Phase II Study to Assess the Safety, Tolerability, and Target Engagement of AMX0035, a Fixed Combination of Sodium Phenylbutyrate and Tauroursodeoxycholic Acid for the Treatment of Alzheimer's Disease

Regulatory Sponsor:	Amylyx Pharmaceuticals Inc.
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Study Product:	AMX0035
Protocol Number:	AMX8000
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Draft or Version Number:	*4.0*

10 April 2020

STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP), and the applicable regulatory requirements, United States Code of Federal Regulations (CFR) Title 45 CFR Part 46 and Title 21 CFR Parts 50, 56, and 312.

SIGNATURE PAGE

I have read the attached protocol entitled, **Phase II Study to Assess the Safety, Tolerability, and Target Engagement of AMX0035, a Fixed Combination of Sodium Phenylbutyrate and Tauroursodeoxycholic Acid for the Treatment of Alzheimer's Disease,** dated April 10, 2020 (Version 4.0) and agree to abide by all described protocol procedures. I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice, applicable FDA regulations and guidelines identified in 21 CFR Parts 11, 50, 56, and 312, local Institutional Review Board (IRB) guidelines and policies, and the Health Insurance Portability and Accountability Act (HIPAA).

Site Investigator: _____

Name Printed: _____

Signed: _____ Date: _____

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event/Adverse Experience
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's disease Assessment Scale – Cognitive Subscale
ALS	Amyotrophic Lateral Sclerosis
b.i.d	Twice a Day
BOLD	Blood Oxygen-Level Dependent Imaging
C-CASA	Columbia Classification Algorithm for Suicide Assessment
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CNS	Central Nervous System
CRF	Case Report Form
CSF	Cerebrospinal Fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DM	Data Management
DSRS	Dementia Severity Rating Scale
eCRF	Electronic Case Report Form
ER	Endoplasmic Reticulum
FAQ	Functional Activities Questionnaire
FDA	Food and Drug Administration
FWA	Federal-wide Assurance
G	Gram
GDS	Geriatric Depression Scale
GCP	Good Clinical Practice
HDAC	Histone Deacetylase
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intention to Treat
LP	Lumbar Puncture
MCI	Mild Cognitive Impairment
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal – Cognitive Assessment

MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
N	Number (typically refers to subjects)
NDA	New Drug Application
NIH	National Institutes of Health
NfL	Neurofilament Light Chain
Ng	Neurogranin
NPI	Neuropsychiatric Inventory
NPI-Q	Neuropsychiatric Inventory Questionnaire
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PAA	Phenylacetate (metabolite of PB)
PB	Sodium Phenylbutyrate
pCASL	Pseudo-Continuous Arterial Spin Labeling
PET	Positron Emission Tomography
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PSC	Protocol Steering Committee
QA	Quality Assurance
QC	Quality Control
ROI	Region of Interest
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SI	Site Investigator
SDT	Source Document Templates
SOP	Standard Operating Procedure
t.i.d	Three Times a Day
TUDCA	Tauroursodeoxycholic Acid
UDCA	Ursodeoxycholic Acid
US	United States
vMRI	Volumetric Magnetic Resonance Imaging

SCHEDULE OF ACTIVITIES

Study table

	Screening	Baseline[1]	Week 1 Phone Call	Week 6[15]	Week 12[16]	Week 18[15]	Week 24[17]/Early Discontinuation[18]	Final Follow-Up Call[14]
	-28 Days	Day 0 +5 Days	Day 7 ±1 Days	Day 42 ±14 Days	Day 84 ±28 Days	Day 126 ±14 Days	Day 168 ±28 Days	Last Dose of IP +14 ±5 Days
Written Informed consent	X							
Inclusion/Exclusion Review	X	X						
Randomization[2]		X						
Medical History/Demographics	X							
AD Diagnosis History	X							
Montreal - Cognitive Assessment (MoCA)	X			X		X	X	
DSRS		X			X		X	
Geriatric Depression Scale	X							
Vital Signs[3]	X	X			X		X	
FAQ		X			X		X	
Physical Exam including Height and Weight[4]	X						X	
Neurology Exam[5]	X						X	
Safety labs[6]	X				X		X	
12-Lead ECG (Electrocardiogram)	X				X		X	
Neuropsychiatric Inventory Questionnaire (NPI-Q)	X[7]				X		X	
ADAS-Cog		X			X		X	
MRI Assessment[8]	X						X	
Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications	X	X		X	X	X	X	X
Dispense Study Drug[9]		X		X	X	X		
Drug Accountability/Compliance			X[10]	X	X	X	X	
Suicide Rating Scale (C-SSRS)[11]	X	X		X	X	X	X	

	Screening	Baseline[1]	Week 1 Phone Call	Week 6[15]	Week 12[16]	Week 18[15]	Week 24[17]/Early Discontinuation[18]	Final Follow-Up Call[14]
	-28 Days	Day 0 +5 Days	Day 7 ±1 Days	Day 42 ±14 Days	Day 84 ±28 Days	Day 126 ±14 Days	Day 168 ±28 Days	Last Dose of IP +14 ±5 Days
Blood draw for biomarker analysis		X			X		X	
Lumbar puncture/CSF draw for biomarkers[12]	X						X	
Blood draw for pharmacokinetics[13]					X		X	
Blood draw for genetic analysis		X						

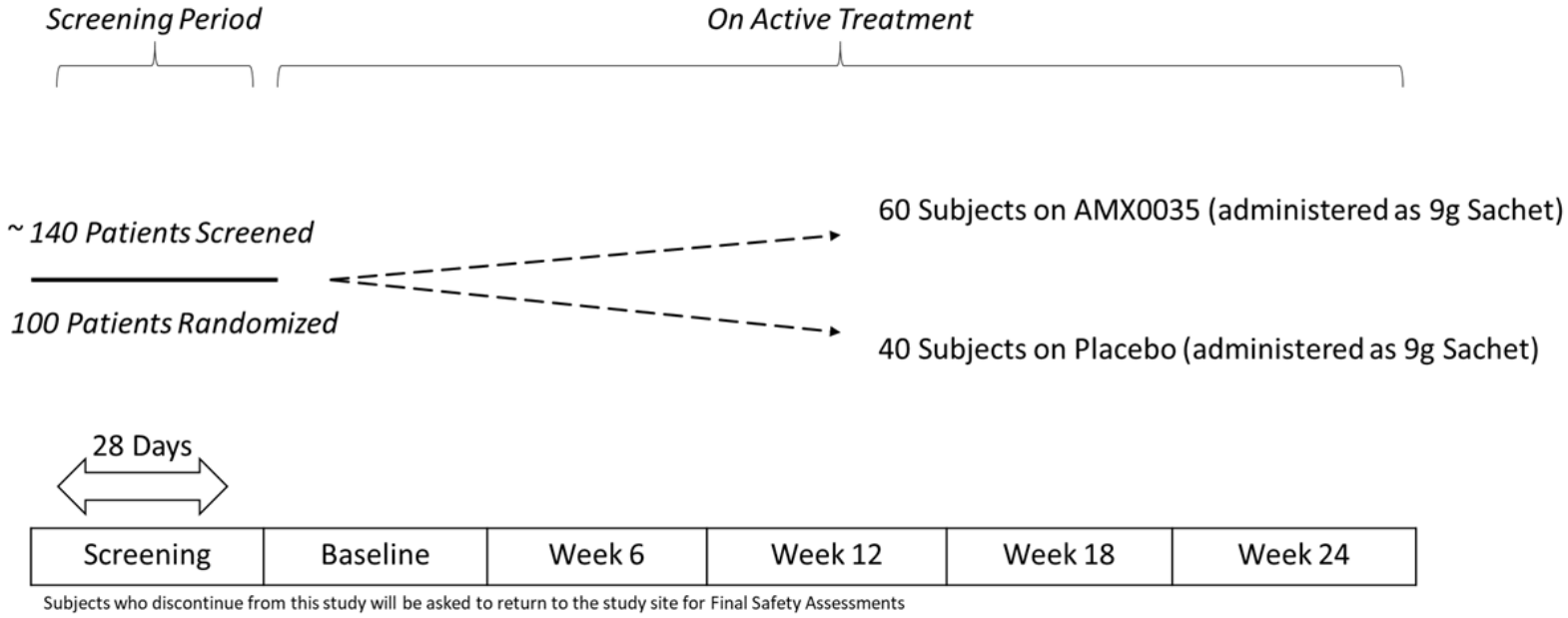
[1]The Baseline Visit can be completed any time after the screening so long as all eligibility criteria are met and occur no more than 28 +5 days after the Screening Visit.
[2]Randomization should occur at the Baseline Visit. Randomization will entail entering a subject's kit number into the electronic data capture system.
[3]Vital signs include systolic and diastolic pressure in mmHg, respiratory rate/minute, heart rate/minute and temperature.
[4]Height is only recorded once at the Screening Visit.
[5]The standard Neurological Exam will be used for all subjects.
[6]Safety labs include Hematology (CBC with differential), Complete Chemistry Panel, Liver Function Tests, B12 and TSH (at Screening Visit only) and Urinalysis.
[7] The NPI-Q Test can be performed either at the screening or baseline visit
[8]The MRI assessment can be completed anytime between the Screening and up to 7 days prior to the Baseline Visit and will have a clinical read done locally.
[9]First dose of study drug will be administered in clinic after ALL Baseline Visit procedures are completed.
[10]Notify subjects of increase from one sachet per day to two sachets per day
[11]C-SSRS Screening Version to be completed at Screening Visit only. C-SSRS Since Last Visit version to be completed at all other visits.
[12]The first LP can be completed anytime between the Screening and up to 7 days prior to the Baseline Visit.
[13]Take a single PK plasma sample on Visits 12 and 24 (same time as lumbar puncture). A PK sample will not be taken on subjects completing the Early Discontinuation Visit if the subject discontinued study drug more than 48 hours before the visit.

[14]The Final Follow-Up Call is to occur 14 ± 5 days after the participant's last dose of study drug. For participants who discontinue treatment early, the Final Follow-Up Call is not required if the Early Discontinuation visit occurs 14 ± 5 days after the last dose of study drug.
[15]To the extent possible, the Week 6 and Week 18 visits may be done remotely. If the visit is done remotely, Drug Accountability/Compliance will occur at the next in-person clinic visit.
[16]It is preferred that the Week 12 visit be conducted at the site with the participant physically present. If it is not possible to complete an in-person Week 12 visit at the site, the safety assessments below must be completed by Week 16/Day 112 for the subject to remain on study drug. Sites may make alternative arrangements to complete these assessments per institutional and IRB policy.

- ECG
- Safety Labs: Hematology (Complete Blood Count with Differential), Complete Chemistry Panel, Liver Function Tests, and Urinalysis
- Vital Signs
- C-SSRS

[17] The window for the Week 24 visit is Day 168 ± 28 days. However, if COVID-19 related restrictions (e.g., site closure, travel restrictions) make it impossible to conduct an in-person clinic visit during the specified window, then any assessment that can be performed remotely should be completed as an unscheduled visit during the Week 24 window. The actual Week 24 visit, with all of the assessments indicated on the SOA, may be postponed for up to 12 weeks and treatment extended. The maximum duration a subject may be on IP is 40 weeks. Safety checks (i.e., ECG, safety labs, vital signs, and C-SSRS) must be completed, at minimum, every 16 weeks/112 days. If safety assessments are performed so that the Week 24 visit may be postponed, the assessments should be documented as an unscheduled visit.
[18]If possible, an Early Discontinuation visit should be done within 14 days of the last dose of IP (i.e., last dose of IP + 14 days). The MRI and lumbar puncture may be done as soon as is practical and, if possible, within 60 days of the last dose of IP (i.e., last dose of IP + 60 days).

STUDY WORKFLOW



1 ETHICS/PROTECTION OF HUMAN SUBJECTS

1.1 Institutional Review Board (IRB)

This study will be conducted in compliance with current Good Clinical Practices (GCP) and Title 21 Part 56 of the United States of America Code of Federal Regulations (CFR) relating to IRBs.

1.2 Ethical Conduct of Study

The study will be conducted in accordance with GCP defined by the International Conference on Harmonization (ICH) and the ethical principles of the Declaration of Helsinki.

1.3 Subject Information and Consent

This study will be conducted in compliance with Title 21 Part 50 of the United States of America CFR, Federal Regulations and ICH Guidance Documents pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, subjects will be informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits. Subjects will be given adequate time to ask questions and become familiar with the study prior to providing consent to participate. Subjects will give their written consent to participate in the study and will be provided with a copy of the fully executed consent form for their records.

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 Alzheimer's Disease (AD) Overview

Alzheimer's disease (AD) is the most prevalent form of dementia affecting more than 5,000,000 subjects in the US and an estimated 20,000,000 people worldwide, according to the Alzheimer's Association. AD causes progressive neuronal degeneration, resulting in progressive memory loss and dementia. AD has no available cure; however, treatments exist that can temporarily slow dementia symptoms. There are five FDA-approved medications for the treatment of Alzheimer's disease. These drugs fall into two categories; acetylcholinesterase inhibitors and NMDA receptor antagonists. Approved acetylcholinesterase inhibitors include tacrine (Cognex®), rivastigmine (Exelon®), galantamine (Nivalin® and Razadyne®), and donepezil (Aricept®). The only approved NMDA receptor antagonist for the treatment of AD is memantine (Namenda®).

Alzheimer's disease is characterized by the loss of neurons and synapses in the cerebral cortex and atrophy in the temporal and parietal lobes. Abnormal aggregates of amyloid plaques and neurofibrillary tangles are two of the primary histopathological findings of AD and have been the target of many recent clinical trials. However, recent studies suggest that amyloid reduction is less able to halt pathology after AD progresses beyond the stage of mild cognitive impairment (MCI). By this point, parallel neuronal death and inflammatory pathways may contribute to disease progression greater than either amyloid or tau. This suggests that there is a significant patient group that may not respond to amyloid-targeted therapies alone, yet may benefit from therapies targeting cell death and inflammation.

2.1.2 AMX0035 Rationale

AMX0035 is a combination of two compounds, Sodium Phenylbutyrate (PB) and Tauroursodeoxycholic Acid (TUDCA), that target the cellular unfolded protein response (UPR) and bioenergetics stress, respectively. Both compounds, at our selected doses are expected to cross the blood-brain-barrier at therapeutic levels based on observed CNS target engagement observed in previous *in vivo* studies[3,4,7,11,14] and are hypothesized to prevent neuronal death through distinct pathways.

Each compound has exhibited strong efficacy in several cellular and animal models of AD, as well as models of endoplasmic reticulum (ER) stress and mitochondrial dysfunction. Amylyx has demonstrated robust synergy when PB and TUDCA are dosed simultaneously and found the combination to be efficacious in many preclinical models.

PB is a class I and class II HDAC inhibitor that ameliorates ER stress through upregulation of DJ-1, a master chaperone regulator[1], and other chaperone proteins[2]. The epigenetic and cellular stress

response activities of PB have been demonstrated to modify the AD phenotype in the Tg2576 mouse model of AD, through a prevention of neuronal loss in the hippocampus and increased clearance of Aβ deposits[3,4]. PB has been shown to reduce cortical and hippocampal amyloid plaque burden in the APP/PS1 double-transgenic model of AD, resulting in increased cognitive performance of the mice in spatial memory tasks[5]. PB was shown to reduce tau hyperphosphorylation in *in vivo* studies of AD through reduction of ER-stress dependent kinase activity[6]. PB has been tested in many other *in vivo* models of neurodegenerative diseases and has been demonstrated to increase survival in the G93A SOD1 mouse model of ALS[7] and the N171-82Q mouse model of Huntington's disease[8] through chaperone mediated mechanisms. Finally, as expected by its HDAC inhibition properties, PB has been reported to increase astrocyte BDNF and NT-3 production and secretion in culture and *in vivo* and improve synaptic protein expression and spatial memory in the 5XFAD mouse[9].

TUDCA has been shown to recover mitochondrial bioenergetic deficits through incorporation into the mitochondrial membrane, reducing Bax translocation to the mitochondrial membrane, reducing mitochondrial permeability, and increasing the apoptotic threshold of the cell[10]. TUDCA, through these anti-apoptotic pathways, prevents cognitive decline in the APP/PS1 mouse model of AD, reduces hippocampal and frontal cortex amyloid deposits[11,12] and reduces glial activation[13]. TUDCA has shown efficacy in many oxidative injury models, including mouse models of ischemia[14], the MPTP mouse model of Parkinson's[15], and ALS models of poly(GA)-induced toxicity[16].

ER and mitochondrial stress can both cause neuronal death and a subsequent cytotoxic immune response. Therefore, we combined PB and TUDCA and have since demonstrated that they have synergistic efficacy when dosed at particular ratios. Specifically, the combination of agents resulted in a synergistic increase in neuronal viability in an H_2O_2-mediated insult model. In the assay, H_2O_2 was dosed at 40μM for one hour, a dose causing approximately 50% neuronal death. Administration of TUDCA or PB individually resulted in a modest increase in viability, while the combination returned cell viability nearly to control (>90% viability). To demonstrate the reproducibility of these results, as well as to determine optimal ratios of AMX0035, we repeated the experiment with 20 different combinations of TUDCA and PB. These experiments replicated our previous results and revealed the optimal efficacious concentrations *in vitro*. PB demonstrated optimal efficacy at concentrations between 150μM-500μM and TUDCA at concentrations between 50μM-200μM. These correspond to the clinical dose we are evaluating in a clinical trial in ALS. The combination dose that demonstrated optimal efficacy in the H_2O_2-mediated insult model was evaluated in an acute, pre-plaque Tg2576 mouse model. AMX0035 treatment significantly reduced soluble amyloid beta, preferentially Aβ42 (Figure 1).

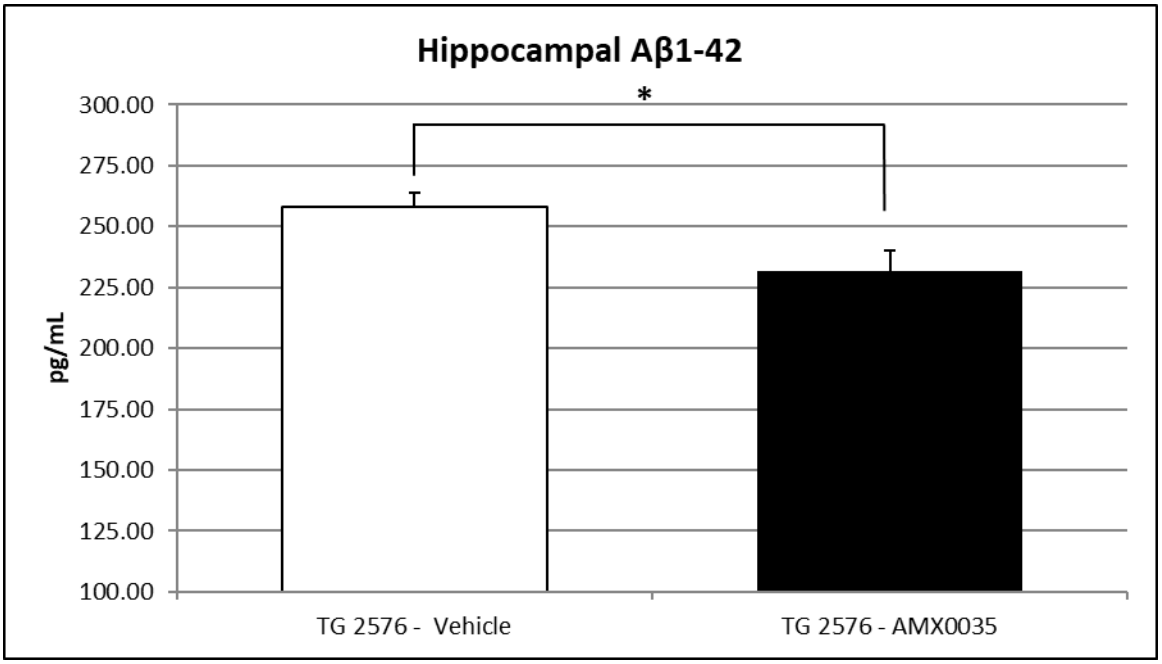


Figure 1: Treatment with AMX0035 at a dose of 200µM TUDCA and 200µM PB reduced levels of $A\beta_{42}$ relative to control in the Tg2576 mouse model of Alzheimer's disease.

2.1.3 Prior Clinical Use of PB and TUDCA in Subjects with Neurodegenerative Disease

Neither PB or TUDCA have been evaluated in subjects with AD or MCI likely related to AD, however, both PB and TUDCA have been evaluated, individually, in subjects with neurodegenerative diseases and were found to be safe, well-tolerated, and exhibited preliminary signs of efficacy. PB was evaluated in a 20-week safety and biomarker study in ALS subjects[17]. This study was a Phase I dose-escalation trial and each subject was scheduled to receive PB at increasing dose from 9 to 21 g/day. A total of 40 subjects were recruited at 8 trial sites in the United States. Twenty-six subjects completed the 20-week treatment phase. Histone acetylation was decreased by approximately 50% in blood buffy-coat specimens at screening and was significantly increased following PB treatment (Figure 2). Blood levels of PB and the primary metabolite, phenylacetate, increased with dosage (Figure 3) with a plateau between the 3 and 6g t.i.d. regimen. While the majority of subjects tolerated higher dosages of PB, the lowest dose (9 g/day, 3g t.i.d) was the most effective at increasing histone acetylation levels in blood (Figure 3). Treatment with PB did not alter blood riluzole levels. Adverse events in subjects taking riluzole and PB together did not occur more frequently.

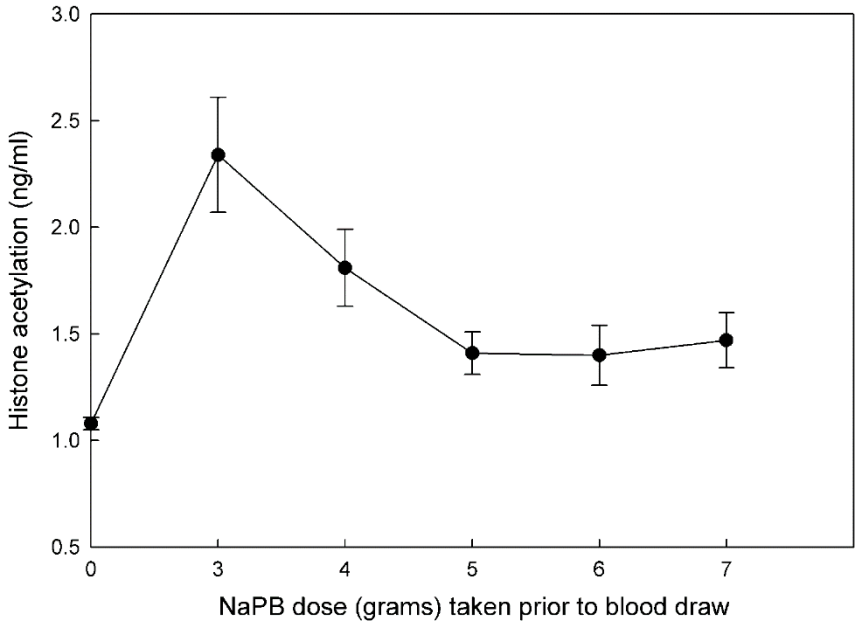


Figure 2: Histone acetylation levels with PB dose. Blood histone acetylation levels are shown compared with dose taken prior to blood draw. The error bars represent standard error. (Doses are repeated t.i.d in this study).

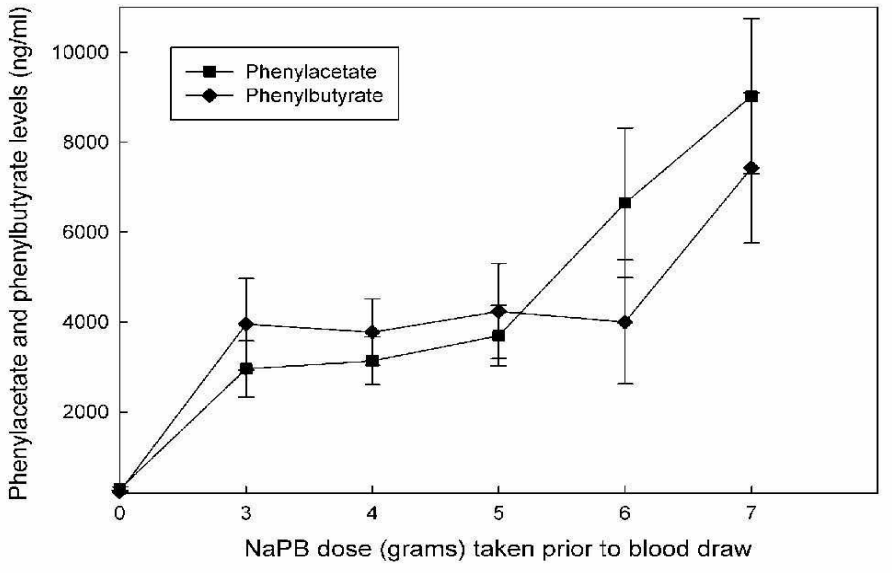


Figure 3: Plasma levels of phenylbutyrate and its metabolite, phenylacetate. Plasma phenylbutyrate and phenylacetate levels are shown compared with dose taken prior to blood draw. The error bars represent standard error (Dosing was t.i.d in this study).

It is not clear why acetylation levels were highest at 9g/day, however the authors noted that in a study of PB in Huntington's disease (HD)[18], the effects of PB on mRNA expression levels of a 12-gene biomarker set were greatest at lowest evaluated dosage (12g/day), indicative of an inverse dose response. Furthermore, in the clinical study of PB in Huntington's disease, the maximum tolerated dose was determined to be 15g/day, with PB at 12-15g/day appearing to be safe and well-tolerated.[19]

TUDCA, dosed at 1g b.i.d., demonstrated a statistically significant slowing of ALSFRS-R progression rate in a 54-week, multi-site, placebo-controlled clinical trial of ALS[209]. In this proof-of-principle trial, 34 ALS subjects under concomitant treatment with riluzole were randomized to receive placebo or TUDCA (1g b.i.d.) for 54 weeks. The proportion of responders (defined as subjects with >15% improvement in ALSFRS-R scale) was higher under TUDCA (87%) than under placebo (43%; P=0.021). At study end, baseline-adjusted ALSFRS-R was significantly higher (P=0.007) in TUDCA than in placebo group. Comparison of the slopes of regression analysis showed slower progression in the TUDCA than in the placebo group (P<0.01) (Figure 4).

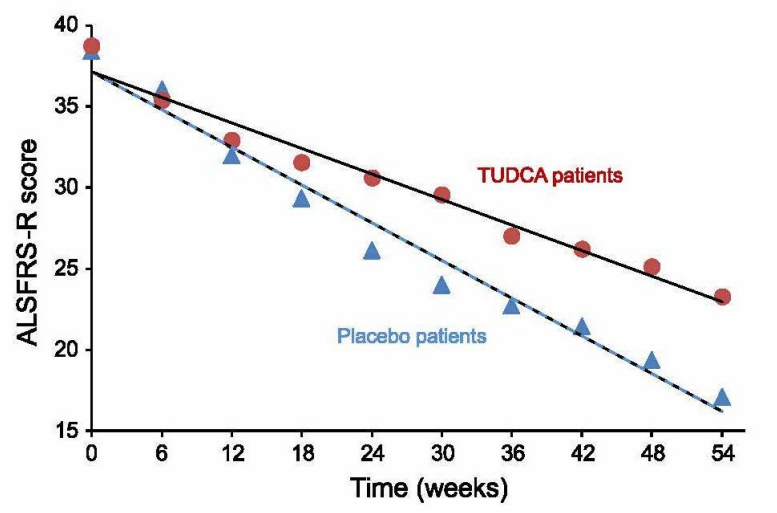


Figure 4: Linear regression analysis of ALSFFRS-R mean scores over time for the TUDCA (circles, slope -0.388) and placebo groups (triangles, slope -0.262).

In this Phase II trial, subject with AD or MCI related to AD will receive 3g PB and lg TUDCA twice a day orally. AMX0035 will be presented as a roughly 10-gram sachet to be suspended in water and taken prior to a meal. Treatment of single agent TUDCA or PB in subjects with other neurodegenerative diseases was very well tolerated. In a study of TUDCA in subjects with ALS subjects[20], the AE profile and laboratory anomalies were not different between the TUDCA and placebo cohort. In the small group of 15 subjects treated with TUDCA, the AEs were limited to diarrhea. In the PB ALS clinical study[17], tolerability was similar to that reported in trials of PB in other indications. There were no changes in safety laboratory tests, ECG or vital signs. The most common AEs were those previously reported with PB, including falls, dizziness, diarrhea, edema, dry mouth, headache, nausea and rash. A single subject interrupted treatment with PB at the 9g per day dose (i.e. a dose higher than that planned in the proposed Phase II) for the occurrence of edema on the feet and under the eyes.

2.1.4 Additional Previous Clinical Experience with Phenylbutyrate

Sodium phenylbutyrate (PB) is generally well tolerated. It is FDA approved for subjects with urea cycle disorders, including deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase. It is indicated in subjects with either neonatal-onset deficiency or late-onset disease. The typical daily dose is 450-600 mg/kg in subjects weighing less than 20kg, or 9.9-13.0 g/day in larger subjects. Detailed information can be found on the package insert for PB[22].

PB is also under development as an anticancer agent. In a dose-escalation study in subjects with refractory solid tumor malignancies, doses of up to 45g/day PB were administered[23]. Due to dose-limiting toxicities, the study concluded that 27g/day was the maximum tolerated dose. Nausea, vomiting, hypocalcemia and fatigue occurred at the 36g/day and 45g/day doses. Gastrointestinal upset (nausea, dyspepsia and vomiting) occurred at the lowest dose of 9g/day and was seen within 30 minutes of drug ingestion. However, 82% of subjects completed the study despite these side effects. Other frequently reported side effects include a "sweat"-like odor, usually noticeable only to the caregiver. Mild neurotoxicity (confusion, lethargy) has been noted at higher doses of close to 30g/day but resolved with dose reduction.

A dose-escalation study of intravenous PB in subjects with myelodysplastic syndromes and acute myelogenous leukemia found a maximally tolerated dose at 375 mg/kg/day (26.3g/day for a 70kg individual) with no serious toxicities detected in subjects receiving doses between 125 and 375 mg/kg/day (8.8 and 26.3g/day for a 70kg individual)[24]. Dose-limiting toxicities (lethargy, confusion, slurred speech) were detected at 440 and 500 mg/kg/day PB (30.8 and 35g/day respectively, for a 70kg individual). Reports of edema have been blamed on the high sodium load associated with the drug. Phase I/II studies in subjects with sickle cell anemia and beta thalassemia report similar side effects.

Another phase I study in subjects with refractory solid tumors tested IV PB doses between 150 to 515 mg/kg/day (up to 36g/day for a 70kg individual) with dose-limiting toxicities (excessive somnolence, confusion) and electrolyte abnormalities resulting at a dose of 515 mg/kg/day (36.0

g/day for a 70kg individual). The maximally tolerated dose of PB was determined to be 410 mg/kg/day (28.7 grams/day for a 70kg individual) as there were no dose-limiting toxicities at this dose and no subjects required dose reductions or escalations.

The most common side effects of PB include: menstrual irregularities, decreased appetite, sweat-like body odor, and bad taste. Less common side effects include: nausea, vomiting, stomach upset, stomach pain, gastritis, headache, and skin rash. Rarely, cases of peptic ulcers, rectal bleeding, constipation, pancreatitis and renal tubular acidosis have been reported. Hypoalbuminemia, metabolic acidosis, alkalosis, hyperchloremia, hyperuricemia, hypokalemia, hypophosphatemia, hyperphosphatemia and hypernatremia have been observed. At higher doses, some subjects experienced confusion and fatigue, both of which resolved with dose reductions. Rarely, the following may occur, but have not been directly linked to sodium phenylbutyrate therapy: anemia, leukopenia, leukocytosis, thrombocytopenia, thrombocytosis, arrhythmia, syncope and depression.

2.1.5 Additional Previous Clinical Experience with TUDCA

Tauroursodeoxycholic acid (TUDCA) is currently marketed in Italy under the brand name Tudcabil® ( ). It is exported to China and Turkey under the brand name Taurolite®. It is used clinically for the indications of treatment of cholesterol gallstones. TUDCA has been used for the treatment of cholestatic liver diseases including primary cirrhosis, pediatric familial intrahepatic cholestasis, and primary sclerosing cholangitis and cholestasis due to cystic fibrosis. To our knowledge there are no other off-label uses of TUDCA.

Ursodeoxycholic acid, which is widely used in the United States under the trade name Ursodiol®, is an endogenous secretion of the liver, most often as a taurine (TUDCA) or glycine (GUDCA) conjugate. Taurine conjugation increases the solubility of UDCA by increasing its hydrophicity. TUDCA is taken up in the distal ileum under active transport and therefore likely has a slightly a longer dwell time within the intestine than UDCA which is more proximally absorbed in the ileum (IND).

TUDCA is used in some countries internationally for the dissolution of cholesterol gallstones. This generally requires long periods of treatment often 1 to 2 years to obtain complete dissolution (IND).

Between 1997 and 2007, 898,000 Tudcabil® tablets were sold in Italy (Product profile contained in referenced IND). There were no reported cases of toxicity related to Tudcabil® capsules. There were no reports of overdose or drug abuse during this period. There were no reports related to its use in pregnancy (all pregnant subjects, and those planning to become pregnant, are excluded from this trial). Common adverse events included mild abdominal pain and diarrhea. There are some cases of pruritus and a very limited number of cases of elevated liver enzymes. It

should be noted that most of the referenced studies were conducted in subjects with chronic liver disease.

TUDCA is contraindicated in subjects with biliary tree infections, frequent biliary colic, or in subjects who have trouble absorbing bile acids (e.g. ileal disease or resection). The only known or theoretical drug interactions are with substances that inhibit the absorption of bile acids such as cholestyramine and with drugs that increase the elimination of cholesterol in the bile (TUDCA reduces biliary cholesterol content) (Please refer to section 6.7.1). Based on similar physicochemical characteristics, it is likely that drug toxicity/interactions are very similar to those of UDCA which are summarized below.

TUDCA has been and is being evaluated in multiple other studies as well. A study at Columbia University of 20 subjects with new onset type 1 diabetes in which subjects are administered 1.75g TUDCA daily for 12 months is ongoing. A study at Washington University in St. Louis assessing the effect of TUDCA on lipid markers and ER stress has been completed in 101 subjects at 1.75g daily for 4 weeks; an additional study arm in this study assessed PB at 20g/day. A study at Washington University assessing subjects with HIV receiving 1.75g daily TUDCA for 30 days is ongoing.

2.2 Potential Risks and Benefits

2.2.1 Potential Risks

The safety profile with PB administration is in large part derived from studies of subjects with urea cycle disorders. Refer to the phenylbutyrate tablet label (Buphenyl®).

In female subjects, the most common clinic adverse event report was amenorrhea/menstrual dysfunction (irregular menstrual cycles), which occurred in 23% of the menstruating subjects. Decreased appetite occurred in 4% of all subjects. Body odor, likely caused by the metabolite, phenylacetate [PAA]) and bad taste or taste aversion were each reported in 3% of subjects.

Other adverse events reported in 2% of fewer subjects were:

- Gastrointestinal: abdominal pain, gastritis, nausea and vomiting; constipation rectal bleeding, peptic ulcer disease, and pancreatitis each occurred in one subject.
- Hematologic: aplastic anemia and ecchymoses each occurred in one subject.
- Cardiovascular: arrhythmia and edema occurred in one subject
- Renal: renal tubular acidosis
- Psychiatric: depression
- Skin: rash
- Miscellaneous: headache, syncope, and weight gain

As previously described (Sections 2.1.3 and 2.1.4), PB has been evaluated in a dose-escalating study in subjects with neurodegenerative diseases and was found to be generally safe and tolerable at significantly higher doses than will be assessed in this study[17,19]. Specifically, the most common AEs included falls or other accidental injury, dizziness, diarrhea, edema, dry mouth, headache, nausea, and rash. Apart from the emergence of headaches in subjects, these AEs occurred at a higher rate compared to the placebo cohort. These events are expected side effects from PB. No clinically significant changes in laboratory values, ECGs, or vital signs were observed. No deaths or unexpected and related serious adverse events occurred. Importantly, these studies evaluated daily dosages of PB between 9-21g and 12-18g while our study will use 6 grams daily[17,19].

Neurotoxicity was reported in cancer subjects receiving intravenous phenylacetate at dosages of 250-300mg/kg/day for 14 days, repeated at 4-week intervals. Manifestations were predominately somnolence, fatigue, and lightheadedness; with less frequent headache, dysgeusia, and hypoacusis, disorientation, impaired memory, and exacerbation of a pre-existing neuropathy. The majority of these adverse events were mild in severity. The acute onset and reversibility following discontinuation of phenylacetate infusion suggest a possible treatment-related effect.

TUDCA is generally well-tolerated. A derivative, UDCA, is approved for subjects with primary biliary cirrhosis. Common adverse events with TUDCA include mild abdominal pain and diarrhea. There are some cases of pruritus and a very limited number of cases of elevated liver enzymes. The most common adverse reactions reported with the use of TUDCA are abdominal discomfort, abdominal pain, diarrhea, nausea, pruritus, and rash.

As previously described (Section 2.1.3) TUDCA was recently evaluated in a 54-week, placebo-controlled study in ALS subjects at 1g b.i.d[20]. The population for safety analysis consisted of 15 subjects who took TUDCA and 14 placebo subjects. Treatment was well tolerated in all subjects. Laboratory parameters did not change in either treatment group during the study. Except for the expected complications related to ALS, no changes in vital signs and laboratory values that could possibly be attributed to the study drug or placebo were recorded. Overall, five AEs were considered by the Site Investigators to be study-related based on the subjects' descriptions. Two events were reported in the 15 TUDCA-treated subjects (13.3%); three events occurred in the 14 placebo-treated subjects (21.4%). Mild diarrhea occurred in two subjects treated with TUDCA and in two treated with placebo. Anorexia was reported in a placebo-treated subject. Four subjects died during the study period, one in the TUDCA group and three in the placebo group. The one death in the treated group was not considered drug related—TUDCA trended towards a survival benefit.

There are potential risks and side effects of lumbar punctures, commonly called a spinal tap. We will draw cerebrospinal fluid (CSF) using a needle inserted in the lower back for analysis of biomarkers and pharmacokinetic analysis. Lumbar punctures will be performed under local anesthesia to numb the area. Collected CSF will be analyzed to assess biomarkers [redacted]

. Lumbar punctures will occur at the Screening or Baseline Visit and again at the Week 24 Visit.

2.2.2 Known Potential Benefits

TUDCA and PB have both been tested individually in clinical trials in patients with neurodegenerative diseases and have met their primary endpoints of safety and tolerability. If successful, this trial will allow further clinical development of AMX0035 for the treatment of Alzheimer's disease. The trial is also assessing multiple biomarkers in concert with clinical outcomes, which will provide a detailed understanding of drug activity and provide a well-curated data set for the Alzheimer's research community to improve our understanding of Alzheimer's disease.

3 OBJECTIVES

3.1 Study Objectives

The primary objectives of the study will be:

1. To compare the safety and tolerability of a fixed-dose combination of AMX0035 (a TUDCA/PB combination) versus placebo in subjects with MCI (high or intermediate likelihood due to AD) or dementia due to AD over an approximate 24-week treatment period;

The secondary objectives of the study will be:

1. To determine the effects of AMX0035 treatment on whole brain and regional brain atrophy, as assessed by volumetric Magnetic Resonance Imaging (vMRI);
2. To measure the effects of treatment on functional MRI measures including connectivity with resting state BOLD;
3. To assess the impact of AMX0035 on clinical symptoms as measured by ADAS-Cog, DSRS, and FAQ;
4. To assess the effect of AMX0035 on measures of neuropsychiatric symptoms, as assessed by the Neuropsychiatric Inventory Questionnaire (NPI-Q)

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

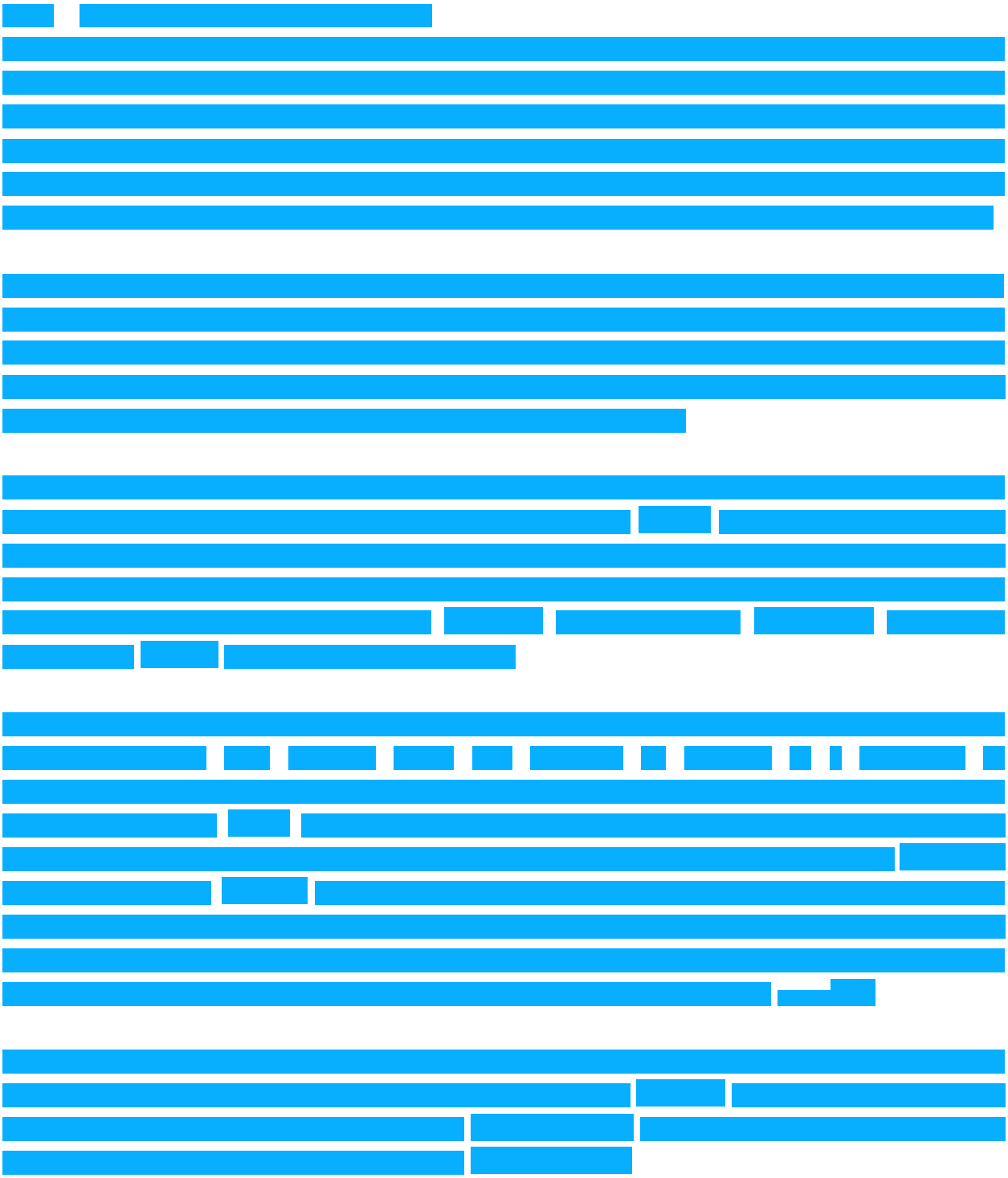
The primary outcome measures for the study will include safety and tolerability of AMX0035 in Alzheimer's disease.

Adverse events (AE), symptomatic, physical exam, neurological exam, and laboratory parameters will be collected prospectively to monitor the safety and tolerability of study drugs. Safety and tolerability will be assessed by the procedures outlined in section 9.

3.2.2 Secondary Outcome Measures

The secondary outcome measures will include neurophysiological biomarker assessments and cognitive and symptom-based measures. The effect of AMX0035 on the rate of cognition (ADAS-Cog and MoCA), functioning (DSRS and FAQ), and neuropsychiatric symptoms (NPI-Q) will be evaluated. Additionally, effects of AMX0035 will be assessed by multi-sequence MRI to evaluate treatment-related changes and will consist of T1 for regional volumetric analyses (especially

hippocampus as primary vMRI outcome), T2 FLAIR for assessment of lesions and white matter hyperintensities, and resting state BOLD to measure posterior and anterior default mode network functional connectivity. Safety outcomes, specifically ARIA-E and ARIA-H, will be monitored by T2 FLAIR and susceptibility-weighted imaging (SWI).



[redacted]

4 STUDY DESIGN

4.1 Overall Study Design and Plan

During the enrollment period, approximately 140 subjects will be screened and around 100 of those subjects will be randomized from approximately 10 AD specialty clinical centers in the US. These subjects will be randomly assigned in a 3:2 ratio to oral twice daily sachet of active combination TUDCA/PB or matching placebo. Treatment duration will be approximately 24 weeks. Subjects will be administered study drug or matching placebo twice daily. Visits will occur at Screening, Baseline, Week 6, Week 12, Week 18, and Week 24. Subjects who dropout of the study will be asked to return for an Early Discontinuation Visit approximately 14 days after last dose of study drug.

If allowable by the local IRB and local regulations, Week 6 and Week 18 visits can take place at the subjects' residence.

All visit windows are consecutive calendar days and are calculated from the day the participant starts study treatment (Day 0 is the day of the Baseline Visit and first day of therapy) except the Final Follow-Up Call. The target date for the Final Follow-Up Call is calculated from the last dose of study drug.

4.1.1 Response to Coronavirus Disease 2019 (COVID-19)

Week 6 and Week 18 may be completed remotely as needed.

It is preferred that the Week 12 visit be conducted at the site with the participant physically present. If it is not possible to complete an in-person Week 12 visit at the site, the safety assessments below must be completed by Week 16/Day 112 for the subject to remain on study drug. Sites may make alternative arrangements to complete these assessments per institutional and IRB policy.

- ECG
- Safety Labs: Hematology (Complete Blood Count with Differential), Complete Chemistry Panel, Liver Function Tests, and Urinalysis
- Vital Signs
- C-SSRS

All reasonable efforts should be made to complete the Week 24 or Early Discontinuation visit at the site with the participant physically present. However, if COVID-19 related restrictions (e.g., site closure, travel restrictions) make it impossible to conduct an in-person clinic visit during the specified window, then any assessment that can be performed remotely should be completed as an unscheduled visit during the Week 24 window. The actual Week 24 visit, with all of the assessments indicated on the SOA, may be postponed for up to 12 weeks and treatment

extended. The maximum duration a subject may be on IP is 40 weeks. Safety checks (i.e., ECG, safety labs, vital signs, and C-SSRS) must be completed, at minimum, every 16 weeks/112 days. If safety assessments are performed so that the Week 24 visit may be postponed, the assessments should be documented as an unscheduled visit.

If possible, an Early Discontinuation visit should be done within 14 days of the last dose of IP (i.e., last dose of IP + 14 days). The MRI and lumbar puncture may be done as soon as is practical and, if possible, within 60 days of the last dose of IP (i.e., last dose of IP + 60 days).

Ideally, remote visits will be conducted using a HIPAA-compliant video conferencing platform. If video conferencing is not available or not feasible, remote visits may be conducted by phone. The Montreal Cognitive Assessment (MoCA) is to be completed to the extent possible given the available technology, and drug accountability/compliance will be performed at the subject's next in-person visit.

Sites may send study drug to participants' residences. When transferring study drug to a participant, all reasonable efforts should be made to maintain the correct temperature. If possible, sites should use the Sponsor-selected vendor who will manage the shipments from the site to the subject using a certified shipping container and temperature monitor. Study drug is to be provided to subjects only after reviewing and documenting concomitant medications and therapies, and Adverse Events. Each subject will be instructed to use study drug from the new kit after receipt and verification of condition, regardless of the amount of study drug remaining from any previous kit in the subject's possession.

The longest period a subject may continue taking study drug without having completed the safety assessments listed below is 16 weeks/112 days.

- ECG
- Safety Labs: Hematology (Complete Blood Count with Differential), Complete Chemistry Panel, Liver Function Tests, and Urinalysis
- Vital Signs
- C-SSRS

4.2 Study Centers

This study will be conducted at approximately 10 specialty AD clinical research centers located in the United States. Sites will be selected based on recruitment record from prior trials, compliance with prior study protocols, clinical research expertise, availability of necessary resources, and enthusiasm for the study design and objectives.

4.3 Study Duration

Subjects will remain on randomized, placebo-controlled, double-blind treatment until the Week 24 Visit. Including the screening and follow-up visits, each subject will be in the study for

approximately 8 months. However, the Week 24 visit may be delayed, and study treatment extended, up to Week 40/Day 280 if COVID-19 restrictions make it impossible to complete the Week 24 visit in window. Therefore, a subject's participation in the study may be up to approximately 11 months.

4.4 Protocol Adherence

Each Site Investigator (SI) must adhere to the protocol detailed in this document and agree that any changes to the protocol must be approved by the NCRI Coordination Center (CC) or their representative prior to seeking approval from the site Internal Review Board (IRB). Each SI will be responsible for enrolling only those study subjects who have met protocol eligibility criteria.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Number of Study Subjects

Approximately 100 subjects will be randomized 3:2 to AMX0035 or matching placebo.

5.2 Inclusion and Exclusion Criteria

5.2.1 Inclusion Criteria

Study subjects should meet all the inclusion criteria during screening evaluations to be entered into the study:

1) Ages 55-89, inclusive, male or female
2) Must have a diagnosis of "Probable Alzheimer's Disease" or “Mild Cognitive Impairment” with a primarily amnestic presentation (deficit in learning and recall of recently learned information) that is accompanied by the presence of documented biomarkers (amyloid PET, CSF AD biomarkers, FDG-PET, or vMRI) supporting that the syndrome is likely due to AD pathology
3) MoCA score ≥8
4) Able to read and write in English sufficiently to complete all study procedures
5) Geriatric Depression Scale <7
6) Willing and able to complete all assessments and study procedures
7) Not pregnant, lactating or of child-bearing potential (women must be >2 years post-menopausal or surgically sterile)
8) Study partner with at least two days per week with contact with the subject willing to accompany patient to visits and complete partner study forms
9) No known hypersensitivity to Tauroursodeoxycholic acid or Phenylbutyrate
10) If on a cholinesterase inhibitor and/or memantine, treatment must have started for no less than 3 months (84 days) prior to baseline and the dosing regimen must have remained stable for 6 weeks (42 days) prior to baseline. The Investigator anticipates that the dosing regimen at baseline will remain unchanged throughout participation in the study.

5.2.2 Exclusion Criteria

Study subjects should not meet any exclusion criteria during screening evaluations or they will be excluded from entry into the study:

1) Any CNS disease other than suspected AD, such as clinical stroke, brain tumor, normal pressure hydrocephalus, multiple sclerosis, significant head trauma with persistent neurological cognitive deficits or complaints, Parkinson's disease, frontotemporal dementia, or other neurodegenerative diseases
2) Abnormal liver function defined as AST and/or ALT > 3 times the upper limit of normal
3) Renal insufficiency as defined by a serum creatinine > 1.5 times the upper limit of normal
4) Recent (less than 1 year) cholecystectomy or the presence of post-cholecystectomy syndrome or biliary obstruction

5) Clinically significant unstable medical condition (other than AD) that in the Site Investigator opinion would pose a risk to the participant if they were to participate in the study
6) Any contraindication to undergo MRI studies such as:
    a. History of a cardiac pacemaker or pacemaker wires
    b. Metallic particles in the body
    c. Vascular clips in the head
    d. Prosthetic heart valves
    e. Severe claustrophobia impeding ability to participate in an imaging study, or MRI findings that show one or more of the following:
    a. More than 4 incidental microhemorrhages
    b. Incidental lacunar infarcts with attributable signs or symptoms and with history of stroke
    c. Incidental meningiomas with attributable signs or symptoms
    d. Newly recognized meningioma
7) Any major active or chronic psychiatric illness (e.g. depression, bipolar disorder, obsessive compulsive disorder, schizophrenia) that is not stable or well controlled within the previous year prior to baseline
8) Any significant neurodevelopmental disability
9) Current suicidal ideation or history of suicide attempt within five years of baseline or significant change from the screening and baseline C-SSRS at the discretion of the Site Investigator
10) History of alcohol or other substance abuse or dependence within the past two years
11) Any significant systemic illness or medical condition that could affect safety or compliance with study at the discretion of the Site Investigator
12) Laboratory abnormalities in B12, TSH, or other common laboratory parameters that might contribute to cognitive dysfunction
13) Current use of medications with psychoactive properties that may deleteriously affect cognition (e.g., anticholinergics, centrally-acting antihistamines, antipsychotics, sedative hypnotics, anxiolytics)
14) Use of any investigational therapy being evaluated for the treatment of AD is prohibited beginning three months (90 days) prior to the Baseline Visit and throughout the study.
16) Use of other investigational agents one month (28 days) prior to the Baseline Visit and for the duration of the trial.

5.3 Treatment Assignment Procedures

Each subject who meets all eligibility criteria will be randomized to receive either therapy by twice daily sachet of AMX0035 (3g PB and 1g TUDCA) oral or matching placebo for approximately 24 weeks of treatment. For the first week of study treatment the subjects will only take a single sachet daily and will be instructed to increase to two sachets daily at the Week 1 Telephone Call.

5.3.1 Randomization Procedures

The randomization scheme will be independently developed and will indicate the treatment assignment and the subject numbers to be used by each site. The randomization scheme will be developed and managed by the biostatistical team.

5.3.2 Reasons for Withdrawal

A study subject will be discontinued from participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, concurrent illness, or other medical condition or situation occurs such that continued participation in the study is not in the best interest of the subject.
- The subject meets any exclusion criteria (either newly developed or not previously recognized).

Subjects are free to withdraw from participation in the study at any time upon request.

5.3.3 Handling of Withdrawals

A subject may choose to discontinue participation in the study at any time. However, the SI or designee will encourage subjects to continue with follow-up, regardless of their compliance with the study drug. If a subject permanently discontinues study drug, the SI or designee will encourage subjects to follow the study protocol under the intent-to-treat principle (ITT). These subjects will be encouraged to follow the study visits, off drug. Loss to follow-up should be prevented whenever possible.

Any subject in the study who needs to begin the use of any prohibited medication (outlined in 6.7.1), must immediately discontinue use of the study drug and should not begin use of the prohibited medication before an appropriate wash-out period occurs (please refer to the Site MOP for additional details). Subjects who permanently discontinue study drug should complete early study drug termination procedures per protocol without any study drug unblinding, if possible. Subjects who must permanently discontinue study drug may continue follow-up, per protocol.

Early termination occurs when a subject withdraws consent, i.e., withdrawing his or her participation in future study procedures. The subject should then return any unused study drug and will be asked to return to the study site for an Early Discontinuation Visit. If possible, the Early Discontinuation visit should be done within 14 days of the last dose of IP (i.e., last dose of IP + 14 days). The MRI and lumbar puncture may be done as soon as is practical and, if possible, within 60 days of the last dose of IP (i.e., last dose of IP + 60 days).

The Final Follow-Up Call is to occur 14 ± 5 days after the participant's last dose of study drug. However, the Final Follow-Up Call is not required if the Early Discontinuation visit occurs 14 ± 5 days after the last dose of study drug.

Subjects who withdraw from the study due to adverse events will continue follow-up per protocol, as noted above.

In the event a subject wishes to no longer have their personal health information used for the analysis of this study, he or she will notify the site in writing and future data will not be included in analysis. All data collected prior to the communication with the subject will be included in analysis.

5.3.4 Termination of Study

This study may be prematurely terminated if, in the opinion of the study PI, medical monitor, or sponsor, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the Site Investigator or sponsor by the terminating party.

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

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Enrollment is unsatisfactory.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Plans to modify, suspend, or discontinue development of the study drug.

If the study is prematurely terminated or suspended, the sponsor will promptly inform the Site Investigators/institutions, and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the Site Investigator/institution, as specified by the applicable regulatory requirement(s).

6 TREATMENTS ADMINISTERED

6.1 Treatments

6.1.1 Study Product Description

AMX0035 is a combination therapy comprising two active pharmaceutical ingredients, Sodium Phenylbutyrate (PB) and Tauroursodeoxycholic acid (TUDCA).

Phenylbutyrate is an approved compound in the United States for urea cycle disorders and is marketed in the US as Buphenyl®. There is an existing USP monograph for this material.
The chemical structure for PB is provided below.

Chemical structure of PB:

The active drug substance, PB, is manufactured by [redacted] under cGMP conditions. The manufacture and controls for PB are described in Drug Master File No. [redacted]. The specifications for PB are identical to those of the Ph.Eur.

The active drug substance, TUDCA, is currently marketed in Italy under the brand name Tudcabil®. TUDCA is exported to China and Turkey under the brand name Taurolite® and is used clinically for the treatment of cholesterol gallstones. TUDCA has been used for the treatment of cholestatic liver diseases including primary cirrhosis, pediatric familial intrahepatic cholestasis and primary sclerosing cholangitis and cholestasis due to cystic fibrosis. To our knowledge, there are no other uses of TUDCA. It is marketed in the United States on websites such as Amazon as a dietary supplement to “promote liver health”.

The chemical structure for TUDCA is provided below.

Chemical structure TUDCA:

The active drug substance TUDCA is manufactured by
The specifications for TUDCA are identical to those used by the supplier.

A powder filled sachet will be used as the AMX0035 drug product. The drug product will be filled under cGMP conditions in an aluminum foil lined sachet.

The sachet will contain 2 active study drug ingredients and excipients.

6.1.2 Placebo

A matching placebo will be used to maintain blinding. The placebo sachets for this study will match the corresponding AMX0035 sachets in size, color, taste, and presentation.

Sachets containing placebo will include sweeteners and excipients, but no active study drug ingredients.

Administration of matching placebo will be the same as for subjects in the treatment group.

6.2 Acquisition

Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in each shipment will be documented in the study files. The Site Investigator must notify the study sponsor of the presence of any damaged or unusable study treatments that were supplied to the site.

6.2.1 Formulation, Packaging, and Labeling

The study drug is prepackaged in kits containing 98 sachets. Each subject will receive, at minimum, a kit at the Baseline, Week 6, Week 12, and Week 18 Visits. Additional kits may be assigned and dispensed with Sponsor approval to accommodate disruptions to the visit schedule because of the COVID-19 pandemic. The SI is responsible for ensuring the integrity of packaged

study drug prior to dispensing. Each individual subject kit must be dispensed as provided with no further repackaging or labeling done at the investigational site, unless required by the institution per institutional polices.

6.2.2 Product Storage and Stability

The SI must ensure that all investigational drug supplies are stored in a locked, safe area at controlled room temperature (15-25°C) with access limited to authorized study staff. Investigational drug supplies should not be repackaged in any way.

Once subjects are given kits, they will be asked to store them away from moisture at room temperature. Stability has been assessed both at ICH standard and accelerated conditions for each of the individual active ingredients. Each active ingredient was found to be stable for over five years. Drug product will receive regular stability testing over the course of the study to ensure product stability. One-month stability will be verified prior to initiation of the proposed trial. Subjects should contact the SI in the case of damaged kits. The SI or site staff will coordinate with sponsor to determine appropriate remediation.

6.3 Dosage, Preparation and Administration of Study Intervention/Investigational Product

Subjects will open the sachet of AMX0035 and add it to a cup or other container. Subjects will then add approximately 8 oz. (1 cup) of room temperature water, stir until the powder is mostly dissolved, and consume the drink completely. It is normal for a small amount of powder to remain undissolved. Subjects should consume within one hour after the powder is added to water. Subjects may consume other beverages after consumption of study drug; however, subjects should not mix study drug with any liquid other than water.

6.4 Modification of Study Intervention/Investigational Product for a Subject

Any dosage adjustment, along with the reason(s) and dates of adjustment, will be documented in the CRF for each subject requiring this manipulation. The SI or designated licensed physician Sub-Investigator may reduce the dosage of study drug or discontinue the study drug for AEs thought to be related to the study drug or for other reasons during the trial (the reason and dates of suspension or dose reduction must be documented in CRF). If the AE is mild or moderate, the dosage may be reduced until the event improves. The SI or designated licensed physician Sub-Investigator may then choose to resume the higher dosage or maintain the subject at a reduced dosage.

If the AE is serious or life threatening, and deemed to be definitely related to drug, the study drug will be discontinued immediately. Study subjects must remain off the study drug permanently. Subjects may not resume study drug. All AEs will be followed to resolution.

6.4.1 Dosage Discontinuation

Reasons for discontinuation of study medication may include an AE, Medical Monitor or SI recommendation, sponsor termination, protocol deviation, loss-to-follow-up, subject request, or death. All serious adverse events (SAEs) that occur in a subject who has discontinued early must be recorded and reported within 24-hours of awareness.

Study subjects who discontinue study drug prematurely (early termination from study) and decide to not remain in the intention-to-treat (ITT) portion of the study will be encouraged to return for a Final Safety/Early Termination Visit and participate in a Follow-Up Telephone Call as outlined in Section 5.3.3. All subjects who discontinue study drug early and choose to remain in the ITT portion of the study will be encouraged to follow the study visits, off drug, up to the time of the Final Follow-up Telephone Call.

6.5 Accountability Procedures for AMX0035

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed, and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6.6 Assessment of Subject Compliance with AMX0035

Subjects will be instructed to return unused study medication containers (optional to return empty sachets) at each on-site clinic visit or the Early Discontinuation Visit. Site personnel will review the unused study medication and log in drug reconciliation form to determine compliance.

In the event that a remote visit occurs, each subject will be instructed to use study drug from the new kit, regardless of the amount of study drug remaining from any previous kit in the subject's possession. Drug accountability and compliance will occur at the next on-site clinic visit.

Non-compliance will be defined as taking less than 80% or more than 125% of study medication as determined by unused sachet counts. If a study subject is non-compliant with study medication, the SI and staff should re-educate and train the subject in administration of study drug. Data indicating non-compliance will be used in the end of study analysis.

6.7 Prior and Concomitant Therapy

Throughout the study, SIs may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care provided that the medications are licensed in the United States. Study subjects should not receive other experimental agents for the duration of the study. This includes marketed agents at experimental dosages that are being evaluated for the treatment of AD. All concomitant medications and/or treatments and significant non-drug therapies including

supplements and assistive devices, received by a subject should be recorded on the appropriate source document and eCRF.

Any small molecule investigational therapy being used or evaluated for the treatment of AD is prohibited beginning 3 months (84 days) prior to the Baseline Visit and throughout the study. Any immunotherapy investigational therapy is prohibited beginning 1 year (365 days) prior to the Baseline Visit and throughout the study.

6.7.1 Prohibited Medications and Contraindications

Prohibited Medications

Throughout the course of the trial, study subjects should not be treated with the following medications. If a Site Investigator learns that a subject has begun therapy with any of these medications, this should be reported to the Coordination Center immediately and action should be taken to discontinue the prohibited medication. If, for safety or health reasons, or by subject choice, the prohibited medication cannot be stopped, then the study medication should be stopped.

Prohibited medications include but are not limited to:

- HDAC Inhibitors including:
    - Valproate
    - Vorinostat (Zolinza)
    - Romidepsin
    - Chidamide
    - Panobinostat
    - Lithium
    - Butyrate
    - Suramin

- Probenecid

- Bile Acid Sequestrants including:
    - Cholestyramine and Cholestyramine Light
    - Questran and Questran Light
    - Welchol
    - Colestid and Colestid Flavored
    - Prevalite

Note on Antacids Within Two Hours of AMX0035 Administration:

Antacids containing Aluminum hydroxide or smectite (aluminum oxide) may not be taken **within two hours of administration of AMX0035** as they inhibit absorption of TUDCA. These include:

- Alamag
- Alumina and Magnesia
- Antacid, Antacid M and Antacid Suspension
- Gen-Alox
- Kudrox
- M.A.H.
- Maalox HRF and Maalox TC
- Magnalox
- Madroxal
- Mylanta and Mylanta Ultimate
- Ri-Mox
- Rulox

Aricept, Exelon, Razadyne, Namenda – If on any of these drugs, treatment must have started for no less than 3 months (84 days) prior to baseline and the dosing regimen must have remained stable for 6 weeks (42 days) prior to baseline. The Investigator anticipates that the dosing regimen at baseline will remain unchanged throughout participation in the study or must not have been discontinued from any of these drugs within one month (28 days) prior to Baseline Visit or start one of these drugs during the course of the study.

Pregnancy & Nursing Mothers

There are no adequate and well-controlled studies in pregnant women. Subjects or partners of male subjects should not become pregnant during the study or 30 days after stopping study drug. If a female subject becomes pregnant, study treatment must be discontinued immediately.

It is not known whether AMX0035 is excreted in human milk. Caution should be exercised; therefore, no subject should nurse an infant while participating in this study.

7 STUDY SCHEDULE

No study procedures should be performed prior to the signing of the informed consent form (ICF). All subjects will sign an ICF prior to undergoing any study tests or procedures. The consenting process must be completed and documented by the SI, Sub-Investigator or by an IRB approved study personnel that has been delegated to consent subjects by the SI.

At the discretion of the SI, the Screening and Week 24/Early Discontinuation visit assessments can be completed on multiple study visits. However, all cognitive testing must be performed on a single day.

Blood samples should be drawn at the end of the visit; however, the order of testing will be at the discretion of each SI.

Visit windows are consecutive calendar days, and the target visit dates, except the Final Follow-Up Call, are calculated from the Baseline Visit (Day 0 of study drug administration). The target date for the Final Follow-Up Call is calculated from the last dose of study drug.

Subjects who withdraw consent or early terminate from the study (i.e., discontinue study drug) will be asked to return for an Early Discontinuation Visit and, as needed, have a Final Follow-Up Call.

Ideally, any remote visit will be conducted using a HIPAA-compliant video conferencing platform. If video conferencing is not available or not feasible, remote visits may be conducted by phone.

Sites may send study drug to participants' residences. When transferring study drug to a participant, all reasonable efforts should be made to maintain the correct temperature. If possible, sites should use the Sponsor-selected vendor who will manage the shipments from the site to the subject using a certified shipping container and temperature monitor. Study drug is to be provided to subjects only after reviewing and documenting concomitant medications and therapies, and Adverse Events. Each subject will be instructed to use study drug from the new kit after receipt and verification of condition, regardless of the amount of study drug remaining from any previous kit in the subject's possession.

The longest period a subject may continue taking study drug without having completed the safety assessments listed below is 16 weeks/112 days.

- ECG
- Safety Labs: Hematology (Complete Blood Count with Differential), Complete Chemistry Panel, Liver Function Tests, and Urinalysis
- Vital Signs
- C-SSRS

7.1 Screening Visit

The following procedures will be performed at an office visit to determine the subject's eligibility for the study and the completion of assessments and parameters will take approximately 3-4 hours:

- Obtain written informed consent from subject
- Assess inclusion and exclusion criteria to determine subject eligibility
- Obtain medical history and demographics
- Review and document concomitant medications and therapies
- Obtain AD diagnosis history, medical history, and demographic information
- Assess and document adverse events (AEs) after subject signs informed consent form (ICF)
- Measure vital signs (blood pressure, heart and breathing rates, temperature) including height and weight
- Perform physical and neurological examinations
- Perform 12-lead ECG (Electrocardiogram)
- Administer Montreal Cognitive Assessment (MoCA)
- Administer the C-SSRS Screening Version questionnaire
- Administer Geriatric Depression Scale
- Administer Neuropsychiatric Inventory Questionnaire (NPI-Q)
- Perform MRI Scan (to be completed anytime between the Screening and up to 7 days prior to the Baseline Visit)
- Collect blood samples for
    - Clinical laboratory assessments including Hematology (CBC with differential),
    - Complete Chemistry Panel, Liver Function Tests
- Collect urine sample for urinalysis
- Perform lumbar puncture to collect CSF for biomarker analysis (to be completed anytime between the Screening Visit and up to 7 days prior to the Baseline Visit, pre-dose)
- Schedule the Baseline Visit

7.1.1 Screen Failures

Any subject who signs consent will be considered enrolled in the study. If a subject fails screening, *at a minimum*, the following information should be captured and entered in the Electronic Data Capture (EDC) System:

- Inclusion/Exclusion Criteria
- Demographics
- Reason for screen failure

7.2 Baseline Visit

This visit will take place no more than 28+5 days after the Screening Visit. The following procedures will be performed and will take approximately 3-4 hours:

- Confirm eligibility criteria are still met
- Randomize subject
- Review and document concomitant medications and therapies
- Review and document Adverse Events

- Measure vital signs (blood pressure, heart and breathing rates, temperature)
- Administer DSRS
- Administer FAQ
- Administer Neuropsychiatric Inventory Questionnaire (NPI-Q) if not performed at screening
- Administer ADAS-Cog
- Administer the C-SSRS Since Last Visit questionnaire
- Collect blood samples for:
    - Biomarkers
    - Genetic analysis
- Administer first dose of study drug. The healthcare staff member will advise the subject on appropriate delivery.
- Dispense 6 weeks of study drug

7.3 Week 1 Phone Call

This visit will take place 7±1 day after the Baseline Visit. The following procedures will be performed and will take approximately 15 minutes:

- Review and document Adverse Events
- Ask about study drug compliance and accountability
- Notify subjects of increase from one sachet per day to two sachets per day

7.4 Week 6 Visit

This visit will take place 42±14 days after the Baseline Visit. The following procedures will be performed and will take approximately 30 minutes –1 hour. To the extent possible, the Week 6 visit may be done remotely. If completed remotely, unused study drug will be collected, and compliance determined, at the next in-person visit. If allowed by local regulations and local IRB this visit can be performed at the subject's residence or preferred location:

- Review and document concomitant medications and therapies
- Review and document Adverse Events
- Administer MoCA
- Administer the C-SSRS questionnaire (Since Last Visit)
- Ask about study drug compliance and accountability
- Collect any unused study drug (optional empty study drug sachets)
- Dispense 6 weeks of study drug
- Schedule next study visit

7.5 Week 12 Visit

This visit will take place 84±28 days after the Baseline Visit.

It is preferred that the Week 12 visit be conducted at the site with the participant physically present. If it is not possible to complete an in-person Week 12 visit at the site, the safety assessments below must be completed by Week 16/Day 112 for the subject to remain on study drug. Sites may make alternative arrangements to complete these assessments per institutional and IRB policy.

- ECG
- Safety Labs: Hematology (Complete Blood Count with Differential), Complete Chemistry Panel, Liver Function Tests, and Urinalysis
- Vital Signs
- C-SSRS

If completed remotely, unused study drug will be collected, and compliance determined, at the next in-person visit.

The following procedures will be performed and will take approximately 2-3 hours:

- Measure vital signs (blood pressure, heart and breathing rates, temperature)
- Review and document concomitant medications and therapies
- Review and document Adverse Events
- Ask about study drug compliance and accountability
- Administer ADAS-Cog
- Administer DSRS
- Administer FAQ
- Administer Neuropsychiatric Inventory Questionnaire (NPI-Q)
- Administer the C-SSRS questionnaire (Since Last Visit)
- Perform a 12-Lead ECG
- Collect blood for:
    - Routine safety lab tests (chemistry and hematology assessment)
    - Biomarkers
    - Pharmacokinetics (PK)
- Collect urine sample for urinalysis
- Collect any unused study drug (optional empty study drug sachets)
- Dispense 6 weeks of study drug
- Schedule next study visit

7.6 Week 18 Visit

This visit will take place 126±14 days after the Baseline Visit. The following procedures will be performed and will take approximately 30 minutes – 1 hour. To the extent possible, the Week 18 visit may be done remotely. If completed remotely, unused study drug will be collected, and compliance determined, at the next in-person visit. If allowed by local regulations and local IRB this visit can be performed at the subject's residence or preferred location:

- Review and document concomitant medications and therapies
- Review and document Adverse Events
- Administer MoCA
- Administer the C-SSRS questionnaire (Since Last Visit)
- Collect any unused study drug (optional empty study drug sachets)
- Ask about study drug compliance and accountability
- Dispense 6 weeks of study drug
- Schedule next study visit

7.7 Week 24 Final Study Visit/Early Discontinuation Visit

This visit will take place 168±28 days after the Baseline Visit.

All reasonable efforts should be made to complete the Week 24 or Early Discontinuation visit at the site with the participant physically present. However, if COVID-19 related restrictions (e.g., site closure, travel restrictions) make it impossible to conduct an in-person clinic visit during the specified window, then any assessment that can be performed remotely should be completed as an unscheduled visit during the Week 24 window. The actual Week 24 visit, with all of the assessments indicated on the SOA, may be postponed for up to 12 weeks and treatment extended. The maximum duration a subject may be on IP is 40 weeks. Safety checks (i.e., ECG, safety labs, vital signs, and C-SSRS) must be completed, at minimum, every 16 weeks/112 days. If safety assessments are performed so that the Week 24 visit may be postponed, the assessments should be documented as an unscheduled visit.
If possible, an Early Discontinuation visit should be done within 14 days of the last dose of IP (i.e., last dose of IP + 14 days). The MRI and lumbar puncture may be done as soon as is practical and, if possible, within 60 days of the last dose of IP (i.e., last dose of IP + 60 days).

The following procedures will be performed and will take 3-4 hours:

- Measure vital signs (blood pressure, heart and breathing rates, temperature) including weight
- Review and document concomitant medications and therapies
- Review and document Adverse Events
- Perform Physical and neurological exam
- Ask about study drug compliance and accountability
- Administer ADAS-Cog
- Administer DSRS
- Administer FAQ
- Administer Neuropsychiatric Inventory Questionnaire (NPI-Q)
- Administer MoCA
- Perform MRI scan
- Perform lumbar puncture to collect CSF for biomarker analysis (can be collected up to 7 days prior to this visit. If the early discontinuation visit occurs up to 7 days after initiation of study drug, then the LP does not need to be completed)
- Administer the C-SSRS questionnaire (Since Last Visit)
- Perform a 12-Lead ECG
- Collect blood for:
    - Routine safety lab tests (chemistry and hematology assessment)
    - Biomarkers
    - PK (will not be done for subjects completing an Early Discontinuation Visit)
- Collect urine sample for urinalysis
- Collect any unused study drug (optional empty study drug sachets)
- Ask about study drug compliance and accountability
- Schedule final follow-up telephone call as needed

7.7.1 Final Follow-up Telephone Call

A follow-up phone call will take place after the Week 24 visit and within 14±5 days after the subject's last dose of study drug. For participants who discontinue treatment early, the Final Follow-Up Call is not required if the Early Discontinuation visit occurs 14 ± 5 days after administration of the last dose of study drug.

The following will be performed and will take approximately 15 minutes:

- Review and document concomitant medications and therapies
- Assess and document AEs, including AEs specified in 9.2.3

7.8 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP). The noncompliance may be either on the part of the subject, the SI, or the study site staff. In the event of deviations, corrective actions are to be developed by the site in conjunction with the coordinating team and implemented promptly.

All deviations from the protocol must be addressed in the subject's source documents. Protocol deviations must be sent to the local IRB per their guidelines and entered in the Protocol Deviations Log in the EDC system.

7.9 Missed Visits and Procedures

Missed visits and any procedures not performed (not attempted) for reasons other than illness, injury or progressive disability (i.e. subject is physically unable to perform test) will be reported as protocol deviations. Multiple missed study procedures, due to COVID-19, that does not affect data integrity or patient safety, will be documented and combined into one (1) minor protocol deviation.

Procedures or visits not performed due to illness, injury or disability, including procedures that were attempted but failed (i.e. blood samples unable to be drawn after multiple attempts, or weight unable to be obtained due to subject immobility) will not be reported as protocol deviations.

Study drug compliance that is outside the limits set in the study operations manual will be reported as a protocol deviation.

Details and specific instructions regarding protocol deviations, including any exceptions to this standard procedure, are found in the study operations manual.

8 CLINICAL ASSESSMENTS AND OUTCOME MEASURES

8.1 Clinical Variables

Assessments will be performed at designated time-points throughout the study for clinical evaluation. In addition to the assessments evaluated below, subjects will provide information related to demographics, medical and AD diagnostic history, and concomitant medication usage.

8.1.1 Vital Signs, Height, & Weight

Vital signs will be obtained after the subject has been in a seated position for several minutes. Vital signs, including blood pressure, heart rate, respiratory rate and body temperature will be assessed at Screening, Baseline, Week 12, and Week 24/Early Discontinuation Visit. Height will only be collected once at the Screening Visit. Weight will be collected when a physical exam is done at the Screening and Week 24/Early Discontinuation Visit.

If the subject cannot attend a visit at the site to have vitals measured because of COVID-19, other arrangements may be made to measure vitals as allowed per institution and local IRB policy.

8.1.2 Clinical Laboratory Assessments

The following laboratory tests will be performed for safety purposes at Screening, Week 12, and Week 24/Early Discontinuation Visits:

- Hematology with differential panel: complete blood count with differential (hematocrit, hemoglobin, platelet count, RBC indices, total RBC, Total WBC, and WBC & differential).
- Blood chemistry panel/liver function tests (LFTs): alanine aminotransferase (ALT (SGPT)), aspartate aminotransferase (AST (SGOT)), albumin, alkaline phosphatase (ALP), bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, magnesium, phosphate, potassium, sodium, total bilirubin and total protein.
- Urinalysis: albumin, appearance, bilirubin, blood, color, glucose, ketones, nitrate, pH, protein, specific gravity, urobilinogen and WBC screen.
- B12 and TSH will be assessed at Screening Visit only as common laboratory assessments that may contribute to cognitive dysfunction.

All subjects will have safety laboratory tests at the designated visits outlined in the protocol. These samples will be analyzed at a central laboratory. The SI may order additional testing, if thought to be necessary, to further assess an adverse event (AE) or if there is any suspicion that a subject may be pregnant, throughout the course of the study.

If the subject cannot attend a visit at the site to have samples collected because of COVID-19, other arrangements may be made for sample collection and analysis as allowed per institution and local IRB policy (e.g., sample may be analyzed by site or third-party laboratory).

8.1.3 Blood Draw and Urine Sample

Subjects will provide additional blood samples at baseline for genetic analysis and at Baseline, Week 12, and Week 24/Early Discontinuation Visits for biomarkers. All samples will be anonymized and labeled with a code that will not include any identifiable information. The samples are for research purposes only. Although genetic information may be analyzed, no genetic information will be given to the subject.

There is no scheduled date by which the samples will be destroyed. Samples may be stored for research until they are used, damaged, decayed, or otherwise unfit for analysis. Subjects have the option of declining participation in this portion of the study at any time by withdrawing their consent to have their sample used. However, it will not be possible to destroy samples that may have already been used.

Additionally, the central laboratory will store ship blood samples for pharmacokinetic analysis. The central laboratory facility will prepare kits for every site detailing the sampling protocol.

8.1.4 12-Lead Electrocardiogram (ECG)

A standard 12-lead ECG will be performed at Screening, Week 12, and Week 24/Early Discontinuation Visits. Tracings will be reviewed by a central ECG reader and a copy of the tracings will be kept at clinic sites as part of source documentation. The central ECG reader will provide standard ECG devices to each site as well as training. Board-certified cardiologists from the central ECG reader will review all ECGs.

If the subject cannot attend a visit at the site to have an ECG performed because of COVID-19, arrangements may be made to complete the ECG elsewhere using a device not provided by the central reader as allowed per institution and local IRB policy.

8.1.5 Physical and Neurological Examination

A physical and neurological examination will be performed at Screening and Week 24/Early Discontinuation Visits. The following systems will be examined: general appearance, head, eyes, ears, nose, throat, neck, chest, heart, abdomen, extremities, edema, peripheral vascular, skin and appendages, musculoskeletal, central nervous system and back.

8.1.6 Geriatric Depression Scale (GDS)

The Geriatric Depression Scale (Short Form) will be performed at the Screening Visit only. The GDS is a questionnaire designed to identify and quantify the presence of depression in the elderly. The scale consists of 15 yes/no questions related to how the subject has felt over the previous week. The GDS includes items to which positive and negative answers are indicative of a symptom of depression. One point is given for each such appropriate answer, with a possible total of 15

points. Total scores of 0-5 are considered normal and scores of 6-15 are considered indicative of depression. A GDS less than 7 is required for inclusion in the study.

8.1.7 Columbia Suicide Severity Rating Scale (C-SSRS)

The US FDA recommends the use of a suicidality assessment instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA)[40]. The C-CASA was developed to assist in coding suicidality data accumulated during the conduct of clinical trials of antidepressant drugs. The Columbia Suicide Severity Rating Scale (C-SSRS)[23] will be utilized in this trial. The C-SSRS involves a series of questions designed to detect possible suicidal thinking and behavior.

At the Screening Visit, the C-SSRS Screening Version will be administered. This version is used to assess suicidality over a specified time-period. The Since Last Visit Version of the C-SSRS will be administered at Baseline, Week 6, Week 12, Week 18 and Week 24/Early Discontinuation Visits. This version of the scale assesses suicidality since the subject's last visit.

8.1.8 Adverse Events

Adverse events (AEs) will be documented at each study visit, including the Screening Visit once the informed consent form has been signed by the subject, and at all study visits, including the Final Follow-up Telephone Call 14 days (± 5 days) after the last dose of study drug. Information on adverse effects of study medication and on inter-current events will be determined at each visit by direct questioning of the subjects, review of concomitant medications, and vital sign results.

8.2 Outcome Measures

8.2.1 Functional Activities Questionnaire (FAQ)

The FAQ is a brief informant-administered rating scale used to determine a subjects' level of functional independence when performing a range of instrumental activities of daily living (IADLs), with repeat assessments useful for monitoring performance in these areas over time[47]. The FAQ total score (ranging from 0-30) reflects the sum of ordinal ratings (0 = fully independent, 1 = has difficulty but does by self, 2 = requires assistance, and 3 = dependent) across ten items assessing a variety of functional activities (i.e., preparing a balanced meal, financial management skills, and shopping), with higher scores indicating increasing levels of dependence. For activities not normally undertaken by a person, a score of 1 is assigned if the informant believes the subject would be unable to complete the task if required, or a score of 0 is assigned if the informant believes the subject could successfully carry out the task if needed. Overall, the FAQ is a sensitive marker of functional impairment among individuals with varying dementia severity[43], and has been shown to differentiate mild cognitive impairment from early Alzheimer's Disease with 80% sensitivity and 87% specificity[49]. The FAQ demonstrates high reliability (exceeding 0.90), takes

about 5 minutes to complete, and requires limited rater training to administer[47]. The FAQ will be administered at the Baseline, Week 12, and Week 24/Early Discontinuation Visits.

8.2.2 Dementia Severity Rating Scale (DSRS)

The DSRS is a brief 12-item questionnaire administered to an informant that assesses a subjects' functional abilities[44] and offers a global characterization of everyday activities that may be impacted by neurodegenerative disease. The DSRS is designed in a multi-choice format with strong concurrent validity and parallel content to material covered on the Clinical Dementia Rating Scale (CDR), a commonly employed dementia staging instrument[46]. The DSRS is a highly reliable scale with an intra-class correlation of >90% for interrater reliability and Cronbach's alpha > 0.70 for internal consistency[48], and has been shown to accurately discriminate between cognitive healthy individuals and dementia subjects of varying severity[44,45]. Further, the DSRS allows for a broad range of scores (total score 0-54) making it suitable to quantify a wide range of functional impairment without being hampered by floor effects seen in more advanced disease, while also making it sensitive to detecting incremental change in functional ability over time[50]. The DSRS takes about 5 minutes to administer, requires minimal rater training, and can be administered over the phone to study subjects if required. The DSRS will be administered at the Baseline, Week 12, and Week 24/Early Discontinuation Visits.

8.2.3 Cognitive Evaluations

Cognitive testing will include evaluations of the ADAS-Cog and Montreal – Cognitive Assessment (MoCA).

The ADAS-Cog is validated and widely used as a primary cognitive outcome measure in AD pharmacotherapy studies. This is a psychometric instrument that evaluates memory (immediate and delayed word recall, word recognition), attention (number cancellation), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope) and constructional praxis (copying geometric designs), and executive functioning (maze completion). Scoring is in the range of 0 to 90 with a higher score indicating greater impairment. This test will be administered by experienced raters at each site at Baseline, Week 12, Week 24/Early Discontinuation Visits. The ADAS-Cog will be the primary cognitive outcome measure for this study.

If the ADAS-Cog is administered remotely, it should be completed to the extent possible given the available technology. If the ADAS-Cog cannot be completed remotely, then it should be documented as a minor deviation.

Montreal Cognitive Assessment (MoCA) is commonly utilized questionnaire in clinical trials and research settings to measure levels of cognitive impairment. The MoCA measures five areas of cognitive function: orientation, visuospatial, attention and calculation, recall, and language. The MoCA will take approximately 10 minutes to complete. The test will be administered by

experienced raters at each site at Screening, Week 6, Week 18, Week 24/Early Discontinuation Visit. See Appendix III (section 13.3) for the worksheet.

The 3 available versions of the MoCA test will be administered by experienced raters at each site. Subjects may be given any version of the MoCA at the Screening Visit as long as they have NOT received the same MoCA version clinically within the last 3 months. A different version of the MoCA should be used at each subsequent visit until Week 24 or Early Termination visit (if applicable). The MoCA version used at a study visit should be accurately documented in Source Document and within the EDC for each visit.

Re-screening: In cases where the subject screen fails due to the MoCA score being out of the required inclusionary range at the Screening Visit, the subject may be re-screened; a minimum of one month must have passed since their original MoCA assessment. If the subject's MoCA score was < 10, they must have had a change in therapy or intervention that (in the opinion of the SI) may have an impact on the subject's cognitive status. Subjects who move forward with a re-screen must be evaluated using a different MoCA version (7.1, 7.2 or 7.3) that was used at the original Screening Visit, and subjects may be re-screened only once.

If the MoCA is administered remotely, it should be completed to the extent possible given the available technology. If the MoCA cannot be completed remotely, then it should be documented as a minor deviation.

8.2.4 Neuropsychiatric Inventory Questionnaire (NPI-Q)

The Neuropsychiatric Inventory (NPI) measures dementia-related behavioral symptoms and is used to assess changes in psychological status. There are several versions of the NPI including the NPI-Questionnaire (NPI-Q), NPI-Clinician (NPI-C) and the NPI-Nursing Home (NPI-NH). All examine 12 sub-domains of behavioral functioning including: hallucinations, delusions, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor activity, eating abnormalities, and night-time behavioral alternations. The NPI-Q is completed by a trained rater through interview with the subject's study partner. It is well-validated and extensively used in clinical trials in AD. The NPI-Q will be administered at the Screening or Baseline, Week 12 and Week 24/Early Discontinuation Visits.

8.2.5 Lumbar Puncture for CSF Biomarker [redacted]

Cerebrospinal fluid (CSF) [redacted] biomarkers [redacted] CSF samples will be collected prior to AMX0035 treatment, anytime between the screening visit and up to 7 days prior to the baseline visit the baseline visit and following 24 weeks of treatment at the final study visit or at the early discontinuation visit.

Subjects will have a fasting morning CSF sample taken anytime between the Screening and up to 7 days prior to the Baseline Visit (pre-dose) and the Week 24 and/or the Early Discontinuation Visit. If the Early Discontinuation Visit occurs within 7 days after the initiation of study drug (Baseline Visit), then the LP does not need to be completed. Lumbar punctures (LPs) will be performed by qualified, experienced practitioners. Standard protocols will be used employing sterile conditions, local lidocaine anesthesia, and preferred use of the Sprotte 24-gauge needles, which minimizes incidence of post-LP headaches. Approximately 15-20 cc of CSF will be collected for CSF biomarker , as well as routine chemistry (protein, glucose) and cell count.

8.2.6 Neuroimaging

MRI Scans: In accordance with secondary study objectives, all subjects will undergo 3T structural and functional MRI will be completed anytime between the Screening and up to 7 days prior to Baseline Visit and Week 24 and/or the Early Discontinuation Visits to assess the effect of treatment on brain volume, cerebral perfusion, and brain connectivity. Each scan session will last approximately 35 minutes and include the following MR pulse sequences: high resolution T1-weighted multi-echo MPRAGE for volumetric analysis, task-free blood oxygen level dependent (BOLD) sequence to measure resting neural connectivity, diffusion tensor imaging (DTI) to quantify white matter structural connectivity, susceptibility-weighted imaging (SWI), and a T2-weighted fluid attenuated inversion recovery (FLAIR) sequence. Radiologist at each site will provide a clinical read. For volumetric analysis, high resolution T1-weighted images will undergo reconstruction and volumetric segmentation using the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/).

8.2.7 Pharmacokinetics

Plasma concentrations of both TUDCA and PB will be assessed at the Week 12 and Week 24 (approximately at the same time as CSF sample, if taken on the same day). The time of the previous two drug administrations and the time of the sample will be noted in the eCRF. A PK sample will not be taken at an Early Discontinuation Visit if the subject discontinued study drug more than 48 hours before the visit.

8.2.8 Training and Validation

All evaluators must be certified by the study PI to perform cognitive and psychiatric outcome assessments. It is strongly preferred that a single evaluator performs all measures with a given instrument throughout the study, if possible. Please refer to Section G of the site MOP for a more detailed description of the training and certification for the outcome assessments.

9 SAFETY AND ADVERSE EVENTS

The adverse event (AE) definitions and reporting procedures provided in this protocol comply with all applicable United States Food and Drug Administration (FDA) regulations and International Conference on Harmonization (ICH) guidelines. The Site Investigator will carefully monitor each subject throughout the study for possible adverse events. All AEs will be documented on CRFs designed specifically for this purpose. It is also important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

9.1 Definitions of AEs, Suspected Adverse Drug Reactions & SAEs

9.1.1 Adverse Event and Suspected Adverse Drug Reactions

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device.

Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs, if there is a suspected causal relationship to the medicinal product.

Examples of adverse events include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (i.e. skin rash, peripheral edema, etc.), or clinically significant abnormal test results (i.e. lab values or vital signs), with the exception of outcome measure results, which are not being recorded as adverse events in this trial (they are being collected, but analyzed separately). Stable chronic conditions (i.e., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered adverse events. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity, would be considered as worsened and therefore would be recorded as adverse events.

Adverse events are generally detected in two ways:

Clinical - symptoms reported by the subject or signs detected on examination.

Ancillary Tests - abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures, the results of which are not being captured as AEs).

For the purposes of this study, symptoms of clinically noteworthy progression/worsening of cognitive, behavioral or functional abilities will be recorded as AEs.

The following measures of disease progression will not be recorded as AEs even if they worsen (they are being recorded and analyzed separately): ADAS-Cog, DSRS, and FAQ.

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Site Investigator and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Site Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by the SI.

Subjects will be monitored for AEs from the time they provide and sign consent until completion of their participation in the study (defined as death, consent withdrawal, loss to follow up, early study termination for other reasons or following completion of the entire study). Any treatment AE still present upon completion of treatment (including early discontinuation) should be monitored until resolution or until the AE is declared a chronic condition.

An unexpected adverse event is any AE in which the specificity or severity of which is not consistent with the current Investigator's Brochure. An unexpected, suspected adverse drug reaction is any unexpected adverse event that, in the opinion of the SI or Sponsor, has a reasonable possibility of being related to the investigational product.

9.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
    a. This serious criterion applies if the study subject, in the view of the Site Investigator or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    a. Hospitalization for an elective procedure or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled "procedure" or a "treatment" is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
    a. This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the subject's ability to carry out normal life functions.

5. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
6. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse experience, and will therefore not be considered an SAE. An example of this would include a social admission (subject admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

A serious, suspected adverse drug reaction is an SAE that, in the opinion of the SI or Sponsor, there is a reasonable possibility is related to the investigational product.

The SI is responsible for classifying adverse events as serious or non-serious.

9.2 Assessment and Recording of Adverse Events

The Site Investigator will carefully monitor each subject throughout the study for possible AEs. All AEs will be documented on source document templates and eCRFs designed specifically for this purpose. All AEs will be reported in the EDC system and compiled into reports for periodic reviewing by the Medical Monitor. The Medical Monitor shall promptly review all information relevant to the safety of the investigational product, including all serious adverse events (SAEs). Special attention will be paid to those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

9.2.1 Assessment of Adverse Events

At each visit (including telephone interviews), the subject will be asked if they have had any problems or symptoms since their last visit in order to determine the occurrence of adverse events. If the subject reports an adverse event, the Site Investigator will probe further to determine:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild, moderate, severe)
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease
6. Action taken regarding investigational product
7. Outcome

9.2.2 Relatedness of Adverse Event to Investigational Product

The relationship of the AE to the investigational product should be specified by the Site Investigator, using the following definitions:

1. Not Related: Concomitant illness, accident, or event with no reasonable association with treatment.

2. Unlikely: The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists.

3. Possibly Related: The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject. (Suspected ADR)

4. Probably Related: The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state. (Suspected ADR)

5. Definitely Related: The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure. (Suspected ADR)

9.2.3 Adverse Events in Prior Human Experience with Each Individual Component

Both TUDCA and PB have been evaluated individually in multiple patient populations. The most commonly reported adverse events are below:

TUDCA:

- A small number of subjects receiving TUDCA have presented with mild diarrhea, abdominal and pain
- Rare incidences of skin rash and vomiting have been observed

PB:

- Menstrual irregularities, decreased appetite, sweat-like body odor, and bad taste Less common side effects include: nausea, vomiting, stomach upset, stomach pain, gastritis, headache, and skin rash. Rarely, cases of peptic ulcers, rectal bleeding, constipation, pancreatitis and renal tubular acidosis have been reported.
- Hypoalbuminemia, metabolic acidosis, alkalosis, hyperchloremia, hyperuricemia, hypokalemia, hypophosphatemia, hyperphosphatemia and hypernatremia have been observed.

9.2.4 Recording of Adverse Events

All clinical adverse events are recorded in the Adverse Event (AE) Log in the subject's study binder. The site should fill out the AE Log and enter the AE information into the EDC system within 48 hours of the site learning of a new AE or receiving an update on an existing AE.

Please Note: Serious Adverse Events (SAEs) must be reported to the MGH Coordination Center within 24 hours of the site learning of the SAE.

Entries on the AE Log (and into the EDC) will include the following: name and severity of the event, the date of onset, the date of resolution, relationship to investigational product, action taken, and primary outcome of event.

9.3 Adverse Events and Serious Adverse Events - Reportable Events

The following are considered reportable events and must be reported to the MGH Coordination Center within 24 hours of the site being notified of the event.

- All events that meet the above criteria for Serious Adverse Events (SAEs)
- Dosage Changes (Dose Management)
  - Investigational Product Suspension, Reduction or Re-challenge
  - Investigational Product Discontinuation

10 DATA SAFETY MONITORING AND STATISTICAL ANALYSIS PLAN

10.1 Medical Monitoring

A Medical Monitor independent of the trial conduct will be identified by the Study Sponsor. The Medical Monitor's responsibilities will include a regular evaluation of the frequency, severity and type of AEs and SAEs reported by all sites in the study. The Medical Monitor will be a physician with expertise in Alzheimer's disease and common chronic medical (e.g., renal and cardiac) conditions in this elderly patient population and with prior experience with the conduct of clinical trials (trial design, safety monitoring, and recruitment). All AEs will be collected and reported in the electronic data capture (EDC) system and compiled into bi-monthly blinded reports for periodic reviewing by the Medical Monitor. Any possibly, probably or definitely study drug related, serious adverse events (i.e. suspected unexpected serious adverse drug reactions, or SUSARs) and any death are considered events of interest and will be reported in real-time (within 1 business day of Coordination Center (CC) awareness) to the Medical Monitor and to members of the PSC. The Medical Monitor will approve the format and content of the periodic safety report. The Medical Monitor shall promptly review all information relevant to the safety of the investigational product, including all serious adverse events (SAEs) and AEs unusual in the context of Alzheimer disease. Special attention will be paid to those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious. The Medical monitor may ask to receive the AE reports more frequently. The Medical Monitor will communicate their recommendations to the PSC.

10.2 Protocol Steering Committee

The Protocol Steering Committee (PSC) is composed of the Principal Investigator of the study (serving as SC Chair), the study biostatistician, independent Investigator members with expertise in Alzheimer's disease and study-related medical (e.g., renal and cardiac) conditions and priorities (trial recruitment and drug supply) and the Sponsor Acting Medical Director. The PSC is responsible for the design of the study protocol and analysis plan and oversees the clinical trial from protocol development to study analysis and publication.

10.3 Statistical Methods

Complete details of efficacy and safety analyses will be provided in a separate Statistical Analysis Plan (SAP).

10.3.1 Sample-Size Determination

A sample size of approximately 100 randomization subjects was chosen based on feasibility and is not based solely in statistical considerations. Subjects will be randomized in a ratio of 3:2 (active versus placebo). In order to maximize study power for evaluation of efficacy end-points, a global test statistic will be used. The global test statistic will be a combination of 3 change-from-baseline to end-of-study endpoints (univariate components), including the following:

- Cognition
- Activities of Daily Living (ADL)
- Total Hippocampal Brain Volume

The global test statistic will be calculated for each subject as a mean percentile score across the above 3 component endpoints for each subject in the study. This mean percentile score will then be analyzed as the primary efficacy outcome variable. For purposes of power calculations, global test statistics can be characterized based on the assumed effect sizes of each of the 3 component endpoints and the correlations between each of the 3 pairs of component endpoints.

Use of a global test statistic can handle the case of correlated univariate endpoints and provide substantially greater power than the use of univariate test statistics, even when the component univariate endpoints have unequal magnitudes of treatment effects in favor of the active treatment. We assume a correlation of 0.4 between the cognitive and ADL component endpoints and a correlation of 0.2 between the total hippocampal volume component endpoint and each of the other two components endpoints (i.e., the cognitive component endpoint and the ADL component endpoint), based upon historical analyses. By using 50% statistical power and the assumed effect sizes as inputs, we can obtain the "expected p-value" for 2 selected combinations of component endpoints of the composite. We do this in 2 stages, first for the combination of ADAS-Cog and ADL component endpoints, which have expected p-values of 0.09409 and 0.20184, respectively, resulting in a 2-component expected p-value of 0.077583. Then we combine the 2-component expected p-value with the expected p-value for Total Hippocampal Brain Volume (0.20184), to get a global test statistic expected p-value of 0.049756.

Each of the 3 component scales may have a different sensitivity with respect to detecting change over time. The sensitivity is quantified using the Mean-to-Standard Deviation Ratio (MSDR), which is calculated by dividing the mean of the change-from-baseline score by the standard deviation of the change-from-baseline score. For change-from-baseline to 6 months, we assume the MSDR values for ADAS-Cog, ADL, Total Hippocampal Volume are 0.8, 0.6, and 0.6, respectively. We assume a 60% value for Percent of Placebo Effect (i.e., the decline for the active treatment group is only 40% of the decline of the Placebo group). This corresponds to effect size (assumed treatment difference divided by the common standard deviation) values of 0.48 for the Cognitive Endpoint, 0.36 for the ADL endpoint, and 0.36 for the Total Hippocampal Brain Volume endpoint. As described previously, using these expected p-values and the assumed correlations between each pair of these 3 endpoints results in an expected p-value of 0.049756 for the global test statistic.

Using 100 randomized subjects (assuming either no subject dropout so that there are 100 completers, or that imputation appropriately accounts for subject dropout), 50% power, a randomization ratio of 1:1, gives an effect size (corresponding to the use of the global test statistic)

of 0.566; this indicates that that under these assumptions use of the global test statistic is equivalent to using a single component test statistic with an effect size of 0.566 (rather than the assumed effect sizes of 0.48 for ADAS-Cog, 0.36 for ADL, and 0.36 for Total Hippocampal Brain Volume). Another way to interpret this is that using of the global test statistic, corresponding to an assumed effect size of 0.566 for a single component endpoint, and using $\alpha = 0.05$ results in a power of approximately 50% (50.1%). So, when the individual components of the global test statistic are in the same direction (and in favor of the active treatment group versus placebo), then use of a global test statistic generally provides more power than use of a single component.

Although the power calculations (see table below) show 80% power for an assumed Percent of Placebo Effect value of 85%, a Percent of Placebo Effect value as small as 50% or 60% would still be clinically relevant and would be an encouraging indication for moving forward into a new study. As described previously, a Percent of Placebo Effect value of 60% corresponds to global test statistic p-value of approximately 0.05 (0.049756, 2-sided), an effect size of 0.566, and a power of approximately 50%. A global test statistic p-value of 0.10 (2-sided) would be an observed trend that would still be suggestive of a signal indicating that moving forward into a new study would be appropriate. This corresponds to Percent of Placebo Effect value of just under 50%: a Percent of Placebo Effect value of 50% corresponds to global test statistic p-value of approximately 0.095 (0.09477, 2-sided), an effect size of 0.479, and a power of approximately 38% at a 2-sided alpha=0.05 level.

Percent of Placebo Effect	Cog. Effect Size	ADL Effect Size	Total Hipp. Brain Volume Effect Size	Cog. Expected p-value (2-sided)	ADL Expected p-value (2-sided)	Total Hipp. Expected p-value (2-sided)	Cog. & ADL Combined Expected p-value (2-sided)	Global Test Statistic Expected p-value (2-sided)	Global Test Statistic Effect Size	Global Test Statistic Power (%)
50%	0.40	0.30	0.30	0.15959	0.27395	0.27395	0.135094	0.09477	0.479	38.3
60%	0.48	0.36	0.36	0.09409	0.20184	0.20184	0.077583	0.049756	0.566	50.1
70%	0.56	0.42	0.42	0.05206	0.14709	0.14709	0.042619	0.024794	0.651	61.7
80%	0.64	0.48	0.48	0.02727	0.09409	0.09409	0.020349	0.009933	0.754	74.4
85%	0.68	0.51	0.51	0.01937	0.07588	0.07588	0.013962	0.006283	0.803	79.5
90%	0.72	0.54	0.54	0.01358	0.06069	0.06069	0.009432	0.003896	0.852	84.0
100%	0.80	0.60	0.60	0.00646	0.03793	0.03793	0.004131	0.001417	0.951	90.9

Some additional examples of the global test statistic under various assumed Percent of Placebo Effect values and corresponding effect sizes (and using the pairwise correlations of 0.4, 0.2, and 0.2 described previously) are given below, along with the examples described previously. (Note that a Percent of Placebo effect value of 0% means that active treatment declines as much as Placebo, a value of 50% means that active treatment declines half as much as Placebo, and a value of 100% means that the active treatment doesn't decline at all over the 6-month treatment period.)

10.3.2 Study Unblinding

After database lock, the responsible statistician will request the treatment codes, the study will be unblinded, and the statistical analysis will be conducted.

10.3.3 Safety Endpoints

10.3.3.1 Safety Endpoints

The primary safety end-point will be the incidence of treatment emergent Grade II-IV adverse events.

Other safety endpoints are:

- Incidence and severity of treatment emergent adverse events (AEs)
- Clinical laboratory tests
- Vital signs
- Physical examinations
- ECGs
- Use of concomitant medications for treatment of AEs
- C-SSRS

10.3.3.2 Primary Efficacy Endpoints

The primary efficacy endpoint will be a global test statistic for change from Baseline to 24 weeks as described in Section 10.2.1 ("Sample-Size Determination").

10.3.3.3 Secondary Efficacy Endpoints

The change in the following assessments from Screening and/or Baseline to each post-baseline visit as described below based on the Schedule of Activities between the AMX0035 treatment group and the placebo treatment group in the ITT population:

- Cognition Endpoint component for the global test statistic (Baseline, Week 12, and Week 24)
- ADL Endpoint component for the global test statistic (Baseline, Week 12, and Week 24)
- Total Hippocampal Brain Volume (Screening/Baseline and Week 24)
    - Additional volumetric MRI brain volume parameters, to be defined in the SAP (Screening/Baseline and Week 24)
- ADAS-Cog (Baseline, Week 12, and Week 24)
- FAQ (Baseline, Week 12, and Week 24)
- DSRS (Baseline, Week 12, and Week 24)
- NPI-Q (Screening/Baseline, Week 12, and Week 24)
- MoCA (Screening, Week 6, Week 18, and Week 24)

Derivation for the Cognition Endpoint component and the ADL Endpoint component for the global test statistic will be designed to optimize sensitivity in the MCI and mild-to-moderate AD populations by using scales specific to each of these two populations (with some overlapping tests and some tests distinct to each population. The process of combining scores for each scale (i.e., Cognition Endpoint component and ADL Endpoint component) across the two populations will be described in detail the SAP.

A Mixed-effects Model for Repeated Measures will be used to calculate differences at 12 and 24 weeks, using baseline assessment as a covariate.

Secondary efficacy endpoints will be assessed using MMRM. For each of the 3 component efficacy endpoints (based on Cognition, ADL, and Total Hippocampal Brain Volume) which are used to calculate the global test statistic, a sensitivity analysis using Pattern Mixture Models (PMM) as described in Section 10.3 ("Missing Data") will be done to impute missing data at Week 24.

10.3.3.4 Volumetric MRI

Observed Case analysis for differences in change of vMRI over 24 weeks.

10.3.3.5 CSF

10.3.4 Analysis Populations

The safety population included all randomized subjects who received at least 1 dose of study medication. Subjects in the safety population will be analyzed based on the treatment they actually received, and not necessarily the one to which they were randomized.

An intent-to-treat (ITT) approach was used to define the primary efficacy analysis population. For a given endpoint, all randomized subjects who received any study medication, had a baseline assessment, and had at least 1 post-baseline efficacy assessment for the primary efficacy endpoint will be included in the ITT population. In the ITT population, subjects who switched treatment groups over the course of the study will be analyzed based on their randomized treatment, and not necessarily the treatment they actually received.

10.3.5 Analysis for Safety

The Safety population will be used for analyses of each of the safety endpoints. All concomitant medications will be tabulated according to drug class and preferred term using the WHO dictionary. The safety data will be summarized by treatment group. Treatment AEs will be coded and graded using MedDRA grading criteria. The treatment groups will be compared with respect to occurrence of each adverse event and incidence of Grade II/IV adverse events. Withdrawal,

abnormal laboratory tests, vital signs and use of concomitant medications used for treatment of AEs will be assessed to characterize the safety profile of the combination of PB and TUDCA. Compliance data will be determined for each visit and by treatment group. The time to subject refusal will be compared between treatment groups to better determine tolerability. This will be accomplished using a method of survival analysis that allows informative censoring due to death. Descriptive statistics denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

10.3.5.1 Adverse Events

Adverse events (AE) occurring after the start of study drug dosing at Baseline will be summarized descriptively for the safety population. All AEs will be coded according to system organ class (SOC) and preferred term (PT) using a Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Summary tables showing the number of subjects and percent within each category will be generated for each of the following types of adverse events and its relationship to study treatment (related to study treatment):

- All events
- Serious events
- Deaths
- Events leading to withdrawal
- Severe events

Treatment AEs will be coded and graded using MedDRA grading criteria. The treatment groups will be compared with respect to occurrence of each adverse event and incidence of Grade II/IV adverse events. Total number of adverse events will be compared between groups using Fisher's exact test. Any treatment AE still present upon completion of treatment (including early discontinuation) should be monitored until resolution or until the AE is declared a chronic condition. AEs will be monitored until they become chronic or have completely resolved.

10.3.5.2 Laboratory Parameters

Laboratory parameters will be summarized by visit. Descriptive statistics denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided. Frequencies of high and low values with respect to the normal range will be displayed, as will shift tables comparing each treatment visit and Baseline visit by time point and treatment group. Abnormal laboratory tests will be compared between groups using Fisher's exact test.

10.3.5.3 Other Safety Parameters

Vital signs will be summarized across groups by visit using descriptive statistics, and at each outcome visit and at end of study. Physical examination findings and number of subjects will be

summarized as the count and percentage of subjects by eCRF pre-defined categories at last visit. Change from baseline at last visit will be summarized in a shift table comparing baseline and last visit results. Concomitant medications will be summarized by treatment group, drug class and preferred term. The change in the C-SSRS score from Baseline to each post-baseline visit will be summarized between the active treatment group and the placebo treatment group.

10.3.6 Analysis for Efficacy

Analysis of primary and secondary efficacy endpoints will be performed on the ITT population.

The primary efficacy analysis will be based on the use of a global test statistic as described in Section 10.3.1 ("Sample-Size Determination"). The null hypothesis will be that there is no difference between the treatment groups, and the corresponding alternative hypothesis is that treatment with AMX0035 will result in a statistically significant difference (in favor of the active treatment group) in the global test statistic score relative to the placebo group at Week 24 in the ITT population. As described in Section 10.3.1, the global test statistic p-value will be calculated using the 3 individual component p-values (corresponding to change from baseline to Week 24 for the Cognition Endpoint, ADL Endpoint, and Total Hippocampal Brain Volume) and the 3 pairwise correlations values between the 3 endpoints.

The primary efficacy analysis using the global test statistic will be based on using the Pattern Mixture Model (PMM) approach described in Section 10.4 ("Missing Data") in order to impute any missing data at Week 24 for the 3 component endpoints (i.e., Cognition Endpoint, ADL Endpoint, and Total Hippocampal Brain Volume). A secondary analysis using the global test statistic will be based on using observed cases.

Analyses for secondary efficacy endpoints will be conducted using mixed models for repeated measures (MMRM). The mixed model analysis will compare the estimated change from baseline (CFB), or change from screening (as applicable), between active treatment and placebo in all efficacy outcome scores at each scheduled post-baseline visit. Separate repeated measures longitudinal models will be used for each efficacy endpoint. This analysis will assess whether there is a difference in estimated CFB values between treatment groups. SAS PROC MIXED will be used to fit the MMRM models, with CFB of each of the efficacy outcomes (e.g., ADAS-cog Total Score) as the response variable and certain covariates and fixed effects as will be specified in the SAP prior to study unblinding. Full details of these analysis will be provided in the SAP.

Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), median, minimum, maximum, first and third quartiles, unless otherwise noted. Frequencies and percentages will be calculated for categorical variables. Percentages will be calculated within each treatment group on the number of non-missing observations.

Subgroup analysis (e.g., based on subgroups defined by gender, age, baseline MoCA score) will be performed in the ITT population.

10.4 Missing Data

Subjects who drop out will have all available post-baseline data included in the analysis. In addition, some subjects may have missing data, because of visits completed remotely during the COVID-19 pandemic. The mixed model for repeated measures is based on an assumption of Missing at Random (MAR) and is designed to handle right-censored data for subjects who drop out of the study. An additional analysis will be performed as a sensitivity analysis in this study and will be a z-score based pattern mixture model (PMM) approach. The PMM will use an MAR assumption, and this sensitivity analysis will use a subject's last observed value and the z-score of that observation as a carried forward value, assuming a pattern of progression similar to subjects within the same treatment group who completed each visit. At each subsequent visit, a value will be imputed such that it has the same z-score relative to that subject's treatment group mean and standard deviation for completers at that visit. The first analysis is intended to estimate the treatment effect expected if all subjects continued on treatment. After imputation for the sensitivity analyses, the estimated change from baseline between active and placebo group will be assessed by fitting an analysis of covariance (ANCOVA) model. Further details for the handling of missing data, as well as a detailed description of the ANCOVA analysis model, will be provided in the SAP.

10.5 Stopping Rules

The Study PI will review safety data throughout the trial and may stop the trial for safety. Any death will lead to prompt review by the Medical Monitor and Global Study PI. Two or more of the same SAE deemed probably or definitely related to study drug by Site Investigators, will lead to prompt review by the Medical Monitor and Study PI.

10.6 Interim Analysis

No interim analysis is planned.

11 DATA COLLECTION, MANAGEMENT AND MONITORING

11.1 Role of Data Management

Data Management (DM) is the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with NCRI policies, and applicable Sponsor and regulatory requirements. Site personnel will collect, transcribe, correct, and transmit the data onto source documents, Case Report Forms (CRFs), and other forms used to report, track and record clinical

research data. Clinical sites will be monitored to ensure compliance with data management requirements and Good Clinical Practices. DM is responsible for developing, testing, and managing clinical data management activities.

11.1.1 Data Entry and Checks

Site personnel are encouraged to enter information into the EDC system within 5 days of a study visit. Data collection is the responsibility of the staff at the site under the supervision of the SI. During the study, the SI must maintain complete and accurate documentation for the study.

The EDC includes password protection. An edit checking and data clarification query process will be put in place to ensure accuracy and completeness of the database. Logic and range checks as well as more sophisticated rules will be built into the EDC to provide immediate error checking of the data entered. The system has the capability to automatically create electronic queries for forms that contain data inputs that are out of range, missing, or not calculated correctly. Sites will only have access to queries concerning their subjects.

11.1.2 Data Lock Process

The application will have the ability to lock the database to prevent any modification of data once the study is closed. Once this option is activated, every user will have Read-Only access to the data. The database can only be locked after each SI has signed off on their subjects and all queries have been resolved.

11.1.3 Quality Assurance

Protocol procedures are reviewed with the SI and associated personnel prior to the study to ensure the accuracy and reliability of data. Each SI must adhere to the protocol detailed in this document and agree that any changes to the protocol must be approved by the Coordination Center prior to seeking approval from the site IRB. Each Site Investigator will be responsible for enrolling only those study subjects who have met protocol eligibility criteria.

11.2 Clinical Monitoring

Study Monitors will visit each study site to review source documentation materials, informed consent forms, and confirm entered data and that data queries have been accurately completed, and again at a study close-out visit. Study Monitors will also verify that SAEs and protocol deviations have been reported appropriately, as required. The Study Monitors will review clinical facilities, resources and procedures for evaluating study subjects and study drug dispensing. Subsequently, the Study Monitors will provide monitoring reports to the Project Manager and, if requested, will provide reports of protocol compliance to the Study PI. Completed informed consent forms from each subject must be available in the subject's file and verified for proper documentation. A document outlining the monitoring plan is provided to each Study Monitor.

11.3 Data Handling and Record Keeping

The SI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Dark ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Source document templates (SDTs) will be provided for use and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents and discrepancies should be explained. The Coordination Center will provide guidance to SIs on making corrections to source documents and eCRFs.

A patient Global Unique Identifier (GUID) will be used as the identifier for the participants included in the study. The GUID is an 11-character string that is generated using encryption technology licensed by the NCRI from the National Institutes of Health (NIH) in 2013.

The GUID is generated on a secure website that utilizes 128-bit Secure Socket Layer (SSL). On the website, the GUID is generated using an irreversible encryption algorithm-it accepts twelve identifying data elements, (e.g. last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth, etc.), and produces a unique random-generated character string, or GUID. No identifying information is stored in the system; it is simply used to generate the GUID. If the same information is entered into the secure website in the future, the same GUID will be generated.

11.3.1 Confidentiality

Study subject medical information obtained in this study is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. All local and federal guidelines and regulations regarding maintaining study subject confidentiality of data will be adhered to.

Data generated throughout study must be made available for inspection by representatives of the US FDA, the Office for Human Research Protections (OHRP), the Sponsor, all pertinent national and local health and regulatory authorities, the Coordination Center or their representative, Study Monitoring personnel, and all local IRBs.

11.3.2 Study Discontinuation

The study can be terminated at any time by the Sponsor, Medical Monitor, or FDA. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to study subjects.
- Study subject enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Sponsor withdraws funding.

11.3.3 Retention of Records

US FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs (if applicable), consent forms, laboratory test results, and medical inventory records, must be retained by the SI for two years after marketing application approval. If no application is filed, these records must be kept for two years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified. The Coordination Center or their representative will notify the Site Investigators of these events. The Site Investigators should retain all study documents and records until they are notified in writing by the Sponsor or their representative.

11.3.4 Publications

The Study PI of the clinical trial, [redacted], along with the sponsor, Amylyx Pharmaceuticals, Inc., will be responsible for publication of results from this trial. Their responsibilities will include the following:

- Analysis and interpretation of data gathered in this study.
- Dissemination of data in the form of a peer-reviewed publication.
- Submit manuscripts to selected journals and address peer reviewers' comments.
- Submit abstracts to selected meetings and present data at the meetings.
- Determine authorship on the basis of the Uniform Requirements for Manuscripts.

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13 APPENDICES

13.1 Appendix I: Columbia-Suicide Severity Rating Scale (C-SSRS) Screening Version

Information obtained from: http://www.cssrs.columbia.edu/

COLUMBIA-SUICIDE SEVERITY

RATING SCALE

(C-SSRS)

Screening

Version 1/14/09

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

Disclaimer:

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

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

For reprints of the C-SSRS contact [redacted] *New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* [redacted]

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 60 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. ***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 <u>some intent to act on such thoughts</u>, 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.	**Yes** **No** □ □

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: _____ _____ _____	
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 you (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop (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 on 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 living with the pain or how you were feeling) (0) Does not apply	____

2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Past 60 Years or Lifetime**
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 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	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

2 = Behavior likely to result in death despite available medical care			

13.2 Appendix II: Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit Version

Information obtained from: http://www.cssrs.columbia.edu/

C-SSRS (COLUMBIA – SUICIDE SEVERITY RATING SCALE – SINCE LAST VISIT)

Since Last Visit Version 1/14/09

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

Disclaimer:
This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.
Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*
For reprints of the C-SSRS contact [redacted] *., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* [redacted]

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). ***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	____

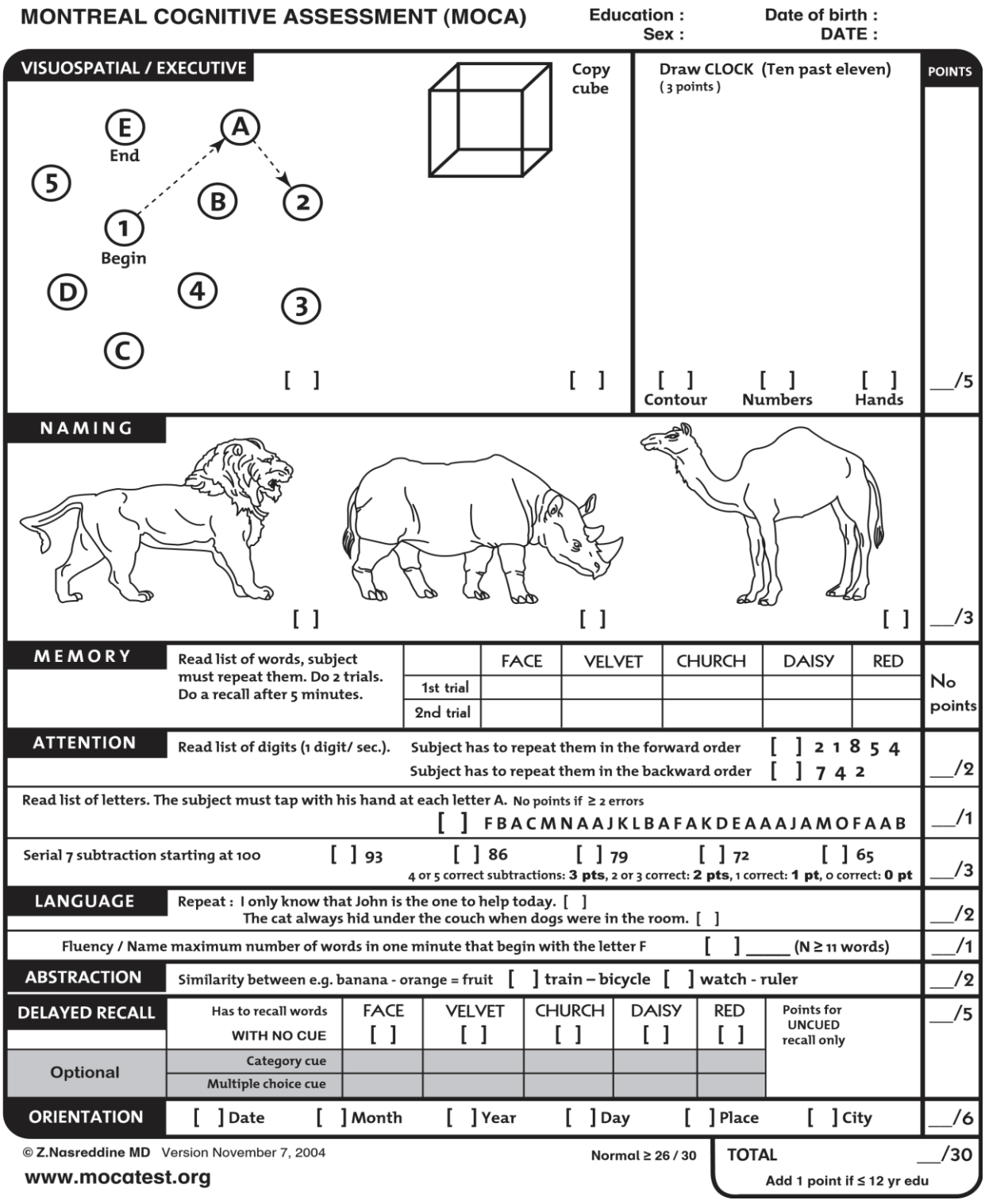
Deterrents *Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?* (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents 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 living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain living with the pain or how you were feeling) (4) Mostly to end or stop the pain (you couldn't go on (5) Completely to end or stop the pain (you couldn't go on (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_____?	Yes No □ □ Total # of Attempts _____ Yes No

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?**	□ □
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* _____

13.3 Appendix III: Montreal Cognitive Assessment (MOCA)



MONTREAL COGNITIVE ASSESSMENT (MOCA)

Education :
Sex :

Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ]

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

13.4 Appendix IV: Dementia Severity Rating Scale (DSRS)

PARTICIPANT'S NAME:_____ DATE:_____
PERSON COMPLETING FORM:_____

Please circle the most appropriate answer.

Do you live with the participant? No Yes
How much contact do you have with the participant? Less than 1 day per week 1 day/week 2 days/week 3-4 days/week
5 or more days per week
Relationship to participant
Self Spouse Sibling Child Other Family Friend Other _____

In each section, please circle the number that **most closely applies** to the participant. This is a general form, so no one description may be exactly right -- please circle the answer that seems to apply most of the time.

Please circle only one number per section, and be sure to answer all questions.

MEMORY
0 Normal memory.
1 Occasionally forgets things that they were told recently.
Does not cause many problems.
2 Mild consistent forgetfulness. Remembers recent events but often forgets parts.
3 Moderate memory loss. Worse for recent events. May not remember something you just told them. Causes problems with everyday activities.
4 Substantial memory loss. Quickly forgets recent or newly-learned things. Can only remember things that they have known for a long time.
5 Does not remember basic facts like the day of the week, when last meal was eaten or what the next meal will be.
6 Does not remember even the most basic things.

SPEECH AND LANGUAGE
0 Normal ability to talk and to understand others.
1 Sometimes cannot find a word, but able to carry on conversations.
2 Often forgets words. May use the wrong word in its place. Some trouble expressing thoughts and giving answers.
3 Usually answers questions using sentences but rarely starts a conversation.
4 Answers questions, but responses are often hard to understand or don't make sense. Usually able to follow simple instructions.
5 Speech often does not make sense. Can not answer questions or follow instructions.
6 Does not respond most of the time.

RECOGNITION OF FAMILY MEMBERS

0 Normal - recognizes people and generally knows who they are.
1 Usually recognizes grandchildren, cousins or relatives who are **not** seen frequently but may not recall how they are related.
2 Usually does not recognize family members who are not seen frequently. Is often confused about how family members such as grandchildren, nieces, or nephews are related to them.
3 Sometimes does not recognize close family members or others who they see frequently. May not recognize their children, brothers, or sisters who are not seen on a regular basis.
4 Frequently does not recognize spouse or caregiver.
5 No recognition or awareness of the presence of others.

ORIENTATION TO TIME
0 Normal awareness of time of day and day of week.
1 Some confusion about what time it is or what day of the week, but not severe enough to interfere with everyday activities.
2 Frequently confused about time of day.
3 Almost always confused about the time of day.
4 Seems completely unaware of time.

ORIENTATION TO PLACE
0 Normal awareness of where they are even in new places.
1 Sometimes disoriented in new places.
2 Frequently disoriented in new places.
3 Usually disoriented, even in familiar places. May forget that they are already at home.
4 Almost always confused about place.

ABILITY TO MAKE DECISIONS
0 Normal - as able to make decisions as before.
1 Only some difficulty making decisions that arise in day-to-day life.
2 Moderate difficulty. Gets confused when things get complicated or plans change.
3 Rarely makes any important decisions. Gets confused easily.
4 Not able to understand what is happening most of the time.

SOCIAL AND COMMUNITY ACTIVITY
0 Normal - acts the same with people as before
1 Only mild problems that are not really important, but clearly acts differently from previous years.
2 Can still take part in community activities without help. May appear normal to people who don't know them.
3 Often has trouble dealing with people outside the home without help from caregiver. Usually can participate in quiet home activities with friends. The problem is clear to anyone who sees them.
4 No longer takes part in any real way in activities at home involving other people. Can

only deal with the primary caregiver.
5 Little or no response even to primary caregiver.

HOME ACTIVITIES AND RESPONSIBILITIES
0 Normal. No decline in ability to do things around the house.
1 Some problems with home activities. May have more trouble with money management (paying bills) and fixing things. Can still go to a store, cook or clean. Still watches TV or reads a newspaper with interest and understanding.
2 Makes mistakes with easy tasks like going to a store, cooking or cleaning. Losing interest in the newspaper, TV or radio. Often can't follow a long conversation on a single topic.
3 Not able to shop, cook or clean without a lot of help. Does not understand the newspaper or the TV. Cannot follow a conversation.
4 No longer does any home-based activities.

PERSONAL CARE - CLEANLINESS
0 Normal. Takes care of self as well as they used to.
1 Sometimes forgets to wash, shave, comb hair, or may dress in wrong type of clothes. Not as neat as they used to be.
2 Requires help with dressing, washing and personal grooming.
3 Totally dependent on help for personal care.

EATING
0 Normal, does not need help in eating food that is served to them.
1 May need help cutting food or have trouble with some foods, but basically able to eat by themselves.
2 Generally able to feed themselves but may require some help. May lose interest during the meal.
3 Needs to be fed. May have trouble swallowing.

CONTROL OF URINATION AND BOWELS
0 Normal - does not have problems controlling urination or bowels except for physical problems.
1 Rarely fails to control urination (generally less than one accident per month).
2 Occasional failure to control urination (about once a week or less).
3 Frequently fails to control urination (more than once a week).
4 Generally fails to control urination and frequently can not control bowels.

ABILITY TO GET FROM PLACE TO PLACE
0 Normal, able to get around on their own. (May have physical problems that require a cane or walker).
1 Sometimes gets confused when driving or taking public transportation, especially in new places. Able to walk places alone.
2 Cannot drive or take public transportation alone, even in familiar places. Can walk alone outside for short distances. Might get lost if walking too far from home.

3 Cannot be left outside alone. Can get around the house without getting lost or confused.
4 Gets confused and needs help finding their way around the house.
5 Almost always in a bed or chair. May be able to walk a few steps with help, but lacks sense of direction.
6 Always in bed. Unable to sit or stand.

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13.5 Appendix V: Functional Activities Questionnaire

Administration

Ask informant to rate patient's ability using the following scoring system:

- Dependent = 3
- Requires assistance = 2
- Has difficulty but does by self = 1
- Normal = 0
- Never did [the activity] but could do now = 0
- Never did and would have difficulty now = 1

Writing checks, paying bills, balancing checkbook
Assembling tax records, business affairs, or papers
Shopping alone for clothes, household necessities, or groceries
Playing a game of skill, working on a hobby
Heating water, making a cup of coffee, turning off stove after use
Preparing a balanced meal
Keeping track of current events
Paying attention to, understanding, discussing TV, book, magazine
Remembering appointments, family occasions, holidays, medications
Traveling out of neighborhood, driving, arranging to take buses

TOTAL SCORE:

Evaluation

Sum scores (range 0-30). Cutpoint of 9 (dependent in 3 or more activities) is recommended to indicate impaired function and possible cognitive impairment.

Pfeffer RI et al. Measurement of functional activities in older adults in the community. J Gerontol 1982; 37(3):323-329. Reprinted with permission of The Gerontological Society of America, 1030 15th Street NW, Suite 250, Washington, DC 20005 via Copyright Clearance Center, Inc.

13.6 Appendix VI: Geriatric Depression Scale

Choose the best answer for how you have felt over the past week:

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

Answers in **bold** indicate depression. Score 1 point for each bolded answer.

A score > 5 points is suggestive of depression.
A score ≥ 10 points is almost always indicative of depression.
A score > 5 points should warrant a follow-up comprehensive assessment.

Source: http://www.stanford.edu/~yesavage/GDS.html
This scale is in the public domain.

The Hartford Institute for Geriatric Nursing would like to acknowledge the original author of this Try This, Lenore Kurlowicz, PhD, RN, CS, FAAN, who made significant contributions to the field of geropsychiatric nursing and passed away in 2007.

13.7 Appendix VII: Instructions to subjects

The following instructions will be provided orally to the patient at the Baseline Visit by a healthcare staff member. Please have the Listerine® products (Pocketpaks® and Pocketmist®) available for demonstration.

- Alert the patient that the study drug has a bitter taste, but that there are ways to make it more palatable (see below).

- Rip open the sachet of study drug and add it to a cup or other container and add approximately 8 oz. (1 cup) of room temperature water and stir vigorously. Study drug may require significant stirring or gentle crushing to dissolve.

- The treatment should be taken within one hour of mixing into water.

- Several things may be done to reduce the bad taste and make the drug more palatable:

    - Use Listerine Pocket Packs® (strips) or a Listerine PocketMist® (spray) immediately before and/or immediately after taking the drug. Use liberally to coat the mouth. This has been found to significantly mask the bitter taste.

    - Take a snack or a meal after taking your treatment.

    - Follow drug immediately with milk to remove taste from the mouth.

    - Avoid drinking fruit juice at the same time as the drug as this may make flavor worse.

    - Mixing the study drug with a liquid other than water should be avoided.