Long-Term Nicotine Treatment of Mild Cognitive Impairment

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADC	Alzheimer's Disease Center
ADCS	Alzheimer's Disease Cooperative Study
ADCS-ADL	ADCS - Activities of Daily Living Inventory
ADEAR	Alzheimer's Disease Education & Referral Center, under the NIA
ADHD	Attention Deficit/Hyperactivity Disorder
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	Adverse Event
APOE/APOE4	Apolipoprotein E (APOE) epsilon 4 (APOE4)
ATRI	Alzheimer's Therapeutic Research Institute
Aβ	Beta Amyloid
C_{max}	Maximum Observed Concentration
CDR/CDR-SOB	Clinical Dementia Rating (CDR) Sum of Boxes (CDR-SOB)
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CNS	Central Nervous System
CPT	Conners Continuous Performance Task (CPT)
CSF	Cerebrospinal Fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CSQ	Client Satisfaction Questionnaire
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDTA	ethylenediamine tetraacetic acid, an anticoagulant
ESS	Epworth Sleepiness Scale
fMRI	Functional MRI
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GMD	Gray Matter Density
HDL	High-Density Lipoprotein (HDL) Cholesterol
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISLT - TIR	International Shopping List Test – Total Immediate Recall
LCMS	Liquid Chromatography Mass Spectrometry

LP	Lumbar Puncture
MCI	Mild Cognitive Impairment
mg	milligram
mL	milliliter
MMSE	Mini-Mental State Examination
MMRM	Mixed Model Repeated Measures
MR/MRI	Magnetic Resonance / Magnetic Resonance Imaging
NIA	National Institute on Aging, under the NIH
NIAGADS	NIA Genetics of Alzheimer's Disease Data Storage Site
NIH	National Institutes of Health
NMR	Nicotine Metabolite Ratio
OABCL	Older Adult Behavior Checklist
OASR	Older Adult Self Report
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PID	Participant ID
PSQI	Pittsburgh Sleep Quality Index
PT/PTT	Prothrombin Time (PT), Partial Thromboplastin Time (PTT)
QC	Quality Control
REB	Research Ethics Board
RT-SE	Reaction Time – Standard Error
RSS	Research Satisfaction Survey
SAE	Serious Adverse Event
SUSAR	Suspected Unanticipated Serious Adverse Reaction
T	Tesla
T_{max}	Time to Reach the Maximum Concentration (C_{max})
TFTs	Thyroid Function Tests
TSH	Thyroid Stimulating Hormone
URG	Underrepresented Groups
WMSR	Wechsler Memory Scale Revised
WTAR	Wechsler Test of Adult Reading
XNAT	eXtensible Neuroimaging Toolkit

SIGNATURE PAGE

(SIGNATURES ON FILE AT COORDINATING CENTER)

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PROTOCOL SYNOPSIS

PROTOCOL TITLE	Long-Term Nicotine Treatment of Mild Cognitive Impairment
PROJECT DIRECTOR	Paul Newhouse, MD
STUDY SPONSOR	National Institute on Aging and Alzheimer's Drug Discovery Foundation
COORDINATING CENTER	Alzheimer's Therapeutic Research Institute (ATRI)
STUDY DESIGN	A Phase 2 multi-center, randomized, double-blind, placebo-controlled study in approximately 380 participants with MCI
DURATION OF STUDY PARTICIPATION	Each participant will have up to a 28-day screening period, followed by 24 months and 3 weeks of treatment
SUMMARY OF INVESTIGATIONAL PRODUCT	21mg Nicotine, or placebo, transdermal patches worn during waking hours. Active dose will titrate up from 3.5mg to 21mg in the first 6 weeks of treatment, remain at 21mg for 22.5 months, and then taper down in the final 3 weeks of treatment
SUMMARY OF KEY ELIGIBILITY CRITERIA	• Age 55+ • Logical Memory below education adjusted cut-offs • MMSE 24-30 (inclusive) • CDR 0.5, Mild Cognitive impairment (MCI)
PRIMARY OUTCOME MEASURE	Cogstate Battery International Shopping List Test - Total Immediate Recall (ISLT-TIR)
OTHER OUTCOME MEASURES	MCI-CGIC, Cogstate battery, NYU Paragraph Recall, CDR-SOB, GDS, ADCS-ADL-MCI, OASR/OABCL, RT-SE CPT
OPTIONAL SUB-STUDIES	CSF and MRI/fMRI sub-studies will be performed in approximately 50 participants each

INTRODUCTION

Mild Cognitive Impairment (MCI) is a term that is used to characterize a transitional state between normal cognitive aging and mild dementia[1, 2] While life expectancy is increasing, the quality of that life becomes a major issue. Development of cognitive impairment that leads to dementia has become an active area of research and clinical investigation. Efforts are moving from focusing only on the treatment of already identified demented patients to developing effective treatments to alleviate symptoms and prevent or slow progression to a demented status. By encouraging early treatment to improve symptoms and/or retard progression of cognitive impairment, the course of dementing illness could be altered.

With the aging of the population, MCI will become a greater burden, which increases the importance of finding cost-effective treatments. Cholinergic system integrity appears to be critical for maintaining normal cognitive functioning in aging. Stimulation of cholinergic receptors remains the principal effective treatment for Alzheimer's disease (AD), despite advancing knowledge of the underlying molecular derangements and targeted treatments, which thus far have been unsuccessful.

This study is a multi-site clinical trial of the safety and efficacy of transdermal nicotine in alleviating symptoms of MCI, designed to test the hypothesis that nicotinic cholinergic receptor stimulation reliably produces enhancement in attentional functioning and memory. If the hypotheses are validated, these findings will support a novel, broadly available, and inexpensive repurposed intervention for MCI.

The trial will consist of 24 months (plus a 3 week tapering off period) of randomized double-blind placebo-controlled treatment with nicotine or placebo in approximately 380 participants with MCI (190 per arm). This would be the longest trial of nicotine or nicotinic agonists to date and if successful would lead to combined trials with other symptomatic agents and/or agents that might directly interact with Aβ or tau-related mechanisms. Success of the pilot trial is encouraging and justifies cautious but significant optimism for sustained success in this proposed study.

1.1 Study Aims

Aim 1.

To test whether daily transdermal nicotine will produce sustained cognitive, clinical, and functional benefits for patients with MCI in a 2-year multi-center clinical trial.

Aim 2.

To assess whether nicotine will influence the underlying biology related to MCI/AD by monitoring putative biological markers for AD development including structural/functional brain imaging and measures of AD pathology in spinal fluid.

1.2 Outcome Measures

Primary:

Cogstate Battery International Shopping List Test - Total Immediate Recall (ISLT-TIR)

Key Secondary:

- Clinical Global Impression of Change (MCI-CGIC)

Other Secondary:

- Cogstate Battery: The change in delayed word recall from the Verbal Learning and Delayed Verbal Recall (International Shopping List Task), Simple Reaction Time (Detection task), Choice Reaction Time (Identification Task), Working Memory (One-back Task), Recognition Memory (One Card Learning Task); Immediate and Delayed Paragraph Recall
- RT-SE CPT, CDR-SOB, GDS, ADCS-ADL-MCI scale, OASR/OABCL

Safety:

- Adverse experiences, vital signs, physical examinations, laboratory tests

2.0 PRELIMINARY STUDIES

2.1 Mild Cognitive Impairment

There is currently no accepted treatment for MCI, nor is there any treatment that has been demonstrated to prevent progression to Alzheimer's disease (AD). Many treatment and/or prevention trials have been conducted and include acetylcholinesterase inhibitors such as donepezil[3] and rivastigmine[4], antioxidants such as vitamin E[5], ginkgo biloba[6], anti-inflammatory agents, and others. No trials have as yet demonstrated substantial efficacy[7].

2.2 Nicotine

The plant alkaloid nicotine may represent a promising agent to test for its ability to improve the cognitive symptoms of MCI and delay progression to dementia. Studies by Kellar and colleagues[8, 9] established the importance of changes in nicotinic receptors in Alzheimer's disease. The importance of the loss of nicotinic receptors for the cognitive disturbances of Alzheimer's disease was demonstrated by showing that blockade of CNS nicotinic receptors produces impairment of attention, acquisition of information, and decision-making[10]. Several decades of research in humans have shown that nicotine and/or nicotinic stimulation produces improved attention, speed of information processing, reaction time, and sustained attention[11]. Furthermore, nicotine decreases errors on a variety of cognitive tasks, particularly those that require attention and concentration[12, 13]. Nicotinic stimulation has shown positive cognitive effects in a number of disorders with memory and/or attentional impairment including Alzheimer's disease[12, 14, 15], Parkinson's disease[16], schizophrenia[17], attention deficit-hyperactivity disorder[18, 19], and Tourette's syndrome[20].

Nicotine treatment has also been shown to be beneficial even when no signs of cognitive decline are yet present, as a study with low dose nicotine patch[21] showed improvement in verbal learning and recall, that correlated with the plasma nicotine level. A recent study showed[22] that six months of nicotine treatment improved attention and episodic memory in patients with MCI with excellent safety and no abuse liability. Furthermore, in the open-label extension of this study results were sustained in the group initially treated with nicotine, suggesting that earlier intervention may be an important factor in determining the effectiveness of nicotine treatment[23]. The effects of nicotine on the cognitive symptoms of dementia thus show improved attention and learning ability and reduced errors (see [24] for a review).

3.0 BACKGROUND AND SIGNIFICANCE

3.1 Rationale for Study

MCI is defined as a subjective and objective decline in cognition and function that does not meet criteria for a diagnosis of dementia and that represents a transitional state between the cognition of normal aging and mild dementia [1, 2, 25]. The overall population risk for the development of MCI is substantial, rising from 3.6% at age 70 to 13.5% by age 85[26]. The cognitive impairment of MCI is not considered part of normal cognitive aging and appears in many cases to represent the prodromal phase of a degenerative neuropathologic condition. Patients with MCI are at high risk for subsequently developing dementia. Amnestic MCI is the condition most likely to progress to AD, whereas individuals who have multiple domains or non-memory domains may progress to AD and/or other types of dementias. Thus, the term MCI is generally used to refer to the symptomatic pre-dementia phase of Alzheimer's disease (AD).

The core clinical criteria, as recently updated[2, 25] include evidence of concern regarding a change in cognition, either from the patient or an informant. The impairment in one or more cognitive domains, as well as episodic memory loss are seen most commonly in patients with MCI who subsequently progress to AD[25]. These cognitive changes are sufficiently mild that there is no significant impairment in social or occupational functioning. There may be mild functional impairment for complex tasks but basic activities of daily living are preserved. Recognizing that not all cases of MCI may be due to AD, there has recently been an attempt to probabilistically define "MCI due to Alzheimer's disease" by requiring evidence of biomarkers of neuronal injury, including cerebral spinal fluid (CSF) changes such as elevated tau or reduced Aβ42, or hippocampal atrophy on MRI[2].

In many respects, MCI may be the optimal diagnosis for which to test the efficacy of nicotinic therapy. The likelihood of relatively large numbers of preserved nicotinic receptors[27, 28], preservation of attentional, acquisition, encoding, and retrieval mechanisms with the evidence for substantial neuroprotective effects of nicotinic stimulation make MCI an ideal diagnosis to test the efficacy of long-term, low dose nicotinic stimulation. The large number of controlled efficacy smoking cessation

trials in healthy and diseased participants and their accompanying enormous safety database give confidence that this treatment will be well-tolerated and safe.

Nicotine may enhance cognitive functioning, enhancing efficiency in frontal attention and executive function/cognitive control networks, while simultaneously decreasing activity in default mode network nodes in frontal lobe, cingulate, and parietal regions. These together enhance attention, response inhibition and processing speed which will lead to improvements in attention to environmental stimuli, decreased internally focused processing, and enhanced encoding of new information leading to improved memory.

The concept of chronic nicotinic receptor stimulation for cognitive enhancement for non-smoking individuals with memory loss has never been explored, especially with the proposed length of this trial (24 months). If the study results were positive, the immediate availability of a repurposed, inexpensive, well-tolerated treatment would be highly innovative for this ubiquitous disorder. This would likely have significant benefits for large numbers of individuals even without the United States Food and Drug Administration (FDA) registration (e.g. many oncology medications are prescribed "off label"); additionally nicotine is available over-the-counter, which generally increases dissemination.

Stimulation of nicotinic cholinergic receptors with nicotine may be a promising strategy to ameliorate symptoms of MCI and/or slow progression to dementia.

3.2. Rationale for Dosage Selection

Maximal dosage of nicotine patch was used in the pilot study (after up titration) and was associated with significant cognitive and clinical benefit. Thus this study plans to titrate participants gradually up to the highest dose (21 mg) nicotine patch. As the planned patch used for this study is a 24-hour patch (as compared to a 16 hour patch in the pilot study), the patch will be used for 16 hours only to produce similar dose exposure to the patch used in the pilot study[48].

3.3. Rationale for Outcomes and Study Procedures

3.3.1 Rationale for Primary and Key Secondary Outcome

The primary outcome measure has been changed from the Continuous Performance Task Reaction Time Standard Error (CPT-RTSE) to the Cogstate Battery International Shopping List Test - Total Immediate Recall (ISLT-TIR). ISLT-TIR is a widely used and well validated episodic memory task which has performed well in a number of previous therapeutic trials in Alzheimer's disease, with appropriate adjustments for age and sex. The key secondary outcome measure is the MCI-CGIC (Clinical Global Impression of Change) score. This showed a trend of improvement associated with nicotine treatment in the pilot trial. Additional secondary measures include delayed recall from the Cogstate battery. Delayed recall showed nicotine treatment-associated improvement in the pilot trial. Additional measures from the Cogstate battery and paragraph recall will be collected that are test cognitive domains used in the pilot trial and were responsive to nicotinic treatment.

3.3.1.1 Rationale for Change to the Primary Outcome

A decision to change the primary cognitive outcome measure from the Continuous Performance Task reaction time standard error (CPT-RTSE) to the International Shopping List Test - Total Immediate Recall (ISLT-TIR) was done based on a careful analysis and evaluation of the baseline (pre-treatment only) anomalous data from the baseline CPT and difficulties in CPT administration due to computer version changes and lack of support of the vendor.

The CPT task has turned out to be more problematic than originally anticipated for several reasons. Significant hardware challenges have occurred with computer failures leading to a necessity to reinstall software on new equipment. However, the developer of the CPT declined to support the version that was used in this trial and had migrated all of their software and support to a newer version of the software that was incompatible due to changes in the stimuli presentation and timing. Due to this loss of support, we have been unable to reinstall the version of the software that was initially chosen for this trial at certain sites, which led to loss of data from participants at those sites. Furthermore, analysis of the baseline data revealed problematic differences that were not seen in the pilot trial including altered levels of omission errors which appear to have changed the distribution of the data from what was seen in the pilot study and large numbers of outliers observed in the baseline data that would impact data quality. After review by the study statisticians, it was concluded that retaining the CPT-RTSE as the primary cognitive outcome measure would jeopardize the ability of the study to arrive at a definitive conclusion regarding treatment efficacy.

The ISLT has significant face validity and the software has been stable throughout this trial and analysis of missing data pattern show significantly better consistency of administration than the CPT. Analysis of baseline data suggests that the Total Immediate Recall (TIR) shows a reasonably normal distribution with few outliers and this is more amenable to a measurement of change with treatment. This verbal recall measure is similar to a verbal recall test found to be sensitive to chronic nicotine treatment effects in our pilot trial. Thus, we propose to replace the CPT-RTSE with the ISLT-TIR as the primary cognitive outcome measure for this trial. This decision was made without any of the scientific team seeing follow-up data for alternate outcome. All analyses were done in aggregate only.

3.3.2. Rationale for fMRI of Nicotinic Response to Treatment

Nicotinic stimulation appears to deactivate midline cortical structures involved in resting state activity such as the default mode network and mostly activate task-related structures[29, 30]. This deactivation-activation pattern appears to be in the service of reorienting cortical systems towards external versus internal processing and/or preparing cortical systems to receive external input. Deactivation of default mode network structures may serve as a biomarker for the effects of nicotinic agents, particularly if such activities correlate with cognitive or behavioral performance. Resting state fMRI and task-related fMRI at the substudy sites (that can be shown to produce replicable, harmonious fMRI data) will be used to

investigate nicotinic treatment effects on resting state activity and task-related activity and correlate these measures with clinical outcomes.

3.3.4. Rationale for Genetics

APOE polymorphisms are an important genetic risk factor for AD. Individuals with one or two APOEε4 alleles have a higher risk of developing AD and an earlier age of onset. Furthermore, those with one or two APOEε4 alleles exhibit a more rapid rate of clinical change in some, but not all studies. APOE genotyping will allow secondary analyses of data on the impact of APOE on putative biomarkers of AD, clinical outcome measures, and adverse events.

Genetic variants in CYP2A6 are associated with differences in nicotine pharmacokinetics, thus the specific polymorphisms that explain most variability in nicotine metabolism will be examined.

Banked DNA may be used to examine additional cholinergic genes; other genes related to Alzheimer's disease, and additional risk genes in terms of their relationship to therapeutic effects of nicotine and imaging effects. For example, a meta-analysis of copy number variants in CHRFAM7A that influences CHRNA7, the gene that codes for the α7 nicotinic receptor, indicated a significant association of the gene with AD and/or MCI risk ($p = 0.006$, $OR = 3.986$)[49].

4.0 POTENTIAL RISKS AND BENEFITS ASSOCIATED WITH THIS INVESTIGATIONAL PRODUCT

4.1 Potential Risks and Benefits Associated with This Investigational Product

4.1.1 Potential Benefits

Nicotine may improve the cognitive symptoms of MCI and delay progression to dementia. The results of the study might help people with a similar condition in the future.

4.1.2 Potential Risks

The inclusion and exclusion criteria are designed to minimize the anticipated adverse effects of nicotine patches or any drug-drug interactions that could arise from the use of nicotine products.

At the nicotine doses proposed in this study, the major peripheral action of nicotine is facilitation of impulses through all autonomic ganglia, stimulation of the adrenal medulla and stimulation of sensory receptors including chemoreceptors in the carotid body. Ganglionic depression occurs at higher nicotine levels. In cardiovascular systems, mild increases in heart rate and blood pressure from sympathetic ganglion stimulation, catecholamine release from adrenal medulla, and aortic and carotid body chemoreceptor stimulation may occur. A mild parasympathetic response may be seen in the gastrointestinal tract and bladder (increased tone and motor activity), with increased secretion of exocrine glands. Nausea and vomiting can occur from peripheral (bowel activity and vagal efferent nerve stimulation) and central (medullary emetic chemoreceptor trigger zone

stimulation) causes. Low dose stimulation of the CNS could in theory produce tremors and respiratory stimulation, although this is rarely seen except in patients with tremor disorders. Toxic nicotinic doses result in CNS depression. With use, tolerance develops to virtually all acute adverse effects.

The risks are completely described in the package insert.

4.2 Relationship of this intervention to current treatment practices in MCI

Currently, there is no approved/accepted treatment for MCI.

5.0 SAMPLE SIZE AND STATISTICAL PLAN

5.1 Randomization

Participants who have signed an informed consent and meet screening eligibility requirements will be randomly assigned using a 1:1 allocation ratio to nicotine or placebo by a random permuted block treatment assignment method, stratified by site.

5.2 Power and Sample Size Determination

Power calculations were conducted using a two-sided, two-sample, equal-variance t-test, based on mean ISLT- TIR from baseline to 24 months between the nicotine and placebo groups. Power is expressed in terms of standardized effect sizes defined as difference in mean change score between the two groups divided by the pooled standard deviation of change. With a sample size of 102 participants in each intervention group (204 total), the study has 80% power to detect a standardized effect size of d=0.39, assuming a two-sided Type 1 Error of 0.05. The sample size is increased to 171 per group (342 total) due to an approximate 30% dropout rate to date, attributed to COVID-19 pandemic disruptions, and we anticipate an overall attrition rate of approximately 40% for the study.

5.3 Statistical Analysis Plan

In general, biomarker and clinical outcome analyses will incorporate the modified intent-to-treat principle, namely, all randomized participants with both a baseline and at least one post-baseline measurement will be included in the analysis while the safety analysis will be conducted on the intent-to-treat population (all randomized participants). All results will be reported as point estimates (proportions or mean differences across groups, as appropriate) and interval estimates (95% confidence intervals) with two-sided p-values denoting significance. No adjustments for multiple comparisons on secondary outcomes will be made and a p-value of 0.05 will be considered significant. Statistical analysis will be conducted using the statistical software R (www.r-project.org) or SAS.

5.3.1 Demographics and Baseline Characteristics

Baseline demographics and clinical characteristics will be summarized by frequencies and percentages for categorical variables; continuous variables will be summarized by mean and standard deviation as well as quartiles. Group comparisons will be performed using Student t-tests for continuous variables.

Assumptions of normality (using Shapiro-Wilk tests) and equal variances (using F-tests) will be tested, and if violated, the alternative non-parametric Wilcoxon-rank sum test will be used. Fisher's Exact test will be used for categorical data.

5.3.2 Safety Outcome

Tolerability and safety will be determined by counting specific adverse events, counting dropouts due to adverse events, and by determining how often there is a need to reduce the dose of nicotine/placebo as determined by the participant and the physician. Abnormalities in vital signs, physical examination, and laboratory tests will be collected by treatment. Adverse events will be recorded and categorized by body system, event type, attribution, frequency, severity, and course. Rates of adverse events or other abnormalities between groups will be assessed using Fisher's exact tests. Appropriate transformations and/or models will be used (e.g. Poisson regression) for non-normally distributed data, if appropriate.

5.3.3 Primary Outcome: Cognitive Performance

The primary objective of this study is to test the hypothesis that nicotine patch treatment will improve cognitive function in MCI compared with placebo at 24 months. A constrained Longitudinal Data Analysis (cLDA) Natural Cubic Spline (NCS) analysis (referred to as NCS henceforth) with 2 degrees of freedom will be used to assess the difference between treatment groups in change from baseline for performance on the Cogstate Battery ISLT -TIR. Participants will be included in the model if they have both a baseline and at least one post-baseline ISLT – TIR answer. Change from baseline at each post-baseline visit for the ISLT – TIR will be the dependent variable. Time will be treated as continuous variable. We will assume a heterogeneous Toeplitz covariance structure, where the time values are mapped back to the corresponding visits. Fixed effects in the model will include the following terms: (i)NCS basis expansion terms (two terms), (ii) NCS basis expansion terms-by-treatment interaction (two terms), (iii) age, (iv) sex, and (v) APOEε4 genotype (Yes/No). Visits will be treated as a categorical variable. The null hypothesis is that the treatment difference between nicotine and placebo for the ISLT-TIR at month 24 is equal to zero.

5.3.4 Key Secondary Outcome: Global Ratings (MCI-CGIC)

For this study, the MCI-CGIC measure will be defined as a binary variable (improvement versus no improvement). Analysis of the MCI-CGIC will compare global ratings for nicotine and placebo utilizing a mixed-effects regression model for binary data. The CGIC rating at each follow-up visit for each participant will be used as the dependent variable. Treatment, time (as a categorical variable), time-by-treatment interaction and APOEε4 genotype (Yes/No) will be included in the model as covariates. Sensitivity analysis treating MCI-CGIC as a three-category variable (any deterioration, no change, any improvement) and as a continuous variable will be conducted using mixed-effects regression models for ordinal and continuous data respectively.

5.3.5 Other Secondary Outcomes: Behavioral/Functional Assessments

Similar models to the primary analysis will be used for the analysis of all secondary behavioral/functional assessments.

5.3.5 Biomarker and Imaging Outcomes

Biomarker outcomes:

Markers, including T-Tau, P-Tau217, Aβ42, and Aβ42/tau ratio, will be evaluated. Change from baseline will be compared by treatment group using an analysis of covariance (ANCOVA) model with change score as the dependent variable and the baseline measure, treatment and APOEε4 status as independent variables in the model. Correlations with clinical outcomes and progression will be examined for treatment effects using linear regression modeling.

Imaging Outcomes:

Mean left and right hippocampal volume and gray matter density (GMD) adjusted for total intracranial volume, age and sex, will be compared between treatment groups using an MMRM approach. A comprehensive set of brain regions of interest for volume, cortical thickness and GMD will be available for additional outcome and exploratory analyses.

5.4 Criteria for the termination of the trial

The trial may be terminated by the Project Director(s) based on issues of safety, feasibility, and DSMB recommendations.

6.0 STUDY DRUG AND CONCOMITANT MEDICATIONS

6.1 Name and Description of IP and Comparator

Nicotine will be administered as a transdermal patch. The technical description of this transdermal patch is as follows:

Nicotine will be delivered by a transdermal patch which is a transdermal delivery system for topical application, available in sizes of 10, 20, and 30 cm^2 each containing 1.75 mg/cm^2 of nicotine, releasing 7 mg, 14 mg and 21 mg respectively over 24 hours. Each patch is rectangular in shape and comprises 3 distinct layers; an outer beige matte finish backing layer, a patterned silvery middle layer and an inner clear release liner, which is removed prior to use. Each patch is packaged in a heat sealed multi-laminate sachet. Taking into account the residual concentration of nicotine in the transdermal system, the nicotine released from the system is efficiently absorbed: a bioavailability of between 80-108% has been reported. There is no clinically significant difference in bioavailability when the patch is applied to the hip, upper arm or chest. T_{max} of nicotine after application of a 30 cm^2 nicotine transdermal system has been shown to be 3.8 hours; C_{max} has been shown to be 21.9 ng/ml for the 21 mg patch[48]. No differences in these pharmacokinetic parameters have been observed between males and females.

Matching placebo patches will be used.

6.2 Dosage

During the first 6 weeks of treatment, the nicotine treatment group will have their dose level slowly increased (according to the table below) from 3.5mg to 21mg nicotine per day, administered via transdermal patch. They will remain at 21mg

until the Month 24 visit, when they begin a 3-week tapering off period (according to the table below).

Study Period	Visit Interval	Prescribed Dose/Patch Type Per Day
Titration	Baseline – Week 5	Week 1: 3.5mg (½ of 7mg patch)
		Week 2: 7mg patch
		Week 3: 7mg patch
		Week 4: 14mg patch
		Week 5: 14mg patch
Maintenance	Week 5 – Month 24	21mg patch
Taper	Post-Month 24	Week 1: 14mg patch
		Week 2: 14mg patch
		Week 3: 7mg patch

The placebo group will receive the placebo comparator for the duration of the study.

Patches will be applied in the morning and removed at bedtime each day (worn for approximately 16 hours). The application site should be changed daily and not reused within 7 days. If the participant forgets to apply a patch, it should be applied later that day when remembered, and removed as usual at bedtime. If a patch is left on overnight, it should be removed in the morning and a new patch applied as usual. More than one patch should never be worn at the same time.

If tolerability issues arise, the site clinician may alter the timing of the next dose level increase and/or reduce the prescribed dose, consulting with the Medical Monitor as needed. If a study drug dose reduction is deemed necessary, it could be achieved by decreasing the size of the patch (e.g., reducing to ¾ or ½ of a patch). Decreasing the duration that the patch is applied is not an acceptable method for reducing the dose. If the investigator elects to reduce the dose and the adverse symptoms resolve, the participant should be re-challenged with the original dose or titrated back up to the original dose within a few days thereafter. If tolerability issues persist, consult with the Medical Monitor. Such cases are expected to be rare and will be managed on a case-by-case basis.

If dosage is interrupted over an extended period of time, sites must consult with the Medical Monitor for possible re-titration.

6.3 Blinding

This is a double-blind study in which participants and site personnel will be blinded to treatment assignment. In order to maintain the blind, placebo patches will be manufactured to have the same size and packaging as each of the doses of active nicotine patches that will be used. During the titration and tapering phases, both treatment groups will follow the same schedule for adjusting the patch type.

6.4 Packaging/Dispensing/Labeling

Study drug will be packaged, labeled, and dispensed according to the table below. Within each package, the central packaging vendor will seal individual patches in opaque, foil, multi-laminate sachets. Titration Pack 1 and the Taper Pack will include pouches labeled by week as described below.

The dosing schedule described in Section 6.2 will be clearly explained to the participant and study partner before dispensing the study drug and it will be printed on the labels.

Dispensing Visit	Package Type	Nicotine or Placebo patches dispensed
Baseline	Titration Pack 1	Week 1: 7 – 7mg patches
		Week 2: 7 – 7mg patches
		Week 3: 7 – 7mg patches
		Week 4: 7 – 14mg patches
		Week 5: 7 – 14mg patches
		Overage: 7 – 7mg patches, 7 – 14mg patches
Week 5	Titration Pack 2	70 – 21mg patches
Months 3, 6, 9, 12, 15, 18, 21	Maintenance Pack	107 – 21mg patches
Month 24	Taper Pack	Week 1: 7 – 14mg patches
		Week 2: 7 – 14mg patches
		Week 3: 7 – 7mg patches
		Overage: 7 – 7mg patches

At Baseline, if a participant passes the eligibility criteria, sites will manually assign a Randomization ID using the Randomization List mailed to them from the Coordinating Center. The site must strictly adhere to the instructions for randomization provided by the Coordinating Center. The corresponding Randomization ID will be printed on each study drug package by the central depot to allow for proper dispensing of study medication to each participant. Sites must verify that the Randomization ID on the study drug package matches the next ID in sequence on the Randomization List prior to Randomization ID assignment to the participant. A second person must verify the randomization information across the study drug package, Randomization List, and Accountability Log to ensure accuracy.

6.5 Storage

Study drug should be stored in a facility at the site to which only the investigator and his/her designees will have access. Study medication must be stored at a controlled temperature (15 – 30° C, 59-86° F).

6.6 Drug Accountability

Study drug will be accompanied by a shipping manifest when shipped to study sites from a central depot. Sites will inspect each shipment to ensure that 1) the contents are not damaged and 2) the packages received match the shipping manifest. Once the shipment has been reviewed, the manifest must be initialed and dated by the

personnel who conducted the review, saving a record of this activity for monitor review. The investigator or designee must receive and store study drug supplies in a secure area and dispense according to protocol.

Prior to dispensing a drug package, sites will check that 1) the study drug has not expired; and 2) the package will not expire during dosing period.

Expiring study drug will be quarantined and recorded in the Not Dispensed Log. Monitors will inspect the log and sign off before study drug destruction.

The participant will be advised to return all unused study drug and used patch sachets to the investigator for documentation of accountability and calculation of compliance. All returned supplies will be counted and verified by a clinical monitor prior to being destroyed according to local site procedures.

6.7 Assessment of Compliance

Site personnel will assess compliance at every visit after Baseline. Participants and study partners will be instructed to return all empty sachets and unused study drug patches to the site at each visit. When study drug is returned, site personnel will perform a count of the items for compliance evaluation. If study drug is not returned, site personnel will discuss adherence to study drug regimen with the participant and study partner. Participants found to be < 80% or > 120% compliant will receive specific instruction from site personnel, including re-instruction on study procedures and additional telephone contact between visits.

6.8 Breaking the Blind

Only when knowledge of whether the patient has received the investigational product is essential for the clinical management or welfare of the patient may the Investigator request to intentionally unblind a patient's treatment assignment. If the Investigator needs the blind to be unmasked for any reason, the Investigator must the Medical Monitor (and/or Project Director) to obtain an approval.

Unintentional breaking of the blind (when, for example, study staff inadvertently discovers whether the participant is on placebo or active study drug) must be reported to the Coordinating Center within 5 business days. The report should include the date for when the blind was broken, each site personnel exposed to the treatment assignment, and the reason for breaking the blind. Refer to the study Procedures Manual for more detailed procedures related to breaking the blind and reporting.

6.9 Concomitant Medications

6.9.1 Concomitant Cognitive Enhancing Medications

This protocol allows concomitant treatment with memantine and/or cholinesterase inhibitors if on stable doses for 12 weeks prior to screening.

Putative non-prescription cognitive enhancers (e.g. gingko) are discouraged.

Initiation of or modifications to concomitant cognition-enhancing medications during the course of the study should be discouraged. However, if a change occurs

or a new medication is planned to be initiated, the site should consult with the Project Director and/or Medical Monitor for further guidance.

6.9.2 Prohibited Concomitant Medications

Use of the following medications is prohibited within 4 weeks of screening and throughout the study except as noted in Section 6.10.3:

- medications with significant central anti-cholinergic activity, which can include:
  - tricyclic antidepressants
  - antipsychotics (except risperidone ≤1.5 mg/day, quetiapine ≤100 mg/day, olanzapine ≤5 mg/day, and aripiprazole ≤10 mg/day)
- mood-stabilizing psychotropic agents (e.g. lithium salts)
- psychostimulants
- opiate analgesics
- antiparkinsonian medications (except for non-parkinsonian indications)
- anticonvulsant medications (except gabapentin and pregabalin for non-seizure indications)
- systemic corticosteroids
- anxiolytics or sedative hypnotics: Use of some short- to medium-acting benzodiazepines for treatment for insomnia or anxiety is permitted (see Prohibited and Cautionary Medications List). Use of sedatives or hypnotics should be avoided for 24 hours (8 hours, if used chronically) before administration of cognitive tests.

Use of the following medications prior to screening is prohibited:

- aducanumab (or other approved AD disease modifying treatments)

Initiation of prohibited medications during the course of the study should be discouraged, however, if an excluded medication is initiated after screening, the site should consult with the Project Director and/or Medical Monitor for further guidance.

Notify the Medical Monitor if aducanumab (or other approved AD disease modifying treatments) is started during the course of the study. Participants who have started aducanumab (or other AD disease modifying treatments) prior to screening will not be eligible for the study.

Investigational agents are prohibited 4 weeks or 5 half-lives, whichever is longer, prior to entry and for the duration of the trial. Also exclusionary is previous treatment with an investigational small molecule with anti-amyloid properties or passive immunization against amyloid within 6 months of entry or any previous treatment with an active immunization against amyloid.

Current use of warfarin or other anticoagulants are exclusionary for CSF substudy only.

6.9.3 Permitted Concomitant Medications

Gabapentin and pregabalin for non-seizure indications are permitted.

Use of short- to medium-acting benzodiazepines for treatment for insomnia or anxiety is permitted. Use of sedatives or hypnotics should be avoided for 24 hours (8 hours if used chronically) before administration of cognitive tests.

Stable doses of antidepressants lacking significant anticholinergic side effects are allowable (if the participant is not currently depressed and does not have a history of major depression within the past 1 year).

7.0 STUDY POPULATION

The study will randomize approximately 380 individuals with MCI as specified in the entry criteria below. Participants who do not meet all inclusion criteria, disease diagnostic criteria, or who meet any exclusion criteria may not be randomized into the study. Exceptions may be considered on a case-by-case basis by the Project Director and/or Medical Monitor. Two sub-studies (CSF and MRI/fMRI) will be set up to enroll approximately 50 participants each at select sites.

7.1 Inclusion Criteria

Participants must meet the following criteria:

1. Participant must have a subjective memory concern as reported by participant, study partner, or clinician
2. Abnormal memory function documented by scoring within the education adjusted ranges on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale – Revised:
    - Less than or equal to 11 for 16 or more years of education
    - Less than or equal to 9 for 8 - 15 years of education
    - Less than or equal to 6 for 0 - 7 years of education
3. Mini-Mental State Exam score between 24 and 30, inclusive
4. Clinical Dementia Rating (CDR) Global = 0.5. Memory Box score must be at least 0.5
5. General cognition and functional performance sufficiently preserved such that a diagnosis of Alzheimer's disease dementia cannot be made by the site clinician at the time of the screening visit
6. Age 55-90 (inclusive)
7. Stable permitted medications for 4 weeks or longer as specified in Section 6.10, including:
    - Memantine and cholinesterase inhibitors are allowable if stable for 12 weeks prior to screen
8. Geriatric Depression Scale score of less than or equal to 14
9. Study Partner is available who has frequent contact with the participant (e.g. an average of 10 hours per week or more), and can accompany the participant to most visits to answer questions about the participant
10. Adequate visual and auditory acuity to allow neuropsychological testing

11. Good general health with no additional diseases/disorders expected to interfere with the study
12. Participant is not pregnant, lactating, or of childbearing potential (i.e. women must be two years post-menopausal or surgically sterile)
13. Completed six grades of education or has a good work history
14. Fluent in English or Spanish

7.2 Exclusion Criteria

Participants must not meet the following criteria:

1. Any use of tobacco or nicotine products within the past year, such as smoking (cigarettes, pipes, cigars, etc.) or use of other nicotine products (chewing tobacco, e-cigarettes, nicotine patches, gum, sprays, etc.).
2. Any significant neurologic disease such as Alzheimer's disease dementia, Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities.
3. Major depression, bipolar disorder as described in DSM-V within the past 1 year or psychotic features, agitation or behavioral problems within 3 months, which could lead to difficulty complying with the protocol
4. History of schizophrenia (DSM V criteria)
5. History of alcohol or substance abuse or dependence within the past 2 years (DSM V criteria)
6. Clinically significant or unstable medical condition, including uncontrolled hypertension, uncontrolled diabetes, or significant cardiac, pulmonary, renal, hepatic, endocrine, or other systemic disease in the opinion of the Investigator, may either put the participant at risk because of participation in the study, or influence the results, or the participant's ability to participate in the study.
7. Has had a history within the last 5 years of a primary or recurrent malignant disease with the exception of non-melanoma skin cancers, resected cutaneous squamous cell carcinoma in situ, basal cell carcinoma, cervical carcinoma in situ, or in situ prostate cancer with normal prostate-specific antigen post-treatment
8. Clinically significant abnormalities in B12 or TFTs that might interfere with the study. A low B12 is exclusionary, unless the required follow-up labs (homocysteine (HC) and methylmalonic acid (MMA)) indicate that it is not physiologically significant.
9. Clinically significant abnormalities in screening laboratories or ECG.
10. Residence in a skilled nursing facility.
11. Use of any excluded medication as described in Section 6.10, including:
    - Use centrally acting anti-cholinergic drugs
    - Use of any investigational drugs within 4 weeks or 5 half-lives, whichever is longer, prior to screening.
12. For CSF sub-study participants, a current blood clotting or bleeding disorder, or significantly abnormal PT or PTT at screening

13. For MRI sub-study participants, contraindications for MRI studies, including claustrophobia, the presence of metal (ferromagnetic) implants, or cardiac pacemaker.
14. Participants whom the Site PI deems to be otherwise ineligible.

Deviations from the inclusion/exclusion criteria will be considered on a case-by-case basis. Contact the ATRI Medical Monitor for review and approval.

7.3 Recruitment and Retention Strategies

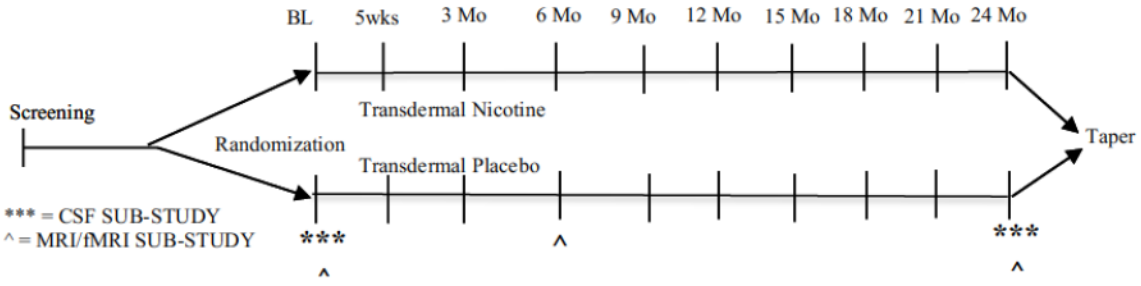
Study-wide recruitment efforts will be overseen by a recruitment team at the Coordinating Center, which has developed a coordinated recruitment plan to ensure that enrollment occurs in a timely fashion. The overall goals of the plan are to raise awareness of the trial among targeted populations to ensure adequate enrollment. The Coordinating Center partners with NIA and coordinates with its ADEAR Center to leverage existing resources. The recruitment and retention team will develop materials specific to the trial for use by the study sites, provide ongoing recruitment assistance and support, and develop tracking procedures to monitor effectiveness of recruitment efforts. The recruitment plan for the trial will include both the utilization of participants existing at clinical trial centers and the recruitment of additional populations by methods of outreach. Efforts will be made to target at least 20% enrollment of underrepresented groups (URGs), which will be facilitated through special URG effort coordinated by the Coordinating Center.

8.0 STUDY TIMELINE

The approximate timeline for this study is projected as follows: 1) approximately 6 months for study startup activities, site IRB and regulatory approvals, and the Investigator training meeting; 2) approximately 24 months for screening; 3) 2.5 years for treatment period and analysis.

9.0 DESCRIPTION OF STUDY VISITS

Study visits will occur according to the following diagram. For a complete list of all visit procedures, refer to the Schedule of Events (Appendix 1).



9.1 Pre-screening

During the prescreen phase, sites will identify potential participants through a variety of mechanisms (i.e. reviewing patients enrolled in ADCs, de novo recruitment, and referrals) and assess if they may potentially qualify for the study following the site's standard practice.

9.2 Screening

The purpose of this visit is to determine initial study eligibility. Potential participants, or legally authorized representatives, and their study partners must sign an informed consent form prior to administration of any study-related procedures. Information regarding the participant's demographics, concurrent medications, and medical history will be gathered along with cognitive, clinical, and safety assessments. For a complete list of all Screening Visit procedures, refer to the Schedule of Events (Appendix 1).

Important: If participant has ever had any prior exposure to the Logical Memory story, an alternate paragraph will be used instead.

All Screening procedures must be completed and all information related to eligibility, including screening lab results, must be reviewed by the investigator or qualified designee for assessment of the participant's eligibility.

Monitor review is required prior to randomization.

9.2.1 Screen Failures and Re-screens

Unless otherwise approved by the Project Director, a participant may only be re-screen once, should the original screen be a failure. The re-screen should typically occur at least 3 months after the original screen failure.

9.3 Baseline Visit

The Baseline visit may only be initiated following completion of all Screening assessments and required approvals. All Baseline procedures, including randomization must be completed within 28 days of initiation of Screening Visit procedures.

Baseline procedures include cognitive and functional assessments, safety assessments, review of concurrent medications and adverse events, biofluid collection (blood, plasma, and optional CSF), and optional MRI. For a complete list of all Baseline procedures, refer to the Schedule of Events (Appendix 1).

Baseline cognitive assessments for CSF sub-study participants must be done prior to, or at least 48 hours after, the lumbar puncture. In no instance should cognitive assessments be performed while the participant is in a fasted state. If a participant happens to enroll in both the CSF and MRI sub-studies, the LP must occur after (or a minimum of 72 hours prior to) the MRI scan.

For further information regarding specific visit procedures, refer to Section 12.

Following completion of all Baseline procedures, participants who continue to meet all protocol inclusion criteria and no exclusion criteria, will be randomized and

dispensed study medication. Refer to Section 6 for study drug dosing schedule and instructions.

9.4 Treatment Period

Evaluations of safety and tolerability, clinical and biomarker assessments, and study drug dispensing will be performed throughout the remaining treatment period. For a complete list of all study visits and study visit procedures, refer to the Schedule of Events (Appendix 1).

9.4.1. Titration Period

The initial study period includes titrating participants up to the maintenance dose level. Refer to Section 6 for study drug dosing schedule and instructions, including how to detail with tolerability issues that may arise.

9.4.2. Extra Efficacy Clinic Visit

Aducanumab treatment may be started after completion of the Baseline Visit and at any point during the study drug treatment period (Week 5 – Month 24). If the participant reports they will start aducanumab treatment, conduct the Extra Efficacy Clinic Visit if at all possible prior to the participant starting aducanumab treatment and prior to conducting the next scheduled study visit. Depending on the timing of the Extra Efficacy Clinic Visit, visit windows for the next scheduled study visit may need to be adjusted, contact the Coordinating Center for guidance on scheduling.

9.4.3. Phone Follow-ups

An interval history will be performed by telephone following the Baseline and Week 5 visits. The purpose of the phone call is to discuss with the participant their experience in administering the study drug, answer questions, and assess any adverse events that the participant may have experienced. The participant should be reminded about the proper technique for applying the patches.

9.4.4. Taper Period

During the 3 weeks following the Month 24 visit, the dose will be tapered down from the maintenance dose level. Refer to Section 6 for study drug dosing schedule and instructions.

9.4.5. Visit Timing and Procedures

Procedures for each follow-up visit may be completed over multiple days, but must occur within the study visit window. The schedule and visit windows for each treatment period visit are as follows:

Visit	Target date	Visit Window
Baseline Phone Follow-up	7 days from Baseline	+/- 2 days
Week 5 Visit	5 weeks from Baseline	+ 7 days
Week 5 Phone Follow-up	7 days from Week 5	+/- 2 days
Months 3-24 Visits	Specified months from Baseline	+/- 14 days
Taper Visit	3 weeks from Month 24	+7 days

If done on the same day, cognitive assessments must be done prior to MRI scan for MRI sub-study participants.

Cognitive assessments for CSF sub-study participants must be done at least 48 hours after the lumbar puncture. In no instance should cognitive assessments be performed while the participant is in a fasted state. CSF sub-study participants who did not have a successful CSF collection at Baseline should still attempt a collection at Month 24. If a participant happens to enroll in both the CSF and MRI sub-studies, the LP must occur after (or a minimum of 72 hours prior to) the MRI scan.

For further information regarding specific visit procedures, refer to Section 12.

10.0 EARLY TREATMENT/STUDY DISCONTINUATION

The investigators at each site will make every reasonable effort to maximize participant retention. However, if an investigator removes a participant from treatment or study, or if a participant declines further treatment or study participation, an Early Discontinuation Visit will be completed as soon as possible following discontinuation of the study drug and or at time of study discontinuation.

The Early Discontinuation Visit will contain the same assessments as the Month 24 visit, to allow collection of the main outcome measures. Depending on when the last study visit was conducted, the sub-study procedures (e.g. LP, MRI scan) may not be required at the Early Discontinuation Visit. Refer to the Procedures Manual for further guidance. If an in-person visit is not possible, site personnel will complete as much of the Early Discontinuation Visit as possible by telephone. All early treatment discontinuation participants will be strongly encouraged to complete all remaining study visits.

The decision whether to taper down from the maintenance dose level, similar to what would be done following the Month 24 visit, will be left to the discretion of the site clinician.

Replacement participants are not required for those who discontinue from treatment or study (i.e. an additional participant does not need to enroll in the study for every participant discontinued).

10.1 Reasons for Early Discontinuation

Participants may be discontinued from treatment/study for reasons such as the following:

- Adverse experience: The participant has experienced an adverse event that, in the opinion of the investigator, requires early termination. This may include abnormal laboratory values.
- Death
- Safety risk: Any participant who becomes a safety risk during the trial will be withdrawn.
- Protocol violation: The participant fails to meet protocol entry criteria or did not adhere to protocol requirements.

- Non-compliance: The participant is non-compliant with completion of study-related evaluations and or use of study drugs.
- In the investigator's judgment, it is in the participant's best interest to discontinue participation in the treatment/study.
- Consent is withdrawn. The participant wishes to withdraw from the study, or the legally authorized representative wish the participant to be withdrawn.
- The study is terminated by the Project Director/Coordinating Center, alone or at the recommendation of the Data Safety Monitoring Board.
- Lost to follow up. Participant could not be recalled back to conduct follow up visits.
- Loss of informed study partner. The participant no longer has a responsible study partner to oversee participant visits and administration of study drug.
- Coordinating Center Request. The coordinating center determines it is in the participant's best interest to discontinue participation from the treatment and or study.

11.0 INSTRUMENTS

11.1 Cognitive Evaluations

11.1.1 Conners Continuous Performance Test (CPT)

This test was originally validated as an assessment tool for diagnosing attention deficit/hyperactivity disorder (ADHD). Investigators have previously found it to be sensitive to nicotine-induced attentional improvements in people with schizophrenia[17], ADHD[32], (Levin et al. 1996) and normal young adults as well as in the nicotine-MCI pilot study. Participants will be asked to monitor a computer screen and indicate (by pressing a button) whenever the target stimulus (any letter except for the X) appears. Participants are asked to refrain from responding to the X, or the non-target stimulus. Task duration is 15 minutes. Dependent variables include correct responses (hits), misses, errors of commission, and reaction time for all types of responses. Reaction Time-Standard Error (RT-SE), a measure from this task, reflects the variability in attending to a stimulus and is sensitive to cognitive impairment, impairment of attention, and cognition-enhancing drug treatment.

11.1.2 Cogstate Battery

This battery will be used for the purpose of assessing the cognitive status of the participants and will assist in documenting multiple domains of cognitive impairment. Preference was given to measures with adequate temporal stability for the measurement of long-term changing cognitive functioning, and with difficulty levels appropriate for measuring change in cognitive functioning among persons of diverse education and cultural backgrounds. The battery used will be in large part based on the Cogstate computerized battery, and will include the following cognitive measures: Immediate Word Recall (shopping list task), Simple Reaction Time (Detection task), Choice Reaction Time (Identification Task), Working Memory (One-back Task), Recognition Memory (One Card Learning Task), Delayed Verbal

Recall (Shopping List Task). The Cogstate Battery will be administered via tablet in-clinic.

11.1.3 Immediate and Delayed Paragraph Recall (NYU Version)

This test measures immediate and delayed verbal recall of a brief story. Immediate recall is assessed after reading the paragraph to the participant followed by a second reading of the paragraph. After at least five minutes of intervening tests, delayed recall for the paragraph is assessed. This test assesses the effects of aging and cognitive impairment and may predict conversion to Alzheimer's disease in participants with MCI. Different versions of the test will be used at each administration.

11.1.4 Logical Memory II (Delayed Paragraph Recall)

Logical memory II, a measure of episodic memory is a sub-test of the Wechsler Memory Scale Revised (WMSR). The participant is immediately asked to retell a story from memory and then asked following a 30-minute delay. The delayed measure is used as a clinical measure of episodic memory.

11.1.5 Mini-Mental State Examinations (MMSE)

The MMSE[35] is a brief, frequently used screening instrument for Alzheimer's disease drug studies. The MMSE scale evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy two overlapping pentagons. The MMSE is scored as the number of correctly completed items with a lower score indicative of poorer performance and greater cognitive impairment. The total score ranges from 0 (worse) to 30 (perfect performance).

11.1.6 Wechsler Test of Adult Reading (WTAR)

The WTAR allows the measurement of pre-morbid level of intellectual functioning for individuals ages 16 to 89 years. This reading test is composed of a list of 50 irregularly spelled words and the participant is prompted to pronounce each; the irregular grapheme-to-phoneme translations (such as the "gh" in the word *tough*) in the prompts make it difficult to pronounce without having previously learned the word. Since the participant cannot apply standard pronunciation rules to complete the task, the examiner can assess their vocabulary by their ability to pronounce the irregularly spelled words, and by extension, estimate their premorbid IQ. Unlike many intellectual and memory abilities, reading recognition is relatively stable in the presence of cognitive decline associated with normal aging or brain injury. Administration of the WTAR takes less than 10 minutes and involves asking the participant to read out loud 50 words. Pronunciations are provided on the record form for scoring accuracy; the total score is the number of words read correctly.

11.2 Clinical and Functional Evaluations

11.2.1 Mild Cognitive Impairment – Clinical Global Impression of Change (MCI-CGIC)

The MCI-CGIC is the MCI version of the clinician's global impression of change. In this trial it will measure change in the participant's condition between the baseline

visit and subsequent visits. The clinician rates the participant on a seven-point scale ranging from 1 (marked improvement) to 7 (marked worsening). The clinician collects information from both participant and the informant through an interview format. At the baseline visit only, the clinician may review the participant's prior medical history and test scores in order to develop a comprehensive impression of the participant's cognitive abilities and deficits, behavior, and activities of daily living. At each visit the clinician's assessments should be made without referring to the test scores. At each visit at which the evaluation is performed, the MCI-CGIC should be administered without knowledge of the participant's adverse events and should focus on observations of the participant's cognitive, functional, and behavioral performance at the time of the evaluation and during the prior three months.

11.2.2 Activities of Daily Living (ADCS-ADL) - MCI

The Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale (ADCS - ADL) is an activities of daily living questionnaire aimed at detecting functional decline in people with Mild Cognitive Impairment (MCI) [50]. It was adapted from an inventory developed by the ADCS to assess functional performance in participants with Alzheimer's disease [36]. In a structured interview format, informants are queried as to whether participants attempted each item in the inventory during the prior 4 weeks and their level of performance. The ADCS-ADL scale discriminates well between normal controls and participants with mild AD or MCI and has good test-retest reliability. The questions focus predominantly on instrumental activities of daily living scales (e.g. shopping, preparing meals, using household appliances, keeping appointments, reading).

11.2.3 Clinical Dementia Rating Scale (CDR)

The CDR[37, 38] is a clinical scale that rates the severity of dementia as absent, questionable, mild, moderate, or severe (CDR score of 0, 0.5, 1, 2, or 3, respectively). The score is based on interviews with the participant and study partner, using a structured interview that assesses six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The ratings of degree of impairment obtained on each of the 6 categories of function are synthesized into one global rating of dementia (ranging from 0 to 3), with more refined measure of change available by use of the Sum of Boxes. Reliability and validity has been established, as has high inter-rater reliability.

11.2.4 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the corresponding assessment period. The scale includes suggested questions to elicit the type of information needed to determine if a suicide-related thought or behavior occurred. If a suicide-related thought to behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided.

11.2.5 Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a scale intended to measure daytime sleepiness that is measured by use of a very short questionnaire. The questionnaire

asks the participant to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives, though not necessarily every day. The scores for the eight questions are added together to obtain a single number. A number in the 0–9 range is considered to be normal while a number in the 10–24 range indicates sleep difficulties. The author of the ESS recommends that the administrator of the questionnaire does not discuss the results of the ESS with the participant until it is completed, as this may affect the participant's responses on the questionnaire.

11.2.6 Geriatric Depression Scale (long form)

The Geriatric Depression Scale (GDS) is a 30-item self-report assessment used to identify depression in the elderly[39]. The GDS questions are answered "yes" or "no". This simplicity enables the scale to be used with ill or moderately cognitively impaired individuals. One point is assigned to each answer and the cumulative score is rated on a scoring grid. The grid sets a range of 0-9 as "normal", 10-19 as "mildly depressed", and 20-30 as "severely depressed".

11.2.7 Older Adult Self Report (OASR) and Older Adult Behavior Checklist (OABCL)

The OASR (completed by the participant) and the OABCL (completed by the informant) are approximately 145-item comprehensive self-rating instruments. It allows multi-informant perspective (both patient and informant). The items are focused on common elderly emotional, functional, or medical problems. These items were constructed and/or selected from other scales and clinical experience. The scales also include a large number of additional items assessing basic demographic and social information (education, marital status, marital relationship, and friendships) as well as assessing substance use, physical illness and functional abilities. Most of the questions are answered in a 0,1,2 format (not true, sometimes true, often true). There is space at the end of the scale for additional written comments by the participant. These scales have been validated in dementia[40] and were used in the pilot nicotine-MCI study.

11.2.8 Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is a self-report questionnaire that assesses sleep quality over a 1-month time interval. It consists of 19 individual items generating seven “component” scores: subjective sleep quality, sleep latency (i.e., how long it takes to fall asleep), sleep duration, habitual sleep efficiency (i.e., the percentage of time in bed that one is asleep), sleep disturbances, use of sleeping medication, and daytime dysfunction. The survey contains 19 questions, each weighted on a 0-3 interval scale. A global PSQI score is taken from the survey, with lower scores correlating to better sleep quality.

11.2.9 Research Satisfaction Survey

The Research Satisfaction Survey (RSS) was adapted from the work of Larsen et al[42] to measures the satisfaction of elderly volunteers in clinical trials to treat or prevent cognitive loss or dementia. The RSS builds on the Client Satisfaction Questionnaire (CSQ-8), which demonstrates a high degree of validity and internal consistency and measured consumer satisfaction with health and human service programs. Higher scores on the CSQ indicate a greater level of satisfaction in service programs[44];

conversely, lower CSQ-8 scores have been associated with higher dropout rates[44] and missed appointments in treatment settings[43] and in urban Community Mental Health program[42]. Open-ended questions about satisfaction are part of the CSQ, and allow participants to provide feedback about specific operational procedures of a particular service program[42]. The RSS is similarly designed with a 7- item survey and may include additional items to inquire about the specific aspects of a given trial. Four items are designed to be answered with a modified likert scale and can be used to create a summary score with a range of 4-16, which can be analyzed with parametric statistics; three items provide for open ended responses about the intervention, the assessments and the frequency of visits and may be used to understand retention rates.

11.2.10 Treatment Blinding Questionnaire

The Treatment Blinding Questionnaire assesses the perception of blind being maintained until the end of the study. The questionnaire is to be completed by the study participant, study partner, and principal investigator at the end of study.

12.0 PROCEDURES

12.1 Safety Assessments

12.1.1 Physical and Neurological Examination

A medically qualified professional will perform a brief physical examination that consists of a review of the major body systems (i.e. skin, HEENT (head/ears/eyes/nose/throat), cardiovascular, pulmonary, abdomen, musculoskeletal, and extremities). Neurological examination will include an assessment of cranial nerves, strength, coordination, reflexes, sensation, tremor, gait and mental status.

12.1.2 Vital Signs

Vital signs will include seated blood pressure, pulse, temperature, respiration rate, weight, and, at the screening visit, height.

12.1.3 Electrocardiogram (ECG)

An appropriately qualified individual will conduct a standard 12-lead resting ECG. The ECG report must be reviewed, signed, and dated by the site Principal Investigator (or a medically-qualified individual delegated by the PI). Those with clinically significant ECG findings will be referred for follow-up as deemed appropriate by the investigator and may be excluded from the study.

12.1.4 Clinical Laboratory Evaluations

All routine laboratory samples will be analyzed by a central laboratory, which will provide a procedures manual and supplies. Lab reports will be reviewed, signed and dated by the site Principal Investigator (or a medically-qualified individual delegated by the PI). If a value is outside of the laboratory's normal range, the clinician will indicate if it is clinically significant or not. Those results that are deemed clinically significant may need to be repeated and follow up with the participant's primary care physician for further evaluation should occur.

Screening visit labs include: Hematology, Chemistry Panel, TSH, Vitamin B12, Cholesterol (total and HDL), and urinalysis. In the event of a low B12 result at screening, the homocysteine (HC) and methylmalonic acid (MMA) reflex tests must be performed to assess eligibility. Follow-Up labs include: Hematology and Chemistry Panel. At Screening and Month 24, PT/PTT will also be collected for CSF sub-study participants.

12.2 Research Biospecimens

All research laboratory samples will be stored and analyzed by central research laboratories. Detailed collection and shipment procedures, as well as information regarding provision of supplies by the Coordinating Center, will be provided in the study specific procedures manual.

12.2.1 Blood for Plasma Biomarkers

Blood for plasma biomarkers will be collected in a uniform fashion after an 8-hour fast into 10ml lavender top EDTA tubes and shipped overnight at ambient temperature to the central research laboratory. Blood samples will be processed for plasma and used for analysis of AD biomarkers (e.g. Aβ40 & 42, exploratory biomarkers).

12.2.2 Blood for Treatment Related Markers

Blood for treatment related markers will be collected in a uniform fashion after an 8 hour fast into 10ml lavender top EDTA tubes and shipped overnight at ambient temperature to the central research laboratory. Blood samples will be processed for plasma and used for analysis of nicotine, cotinine, and 3hydroxycotinine by LCMS, and the Nicotine Metabolite Ratio (NMR, 3hydroxycotinine/cotinine) will be derived.

12.2.3 Blood for Genetics

Blood for genetic analyses will be collected in a uniform fashion into 10ml lavender top EDTA tubes and shipped overnight at ambient temperature to the central research laboratory. The sample will be used to extract DNA for analysis of APOE genotype and nicotine-pharmacology related genes including those in the main nicotine-metabolizing enzyme, CYP2A6.

12.2.4 Lumbar Puncture/CSF Substudy

Participants at a subset of sites will have the option to participate in the CSF Sub-study.

All samples will be collected after an 8-hour fast, preferably in the morning. Efforts should be made to conduct the follow-up LP at the same time of day as the Baseline LP.

Prior to lumbar puncture (LP), a coagulation panel will be obtained to rule out a clotting disorder. Participants taking an anti-platelet agent (e.g. aspirin) may be discontinued from that agent for a period of time before and after the LP at the discretion of the PI (or qualified designee). Participants who are taking anticoagulants (e.g. warfarin (Coumadin) and/or dabigatran (Pradaxa)) may not undergo an LP and are not suitable to participate in this substudy.

When done at the same visit, the LP must always occur after (or a minimum of 72 hours prior to) the MRI scan. LP under fluoroscopy is permitted, if needed. Site personnel should advise the participant that use of fluoroscopy (x-rays) involves exposure to radiation.

A total volume of 20 mL of CSF should be collected for each LP. To clear blood associated with needle insertion, the first 1-2 mL (or more if needed) of CSF should be discarded. 1-2 mL CSF (or volume per local laboratory requirements) will be sent to the local laboratory for protein, glucose, and cell counts. Remaining CSF will be frozen on dry ice or in a -80 freezer and shipped overnight frozen to the central research laboratory for processing and analysis. Analyses will include AD biomarkers (e.g. Aβ and tau, exploratory biomarkers).

Each study participant or a person designated to speak for them will be contacted by phone one day after the LP to confirm participant well-being and to query about any adverse events.

12.3 Magnetic Resonance Imaging (MRI) Substudy

Participants at a subset of sites will have the option to participate in the MRI Sub-study.

Details regarding site qualification, scan acquisition and scan submission will be included in the study-specific MRI technical manual.

12.3.1 MRI Scanner Qualification

MRI scanners at each site will be subjected to a pre-qualifying process that includes an evaluation for excessive vibration or other image artifact revealed through submitted MR images of an American College of Radiology phantom obtained by applying the study's standardized protocol. If the MRI scanner has not been used previously in an applicable trial, then an additional qualification step will require the scanning of a human volunteer. If the MRI scanner was previously used in an applicable trial, the qualification process may be shortened and a human volunteer may not be needed. Sites must demonstrate the ability to follow the imaging protocol as prescribed in the MRI technical manual and to provide images using the procedures for uploading scans. The QC results will be examined centrally to assess suitability for analyses.

12.3.2 Data Acquisition

The MRI will be performed using a 3.0 Tesla magnet. The MRI will take approximately 1 hour to complete and injectable contrast agents will not be used. The protocol for image acquisition will include structural and functional MRI (both resting state and task-based).

Conscious sedation will not be allowable. When done at the same visit, the MRI scan must always occur prior to (or at least 72 hours after) an LP.

Because longitudinal analyses will be used in this study, sites will be required to use the same qualified scanner for all scans of a particular participant.

Well-standardized multi-center MRI methods developed by the MRI Core of the Alzheimer's disease Neuroimaging Initiative (ADNI) will be used as the basis for the structural imaging. The volumetric analysis procedure will include corrections for gradient nonlinearities[45] and intensity non-uniformity[46, 47] using methods developed within the Morphometry Biomedical Informatics Research Network (mBIRN; http://www.birncommunity.org/).

Intrinsic resting state functional connectivity (rsFC) will be assessed during a 10-min period in which participants are instructed to keep their eyes open and focus on a fixation cross presented in the center of the screen. The N-Back Test will be used as a test of working memory. The participant sees a string of consonant letters (except L, W, and Y), one every three seconds. Multiple conditions are presented, in which the task is to decide whether the letter currently on the screen matches the item that had been presented some number (e.g. 0, 1, or 2) back in the sequence. The N-back has multiple equivalent versions and has been thoroughly tested with older adults to ensure there is neither ceiling nor floor effects for performance and has been shared with comparable data across multiple labs and scanner platforms.

12.3.3 Clinical Read of MRIs

Each site will be required to procure a local clinical read of each participant's MRI scan by qualified personnel. MRI scan findings of clinical significance, as determined by the local clinical read and the site PI, may be shared with the study participant and the participant's local physician.

12.3.4 Data Management and Quality Control

MRI data will be coded by removing all PHI from the imaging headers except acquisition dates and the numerically coded ID. The MRI image file will then be uploaded by each site to a central XNAT (eXtensible Neuroimaging Toolkit) system. In addition to secure, multi-site access to data resources, this XNAT system provides automated processing for QC analysis. The QC results will be reviewed by a human for any gross errors.

Quality control for MRI will result in failure of some scans, which may need to be repeated. Repeat scans must be scheduled within four weeks of the visit date.

MRI scanner performance will be routinely assessed with the standardized ADNI phantom QC procedures at each substudy site.

13.0 PERSONNEL REQUIREMENTS

The Protocol Principal Investigator (PI) is responsible for the overall conduct of the study at the site. The PI is to supervise project personnel and ensure that clinical raters maintain a high level of skill and accuracy in conducting assessments. Additionally, the PI will perform or supervise clinical evaluation of all participants and ensure protocol adherence. Additional key personnel may be required, as specified in the procedures manual.

The CGIC rater must not be a cognitive rater and must remain blinded to AE data. Sites who are unable to maintain this blinding throughout the study should consult with the Coordinating Center for guidance and appropriate handling of the situation.

14.0 ADVERSE EVENTS

14.1 Definition

An adverse event (AE) is defined as per the Code of Federal Regulation Title 21 Part 312:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32

Adverse events which occur after informed consent is signed and up to 30 days after the study drug has been discontinued, include but are not limited to: (1) worsening or change in nature, severity, or frequency of conditions or symptoms present at the start of the study; (2) participant deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. An abnormal laboratory value will only be reported as an AE if the investigator considers it to be clinically significant, or if it leads to the participant being withdrawn from the study.

The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs or symptoms. Symptoms and conditions present at the beginning of the study will be characterized, so that AEs can be defined as any new symptom, or any increase in frequency or severity of an existing symptom. Adverse events should be described with medical terminology so that the event can be matched against a medical coding dictionary, such as MedDRA (Medical Dictionary for Regulatory Activities).

Investigators should report their assessment of the potential relatedness of each AE to the protocol procedure(s) and also to the investigational product.

Following questioning and evaluation, all AEs, whether determined to be related or unrelated to the study drug by a medically qualified site PI or clinician must be documented in the participant's records, in accordance with the investigator's normal clinical practice, and on the AE eCRF.

14.2 Following Up on AEs

The investigator is obliged to follow participants with AEs until the events have subsided, the conditions are considered medically stable, or the participants are no longer available for follow up. Participants who discontinue due to adverse experiences will be treated and followed according to established medical practice. All pertinent information will be entered into the eCRF.

15.0 SERIOUS ADVERSE EVENTS (SAE)

15.1 Definition

A serious adverse event is defined as per the Code of Federal Regulation Title 21 Part 312:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32

Medical and scientific judgment should be exercised in deciding whether reporting a serious adverse event is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the code of Federal Regulations Title 21 Part 312.

Hospitalizations that fulfill one of the following conditions will not have to be reported as SAE:

- Admission for treatment of a pre-existing condition that is not associated with the development of a new AE or with a worsening of the pre-existing condition (i.e., work-up for persistent lab abnormality that occurred prior to the study)
- Social admission (i.e., participant has no place to sleep)
- Administrative admission (i.e., yearly physical exam)
- Protocol-specified admission (i.e., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (i.e., pre-planned treatments, elective cosmetic surgery)

15.2 Reporting SAEs

The principal investigators and Coordinating Center staff will monitor the study procedures for this trial for overall safety and scientific relevance on an ongoing basis. The local site PI (in conjunction with, as needed, the Medical Monitor, the Project Director, and the data safety monitoring board (DSMB)) will evaluate each serious adverse event for safety and causality, and will determine whether the adverse event affects the risk/benefit ratio of the study and whether modifications to the protocol or consent form are required.

Any serious adverse event which occurs during the course of the investigation (i.e. anytime after informed consent, regardless of study drug exposure) or within 30 days of receiving the last dose or last study visit must be reported to the Project Director and the Coordinating Center within 24 hours of learning of the event. Coordinating Center personnel will work with the Protocol Project Director, to generate a report, which will be distributed to all participating site. Sites will inform their IRB of the event based on local IRB requirements.

15.3 Unanticipated Problems

The Office for Human Research Protections considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

ATRI will manage these unanticipated problems as SUSARs that involve the project director and DSMB or as AEs of Medical Interest, which would be reported in local IRB reports from sites.

16.0 DATA AND SAFETY MONITORING BOARD (DSMB)

The DSMB is an independent advisory group to the Coordinating Center Director, the Project Director, and the NIA. No investigator involved in the trial is a member of the DSMB.

The initial task of the DSMB will be to review the protocol to identify any necessary modifications. If modifications are necessary, revisions will be reviewed by the DSMB prior to its recommendation on initiation of the project. The DSMB, based on its review of the protocol, will work with the Coordinating Center personnel to identify the study-specific data parameters and format of the information to be regularly reported. All adverse events and serious adverse events will be reported to the DSMB. The DSMB will initially be provided with data masked to treatment assignment, but they may request unblinded data if there is a safety concern. The DSMB and NIA representative will meet in person or by conference call on a quarterly basis. Additionally, the DSMB will be informed of the occurrence of any Suspected Unexpected Serious Adverse Reactions (SUSARs) or other SAEs of particular significance, within 7 days of being reported to the Coordinating Center. The DSMB may at any time request additional information from the Coordinating Center.

Based on the review of safety data, the DSMB will make recommendations regarding the conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study or continuing the study as designed. For further details please refer to the DSMB charter.

17.0 DATA AND SPECIMEN STORAGE

17.1 Study Data Collection and Storage

Study data will be collected in the following ways:

- the Principal Investigator or designee will record data collected (either written or electronic record of data)
- the participant or study partner will complete assessments on paper
- the participant or study partner will use a computer or tablet to complete assessments

Written or electronic data of record must be entered on the electronic Case Report Form (eCRF) provided for that purpose, except where instructed to use only the computerized system for capture of a particular assessment. In some instances no prior written or electronic record of data may exist and data recorded directly on the eCRF is considered source data. The site will be suitably trained on the use of the eCRF and other computerized systems used for data collection and appropriate site personnel will be authorized to provide electronic signatures. The Principal Investigator is responsible to verify the integrity of the data and acknowledge as such by signature.

All data will be collected in secure web sites or computer systems and the Principal Investigator will review the records for completeness. If corrections are necessary to the eCRFs or data collected via other systems, the Principal Investigator or designee will correct the data and provide documentation for the reason for change.

Sites will complete eCRFs and administer and submit data from computerized assessments according to the Coordinating Center's instructions. The Coordinating Center will review all data to determine their acceptability. If necessary, data correction requests will be generated for resolution by the study site.

17.2 Study Files and Participant Source Documents

Participant confidentiality is strictly held in trust by the participating investigators and research staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsoring institution. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records. Any data, specimens, forms, reports, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in

a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant HIPAA Authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. Each site PI, under the guidance of his/her IRB, is responsible for ensuring that all applicable HIPAA regulations and State laws are met.

17.3 Research Biospecimens and Genetic Material Storage

All research biospecimens, including DNA and other residual samples and derivatives from processing and analysis, will be coded and stored securely by the central research laboratories. Sample tubes will be identified only by a code number and descriptive data (such as the participant's age and gender). No other personal identifying information will be attached to the samples.

Samples collected from participants who do not consent to banking of those samples for future analysis as described in Section 22 will be destroyed after all protocol-related analyses are completed.

17.4 MRI Imaging Data Storage

MRI scans will be labeled according to each site's imaging machine capabilities using Participant ID and scanner specific series descriptions as detailed in the Technical Manual. All imaging data will be coded using participant identifiers as detailed in the Technical Manual and checked centrally to confirm the absence of participant identifying information.

18.0 ETHICS AND REGULATORY CONSIDERATIONS

18.1 Good Clinical Practice

This study will be conducted in compliance with the protocol, in accordance with GCP guidelines, and in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46 – Protections of Human Participants, 24 CFR Part 50 – Protection of Human Participants, 21 CFR Part 56 –

IRBs, and/or the ICH E6, HIPAA, State and Federal regulations and all other applicable local regulatory requirements and laws.

Study personnel involved in conducting this study will be qualified by education, training and experience to perform their respective task(s) in accordance with GCP.

No study document shall be destroyed without prior written agreement between the Coordinating Center and the investigator. Should the investigator wish to assign study records to another party or move them to another location, he/she may do so only with the prior written consent of the Coordinating Center.

18.2 Institutional Review Board (IRB) / Research Ethics Boards (REB)

Institutional Review Boards and Research Ethics Boards must be constituted and their authority delegated through the institution's normal process of governance according to applicable State and Federal requirements for each participating location. Each participating institution must provide for the review and approval of this protocol, the written informed consent form and any other written information to be provided to participants by an appropriate IRB registered with the Office for Human Research Protections (OHRP). In the United States, only institutions holding a current US Federalwide Assurance issued by OHRP may participate. Refer to: http://www.hhs.gov/ohrp/assurances/.

Amendments to the protocol and informed consent form amendments can be made only with the prior approval of the Coordinating Center and must also be approved by an appropriate IRB before they are placed into use. The investigator may not implement any protocol deviation without prior notification to the Coordinating Center and prior review and documented approval of the IRB, except where necessary to eliminate an immediate hazard to study participants, or when change(s) involve only logistical or administrative aspects of the trial (ICH 4.5.4). The investigator shall notify the IRB of deviations from the protocol or serious adverse events occurring at the site, in accordance with local procedures.

18.3 Informed Consent and HIPAA Compliance

Informed consent will be obtained in accordance with US 21 CFR 50.25, the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada and ICH Good Clinical Practice. Applicable HIPAA privacy notifications will be implemented and HIPAA authorizations signed before protocol procedures are carried out. Information should be given in both oral and written form as deemed appropriate by the Site's IRB.

Consent forms must be in a language fully comprehensible to the prospective participants and/or their authorized representatives and study partners. Participants, their relatives, guardians, or authorized representatives and study partners will be given ample opportunity to inquire about the details of the study. Prior to a participant's participation in the trial, the written informed consent form should be signed and personally dated by the participant or by the participant's legally acceptable representative, and by the person who conducted the informed consent discussion. Participants should be provided a copy of the signed ICF.

The informed consent will not only cover consent for the trial itself, but for broad sharing of all study data (including clinical, cognitive, imaging, biomarker and genetic data), as well as storage of biological samples for future research.. Consent forms will specify that DNA and biomarker samples are for research purposes only; the tests on the DNA and biomarker samples are not diagnostic in nature and participants will never receive results.

18.4 Certificate of Confidentiality

A Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

18.5 Inclusion of Children as Participants

Children will not be included.

18.6 Study Monitoring

The clinical monitor is responsible for inspecting the electronic case report forms and source documentation at regular intervals throughout the study to verify adherence to the protocol, completeness and accuracy of the data, and adherence to local regulations on the conduct of clinical research. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities. The Site Investigator will cooperate in the monitoring process by ensuring the availability of the eCRFs, source documents and other necessary documents at the time of the monitoring visits. Site Investigator will promptly address any matters brought to his/her attention by the monitor. The Site Investigator may also be asked to meet in-person with the site monitor during certain visits.

19.0 AUDIT

In accordance with ICH GCP, representatives of the Coordinating Center and/or regulatory agency may select this study for audit. The Investigator and study staff are responsible for maintaining the site master file containing all study-related documentation which is subject to inspection at any time by the Coordinating Center, its designees, and/or regulatory agencies. Inspection of site facilities (e.g., pharmacy, laboratories) to evaluate the trial conduct and compliance with the protocol may also occur.

20.0 RECORD RETENTION

Clinical sites will maintain study documents in an organized and accessible manner to facilitate study management and for audit and inspection purposes. Clinical sites will follow minimum requirements for record retention as specified in your study contract. Clinical sites are considered covered entities and as such must comply with the HIPAA Privacy Rule which stipulates that HIPAA covered documents must be retained for a minimum of six (6) years from when the document was created, or – in the event of a policy – from when it was last in effect (45 CFR 164.316(b)(2)(i)). Record retention requirements of 45 CFR 164 (HIPAA) are in addition to HHS and FDA requirements.

Clinical sites may be required to comply with additional regulations and policies (e.g., NIH, HHS, FDA CFR, HIPAA) and should follow the rule that has the longest period for document retention. It is advised that institutions and site investigators consult their institution's policies and procedures, HIPAA Privacy and Security officials, and legal counsel and/or risk management personnel to determine record retention requirements under HIPAA.

21.0 PUBLICATION POLICY

The results of this study will be published. To coordinate dissemination of data from this study, a publication committee will be formed. The committee will consist of Dr. Newhouse, appropriate Coordinating Center personnel, and others at the discretion of Dr. Newhouse and the Coordinating Center director. The committee will solicit input and assistance from other Investigators as appropriate and adhere to all Coordinating Center Publications Policies.

22.0 SHARING OF RESEARCH DATA AND SPECIMENS

22.1 Sharing of Study Data

Data from this research will be shared with other researchers pursuant to the 02/26/2003 "NIH Final Statement on Sharing Research Data" and pursuant to the 8/24/2014 "NIH Genomic Data Sharing Policy". The NIH policies can be found at:

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-124.html.

NIH believes that data sharing is important for further translation of research results into knowledge, products, and procedures to improve human health. The NIH endorses the sharing of final research data to serve these and other important scientific goals. To protect participants' rights and confidentiality, identifiers will be removed from the data before they are shared.

NIH/NIA Databases

For genetics, genomics, and related data, data may be shared with other researchers pursuant to the NIA Alzheimer's Disease Genetics Sharing Plan: http://www.nia.nih.gov/research/dn/alzheimers-disease-genetics-sharing-plan.

NIAGADS, along with other NIA-approved sites, will make these genetic data and associated phenotypic data available to qualified investigators in the scientific community for secondary analysis in accordance with standards established by NIA. These data repositories are under strict security provisions, including multiple firewalls, separate servers, and data encryption protocols. Investigators and their sponsoring institutions seeking access to data from the NIA-approved data repository must submit a data access request that specifies both the data to which access is sought and the planned research use, and agree to the terms of access set forth in the Data Use Certification (DUC). Investigators are approved by a Data Access Committee (DAC) for access to specific datasets for a specific use(s). In addition, the DUCs include a provision that approved users and their institutions agree to store the requested data securely and to not share the requested data with third parties.

22.2 Sharing of Biospecimens and Genetic Material

Research biospecimens and DNA from consenting participants will be banked and may be shared with other researchers studying AD, aging, or other health conditions to facilitate future research. Banking of these samples will permit qualified investigators to probe candidate biomarkers and genetic polymorphisms as predictors of outcome in future studies.

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APPENDIX 1 SCHEDULE OF EVENTS

Procedure \ Visit [a]	Screening	Baseline	Phone Call	Week 5	Phone Call	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24 [b]	Extra Efficacy Clinic Visit [d]	Taper
Explain Study, Informed Consent	X														
Demographics and Family History	X														
Medical History	X														
ECG	X								X				X	X	
Physical and Neurological Exam	X						X		X		X		X	X	
Vital signs	X	X		X		X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X		X		X	X	X	X	X	X	X	X	X	X
Adverse Events		X		X		X	X	X	X	X	X	X	X	X	X
OASR/OABCL		X					X		X				X	X	
Geriatric Depression Scale	X			X		X	X		X		X		X	X	
Columbia Suicide Severity Rating Scale		X		X		X	X	X	X	X	X	X	X	X	X
Pittsburgh Sleep Quality Index		X		X		X	X		X		X		X	X	
Epworth Sleepiness Scale		X		X		X	X		X		X		X	X	
MCI-CGIC		X				X	X		X		X		X	X	
ADCS-ADL-MCI		X					X		X		X		X	X	
CDR	X								X				X	X	
Logical Memory (WMS-R)	X														
Wechsler Test of Adult Reading (WTAR)		X													
MMSE	X								X				X	X	
Cogstate Battery	X	X		X		X	X		X		X		X	X	
NYU-Paragraph Recall		X		X		X	X		X		X		X	X	
Conners CPT		X		X		X	X		X		X		X	X	
Treatment Blinding Questionnaire													X		
Research Satisfaction Survey		X											X		
Blood for Clinical Labs	X								X				X	X	
Blood for Genetics		X													
Blood for AD Biomarkers		X											X	X	
Blood for Treatment Related Markers						X	X						X	X	
Dispense Medication		X		X		X	X	X	X	X	X	X	X		
Compliance/Medication Count				X		X	X	X	X	X	X	X	X		X
Interval History			X		X										
3T MRI/fMRI [c]		X					X						X	X[e]	
Lumbar Puncture [c]		X											X	X[e]	

[a] See section 9.4 for definition of visit windows.
[b] The Early Discontinuation Visit will contain the same assessments as the Month 24 visit.
[c] If consented to relevant optional sub-study.

[d] Aducanumab treatment may be started after completion of the Baseline Visit and at any point during the study drug treatment period (Week 5 – Month 24). If the participant reports they will start aducanumab treatment, conduct the Extra Efficacy Clinic Visit if at all possible, prior to the participant starting aducanumab treatment and prior to conducting the next scheduled study visit. Depending on the timing of the Extra Efficacy Clinic Visit, visit windows for the next scheduled study visit may need to be adjusted, contact the Coordinating Center for guidance on scheduling.

[e] Depending on timing of the Extra Efficacy Clinic Visit, procedure may not be conducted; contact the Coordinating Center for approval.

APPENDIX 2 REVISION HISTORY

Protocol Version	Summary of Changes
V2.0 **26-SEPT-2018**	• Allowance of cholinesterase inhibitors if stably treated • Addition of ADDF as a sponsor • Expansion on IP management and accountability • Categorization of imaging and biospecimens as coded data • Specified guidance for planned and unplanned blind break
V3.0 **06-SEPT-2019**	• Inclusion criteria - GDS score raised from 9 to 14 • Language on protocol exception clarified • Update to Medical Monitor contact • Clarification to Exclusion 8 and required follow up labs for low B12 results • Clarification to Section 19.0 Audit on inspections of study-related documents
V4.0 **10-SEPT-2021**	• Clarified that aducanumab (or other approved AD disease modifying treatments) is permitted if started after completion of the Baseline Visit. • Added the Extra Efficacy Clinic Visit to be conducted at any point during the study drug treatment period prior to starting aducanumab treatment.
V5.0 **08-APR-2022**	• Updated number of participants enrolled from 300 to 380 (190 per arm) • Updated inclusion critera #14 to indicate participants must be fluent in English or Spanish • Added language to specify that deviations from the inclusion/exclusion criteria will be considered on a case-by-case basis • Updated sample size justification with COVID-19 pandemic related disruptions to potentially account for increased attrition

V6.0 **16-DEC-2024**	• Updated Medical Monitor contact information on the title and signtature page • Added ISLT – TIR to the List of Abbreviations • Updated the primary outcome measure to the Cogstate Battery International Shopping List Test - Total Immediate Recall (ISLT-TIR) • Added RT-SE CPT to the list of other secondary outcome measures • Updated Section 3.3 to reflect the rationale for changing the primary outcome measure from the Continuous Performance Task Reaction Time Standard Error (CPT-RTSE) to the Cogstate Battery International Shopping List Test - Total Immediate Recall (ISLT-TIR) • Updated the Power and Sample Size Determination in Section 5.2 • Updated Sections 5.3.3, 5.3.4, and 5.3.5 to reflect changes to the Statistical Analysis Plan for the primary, secondary, and other secondary outcome measures • Added T-Tau and P-Tau217 to the list of biomarker outcomes being evaluated in Section 5.3.5 • Minor grammatical changes throughout