procedures should be performed first in order to be more efficient in eliminating subjects who do not meet the study entry criteria at Screening and Baseline. In addition, for the following assessments: MMSE, ADAS-Cog, CDR-SB, ADCS-ADL, NPI, C-SDD, and C-SSRS, one rater should be assigned for each of the listed assessments for each subject and score the same assessment for the entire study. Different raters can be assigned to each subject for different assessments, but only one rater should score the same assessment for each subject for the entire study. This may improve consistency in the scoring of assessments throughout the study.

Change 8: Format for the ADAS-Cog and ADCS-ADL assessments were revised to be consistent with the study worksheets and the eCRF. These forms comply with the standard forms but are different in presentation.

Section of protocol affected:

- Appendix 1: 11-Item Alzheimer's Disease Assessment Scale - Cognitive Behavior (ADAS-Cog)
- Appendix 4: Alzheimer's Disease Co-Operative Study Activity of Daily Living

Appendix 1: 11-Item Alzheimer's Disease Assessment Scale - Cognitive Behavior (ADAS-Cog):

Previous text:

~~**1. WORD RECALL TASK:**~~

~~Indicate the total number of ***correct*** responses for each trial~~

~~Trial 1~~	~~Trial 2~~	~~Trial 3~~

~~**2. NAMING OBJECTS AND FINGERS:**~~

~~Check each object/finger named ***correctly*** or check "NONE."~~

~~☐ NONE~~

~~☐ Flower~~ ~~☐ Rattle~~ ~~☐ Wallet~~

☐ Bed	☐ Stethoscope	☐ Index
☐ Mask	☐ Pencil	☐ Ring
☐ Harmonica	☐ Comb	☐ Pinky
☐ Whistle	☐ Tongs	☐ Middle
☐ Scissors	☐ Thumb	

3. COMMANDS:

Check each command performed ***correctly*** or check "NONE."

☐ NONE
☐ Make a fist.
☐ Point to the ceiling, then to the floor.
☐ Put the pencil on top of the card, then put it back.
☐ Put the watch on the other side of the pencil and turn over the card.
☐ Tap each shoulder twice with two fingers keeping your eyes shut.

4. CONSTRUCTIONAL PRAXIS:

Check each figure drawn ***correctly***.

☐ NONE: attempted but drew no forms correctly.
☐ Patient drew no forms; scribbled; wrote words.
☐ Circle
☐ Two overlapping rectangles
☐ Rhombus
☐ Cube

5. IDEATIONAL PRAXIS:

Check each step completed ***correctly*** or check "NONE"

☐ NONE
☐ Fold a letter.
☐ Put letter in envelope.
☐ Seal envelope.
☐ Address envelope.
☐ Indicate where stamp goes.

6. ORIENTATION:

Check each item answered ***correctly*** or check "NONE."

☐ NONE
☐ Full name
☐ Month
☐ Date
☐ Year
☐ Day
☐ Season
☐ Place
☐ Time of day

~~**7. WORD RECOGNITION TASK:**~~

~~Indicate the total number of ***correct*** responses for each trial~~

~~Trial 1~~	~~Trial 2~~	~~Trial 3~~

~~**8. LANGUAGE:**~~

~~Check level of impairment.~~

- ☐ ~~**None**: patient speaks clearly and/or is understandable.~~
- ☐ ~~**Very Mild**: one instance of lack of understandability.~~
- ☐ ~~**Mild**: patient has difficulty < 25% of the time.~~
- ☐ ~~**Moderate**: patient has difficulty 25–50% of the time.~~
- ☐ ~~**Moderately Severe**: patient has difficulty more than 50% of the time.~~
- ☐ ~~**Severe**: one- or two-word utterances; fluent, but empty speech; mute.~~

~~**9. COMPREHENSION OF SPOKEN LANGUAGE:**~~

~~Check level of impairment~~

- ☐ ~~**None**: patient understands.~~
- ☐ ~~**Very Mild**: one instance of misunderstanding.~~
- ☐ ~~**Mild**: 3–5 instances of misunderstanding.~~
- ☐ ~~**Moderate**: requires several repetitions and rephrasing.~~
- ☐ ~~**Moderately Severe**: patient only occasionally responds correctly; i.e., yes–no questions.~~
- ☐ ~~**Severe**: patient rarely responds to questions appropriately; not due to poverty of speech.~~

~~**10. WORD FINDING DIFFICULTY:**~~

~~Check one response.~~

- ☐ ~~**None**.~~
- ☐ ~~**Very Mild**: 1 or 2 instances, not clinically significant.~~
- ☐ ~~**Mild**: noticeable circumlocution or synonym substitution.~~
- ☐ ~~**Moderate**: loss of words without compensation on occasion.~~
- ☐ ~~**Moderately Severe**: frequent loss of words without compensation.~~
- ☐ ~~**Severe**: nearly total loss of content words; speech sounds empty; 1– to 2-word utterances.~~

~~**11. REMEMBERING TEST INSTRUCTIONS:**~~

~~Check level of impairment.~~

- ☐ ~~**None**.~~
- ☐ ~~**Very Mild**: forgets once.~~
- ☐ ~~**Mild**: must be reminded 2 times.~~
- ☐ ~~**Moderate**: must be reminded 3–4 times.~~
- ☐ ~~**Moderately Severe**: must be reminded 5–6 times~~
- ☐ ~~**Severe**: must be reminded 7 or more times.~~

Revised text:

See Appendix 1.

Appendix 4: Alzheimer's Disease Co-Operative Study Activity of Daily Living:

Previous text:

1. Regarding **eating**, which best describes {P} usual performance during the past 4 weeks?
   - ☐ 3: ate without physical help, and used a knife
   - ☐ 2: used a fork or spoon, but not a knife, to eat
   - ☐ 1: used fingers to eat
   - ☐ 0: usually or always was fed by someone else
2. Regarding **walking** (or getting around in a wheelchair), in the past 4 weeks, which best describes his/her **optimal** performance:
   - ☐ 3: mobile outside of home without physical help
   - ☐ 2: mobile across a room without physical help
   - ☐ 0: transferred from bed to chair without help
   - ☐ 0: required physical help to walk or transfer
3. Regarding bowel and bladder function **at the toilet**, which best describes his/her **usual** performance in the past 4 weeks:
   - ☐ 3: did everything necessary without supervision or help
   - ☐ 2: needed supervision, but no physical help
   - ☐ 1: needed physical help, and was usually continent
   - ☐ 0: needed physical help, and was usually incontinent
4. Regarding **bathing**, in the past 4 weeks, which best describes his/her **usual** performance:
   - ☐ 3: bathed without reminding or physical help
   - ☐ 2: no physical help, but needed supervision/reminders to bathe completely
   - ☐ 1: needed minor physical help (e.g., with washing hair) to bathe completely
   - ☐ 0: needed to be bathed completely
5. Regarding **grooming**, in the past 4 weeks, which best describes his/her **optimal** performance:
   - ☐ 3: cleaned and cut fingernails without physical help
   - ☐ 2: brushed or combed hair without physical help
   - ☐ 1: kept face and hands clean without physical help
   - ☐ 0: needed help for grooming of hair, face, hands, and fingernails
6. Regarding **dressing, in the past 4 weeks**,

   A) Did {P} select his/her first set of clothes for the day?
   - ☐ 0: no or don't know

   If yes, which best describes his/her usual performance:
   - ☐ 3: without supervision or help
   - ☐ 2: with supervision
   - ☐ 1: with physical help

   B) Regarding physically getting dressed, which best describes his/her usual performance in the past 4 weeks:
   - ☐ 4: dressed completely without supervision or physical help
   - ☐ 3: dressed completely with supervision, but without help
   - ☐ 2: needed physical help only for buttons, clasps, or shoelaces
   - ☐ 1: dressed without help if clothes needed no fastening or buttoning

☐ 0: always needed help, regardless of the type of clothing

7. In the past 4 weeks, did {P} use a telephone?

☐ 0: no or don't know

If yes, which best describes his/her **highest** level of performance:

☐ 5: made calls after looking up numbers in white or yellow pages, or by dialing directory assistance

☐ 4: made calls only to well-known numbers, without referring to a directory or list

☐ 3: made calls only to well-known numbers, by using a directory or list

☐ 2: answered the phone; did not make calls

☐ 1: did not answer the phone, but spoke when put on the line

8. In the past 4 weeks, did {P} watch television?

☐ 0: no or don't know

If yes, ask all questions:

Did {P}:

d. usually select or ask for different programs or his/her favorite show?

☐ 0: no or don't know

☐ 1: yes

e. usually talk about the content of a program while watching it?

☐ 0: no or don't know

☐ 1: yes

f. talk about the content of a program within a day (24 hours) after watching it?

☐ 0: no or don't know

☐ 1: yes

9. In the past 4 weeks, did {P} ever appear to pay attention to conversation or small talk for at least 5 minutes?

Note: {P} did not need to initiate the conversation.

☐ 0: no or don't know

If yes, which best describes his/her usual degree of participation:

☐ 3: usually said things that were related to the topic

☐ 2: usually said things that were not related to the topic

☐ 1: rarely or never spoke

10. Did {P} clear the dishes from the table after a meal or snack?

☐ 0: no or don't know

If yes, which best describes how he/she usually performed:

☐ 3: without supervision or help

☐ 2: with supervision

☐ 1: with physical help

11. In the past 4 weeks, did {P} usually manage to find his/her personal belongings at home?

☐ 0: no or don't know

If yes, which best describes how he/she usually performed:

☐ 3: without supervision or help

☐ 2: with supervision

☐ 1: with physical help

12. In the past 4 weeks, did {P} obtain a hot or cold beverage for him/herself? (A cold beverage includes a glass of water.)

☐ 0: no or don't know

If yes, which describes his/her highest level of performance

☐ 3: made a hot beverage, usually without physical help

☐ 2: made a hot beverage, usually if someone else heated the water

☐ 1: obtained a cold beverage, usually without physical help

13. In the past 4 weeks, did {P} make him/herself a meal or snack at home?

☐ 0: no or don't know

If yes, which best describes his/her highest level of food preparation:

☐ 4: cooked or microwaved food, with little or no help

☐ 3: cooked or microwaved food, with extensive help

☐ 2: mixed or combined food items for a meal or snack, without cooking or microwaving (e.g., made a sandwich)

☐ 1: obtained food on his/her own, without mixing or cooking it

14. In the past 4 weeks, did {P} dispose of garbage or litter in an appropriate place or container at home?

☐ 0: no or don't know

If yes, which best describes how he/she usually performed:

☐ 3: without supervision or help

☐ 2: with supervision

☐ 1: with physical help

15. In the past 4 weeks, did {P} get around (or travel) outside of his/her home?

☐ 0: no or don't know

If yes, which best describes his/her optimal performance:

☐ 4: alone, went at least 1 mile away from home

☐ 3: alone, but remained within 1 mile of home

☐ 2: only when accompanied and supervised, regardless of the trip

☐ 1: only with physical help, regardless of the trip

16. In the past 4 weeks, did {P} ever go shopping?

☐ 0: no or don't know

If yes, ask A and B:

A) Which one best describes how {P} usually selects items:

☐ 3: without supervision or physical help?

☐ 2: with some supervision or physical help?

☐ 1: not at all, or selected mainly random or inappropriate items?

B) Did {P} usually pay for items without supervision or physical help?

☐ 0: no or don't know

☐ 1: yes

17. In the past 4 weeks, did {P} keep appointments or meetings with other people, such as relatives, a doctor, the hairdresser, etc.?

☐ 0: no or don't know

If yes, which best describes his/her awareness of the meeting ahead of time:

□ 3: usually remembered, may have needed written reminders e.g. notes, a diary, or calendar

□ 2: only remembered the appointment after verbal reminders on the day

□ 1: usually did not remember, in spite of verbal reminders on the day

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Note: 1. Do not ask question 18 if the {P} is institutionalized; check here □

2. Being taken to day care or having a sitter at home does not constitute being left alone

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18. In the past 4 weeks, was {P} ever left on his/her own?

□ 0: no or don't know

If yes, ask all questions:

Was {P} left:

a) away from home, for 15 minutes or longer, during the day?

□ 0: no or don't know

□ 1: yes

b) at home, for an hour or longer, during the day?

□ 0: no or don't know

□ 1: yes

c) at home, for less than 1 hour, during the day?

□ 0: no or don't know

□ 1: yes

19. In the past 4 weeks, did {P} talk about current events?
(This means events or incidents that occurred during the past month.)

□ 0: no or don't know

If yes, ask all questions:

Did {P} talk about events that:

a) he/she heard or read about or saw on TV but did not take part in?

□ 0: no or don't know

□ 1: yes

b) he/she took part in outside home involving family, friends, or neighbors?

□ 0: no or don't know

□ 1: yes

c) events that occurred at home that he/she took part in or watched?

□ 0: no or don't know

□ 1: yes

20. In the past 4 weeks, did {P} read a magazine, newspaper or book for more than 5 minutes at a time?

□ 0: no or don't know

If yes, ask all questions:

Did {P} usually:

a) talk about details of what he/she read while or shortly (< than 1 hour) after reading?

□ 0: no or don't know

□ 1: yes

b) talk about what he/she read 1 hour or longer after reading?

☐ 0: no or don't know

☐ 1: yes

21. In the past 4 weeks, did {P} ever write things down?

Note: If {P} wrote things only after encouragement or with help, the response should still be 'yes.'

☐ 0: no or don't know

If yes, which best describes the most complicated things that he/she wrote:

☐ 3: letters or long notes that other people understood

☐ 2: short notes or messages that other people understood

☐ 1: his/her signature or name

22. In the past 4 weeks, did {P} perform a pastime, hobby or game?

☐ 0: no or don't know

If yes, which pastimes did he/she perform:

Ask about all of the following, check all that apply:

☐ card or board games (including bridge, chess, checkers)

☐ bingo ☐ crosswords ☐ art ☐ musical ☐ instrument

☐ knitting ☐ sewing ☐ reading ☐ gardening ☐ golf

☐ tennis ☐ workshop ☐ fishing

☐ other _____

Note: Walking does NOT count as a hobby/pastime for this scale.

☐ **If {P} performs hobbies/pastimes only at day care, check here.**

If yes, how did {P} usually perform his/her most common pastimes:

☐ 3: without supervision or help

☐ 2: with supervision

☐ 1: with help

23. In the past 4 weeks, did {P} use a household appliance to do chores?

Ask about all of the following, and check those that were used:

☐ washer ☐ dryer ☐ vacuum ☐ dishwasher ☐ toaster

☐ toaster oven ☐ range ☐ microwave ☐ food processor

☐ other _____

If yes, for the most commonly used appliances, which best describes how {P} usually used them:

☐ 4: without help, operating more than on-off controls if needed

☐ 3: without help, but operated only on/off controls

☐ 2: with supervision, but no physical help

☐ 1: with physical help

Total Score (0-78): ___

Number of "Don't Know" Responses: ___

Revised text:

See Appendix 4.

Rationale for changes: The ADAS-Cog and ADCS-ADL assessments in the appendices were not consistent with the study worksheets and the eCRF. The format in the worksheets and eCRF are easier to score and provide scoring instructions.

Change 9: Items that required clarification of what was intended in Version 1 of the protocol

Sections of protocol affected:

- Synopsis, Design
- Synopsis, Treatment
- 3.1 Overview
- 5.1.1 Investigational Treatment: SUVN-502 and Matching Placebo
- 5.1.2 Other Study Drugs
- 5.6 Compliance
- 6.2.1.4 Recording Adverse Events
- 6.2.1.5 Reporting Serious Adverse Events
- 7.2.1 Screening (Visit 1, Day -28 to -14)
- 7.2.2 Baseline Visit (Visit 2, Day 1)
- 7.2.3 Week 4 Visit (Visit 3, Day 28)
- 7.2.4 Week 13 Visit (Visit 4, Day 91)
- 7.2.5 Week 26 Visit (Visit 5, Day 182)
- 7.2.6 Week 30 Visit (Visit 6, Day 210)
- 8.1.1 Disposition of Subjects

Item 1: Changes related to washout period:

Synopsis, Design (2nd paragraph) and *Section 3.1 Overview (2nd paragraph):*

Added text:

…..4-week **single-blind** placebo washout period.

Synopsis, Treatment (3rd paragraph); Section 3.1 Overview (2nd parargraph, 1st sentence, and *7th paragraph, 1st sentence); Section 5.1.1 Investigational Treatment: SUVN-502 and Matching Placebo (2nd paragraph); Section 5.1.2 Other Study Drugs (1st paragraph); Section 6.2.1.4 Recording Adverse Events (1st paragraph, 1st sentence);* and *Section 6.2.1.5 Reporting Serious Adverse Events (4th paragraph, 1st sentence):*

Added text:

….. **single-blind placebo** washout period.

Item 2: Change to clarify when subjects should return medication if they discontinue the study medication early:

Section 5.6 Compliance (6th paragraph, 1st sentence):

Added text:

For subjects who discontinue study medication early ……the subject returns all study medication **at the early termination visit**.

Rationale for changes: These changes were made for clarification purposes only, reflect was what intended in Version 1 of the protocol, and do not involve in changes of the study design or procedures.

Item 3: Change to clarify definition of study completers:

Section 8.1.1 Disposition of Subjects (2nd paragraph):

Previous text:

A subject who completes all visits up to ~~Week 26~~, will be considered to have completed the study.

Revised text:

A subject who completes all visits up to **Week 30**, will be considered to have completed the study. **For evaluation of efficacy, a completed subject is defined as any subject who completes all visits up to Week 26.**

Item 4: Change to clarify which version of the C-SSRS should be used for each visit.

Section 7.2.1 Screening (Visit 1, Day -28 to -14) [2nd bullet, last sub-bullet]:

Added text:

- C-SSRS **(screening version)**

Section 7.2.2 Baseline Visit (Visit 2, Day 1) [10th bullet], Section 7.2.3 Week 4 Visit (Visit 3, Day 28) [11th bullet], Section 7.2.4 Week 13 Visit (Visit 4, Day 91) [10th bullet], Section 7.2.5 Week 26 Visit (Visit 5, Day 182) [11th bullet], and *Section 7.2.6 Week 30 Visit (Visit 6, Day 210) [7th bullet]:*

Added text:

- C-SSRS **(since last visit version)**

Change 10: Editorial changes

Item 1: Change in scoring in Appendix 6 for "Unable to evaluate"

Section of protocol affected:

- Appendix 6: Cornell Scale for Depression And Dementia

Appendix 6: Cornell Scale for Depression and Dementia (scoring system):

Previous text:

~~a~~=Unable to evaluate; 0=Absent; 1=Mild to Intermittent; 2=Severe.

…….~~a~~ 0 1 2

Revised text:

9999=Unable to evaluate; 0=Absent; 1=Mild to Intermittent; 2=Severe.

…….**9999** 0 1 2

Rationale for change: This change was made to the Appendix 6 to be consistent with the study worksheets and the eCRF.

Item 2: Change of the abbreviation used for Alzheimer's Disease Assessment Scale for Cognitive Behavior (ADAS-Cog) to be consistent throughout the document

Section of protocol affected:

- Multiple

Description of change: Multiple abbreviations were used for Alzheimer's Disease Assessment Scale for Cognitive Behavior : "ADAScog-11" and "ADAS-COG". All have been changed to ADAS-Cog.

Rationale for change: Consistency.

Item 3: Change for the description of donepezil and memantine to donepezil HCl and memantine HCl

Section of protocol affected:

- Multiple

Description of change: "Donepezil" was changed to "donepezil HCl" and "memantine" to "memantine HCl", except when describing plasma or drug concentrations.

Rationale for change: Consistency.