# A multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of AGB101 (low-dose levetiracetam, 220 mg, extended release tablet) on slowing progression of mild cognitive impairment due to Alzheimer's disease

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| **Protocol Title:** | A multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of AGB101 (low-dose levetiracetam, 220 mg, extended release tablet) on slowing progression of mild cognitive impairment due to Alzheimer's disease |
| **Protocol Number:** | AGB101 MCD |
| **Clinical Phase:** | 2B |
| **Protocol Version and Date:** | Version 6.1 19Dec2020 |
| **US Investigational New Drug (IND) Number:** | 113798 |
| **Sponsor:** | AgeneBio, Inc.<br>1340 Smith Ave., Suite 200<br>Baltimore, MD 21209<br>Phone: (410) 779-1260 |

**SIGNATURE PAGE**

Protocol title: A multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of AGB101 (low-dose levetiracetam, 220 mg, extended release tablet) on slowing progression of mild cognitive impairment due to Alzheimer's disease.

The undersigned have reviewed the format and content of this protocol and have approved the clinical study protocol.

Any modifications of the clinical study protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

Sponsor Approval:

Signature: DocuSigned by: Michela Gallagher Date: 1/8/2021

Signer Name: Michela Gallagher
Signing Reason: I approve this document
Signing Time: 1/8/2021 | 8:38:43 AM PST
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Name (print): Michela Gallagher

Title: CEO AgeneBio, Inc.

Investigator Agreement:

I have read the clinical study protocol and agree to conduct the study as outlined herein.

Signature: _____ Date: _____

Name (print): _____

**SYNOPSIS**

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| **Protocol Title:** | A multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of AGB101 (low-dose levetiracetam, 220 mg, extended release tablet) on slowing progression of mild cognitive impairment due to Alzheimer's disease. |
| **Protocol Number:** | AGB101 MCD |
| **Investigator(s)/Study Center(s):** | This study will be conducted at approximately 98 study sites in the Americas and Europe. Worldwide Clinical Trials, a contract research organization, will oversee operational aspects of this study on behalf of AgeneBio, Inc., the sponsor of the study. |
| **Phase of Development:** | Phase 2B |
| **Objectives:** | The objectives of this study are as follows:<br>**Primary objective**<br>• To assess the efficacy of AGB101 (low-dose levetiracetam, 220 mg, extended release tablet) compared to placebo in subjects with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) using Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores.<br>**Secondary objectives**<br>• To assess the efficacy of AGB101 compared to placebo on daily functioning and cognition using Functional Activities Questionnaire (FAQ) and Mini Mental State Examination (MMSE) scores.<br>• To assess the effect of AGB101 compared to placebo on neuronal injury, as measured by a change in the entorhinal cortex (EC) thickness, using magnetic resonance imaging (MRI).<br>**Additional secondary objectives**<br>• To assess the efficacy of AGB101 compared to placebo using CDR (global, memory box), Behavioral Pattern |

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| | Separation-Object (BPS-O) task, and International Shopping List Test (ISLT) scores.<br>• To assess the effect of AGB101 compared to placebo on hippocampal volume using MRI.<br>• To assess the effect of AGB101 compared to placebo on the levels of tau protein in the brain using the tau positron emission tomography (PET) marker 6-[$^{18}$F]fluoro-3-(1H-pyrrolo[2,3-c]pyridin-1-yl)isoquinolin-5-amine ([$^{18}$F]MK-6240) in a subpopulation of approximately 56 subjects.<br>**Exploratory Objective**<br>• To assess the effect of AGB101 on blood-based biomarkers of neurodegeneration using samples collected at week 78 or the early termination visit.<br>**Exploratory Objective *(optional procedure to be performed only at Johns Hopkins University)***<br>• To assess the efficacy of AGB101 compared to placebo on hippocampal overactivity in subjects with MCI due to AD.<br>**Safety objective**<br>• To assess the safety and tolerability of AGB101 compared to placebo in subjects with MCI due to AD. |
| **Study Design:** | This is a multicenter, randomized, double-blind, placebo-controlled, 78-week, fixed-dose study evaluating AGB101 versus placebo as a treatment for slowing the progression of MCI due to AD. |
| **Planned Sample Size:** | A total of 160 subjects will be randomized (80/treatment group). |
| **Subject Selection Criteria:** | **Eligibility criteria**<br>**Inclusion criteria**<br>Subjects must meet all of the following inclusion criteria at screening:<br>1. Subjects between 55 and 85 years old (inclusive) in good general health: |

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| | a. Willing and able to consent and participate for the duration of the study.<br>b. Have eighth-grade education or good work history sufficient to exclude mental retardation.<br>c. Have visual and auditory acuity adequate for neuropsychological testing.<br>d. Have proficient fluency of the native local language to participate in all the neuropsychological test assessments.<br>2. Have a study partner who has sufficient contact with the subject to be able to provide assessment of memory changes, who can accompany the subject to the screening and all major clinic visits for the duration of those visits, and who is able to provide an independent evaluation of the subject's functioning.<br>3. Have MCI due to AD as defined by all of the following criteria and consistent with the National Institute on Aging-Alzheimer's Association criteria:<br>a. MMSE scores between 24 and 30 (inclusive; exceptions may be made for subjects with < 8 years of education at the discretion of the sponsor).<br>b. A memory complaint reported by the subject or his/her study partner.<br>c. Evidence of lower memory performance based on the delayed recall portion of the ISLT.<br>d. A Clinical Dementia Rating (CDR) score of 0.5 with a memory box score of ≥ 0.5.<br>e. Essentially preserved activities of daily living.<br>f. Cognitive decline not primarily caused by vascular, traumatic, or medical problems (alternative causes of cognitive decline are ruled out).<br>4. Permitted medications:<br>a. With potential pro-cognitive effects, such as cholinesterase inhibitors and memantine, must be at a stable dose for ≥ 3 months prior to screening and |

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| | expected to remain stable throughout the study; estrogen replacement therapy, Ginkgo biloba, and vitamin E must be at a stable dose for ≥ 4 weeks prior to screening and expected to remain stable throughout the study.<br>b. Other psychotropics, such as antidepressants and antipsychotics, must be at a stable dose for ≥ 3 months prior to screening and expected to remain stable throughout the study.<br>5. Willing and able to undergo imaging procedures:<br>a. An amyloid-imaging PET scan with Neuroceq (florbetaben), Amyvid (florbetapir) or Vizamyl (flutemetamol) ([$^{18}$F] isotope diagnostic agents) or documented evidence of an amyloid-positive PET scan.<br>The amyloid PET scan performed at baseline must be read by a qualified physician with experience in reading amyloid PET scans, and it should be consistent with the presence of amyloid plaques.<br>b. Repeated MRI scans (3 Tesla) with no contraindications to MRI.<br>The MRI scan performed at baseline must be read by a physician with experience in evaluating brain-imaging studies in dementia. MRI scan results are consistent with the diagnosis of amnestic MCI due to AD with no clinically significant findings of non-AD pathology that could account for the observed cognitive impairment.<br>6. Willing to allow collection of blood for apolipoprotein E (ApoE) genotyping (all sites).<br>**<u>Exclusion criteria</u>**<br>Subjects must not meet any of the following exclusion criteria at screening:<br>1. Use of anticonvulsant medications or excluded psychotropic medications within 3 months prior to the baseline visit. |

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| | 2. Participation in a therapeutic clinical study for any medical or psychiatric indications within 3 months (6 months for biologics) of the screening visit, or at any time during the study.<br>Subjects must understand that they may only enroll in this clinical study once; they may not enroll in any other clinical study while participating in the current study, and they may not participate in a clinical study of a drug, biologic, therapeutic device, or medical food, in which the last dose/administration was received within 3 months (6 months for biologics) prior to screening.<br>3. History of hypersensitivity or lack of tolerability to AGB101 (levetiracetam).<br>4. Severe renal impairment (creatinine clearance of < 30 mL/minute) or undergoing hemodialysis.<br>5. Any significant neurological disease other than suspected incipient AD, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder (lifetime history; infant febrile seizures are not exclusionary), subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits, or known structural brain abnormalities.<br>6. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments, or foreign objects in the eyes, skin, or body that constitute a contraindication to having an MRI scan.<br>7. Diagnosis of bipolar disorder, or major depression within the past 3 years, as described in the Diagnostic and Statistical Manual of Mental Disorders, 5th Ed (DSM-5). Psychotic features, agitation, or behavioral problems within the last 3 months that could lead to difficulty complying with the protocol. Subjects must not have a major depressive disorder or other types of depression that could confound diagnosis of MCI due to AD, or clinical assessments, in the opinion of the investigator. The Geriatric Depression Scale (long form score > 9 suggests |

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| | depression) results should be reviewed by the investigator to assist in this determination.<br>8. Modified Hachinski Ischemic Scale (HIS) score > 4.<br>9. History of schizophrenia (DSM-5 criteria).<br>10. History of alcohol or substance abuse or dependence within the past 3 years (DSM-5 criteria).<br>11. Any significant systemic illness or unstable medical condition that could lead to difficulty in complying with the protocol requirements.<br>12. Any unstable medical condition that is likely to require new medical or surgical treatment during the course of the study and where such treatments might affect the collection of efficacy data.<br>13. Clinically significant abnormalities in B12 or thyroid function test that might interfere with the study.<br>A low B12 (below normative range for elderly) is exclusionary, unless follow-up labs (homocysteine and methylmalonic acid) indicate that it is not physiologically significant. If the B12 deficiency is treated, subjects may become eligible to participate in the study.<br>14. Residence in a skilled nursing facility.<br>Individuals in independent living communities, assisted living facilities, residential care facilities, or continuing care communities are eligible provided they engage in a sufficient spectrum of activity to permit assessment of all 6 domains contributing to the Clinical Dementia Rating-Sum of Boxes (CDR-SB). Individuals in these facilities must also have a study partner who has the ability to observe the subject during the study and can participate in clinical evaluations.<br>15. Any use of excluded medications (eg, antiepileptics, certain antidepressants or antipsychotics, antihistamines with anticholinergic properties, opiates).<br>16. Participation in clinical studies using the ISLT, BPS-O task, or the trail making test (A, B) within 1 month of screening. |

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| | 17. Female subjects must not be pregnant, lactating, or of childbearing potential (ie, they must be 2 years postmenopause or surgically sterile). |
| **Study Drug(s):** | Subjects will receive AGB101 or placebo in the morning in identically appearing oral dosage forms. One dose of AGB101 will contain 220 mg of levetiracetam. |
| **Duration of Treatment:** | The duration of treatment will be 78 weeks. |

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| **Main Parameters of Efficacy:** | **<u>Primary endpoint</u>**<br>Change in CDR-SB score from baseline to 78 weeks.<br>**<u>Secondary endpoints: cognitive/functional</u>**<br>• Change in FAQ score from baseline to 78 weeks.<br>• Change in MMSE score from baseline to 78 weeks.<br>**<u>Secondary endpoints: neuronal injury</u>**<br>• Change in EC thickness on MRI from baseline to 78 weeks.<br>**<u>Additional secondary endpoints</u>**<br>• Change in CDR global score from baseline to 78 weeks.<br>• Change in CDR memory box score from baseline to 78 weeks.<br>• Change in BPS-O task score from baseline to 78 weeks.<br>• Change in ISLT score from baseline to 78 weeks.<br>• Change in EC volume on MRI from baseline to 78 weeks.<br>• Change in hippocampal volume on MRI from baseline to 78 weeks.<br>• Change in [$^{18}$F]MK-6240 in the brain from baseline at week 78.<br>**<u>Exploratory endpoint:</u>**<br>• Difference between treatment groups in blood-based biomarkers collected at week 78 or early termination visit.<br>**Exploratory endpoint: Functional MRI (*optional procedure to be performed only at Johns Hopkins University*)**<br>• Confirmation of target engagement demonstrated by reduction in hippocampal overactivity. |
| **Main Parameters of Safety:** | **<u>Safety endpoints</u>**<br>• Change from baseline in vital signs (heart rate, respiratory rate, and blood pressure). |

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| | • Change from baseline in physical and neurological exams.<br>• Change from baseline in safety labs and urinalysis.<br>• Change from baseline in Columbia Suicide Severity Rating Scale.<br>• Incidence of adverse events. |
| **Pharmacokinetic Parameters:** | AGB101 plasma pharmacokinetic sampling will be performed during the 26, 52, and 78-week visits. Time since the last dose will be recorded. |
| **Statistical Analyses:** | The primary goal of the study is to estimate the average treatment effect defined as the difference between the population mean outcome of the primary endpoint (CDR-SB change score from baseline to 78 weeks) comparing treatment to control. The primary null hypothesis is that the average treatment effect is zero. The alternative hypothesis is that the average treatment effect is not equal to zero.<br>In the primary analysis, we will use a pre-specified, intention-to-treat estimator that simultaneously (i) adjusts for 78-week outcomes missing at random (due to subject loss to follow up), and (ii) adjusts for chance imbalances in key baseline variables between the study arms. One advantage of this estimator is that it is consistent under weaker assumptions on missing outcomes than needed for the unadjusted estimator to be consistent. The nonparametric bootstrap (bias-corrected and accelerated method) will be used to construct 95% confidence intervals for the average treatment effect. Similar analyses will be conducted for each of the secondary endpoints, along with a gate-keeping multiple testing procedure for an ordered sequence of null hypotheses.<br>ApoE genotyping will be used for post hoc subject stratification. There will be a preplanned subgroup analysis in which each efficacy measure will be looked at separately by ApoE genotype with two subgroups, those carrying one or more ApoE4 alleles and those with no ApoE4 alleles. |

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| Abbreviation | Definition |
|---|---|
| [$^{18}$F]MK-6240 | 6-[$^{18}$F]fluoro-3-(1H-pyrrolo[2,3-c]pyridin-1-yl)isoquinolin-5-amine |
| 3T | 3 Tesla |
| Aβ | beta amyloid |
| AD | Alzheimer's Disease |
| ADNI | Alzheimer's Disease Neuroimaging Initiative |
| ADR | adverse drug reaction |
| AE | adverse event |
| AED | antiepileptic drug |
| AGB101 | low-dose levetiracetam, 220 mg, extended release tablet |
| aMCI | amnestic mild cognitive impairment |
| ApoE | apolipoprotein E |
| $AUC_{0-24}$ | area under the plasma concentration-time curve during 24 hours |
| $AUC_{extrap}$ | area under the plasma concentration-time curve extrapolated from time zero to time of last measurable concentration |
| $AUC_{inf}$ | area under the plasma concentration-time curve extrapolated from zero to infinity |
| $AUC_{last}$ | area under the plasma concentration-time curve from time of dosing to last measurable concentration |
| BCa | bias-corrected and accelerated method |
| BID | twice a day |
| BOLD | blood oxygen level dependent |
| BP | blood pressure |

| Abbreviation | Definition |
|---|---|
| BPS-O | Behavioral Pattern Separation-Object |
| CBC | complete blood count |
| CDR | Clinical Dementia Rating |
| CDR-SB | Clinical Dementia Rating-Sum of Boxes |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CL/F | apparent total clearance of the drug from plasma after oral administration |
| $C_{last}$ | last measurable plasma concentration |
| $C_{max}$ | maximum plasma drug concentration |
| CNS | central nervous system |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, 5$^{th}$ Edition |
| DSMB | Data Safety and Monitoring Board |
| EC | entorhinal cortex |
| ECG | Electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EU | European Union |
| FAQ | Functional Activities Questionnaire |
| FDA | Food and Drug Administration |

| Abbreviation | Definition |
|---|---|
| FLAIR | fluid attenuation inversion recovery |
| fMRI | functional magnetic resonance imaging |
| GCP | Good Clinical Practice |
| GDS | Geriatric Depression Scale |
| HIS | Hachinski Ischemic Scale |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IR-SPGR | radiofrequency-spoiled gradient echo |
| ISLT | International Shopping List Test |
| ITT | intention-to-treat |
| IWRS | interactive web response System |
| JHU | Johns Hopkins University |
| $\lambda_z$ | terminal disposition rate constant |
| MCI | mild cognitive impairment |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMS | Mini Mental State |
| MMSE | Mini Mental State Examination |
| MP-RAGE | magnetization-prepared gradient echo |

| Abbreviation | Definition |
|---|---|
| MRI | magnetic resonance imaging |
| MTL | medial temporal lobe |
| NIA-AA | National Institute on Aging-Alzheimer's Association |
| PET | positron emission tomography |
| PK | pharmacokinetic(s) |
| RPM | revolutions per minute |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SEM | standard error of the mean |
| SPGR | radiofrequency-spoiled gradient echo |
| SUSAR | Suspected Unexpected Adverse Reactions |
| $T_{½}$ | elimination half-life |
| $T_{last}$ | time to last measurable plasma concentration |
| $T_{max}$ | time to reach maximum plasma concentration following drug administration |
| TEAE | treatment-emergent adverse event |
| TMLE | targeted minimum loss based estimators |
| US | United States |
| WCT | Worldwide Clinical Trials |

**ADMINISTRATIVE STRUCTURE**

Medical Monitor: Stephen Kirzinger, MD
Senior Medical Director
Medical & Scientific Affairs
Worldwide Clinical Trials (WCT)
1000 Continental Drive
King of Prussia, PA 19406
Phone: (502)419-4732
Email: stephen.kirzinger@worldwide.com

# 1 INTRODUCTION

## 1.1 Background

No effective therapies exist to halt or reverse Alzheimer's disease (AD). With a predicted prevalence of AD cases rising to >100 million worldwide by 2050 (Wimo and Prince 2010), the need for such therapies is urgent. Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and other sources support the notion of existing AD pathology in the brain for at least a decade before a clinical diagnosis of AD is made (Perrin, Fagan, and Holtzman 2009; Tarawneh and Holtzman 2010; Weiner et al. 2015). By the time an AD diagnosis is made using clinical criteria for dementia, significant irreversible neurodegeneration has already occurred (Gómez-Isla et al. 1996). It is widely acknowledged that therapeutic intervention in the early stages of AD has the best prospect for modifying disease progression (Sperling et al. 2011). No such therapies have been approved based on studies in conditions that are precursors for dementia, such as in prodromal AD.

By clinical, cognitive, and functional criteria, mild cognitive impairment (MCI) is an intermediate state between normal aging and a diagnosis of dementia, including probable AD. Impairment of episodic memory, that is the ability to acquire and retain information about life events that is greater than expected for a person's age, is most commonly observed in subjects with MCI who progress to AD, and it has been used to define a subtype of MCI called amnestic mild cognitive impairment (aMCI) (Petersen 2011).

In addition, evidence for the pathophysiology of AD, such as neuronal injury or neurodegeneration in specific loci in the brain (eg, temporal lobe) or evidence for amyloid by positron emission tomography (PET) imaging, was proposed for a diagnosis of MCI due to AD (Albert et al. 2011). MCI is a medical diagnosis as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM), 4$^{th}$ Ed, or a mild neurocognitive impairment due to AD as defined in the DSM 5$^{th}$ Ed (DSM-5). Currently, there are no approved treatments for MCI, including MCI due to AD. Thus, MCI due to AD represents an unmet medical need, which is both symptomatically and as a clinical diagnosis suitable for intervention to modify disease progression, in subjects at high risk for AD dementia.

## 1.2 Study Rationale

The current study will enroll subjects with a diagnosis of MCI due to AD, as defined by the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria (Albert et al. 2011).

A distinctive condition in the MCI due to AD population is neural over-activity localized to the hippocampal formation by functional magnetic resonance imaging (fMRI) (Ewers et al. 2011; Sperling et al. 2011; Albert et al. 2011). Although modest

hippocampal over-activity is observed in preclinical (asymptomatic) conditions in older adults, (O'Brien et al. 2010; Yassa et al. 2011) a very prominent increase in hippocampal over-activity occurs in subjects with MCI due to AD compared with age-matched controls (Yassa et al. 2011; Bakker et al. 2012; Huijbers et al. 2015). In clinical studies, the magnitude of such hippocampal over-activity longitudinally predicts subsequent cognitive decline/conversion to dementia, (Dickerson et al. 2005; Miller et al. 2008; Sperling 2007) and hippocampal over-activity in subjects with MCI due to AD is significantly correlated with the extent of neuronal injury affecting AD-specific regions of the brain. Putcha et al. 2011 reported a significant correlation between greater hippocampal activation (fMRI) and more pronounced medial temporal lobe (MTL) atrophy (cortical thinning) indicative of AD-related neurodegeneration in subjects with MCI due to AD with a Clinical Dementia Rating (CDR) score of 0.5 selected by ADNI-1 criteria. This supports a therapeutic rationale to reduce over-activity in order to slow or prevent neuronal injury.

Current evidence from basic scientific research indicates a convergence of pathways involving the beta amyloid (Aβ) protein, the tau protein, and the process of aging itself that boosts hippocampal over-activity, contributing to the condition of MCI due to AD in subjects at high risk for progression to dementia. Levetiracetam has been shown to preserve synaptic function and control very early AD pathophysiology tied to Aβ and tau (Shi et al. 2013; Hall et al. 2015). It reduces aberrant over-activity in specific brain circuits that are highly vulnerable to early neurodegeneration caused by AD (Shi et al. 2013; Hall et al. 2015).

In animal models of age-related memory impairments and AD (Morris water maze, radial arm maze), levetiracetam reverses deficits in cognition and reductions of reelin expression in the entorhinal cortex (EC) of aged rats with memory impairments (Koh et al. 2010; Rose and Corbin 2010; unpublished data Gallagher M). The effect of levetiracetam on reelin expression is notable in light of evidence indicating that reelin reduction accelerates amyloid and tau pathology in the hippocampus (Kocherhans et al. 2010). Reduced levels of reelin have also been shown in the EC of age-impaired (but not age-unimpaired) rhesus monkeys (Long et al. 2014). Reelin was shown to delay Aβ fibril formation and rescue cognitive deficits in a model of AD (Pujadas et al. 2014). Evidence of aberrant excitatory activity has been observed in experimental animal models relevant to AD, a condition first described in hAPP mice J20 (Palop et al. 2007; Busche et al. 2012; Minkeviciene et al. 2009; Tabuchi et al. 2015). Levetiracetam administered at low doses to transgenic hAPP J20 mice resulted in an improved hippocampal system (eg, synaptic function, molecular markers, double-strand DNA breaks) and memory performance (Sanchez et al. 2012; Suberbielle et al. 2013).

More recently, chronic use of low-dose levetiracetam (50 mg/kg/day for 30 days) was reported to reduce both amyloid and tau pathology in APPswe/PS1dE9 mice

(Shi et al. 2013). It is noteworthy that the effects of levetiracetam were not observed (no effect on brain markers or behavior) in control non-transgenic mice given the same drug treatment. Consistent with clinical and preclinical data, low-dose administration of levetiracetam was effective, while high dose had no effect (Sanchez et al. 2012). Importantly, a spectrum of other antiepileptic drugs (AEDs) with mechanisms of action different from levetiracetam (eg, ethosuximide, gabapentin, phenytoin, pregabalin, and vigabatrin) were ineffective in this AD model. More recently, chronic administration of low-dose levetiracetam rapidly and persistently reversed brain dysrhythmia and network hypersynchrony in hTau-A152T mice, suggesting that levetiracetam treatment is able to counteract tau-dependent neural network dysfunction (Das et al. 2018).

### 1.3 Dose Rationale

Preclinical models of age-impaired laboratory rats with memory loss have demonstrated that increased activation in the CA3 subregion of the hippocampus is a dysfunctional condition contributing to memory impairment (Wilson et al. 2005; Wilson et al. 2006). In a preclinical model of memory loss due to aging and mouse models of AD pathology (J20 hAPP and APPswe/PS1dE9 mice), levetiracetam was shown to decrease excess neural activity and improve memory function (Koh et al. 2010; Sanchez et al. 2012; Shi et al. 2013). The levetiracetam dose levels leading to efficacious results in the age-impaired rat model ranged from 1.9 μg/mL to 3.9 μg/mL, and efficacy was lost at a higher exposure of 7.8 μg/mL (Rosenzweig-Lipson et al. 2015).

Based on preclinical efficacy results with low-dose levetiracetam and results from clinical use of Keppra XR (high-dose levetiracetam; 1000 mg/day to 3000 mg/day) for the treatment of epilepsy, a translational, proof-of-concept, phase 2 study was performed in subjects with MCI. This was an 8-week, randomized, double-blind, placebo-controlled, within-subject, crossover study evaluating the effects of low-dose levetiracetam on hippocampal over-activity and memory function in MCI (Bakker et al. 2012). A total of 54 subjects completed the study. Subjects received both levetiracetam (62.5 mg twice a day [BID], 125 mg BID, or 250 mg BID) and placebo separately in periods of 2 weeks each. Twenty subjects completed the study in the 62.5 mg BID dose group, 17 subjects in the 125 mg BID dose group, and 17 subjects in the 250 mg BID dose group. At the end of each treatment period, participants completed a high-resolution fMRI scan while performing the 3 choice memory recognition task designed to assess the function of the hippocampal (DG/CA3) network (Bakker et al. 2008; Lacy et al. 2011). As in the rat model studies, low-dose levetiracetam (62.5 mg BID and 125 mg BID), but not high dose (250 mg BID), attenuated hippocampal over-activity and improved the task-related memory function (Bakker et al. 2015). The lower doses of levetiracetam that improved memory performance in the scanning task also normalized fMRI activation in the EC/DG/CA3 network both by reducing elevated DG/CA3 fMRI activity and by boosting decreased fMRI activation in the EC. Subjects who received the lower doses also showed

significant improvement in memory performance in the fMRI task. Drug blood levels from subjects receiving low-dose levetiracetam in the clinical study closely matched drug blood levels from preclinical aging/AD models (Koh et al. 2010; Sanchez et al. 2012; Bakker et al. 2012). In addition, matching high doses of levetiracetam in both the preclinical aging/AD studies and in subjects with aMCI were demonstrated to lack efficacy (Koh et al. 2010; Sanchez et al. 2012; Bakker et al. 2015) Based on these findings, AGB101 formulations (low-dose levetiracetam, 190 mg and 220 mg, extended release tablets) were developed to allow for once-daily dosing in subjects with aMCI. The current study is the first clinical study undertaken with the novel formulation.

High-dose Keppra XR has been used for the treatment of epilepsy at doses of 1000 mg/day to 3000 mg/day for more 15 years, with a favorable safety and efficacy profile in this subject population. Importantly, effective doses of levetiracetam used in the preclinical models of aMCI and AD are lower than those required clinically for antiepileptic activity. Consistent with preclinical findings, treatment with low-dose levetiracetam (62.5 mg BID or 125 mg BID) concurrently improved behavioral performance in the scanning task for memory function and normalized increased DG/CA3 activity. An analysis of the interaction for performance in the task by planned contrast showed that aMCI subjects who received levetiracetam at doses of 62.5 mg BID or 125 mg BID made fewer incorrect responses of 'old' while concomitantly increasing correct judgments of 'similar', compared with their control group counterparts (aMCI drug versus aMCI placebo by old versus similar; 62.5 mg BID ($F[1,19] = 4.783$, $p = 0.041$; 125 mg BID $F[1,16] = 5.028$, $p = 0.039$). Indeed, performance in the low-dose levetiracetam groups was not significantly different from healthy control subjects (aMCI drug versus control by old versus similar; 62.5 mg BID $F[1,35] = 1.823$, $p = 0.186$; 125 mg BID $F[1,32] = 1.945$, $p = 0.173$).

In contrast, subjects with aMCI who received high-dose levetiracetam (250 mg BID; Keppra starting dose for epilepsy) did not exhibit normalized DG/CA3 activity and did not improve in memory task performance, compared with subjects in the placebo group. In the memory task, they did not alter the proportion of old and similar responses to lures under drug treatment (aMCI drug versus aMCI placebo by old versus similar: $F[1,16] = 1.492$, $p = 0.2396$) and remained significantly different from healthy control subjects (aMCI drug versus control by old versus similar: $F[1,32] = 5.208$, $p = 0.029$).

To confirm the finding that low-dose levetiracetam treatment effectively reduces hippocampal activation, a separate analysis was conducted in which voxel selection was based on a one-way analysis of variance study type in control subjects. This analysis resulted in an area of task-related activation similarly localized to the left DG/CA3 subregion of the hippocampus. The effect of drug treatment was confirmed by comparing fMRI activation in the area of task-related activity in subjects with aMCI in the placebo and levetiracetam groups within each of the 3 aMCI cohorts. Confirming the treatment

effects, the analysis similarly showed that the levetiracetam 62.5 mg BID dose lowered but did not significantly reduce blood oxygen level dependent (BOLD) activation, compared with placebo (t = 1.503, $p = 0.1492$). The levetiracetam 125 mg BID dose significantly reduced BOLD activation during the correctly identified lure trials, compared with placebo (t = 2.192, $p = 0.044$). In contrast, the levetiracetam 250 mg BID dose showed no evidence of reducing activation (t = 0.1773, $p = 0.8615$).

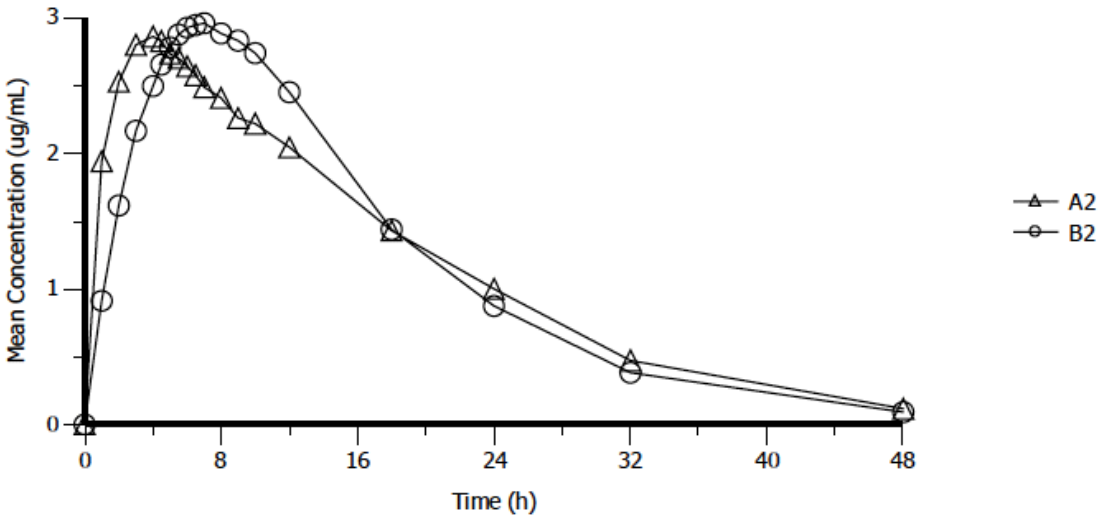
In addition to areas of task-related activity in the DG/CA3, analyses of the functional imaging data also revealed an area of reduced task-related activity in the left EC in both low-dose levetiracetam groups (62.5 mg BID and 125 mg BID). In the left EC, participants in the levetiracetam groups showed significantly decreased BOLD activation during those same lure studies, compared with their healthy control group counterparts (62.5 mg BID, t = 3.443, $p = 0.002$; 125 mg BID, t = 3.278, $p = 0.003$). After treatment, BOLD activation in the left EC was increased and normalized in aMCI participants during the critical lure studies, compared with their placebo counterparts. This increase was statistically significant in the 62.5 BID cohort (t = 3.318, $p = 0.004$) but not statistically significant in the 125 mg BID cohort (t = -1.60, $p = 0.129$). In both groups, fMRI activity in the left EC after drug treatment was no longer different from the activity observed in the left EC in the control subjects.

The effects on BOLD activation in the left DG/CA3 and EC in the levetiracetam 62.5 mg BID and 125 mg BID cohorts were obtained with drug dose levels well below those used clinically for the treatment of epilepsy. Drug levels in aMCI subjects were determined to be 2.9 µg/mL ± 0.29 µg/mL (mean ± standard error of the mean [sem]) for the 62.5 mg BID cohort, 4.4 µg/mL ± 0.53 µg/mL (mean ± sem) for the 125 mg BID cohort, and 7.91 µg/mL ± 0.92 µg/mL (mean ± sem). These drug exposure levels are well below typical ranges reported for efficacy with Keppra (high-dose levetiracetam) as an antiepileptic agent, where doses of 1000 mg/day to 3000 mg/day are typical, resulting in drug levels of 10 µg/mL to 40 µg/mL (Lyseng-Williamson 2011).

**Clinical experience with AGB 101**

Based on the findings from the phase 2 study, a novel extended-release tablet formulation of AGB101 was developed at a dose of 220 mg with a predetermined target plasma exposure range of 1.9 µg/mL to 4.4 µg/mL (based on animal and human aMCI data). A phase 1, 2-group, single-dose, 2-period, 2-way crossover, food-effect study of AGB101 formulation was recently undertaken. The AGB101 maximum plasma drug concentration ($C_{max}$) ranged from 3.02 µg/mL in the fasted condition to 3.16 µg/mL in the fed condition (Figure 1). The elimination half-life ($T_{½}$) was similar under all conditions ranging from 7.56 h to 8.09 h (Table 1), and it was comparable to the reported $T_{½}$ of the levetiracetam extended release (~7 hours). Single-dose $C_{max}$ levels fell within the target range (1.9 µg/mL to 4.4 µg/mL).

**Figure 1: Mean Levetiracetam Concentration-Time Profiles Following Administration of AGB101**




A2 = fasted condition in group 2/treatment A; B2 = fed condition in group 2/treatment B.

**Table 1: Pharmacokinetic Parameters for AGB101 (220 mg)**

| Parameter | Group 2/Treatment A: AGB101 220 mg, Fasted | | | | Group 2/Treatment B: AGB101 220 mg, Fed | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | CV% | n | Mean | SD | CV% |
| $T_{max}$ (h) | 26 | 4.04 | 1.25 | 30.91 | 28 | 6.64 | 1.83 | 27.55 |
| $C_{max}$ (µg/mL) | 26 | 3.02 | 0.569 | 18.88 | 28 | 3.16 | 0.623 | 19.73 |
| $C_{max}$/Dose (µg/mL/mg) | 26 | 0.0137 | 0.00259 | 18.88 | 28 | 0.0143 | 0.00283 | 19.73 |
| $AUC_{last}$ (h*µg/mL) | 26 | 56.33 | 10.42 | 18.49 | 28 | 55.27 | 10.35 | 18.72 |
| $AUC_{last}$/Dose (h*µg/mL/mg) | 26 | 0.2560 | 0.04734 | 18.49 | 28 | 0.2512 | 0.04702 | 18.72 |
| $AUC_{inf}$ (h*µg/mL) | 26 | 57.68 | 10.67 | 18.50 | 28 | 56.63 | 10.53 | 18.59 |
| $AUC_{inf}$/Dose (h*µg/mL/mg) | 26 | 0.2622 | 0.04850 | 18.50 | 28 | 0.2574 | 0.04784 | 18.59 |
| $AUC_{Extrap}$ (%) | 26 | 2.35 | 1.10 | 47.03 | 28 | 2.42 | 1.19 | 48.97 |
| $\lambda_z$ ($h^{-1}$) | 26 | 0.0905 | 0.0123 | 13.63 | 28 | 0.0933 | 0.0126 | 13.50 |
| $T_{1/2}$ (h) | 26 | 7.81 | 1.14 | 14.59 | 28 | 7.56 | 1.01 | 13.32 |
| $T_{last}$ (h) | 26 | 48.01 | 0.06 | 0.13 | 28 | 45.73 | 5.71 | 12.48 |
| $C_{last}$ (µg/mL) | 26 | 0.116 | 0.0442 | 38.18 | 28 | 0.124 | 0.0640 | 51.46 |

$AUC_{extrap}$ = area under the plasma concentration-time curve extrapolated from time zero to time of last measurable concentration; $AUC_{inf}$ = area under the plasma concentration-time curve extrapolated from zero to infinity; $AUC_{last}$ = area under the plasma concentration-time curve from time of dosing to last measurable concentration; $C_{last}$ = last measurable plasma concentration; $C_{max}$ = maximum plasma drug concentration; $\lambda_z$ = terminal disposition rate constant; $T_{½}$ = elimination half-life; $T_{last}$ = time to last measurable plasma concentration; $T_{max}$ = time to reach maximum plasma concentration following drug administration.

Additional modeling studies were performed to predict exposures at a steady state. The AGB101 Cmax increased from 3.02 µg/mL to 3.84 µg/mL under the fasted condition and

from 3.16 µg/mL to 3.66 µg/mL under the fed condition (Figure 2 and Table 2). These maximal exposures all met the target criteria (1.9 µg/mL to 4.4 µg/mL).

**Figure 2: Mean AGB101 (Levetiracetam) Concentration-Time Profiles After Single Dose (Actual Data) and Once-Daily Administration (Simulated Data at Steady State) of AGB101 Under a Fed Condition**

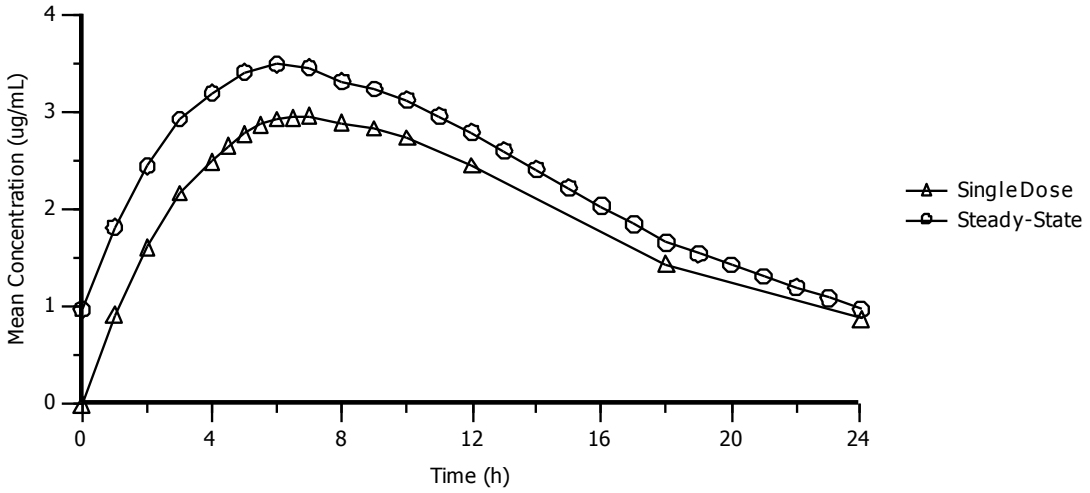


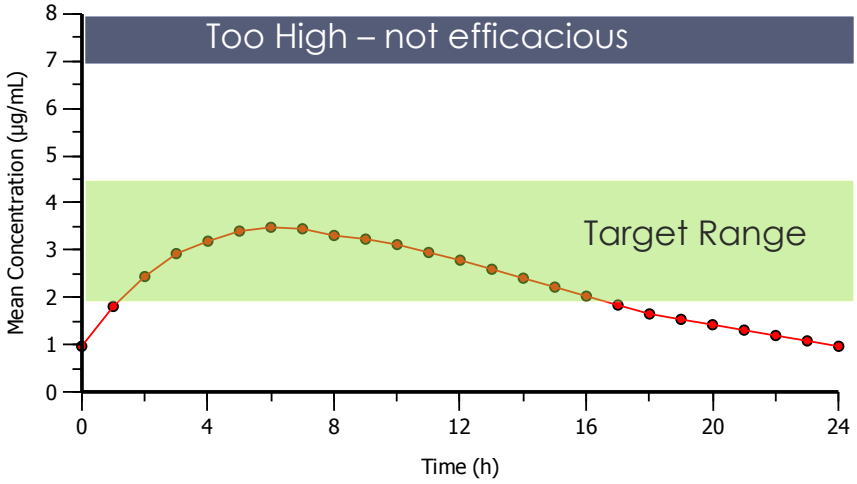

**Table 2: Predicted Pharmacokinetic Parameters of AGB101 (Levetiracetam) at Steady State After Once-Daily Administration of AGB101 Under Fasting and Fed Conditions**

| Parameter | AGB101 220 mg – Fasted (A2) | | | AGB101 220 mg – Fed (B2) | | |
|---|---|---|---|---|---|---|
| | N | Mean | CV% | N | Mean | CV% |
| $C_{max}$ (µg/mL) | 26 | 3.84 | 19.20 | 28 | 3.66 | 17.88 |
| $T_{max}$ (h) | 26 | 3.46 | 23.44 | 28 | 6.11 | 27.95 |
| $AUC_{0-24}$ (h* µg/mL) | 26 | 57.60 | 18.55 | 28 | 56.58 | 18.47 |

$AUC_{0-24}$ = area under the plasma concentration-time curve during 24 hours; $C_{max}$ = maximum plasma drug concentration; $T_{max}$ = time to reach maximum plasma concentration following drug administration.

Figure 3 depicts a steady-state modeling relative to the target range established for the AGB101 over time; the modeling was developed based on results from the phase 2 aMCI study and the age-impaired rat model. AGB101 meets the goal for the target range and maintains exposures between 1.9 µg/mL and 4.4 µg/mL for approximately 14 hours of the day.

**Figure 3: Mean Simulated Steady State AGB101 (Levetiracetam) Concentration-Time Profile of AGB101 Under the Fed Condition (B2)**




Food effect: The presence of food did not significantly alter the pharmacokinetics (PK) of AGB101.

Steady state: In general, based on the simulated mean concentration-time profiles and the mean $C_{max}$ from the simulated profiles, the predicted accumulation of levetiracetam in systemic circulation during once-daily administration of AGB101 formulation (220 mg) is consistent with the theoretical accumulation factor for once-daily administration of a drug with a $T_{½}$ of approximately 8 hours (approximately 1.14), particularly under the fed condition. The simulations based on fasting data suggest a slightly higher accumulation factor (approximately 1.3).

Overall conclusion: AGB101 (220 mg) is a novel extended-release formulation of levetiracetam suitable for once daily dosing in subjects with MCI due to AD. The extended-release formulation maintains exposures within the a priori-defined target range of 1.9 µg/mL to 4.4 µg/mL that aligns to the efficacy observed in the Phase 2 aMCI study. Importantly, the extended-release formulation exposures do not exceed the therapeutic efficacy range and do not approach the high-dose exposures associated with a lack of efficacy. The nominal impact of food on the rate and extent of absorption suggests that AGB101 may be administered without regard to food intake in a clinical study.

### 1.4 Study Endpoint Rationale

The primary efficacy evaluation is the change in Clinical Dementia Rating-Sum of Boxes (CDR-SB) score over the course of treatment. The CDR (global score) is a rating scale used to characterize the degree of dementia severity. It ranges from 0 (“no dementia”) to 3 (“severe dementia”). It is based on semi-structured interviews with both the subject thought to suffer from dementia and a knowledgeable informant (for example, an adult family member). For the CDR-SB score, cognitive functioning is rated in 6 domains:

memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a 5-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment. For subjects with a global score of 0.5, the subsequent "sum of boxes" score can help quantify the severity of cognitive and functional impairment within the range of MCI.

CDR-SB has been shown to markedly progress (worsen) during MCI due to AD. In this regard, episodic memory impairment is related to CDR-SB progression (Albert et al. 2007). Importantly, and consistent with a diagnosis of MCI due to AD, a positive Aβ status predicts greater progression on CDR-SB (Jack et al. 2010; Huijbers et al. 2015). Moreover, hippocampal over-activity also predicts progression on CDR-SB (Miller et al. 2008; Huijbers et al. 2015). If AGB101 is effective in slowing the progression of MCI due to AD, then subjects should show an improvement in (lowering), or a stabilizing of, their CDR-SB scores over the duration of the study (78 weeks).

The secondary efficacy evaluation is the extent of neuronal injury as measured by the change in EC atrophy from baseline to 78 weeks. It has long been known that early pathological changes in the AD cascade occur in the EC (Braak and Braak 1991; Braak and Braak 1995; Braak et al. 1998). Consistent with the localization and spread of pathology, degeneration of EC neurons represents the earliest lesion in the brain that is characteristic of dementia due to AD. Quantitative studies of neuron numbers in autopsy brains well-characterized for AD pathology have shown that a substantial reduction in the numbers of EC neurons is observed in prodromal AD (CDR 0.5), with further progressive loss of EC neurons (> 90%) over the course of the disease (Gomez-Isla et al. 1996). Those findings are consistent with subsequent studies of autopsy brains (CDR 0.5) with 50% or greater layer II neuron loss in the EC, as assessed by stereological analysis, and > 20% regional atrophy in the EC (Kordower et al. 2001; Price et al. 2001). Moreover, Kordower et al. 2001, reported that the layer II neuron loss and EC atrophy were significantly correlated with episodic memory status in neuropsychological tests of delayed recall, and the EC atrophy correlated significantly with performance on the Mini Mental Status Examination (MMSE). This evidence has reliably demonstrated that EC neurodegeneration and EC atrophy occurs in elderly subjects with MCI due to AD prior to the clinical diagnosis of dementia.

In structural neuroimaging with magnetic resonance imaging (MRI), EC atrophy has been identified as a good biomarker for longitudinal progression in MCI due to AD and AD, with greater atrophy predicting more advanced disease severity (Zhou et al. 2015). In subsequent longitudinal studies using MRI, EC atrophy has been repeatedly shown as a strong predictor of further memory impairment and progression to Alzheimer's dementia (Devanand et al. 2007; Burggren et al. 2011; Devanand et al. 2012; Ewers et al. 2012). Additionally, even minimal levels of EC atrophy detected by MRI are associated with

impairment on multiple memory tests, confirming that this atrophy has clinical relevance for individuals with MCI due to AD (Varon et al. 2011).

Another useful biomarker for monitoring the progression of AD is the tau protein PET biomarker 6-[$^{18}$F]fluoro-3-(1H-pyrrolo[2,3-c]pyridin-1-yl)isoquinolin-5-amine ([$^{18}$F]MK-6240). Post-mortem Braak staging, based on the anatomical localization of intraneuronal neurofibrillary tangles comprised of hyperphosphorylated tau protein, is a hallmark pathology defining the severity and progression of AD in the brain (Braak & Braak 1991). Recent studies using tau PET ligands have shown in vivo features in patients characteristic of Braak histopathological stages (Schwartz et al. 2016; Xia & Dickerson 2017). Notably, in patients in the prodromal stage of MCI, the tau PET tracer AV-1451 increased only in the entorhinal cortex (Braak Stage I & II) while patients with AD had increased binding in cortical areas consistent with later Braak stages (Cho et al. 2016). [$^{18}$F]MK-6240 has been developed for in vivo quantification of human neurofibrillary tangles (Collier et al. 2017; Hostetier et al. 2016; Walji et al. 2016) and has demonstrated binding consistent with AD tau pathology with an improved off target profile. Concurrent with the clinical use of tau PET tracers, evidence from AD preclinical models of human tau mutations has now demonstrated that chronically increased neural activity stimulates the release of tau and enhances the spread of tau pathology in the hippocampus and associated cortical circuits in a manner consistent with Braak staging (Wu et al. 2016). The longitudinal data that will be obtained with [$^{18}$F]MK-6240 in a substudy is included to provide possible evidence for slowing of the progression of tau pathology in patients treated with AGB101 targeting excess neural activity compared to patients on placebo. Evidence for reduced progression of tau pathology in the substudy will bridge to patients in the Phase 3 protocol with the acquisition of structural 3T MRI longitudinal data in all subjects; structural atrophy in the brain with 3T MRI scans is expected to be observed in the entorhinal cortex (Tward et al. 2017) where increased binding in tau PET imaging is also expected to occur in the study population (Cho et al. 2016).

For this study, a subpopulation of approximately 56 subjects will participate, on an optional basis, to have the tau PET marker evaluated using the [$^{18}$F]MK-6240 biomarker.

Analyses of the two cognitive/functional secondary endpoints includes a fixed-sequence procedure with Type I error control, in which the Functional Activities Questionnaire (FAQ) and MMSE are separately considered in a sequential fashion (see Section 5.2.6.2). Assessments of EC and hippocampal atrophy are placed outside of this biostatistical gatekeeping process due to residual uncertain linkages between the neuropsychological test performance and structural neuroimaging assessments in this therapeutic area.

A distinctive condition in the MCI due to AD population is neural over-activity localized to the hippocampal formation, as assessed by fMRI (Ewers et al. 2011; Sperling et al. 2011; Albert et al. 2011). In clinical studies, the magnitude of such hippocampal over-

activity longitudinally predicts subsequent cognitive decline/conversion to a dementia diagnosis (Dickerson et al. 2005; Miller et al. 2008; Sperling 2007) and hippocampal over-activity in MCI due to AD subjects is significantly correlated with the extent of neuronal injury affecting AD-specific regions of the brain. With respect to neuronal injury, Putcha et al. 2011 reported a significant correlation between greater hippocampal activation (fMRI) and more pronounced MTL atrophy (cortical thinning) indicative of AD-related neurodegeneration in MCI due to AD subjects. If the primary efficacy evaluation shows significant cognitive improvement, it could be due, in part, to the effects of AGB101 (low-dose levetiracetam) in reducing hippocampal over-activity to slow or prevent neuronal injury. This assessment will verify or dispute that prediction.

### 1.5 Risks and Benefits for Subjects

Keppra is an antiepileptic drug approved for use in the United States (US) since 1999. Doses of 1000 mg/day to 3000 mg/day are typically used for this indication. As of 2011, Keppra was prescribed to nearly one quarter of all individuals with epilepsy. According to a survey of neurologists, Keppra performs best on categories such as safety/tolerability, as well as subject and physician benefits.

In controlled clinical studies of adults with partial-onset seizures, the most frequently reported adverse events (AEs) from Keppra in combination with other AEDs included somnolence, asthenia, infection, and dizziness. Of the most frequently reported AEs, asthenia, somnolence, and dizziness appeared to occur predominantly during the first 4 weeks of treatment with Keppra. AEs were usually mild-to-moderate in intensity.

**Keppra (adult doses 1000 mg/day-3000 mg/day)**

Partial onset seizures

Table 3 lists treatment-emergent adverse events (TEAEs) that occurred in at least 1% of adult epilepsy subjects treated with Keppra who participated in placebo-controlled studies and were numerically more common than in individuals treated with placebo.

**Table 3: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Studies of Adults Experiencing Partial Onset Seizures by Body System**

| Body System/ Adverse Event | Keppra® (N=769) % | Placebo (N=439) % |
|---|---|---|
| **Body as a Whole** | | |
| Asthenia | 15 | 9 |
| Headache | 14 | 13 |
| Infection | 13 | 8 |
| Pain | 7 | 6 |
| **Digestive System** | | |
| Anorexia | 3 | 2 |
| **Nervous System** | | |
| Somnolence | 15 | 8 |
| Dizziness | 9 | 4 |
| Depression | 4 | 2 |
| Nervousness | 4 | 2 |
| Ataxia | 3 | 1 |
| Vertigo | 3 | 1 |
| Amnesia | 2 | 1 |
| Anxiety | 2 | 1 |
| Hostility | 2 | 1 |
| Paresthesia | 2 | 1 |
| Emotional Lability | 2 | 0 |
| **Respiratory System** | | |
| Pharyngitis | 6 | 4 |
| Rhinitis | 4 | 3 |
| Cough Increased | 2 | 1 |
| Sinusitis | 2 | 1 |
| **Special Senses** | | |
| Diplopia | 2 | 1 |

Other events reported by at least 1% of adult Keppra-treated subjects, but as or more frequent in the placebo group included: abdominal pain, accidental injury, amblyopia, arthralgia, back pain, bronchitis, chest pain, confusion, constipation, convulsion, diarrhea, drug level increased, dyspepsia, ecchymosis, fever, flu syndrome, fungal infection, gastroenteritis, gingivitis, grand mal convulsion, insomnia, nausea, otitis media, rash, thinking abnormal, tremor, urinary tract infection, vomiting, and weight gain.

Time course of onset of AEs for partial-onset seizures

Of the most frequently reported AEs in adults experiencing partial-onset seizures, asthenia, somnolence, and dizziness appeared to occur predominantly during the first 4 weeks of treatment with Keppra.

Discontinuation or dose reduction in well-controlled clinical studies

In well-controlled adult clinical studies, 15.0% of subjects receiving Keppra and 11.6% of subjects receiving placebo either discontinued or had a dose reduction because of an

AE. Table 4 lists the most common (> 1%) AEs that resulted in discontinuation or dose reduction.

**Table 4: Adverse Events Most Commonly Resulting in Discontinuation or Dose Reduction**

| | Number (%) | |
|---|---|---|
| | Keppra® (N=769) | Placebo (N=439) |
| Asthenia | 10 (1.3%) | 3 (0.7%) |
| Convulsion | 23 (3.0%) | 15 (3.4%) |
| Dizziness | 11 (1.4%) | 0 |
| Rash | 0 | 5 (1.1%) |
| Somnolence | 34 (4.4%) | 7 (1.6%) |

Myoclonic seizures

In a well-controlled clinical study of adolescents (12 to 16 years of age) and adults with myoclonic seizures, the most frequently reported AEs associated with the use of Keppra in combination with other AEDs were somnolence, neck pain, and pharyngitis; these AEs were not observed an equivalent frequency among placebo-treated subjects.

Other events occurring in at least 5% of Keppra-treated subjects with myoclonic seizures, but as or more frequent in the placebo group, were fatigue and headache.

Keppra use in the elderly

A total of 347 subjects age 65 or older have participated in clinical studies as of March 2015, and results from those studies showed no overall differences in safety-related measures due to age (Keppra XR 2015). Results from a study of 16 elderly subjects (age 61 to 88 years) showed a 28% decrease in total body clearance and an increase of 2.5 hours in $T_{½}$, which were attributed largely to decreases in renal function typically found in the elderly. As Keppra is known to be substantially excreted by the kidneys, special care should be taken when administering Keppra to elderly individuals, as exposures are expected to be higher in that population.

Published data are available on the safety, tolerability, and PK of Keppra in elderly healthy volunteers, elderly cognitively impaired subjects, and elderly subjects with epilepsy with or without comorbidity with AD. While not an exhaustive, the following summary captures important studies in the elderly reported in the literature.

In a review by French et al. 2001, the safety and tolerability of Keppra was evaluated from an integrated summary of safety. In the cognition studies, subjects were randomized to receive Keppra (250 mg/day to 1500 mg/day; n = 394) or placebo (n = 344). The mean

age was 60 years, with 300 subjects (42%) being 65 years or older. The mean Keppra dose in subjects 65 years or older was 828 mg/day, and the average length of treatment was 41 days. Approximately 14% of subjects in the Keppra group and 7% of subjects in the placebo group experienced TEAEs that led to a dose reduction or discontinuation from the study. A higher incidence of AEs, particularly behavioral effects, was reported among subjects with epilepsy than elderly subjects with cognitive disorders who received lower doses of the drug.

In an analysis of the UCB Keppra safety database, Cramer et al. 2003 reported a higher incidence of headache (5.2% versus 0.9%) and tremor (5.2% versus 0.5%) among elderly subjects with anxiety disorders compared with their younger counterparts.

In a 1-year, open-label study, Keppra (1000 mg/day to 3000 mg/day) was administered as add-on therapy to 491 subjects with focal epilepsy age 65 years or older (Werhahn et al. 2011). The mean age was 72 years (range, 65 to 101 years) and the mean daily dose was 1573 mg, 1796 mg, and 2083 mg at 3 months, 6 months, and 12 months, respectively. Overall, Keppra was reported to be well tolerated. A total of 97 AEs were reported in 53 subjects. Fatigue and restlessness were the most common AEs, occurring in 6 subjects each. Eighteen subjects (3.7%) discontinued the study because of intolerable AEs. Of the SAEs reported (n = 35), 1 (lack of efficacy) was regarded as probably related to Keppra, with the other 34 were regarded as unlikely related to the drug.

The safety and cognitive effects of Keppra were evaluated in subjects with epileptic seizures comorbid with AD in a case-control design study (Cumbo and Ligori 2010). Subjects were administered Keppra (n = 38), phenobarbital (n = 28), or lamotrigine (n = 29), and compared with a control group (n = 68) of subjects with AD without epilepsy. The mean age was 72 years, and the mean daily dose of Keppra was 956 mg. AEs were mainly related to the central nervous system (CNS) and were mild in severity. Six (17%) Keppra-treated subjects reported AEs. None of the subjects dropped out of the study due to the AEs. Keppra caused fewer AEs than the other antiepileptic drugs. Keppra also improved cognitive performance related to the level of attention and oral fluency items, compared to baseline.

In a 12-week, open-label, phase 4 study in subjects (n = 24) with epileptic seizures and AD or other cognitive problems, the mean age was 70 years (range, 50 to 84 years) and the median Keppra dose was 625 mg BID (Lippa et al. 2010). MMSE and AD assessment scale-cognitive scores improved relative to baseline. Fatigue was the most common AE. Five (21%) subjects experienced fatigue, and 4 of those subjects discontinued Keppra. Eleven of the 24 subjects were taking memantine, a cholinesterase inhibitor, or both Keppra and memantine. Keppra was regarded as well tolerated in this population.

In a separate study, Contin et al. 2012 reported results on PK parameters in elderly subjects. A total of 105 elderly (age, 66 to 80 years), 70 very elderly (age, 81 to 96 years), and 96 non-elderly (age, 30 to 65 years) subjects with epilepsy who had been

on Keppra for at least 1 month were included in the study. Median weight-normalized apparent total clearance of the drug from plasma after oral administration (CL/F) decreased from 1.23 mL/min kg in the nonelderly to 0.83 mL/min kg in the elderly and 0.59 mL/min kg in the very elderly ($P < 0.001$). No sex differences were observed. Keppra CL/F significantly declined with age, with elderly and very elderly subjects requiring about 30% to 50% lower dose, respectively, compared with nonelderly subjects. Possibly-related AEs included somnolence, fatigue, confusion, irritability, paresthesias, and mental slowing, which were recorded in 14 (14.4%) nonelderly subjects, 14 (13.3%) elderly subjects, and 7 (10.0%) very elderly subjects.

In a recent study, Werhahn et al. 2011 compared the efficacy and tolerability of Keppra to carbamazepine and lamotrigine in elderly subjects (> 60 years) with new onset focal epilepsy. The median daily dose of Keppra was 950 mg. At 58 weeks, the retention rate with Keppra was higher than that observed with carbamazepine and lamotrigine (61.5% versus 45.8% versus 55.6%, respectively). Subjects who received Keppra had a lower discontinuation rate (17.2%) due to AEs (fatigue, renal failure, and epileptic seizures), compared with those who received carbamazepine (32.2%) and lamotrigine (26.3%). The most common AEs (non-epilepsy related) in subjects who received Keppra were dizziness (29.5%), headache (25.4%), fatigue (25.4%), nasopharyngitis (16.4%), and nausea (9%).

Postmarketing

Postmarketing AE information has been obtained from the Keppra XR medication guide (Keppra XR 2015). The following AEs have been reported in subjects receiving Keppra worldwide: abnormal liver function test, agranulocytosis, choreoathetosis, drug reaction with eosinophilia and systemic symptoms, dyskinesia, erythema multiforme, hepatic failure, hepatitis, hyponatremia, leukopenia, muscular weakness, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), panic attack, thrombocytopenia, and weight loss. Alopecia has also been reported with Keppra use in epilepsy; however, recovery was reported in the majority of cases once the drug was discontinued.

**AGB101 (novel extended-release tablet formulation)**

In a recent phase 1, 2-group, single-dose, 2-period, 2-way crossover, food-effect study of AGB101 (190 mg and 220 mg) extended-release tablet formulation, 5 TEAEs were reported by 5 subjects over the course of the study; 2 of the AEs were reported in the 190 mg dose group and 3 AEs were reported in the 220 mg dose group (Table 5). There were no serious AEs (SAEs) or AEs leading to study discontinuation.

**Table 5: Number (%) of Subjects With Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**

| | | Group 1: 190 mg AGB101 | | Group 2: 220 mg AGB101 | |
|---|---|---|---|---|---|
| System Organ Class | Preferred Term | Treatment A (N=28) | Treatment B (N=27) | Treatment A (N=26) | Treatment B (N=28) |
| Ear and labyrinth disorders | Vertigo positional | 0 (0.0%) | 0 (0.0%) | 1 (3.8%) | 0 (0.0%) |
| Gastrointestinal disorders | Nausea | 0 (0.0%) | 0 (0.0%) | 1 (3.8%) | 0 (0.0%) |
| General disorders and administration site conditions | Fatigue | 1 (3.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Nervous system disorders | Somnolence | 0 (0.0%) | 0 (0.0%) | 1 (3.8%) | 0 (0.0%) |
| Psychiatric disorders | Depressed mood | 0 (0.0%) | 1 (3.7%) | 0 (0.0%) | 0 (0.0%) |

A= Fasted condition, B = Fed condition

AGB101 (220 mg) is the formulation that will be used in the current study.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

- To assess the efficacy of AGB101 (low-dose levetiracetam, 220 mg, extended-release tablet) compared to placebo in subjects with MCI due to AD using CDR-SB scores.

## 2.2 Secondary Objectives

- To assess the efficacy of AGB101 compared to placebo on daily functioning and cognition using FAQ and MMSE scores.
- To assess the effect of AGB101 compared to placebo on neuronal injury, as measured by a change in the EC thickness, using MRI.

## 2.3 Additional Secondary Objectives

- To assess the efficacy of AGB101 compared to placebo using CDR (global, memory box), Behavioral Pattern Separation-Object (BPS-O) task, and International Shopping List Test (ISLT) scores.
- To assess the effect of AGB101 compared to placebo on hippocampal volume using MRI.
- To assess the effect of AGB101 compared to placebo on the levels of tau protein in the brain using the tau PET marker [$^{18}$F]MK-6240 in a subpopulation of approximately 56 subjects.

## 2.4 Exploratory Objectives

- To assess the effect of AGB101 on blood-based biomarkers of neurodegeneration at week 78 or the early termination visit
- (*optional procedure to be performed only at Johns Hopkins University*) To assess the efficacy of AGB101 compared to placebo on hippocampal overactivity in subjects with MCI due to AD.

## 2.5 Safety Objective

- To assess the safety and tolerability of AGB101 compared to placebo in subjects with MCI due to AD.

## 2.6 Study Hypothesis

AGB101 is hypothesized to slow the progression of MCI due to AD by restoring the entorhinal/hippocampal network balance. During this phase of the disease, fMRI studies show hippocampal over-activity and EC under-activity. As shown in the phase 2 study, AGB101 restores this network balance by attenuating hippocampal over-activity and restoring EC activity. Hippocampal over-activity predicts progression on CDR-SB (primary endpoint) and on EC atrophy (a neuronal injury secondary endpoint). By

restoring network balance, AGB101 is hypothesized to improve cognitive function (CDR-SB) and reduce neuronal injury (EC atrophy).

# 3 INVESTIGATIONAL PLAN

## 3.1 Overall Study Design and Plan

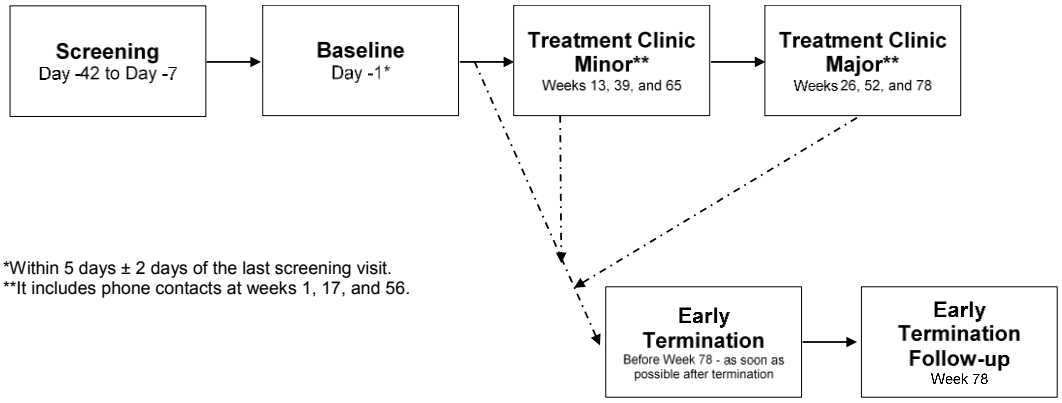
This is a multicenter, randomized, double-blind, placebo-controlled, 78-week, fixed-dose study evaluating AGB101 versus placebo as a treatment for slowing the progression of MCI due to AD.

The screening phase will occur 7 days to 42 days before the baseline visit (see Figure 4). After providing informed consent, subjects who meet entry criteria will be randomized 1:1 during the final baseline visit to receive either placebo or AGB101. A total of 160 subjects will be randomized (80/treatment group). Because of the PK and safety profile of AGB101, dosing will be initiated without titration and will be discontinued without tapering.

The baseline visit will occur 1 day before the study start. Subjects will be given their assigned study drug and instructed to take their 1st dose the next morning. A telephone contact will be made 1 week after the baseline visit to assess the subjects' medical status and inquire about any AEs/SAEs; similar telephone contacts will be made at weeks 17 and 56 with the same purpose. Study clinic visits are divided into minor visits ("clinic minor") at weeks 13, 39, and 65 and major visits ("clinic major") at weeks 26, 52, and 78. The difference between these two types of visits is the number and kinds of assessments performed. The "clinic minor" visits consist of a few basic assessments, while the "clinic major" visits consist of more in-depth testing, neuropsychological testing, and blood draws.

Subjects who enroll and subsequently discontinue the treatment before the 78-week visit will be followed up with a phone call at week 78 to assess their medical status and encourage them to come in to complete the early treatment termination/follow-up visit assessments.

**Figure 4: Study Schema**



## 3.2 Study Duration

The study includes up to a 5-week screening period and a 78-week treatment period consisting of 13 visits (3 screening visits, 1 baseline visit, 3 telephone call visits, and 6 clinic visits).

## 3.3 Selection of Study Population

The study population consists of subjects with a diagnosis of MCI due to AD (see Section 3.3.1 and Section 3.3.2).

### 3.3.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria at screening:

1. Subjects between 55 and 85 years old (inclusive) in good general health:
    a. Willing and able to consent and participate for the duration of the study.
    b. Have eighth-grade education or good work history sufficient to exclude mental retardation.
    c. Have visual and auditory acuity adequate for neuropsychological testing.
    d. Have proficient fluency of the native local language to participate in all the neuropsychological test assessments.
2. Have a study partner who has sufficient contact with the subject to be able to provide assessment of memory changes, who can accompany the subject to the screening visit and all major clinic visits for the duration of those visits, and who is able to provide an independent evaluation of the subject's functioning.
3. Have MCI as defined by all of the following criteria and consistent with the National Institute on Aging-Alzheimer's Association criteria:
    a. MMSE scores between 24 and 30 (inclusive; exceptions may be made for subjects with <8 years of education at the discretion of the sponsor).
    b. A memory complaint reported by the subject or his/her study partner.
    c. Evidence of lower memory performance based on the delayed recall portion of the ISLT.
    d. A CDR score of 0.5 with a memory box score of ≥ 0.5.
    e. Essentially preserved activities of daily living.
    f. Cognitive decline not primarily caused by vascular, traumatic, or medical problems (alternative causes of cognitive decline are ruled out).
4. Permitted medications:
    a. With potential pro-cognitive effects, such as cholinesterase inhibitors and memantine, must be at a stable dose for ≥ 3 months prior to screening and expected to remain stable throughout the study; estrogen replacement therapy,

Ginkgo biloba, and vitamin E must be at a stable dose for ≥ 4 weeks prior to screening and expected to remain stable throughout the study.

b. Other psychotropics, such as antidepressants and antipsychotics, must be at a stable dose for ≥ 3 months prior to screening and expected to remain stable throughout the study.

5. Willing and able to undergo imaging procedures:

   a. An amyloid-imaging PET scan with Neuroceq (florbetaben), Amyvid (florbetapir), or Vizamyl (flutemetamol) ([$^{18}$F] isotope diagnostic agents) or documented evidence of an amyloid-positive PET scan.
   The amyloid PET scan performed at baseline must be read by a qualified physician with experience in reading amyloid PET scans, and it should be consistent with the presence of amyloid plaques.
   b. Repeated MRI scans (3 Tesla) with no contraindications to MRI.
   The MRI scan performed at baseline must be read by a physician with experience in evaluating brain-imaging studies in dementia. MRI scan results are consistent with the diagnosis of amnestic MCI due to AD with no clinically significant findings of non-AD pathology that could account for the observed cognitive impairment.

6. Willing to allow collection of blood for apolipoprotein E (ApoE) genotyping (all sites).

### 3.3.2 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria at screening:

1. Use of anticonvulsant medications or excluded psychotropic medications within 3 months prior to the baseline visit.
2. Participation in a therapeutic clinical study for any medical or psychiatric indications within 3 months (6 months for biologics) of the screening visit, or at any time during the study.
   Subjects must understand that they may only enroll in this clinical study once; they may not enroll in any other clinical study while participating in the current study, and they may not participate in a clinical study of a drug, biologic, therapeutic device, or medical food, in which the last dose/administration was received within 3 months (6 months for biologics) prior to screening.
3. History of hypersensitivity or lack of tolerability to AGB101 (levetiracetam).
4. Severe renal impairment (creatinine clearance of < 30 mL/minute) or undergoing hemodialysis.

5. Any significant neurological disease other than suspected incipient AD, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder (lifetime history; infant febrile seizures are not exclusionary), subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits, or known structural brain abnormalities.
6. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments, or foreign objects in the eyes, skin, or body that constitute a contraindication to having an MRI.
7. Diagnosis of bipolar disorder, or major depression within the past 3 years, as described in the DSM-5.
   Psychotic features, agitation, or behavioral problems within the last 3 months that could lead to difficulty complying with the protocol. Subjects must not have a major depressive disorder or other types of depression that could confound diagnosis of MCI due to AD, or clinical assessments, in the opinion of the investigator. The Geriatric Depression Scale [GDS] (long form score > 9 suggests depression) results should be reviewed by the investigator to assist in this determination.
8. Modified Hachinski Ischemic Scale (HIS) score > 4.
9. History of schizophrenia (DSM-5 criteria).
10. History of alcohol or substance abuse or dependence within the past 3 years (DSM-5 criteria).
11. Any significant systemic illness or unstable medical condition that could lead to difficulty in complying with the protocol requirements.
12. Any unstable medical condition that is likely to require new medical or surgical treatment during the course of the study and where such treatments might affect the collection of efficacy data.
13. Clinically significant abnormalities in B12 or thyroid function test that might interfere with the study. A low B12 (below normative range for elderly) is exclusionary, unless follow-up labs (homocysteine and methylmalonic acid) indicate that it is not physiologically significant. If the B12 deficiency is treated, subjects may become eligible to participate in the study.
14. Residence in a skilled nursing facility. Individuals in independent living communities, assisted living facilities, residential care facilities, or continuing care communities are eligible provided they engage in a sufficient spectrum of activity to permit assessment of all 6 domains contributing to the CDR-SB. Individuals in these facilities must also have a study partner who has the ability to observe the subject during the study and can participate in clinical evaluations.

15. Any use of excluded medications (eg, antiepileptics, certain antidepressants or antipsychotics, antihistamines with anticholinergic properties, opiates).
16. Participation in clinical studies using the ISLT, BPS-O task, or the trail making test (A, B) within 1 month of screening.
17. Female subjects must not be pregnant, lactating, or of childbearing potential (ie, they must be 2 years postmenopause or surgically sterile).

### 3.3.3 Early Termination From Treatment

A subject who discontinues from treatment will complete the early termination visit assessments as shown in Table 7. The investigator will make every attempt to follow the subject to week 78 and complete the early termination/follow-up visit.

A termination electronic case report form (eCRF) page should be completed for every subject who receives the study drug, whether or not the subject completes the study. The reason for early termination should be indicated on this form. The primary reason for early termination should be selected from the following standard categories:

*Adverse event (adverse reaction)*: Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the subject, were grounds for discontinuation. This includes serious and non-serious AEs regardless of relation to the study drug.

*Death:* The subject died.

*Withdrawal by subject*: The subject or legal representative desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawing, it should be recorded in the eCRF.

*Withdrawal by study partner:* The study partner desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the study partner gave a reason for withdrawing, it should be recorded in the eCRF.

*Lack of Efficacy:* The subject or legal representative (or study partner) indicated a lack of efficacy as the primary reason warranting discontinuation from the study.

*Noncompliance with study drug:* The subject was noncompliant in taking the prescribed study drug. Efforts to ensure compliance with the protocol including reminders, phone calls, and counseling should be recorded. Subjects who discontinue treatment will not be automatically discontinued from the study. Every effort should be made to bring subjects back for study visits unless the subject withdraws consent.

*Physician decision:* The study physician may determine that the subject should no longer continue in the study if continuation would pose a safety risk for either the subject, study partner, or another person. In this case, the reason for the concern should be recorded.

*Protocol deviation*: The subject's findings or conduct failed to adhere to the protocol requirements (eg, drug noncompliance, failure to return for defined number of visits). The deviation necessitated early discontinuation from treatment.

*Lost to follow-up*: The subject stopped coming for visits and study personnel were unable to contact the subject. The efforts to contact the subject should be documented.

*Terminated by Sponsor:* The subject was discontinued due to the study being terminated by the sponsor.

*Other*: The subject was discontinued for a reason other than those listed above, such as theft or loss of study drug.

## 3.4 Treatments

### 3.4.1 Details of Study Treatments

Information about the study drugs is provided in Table 6 below.

**Table 6: Details of the Study Drugs**

| | **Study drug** | **Placebo** |
|---|---|---|
| **Name** | AGB101 | Not applicable |
| **Manufacturer** | AgeneBio, Inc. | AgeneBio, Inc. |
| **Dose(s)** | 1 x 220 mg | Not applicable |
| **Route** | Oral | Oral |
| **Formulation** | Light yellow to peach coated capsule shaped tablet debossed with "AGB" | Light yellow to peach coated capsule shaped tablet debossed with "AGB" |
| **Strength(s)** | 220 mg | Not applicable |

AGB101 = low-dose levetiracetam, 220 mg, extended release.

The sponsor will provide all the drug supplies. Subjects will be receiving AGB101 or placebo in the morning in identically appearing oral dosage forms. One dose of AGB101

will contain 220 mg of levetiracetam. A 102-day supply will be provided at each of the clinical visits.

### 3.4.2 Dosage Schedule

Subjects will be administered a single morning daily dose of placebo or AGB101 for 78 weeks. Given the low dose being used, AGB101 dosing will be initiated without titration and will be discontinued without tapering.

### 3.4.3 Treatment Assignment (1:1 Randomization Placebo:AGB101)

A central randomization list will be used for the treatment assignment.

After signing informed consent, subjects will be assigned a unique 10-digit subject identification number (XXX-CC-SSS-EE), with the first 3 digits for the study, the next 2 digits for the country, the next 3 digits for the site, and the last 2 digits for the sequential order of enrollment at a given site. Subjects who are rescreened will receive a new identification number; the previous number will also be recorded by the site. After screening assessments are performed and eligibility is confirmed, eligible subjects will be randomized at baseline. Randomization will be accomplished by the study site using an interactive web response system (IWRS) to assign the next sequential randomization number within the relevant stratum to the eligible subject. Block randomization will be used at each site, with each block having a randomly chosen length of 4 or 6 (each with probability 1/2).

### 3.4.4 Drug Packaging and Blinding

The double-blind study drug will be packaged, labeled, and distributed to study sites by a designated vendor.

The study drug supplied to subjects will be packaged in 3 bottles containing 34 tablets each. The study drug package labels will be in compliance with applicable regulatory requirements and will include the statements “Keep out of reach of children”, “Caution: New Drug – Limited by Federal (United States) law to investigational use”, and/or “For clinical trial use only” as appropriate, as well as any other locally mandated statements. Labels will be translated into the local language.

At a minimum, labels will also include the following information: the name of the sponsor, study code, a unique identifier number, and appropriate contact information. A re-test or expiry date will be included in jurisdictions that require this information.

The investigator may unblind a subject’s treatment assignment. If that happens, the following will apply:

Such a measure should be taken **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study drug is essential for the appropriate clinical management or welfare of the subject, as judged by the investigator.

In the event that a medical emergency or condition requires knowledge of the subject's treatment assignment, the investigator will contact the medical monitor to discuss the potential need for unblinding. Unblinding will be done through the interactive voice response system/IWRS. The procedure for subject unblinding is provided in the study reference manual.

If, for safety reasons, the investigator determines that the subject's treatment must be immediately unblinded to provide adequate medical treatment, the investigator must inform the medical monitor about the unblinding as soon as possible, but without revealing the treatment assignment of the unblinded subject.

The sponsor will be informed immediately of the decision to unblind any subject and will determine whether any additional measures need to be taken for the safety of subjects currently in the study.

Any other requests to reveal a subject's treatment identity must be requested from and approved by the sponsor.

A subject will be withdrawn from the study if his or her treatment code is unblinded by the investigator. The date, time, and reason for the unblinding must be fully documented in the source documents and the eCRF.

The sponsor, or designee, may unblind the treatment assignment for any subject if this is required to fulfill regulatory reporting obligations, such as expedited SAE reporting.

Information about any subject for whom a code break or unblinding occurs will be provided to the Data Safety and Monitoring Board (DSMB) by the sponsor, or designee, within 15 days (within 7 days in the event of a fatal event).

Information regarding unblinding treatment allocation in relation to reporting Suspected Unexpected Adverse Reactions (SUSARs) is provided in Section 4.4.1.

### 3.4.5 Drug Inventory and Accountability

Investigators must keep an accurate accounting of the number of study drug units delivered to the site, dispensed to subjects, returned to the investigator by the subject, and returned to the sponsor or other disposition during and at the completion of the study. Only an appropriately qualified person must dispense the study drug to subjects. The study drug is to be used in accordance with the protocol by subjects who are under the direct supervision of the investigator. Investigators should maintain records that adequately document that the subjects were provided the doses specified by the protocol and reconcile all study drugs received at the site before final disposition. At the end of the study, or as directed, all study drugs, including unused, partially used, and empty containers, will be returned to the sponsor.

### 3.4.6 Treatment Compliance

Study drug containers must be returned at each visit, as compliance will be assessed by tablet count. Noncompliance is defined as taking < 80% or > 120% of the study drug during any outpatient evaluation period (visit to visit). The investigator may use clinical judgement in evaluating noncompliance with the study drug as a reason for early termination from the study. Subjects who discontinue treatment will not be automatically discontinued from the study. Every effort should be made to bring subjects back for study visits unless the subject withdraws consent.

### 3.4.7 Prior and Ongoing Medical History and Treatments

#### 3.4.7.1 Prior and Ongoing Medical History

Investigators should document all significant medical history that subjects experienced within 12 months of screening. Any illness present at the time informed consent is given should be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study should be documented as AEs in the eCRF.

#### 3.4.7.2 Prior and Concomitant Treatments

Prior treatments, defined as those received within 30 days before screening, should be recorded in the eCRF as prior medications. Concomitant treatments, defined as treatments received after the first dose of the study drug, should be recorded in the eCRF as concomitant medications. Any change in medication (including dose or frequency) should be recorded on the "Concurrent Medications Log" for the visit reported. If a subject begins an excluded medication, the site must document this by requesting an exception from the medical monitor.

For a list of accepted and excluded medications, please refer to Appendix 8.1. Note that this is not an exhaustive list. For drugs not included on this list, inquire with the medical monitor. The medical monitor may grant exceptions for infrequent or trivial use.

## 3.5 Assessments

Unless otherwise indicated, all assessments will be performed by the investigator or designated study personnel.

### 3.5.1 Schedule of Assessments

The study procedures are outlined in Table 7 and in Section 3.5.2.

## Table 7: Schedule of Assessments

| Study period | Screening | | | Baseline | Treatment | | | | | | | | | Early termination | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study visit number | S 1[1] | S 2[1] | S 3/B MRI[1] | B[2] | W 1[3] | W 13 | W 17 | W 26 | W 39 | W 52 | W 56 | W 65 | W 78 | ET[4] | ET/ W 78 Follow-up[5] |
| Study day/week | D -42 to D -7 | | | D -1 | D 7 ± 2 | D 91 ± 5 | D 119 ± 5 | D 182 ± 5 | D 273 ± 5 | D 364 ± 5 | D 392 ± 5 | D 455 ± 5 | D 546 ± 5 | N/A | W 78 |
| Visit type | C | I | I | C major | T[6] | C minor | T[6] | C major | C minor | C major | T[6] | C minor | C major | C major | T/C |
| Informed consent | X | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | |
| ApoE genotyping (all sites) and DNA banking (JHU only; optional) | | | | X | | | | | | | | | | | |
| ECG | X | | | | | | | | | | | | X | X | |
| Physical and neurological exams (Height at Screening) [1] | X | | | | | X | | X | X | X | | X | X | X | |
| Vital signs and Body Weight | X | | | X | | X | | X | X | X | | X | X | X | X |
| Serum chemistry | X | | | | | | | X | | X | | | X | X | |
| CBC | X | | | | | | | X | | X | | | X | X | |
| Thyroid panel | X | | | | | | | X | | X | | | X | X | |
| Liver function tests | X | | | | | | | X | | X | | | X | X | |
| Urinalysis | X | | | | | | | X | | X | | | X | X | |

| Study period | Screening | | | Baseline | Treatment | | | | | | | | | Early termination | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study visit number | S 1[1] | S 2[1] | S 3/B MRI[1] | B[2] | W 1[3] | W 13 | W 17 | W 26 | W 39 | W 52 | W 56 | W 65 | W 78 | ET[4] | ET/ W 78 Follow-up[5] |
| Study day/week | D -42 to D -7 | | | D -1 | D 7 ± 2 | D 91 ± 5 | D 119 ± 5 | D 182 ± 5 | D 273 ± 5 | D 364 ± 5 | D 392 ± 5 | D 455 ± 5 | D 546 ± 5 | N/A | W 78 |
| Visit type | C | I | I | C major | T[6] | C minor | T[6] | C major | C minor | C major | T[6] | C minor | C major | C major | T/C |
| Urine drug screen | X | | | | | | | | | | | | | | |
| ISLT[7] | X | | | | | | | X | | X | | | X | X | X |
| MMSE | X[8] | | | X | | | | X | | X | | | X[8] | X[8] | X[8] |
| GDS | X[8] | | | X | | | | | | | | | X[8] | X[8] | X[8] |
| BPS-O task | X[9] | | | X | | | | X | | X | | | X | X | X |
| Trail making test (A, B) | | | | X | | | | | | | | | | | |
| FAQ | | | | X | | | | X | | X | | | X | X | X |
| CDR (participant and study partner) | X | | | X | | | | X | | X | | | X | X | X |
| C-SSRS | X | | | X | X | X | X | X | X | X | X | X | X | X | X |
| HIS score | X | | | | | | | | | | | | | | |
| Amyloid PET scan | | X[10] | | | | | | | | | | | | | |
| MRI structural: MP-RAGE or IR-SPGR | | | X[10, 11] | | | | | X (JHU only) | | X | | | X[10] | | |
| MRI structural: FLAIR, T2 | | | X[10, 11] | | | | | | | | | | | | |
| Randomization | | | | X | | | | | | | | | | | |

| Study period | Screening | | | Baseline | Treatment | | | | | | | | | Early termination | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study visit number | S 1[1] | S 2[1] | S 3/B MRI[1] | B[2] | W 1[3] | W 13 | W 17 | W 26 | W 39 | W 52 | W 56 | W 65 | W 78 | ET[4] | ET/ W 78 Follow-up[5] |
| Study day/week | D -42 to D -7 | | | D -1 | D 7 ± 2 | D 91 ± 5 | D 119 ± 5 | D 182 ± 5 | D 273 ± 5 | D 364 ± 5 | D 392 ± 5 | D 455 ± 5 | D 546 ± 5 | N/A | W 78 |
| Visit type | C | I | I | C major | T[6] | C minor | T[6] | C major | C minor | C major | T[6] | C minor | C major | C major | T/C |
| [$^{18}$F]MK-6240 (Tau protein marker, optional) | | | | X[10] | | | | | | | | | X[10] | | |
| fMRI (JHU only)[12] | | | X | | | | | X | | | | | | | |
| Study drug dispensing | | | | X[13] | | X | | X | X | X | | X | | | |
| PK sampling | | | | | | | | X | | X | | | X | X | |
| Biomarker Blood Draw | | | | | | | | | | | | | X | X | |
| Prior/Concomitant medications[14] | ----------X---------- | | | | | | | | | | | | | | |
| AE/SAE reporting | ----------X---------- | | | | | | | | | | | | | | |

Abbreviations: AE=adverse event; ApoE=apolipoprotein E; B=baseline; B MRI=baseline magnetic resonance imaging; BPS-O=Behavioral Pattern Separation-Object; C=clinic visit; CBC=complete blood count; CDR=Clinical Dementia Rating; C major=major clinic visit; C minor=minor clinic visit; C-SSRS=Columbia Suicide Severity Rating Scale; D=day; DNA = deoxyribonucleic acid; ECG=electrocardiogram; ET=early termination; FAQ=Functional Activities Questionnaire; FLAIR=fluid attenuation inversion recovery; fMRI = functional magnetic resonance imaging; GDS=Geriatric Depression Scale; HIS=Hachinski Ischemic Scale; I=imaging visit; IR-SPGR=radiofrequency-spoiled gradient echo; ISLT=International Shopping List Test; JHU = Johns Hopkins University; M=month; MMSE=Mini Mental State Examination; MP-RAGE=magnetization-prepared gradient echo; MRI=magnetic resonance imaging; N/A=not applicable; PET=positron emission tomography; PK=pharmacokinetic; S=screening; SAE=serious adverse event; T=telephone contact; T/C=telephone contact/clinic visit; W=week.

1 The screening phase (S1, S2, S3/B MRI) will occur 7 days to 42 days prior to baseline. Subjects must meet all the criteria during all the screening visits in order to be enrolled in the study. Height without shoes will be recorded in inches or meters.

2 Baseline visit will occur on day -1 within 12 days ± 2 days of the S3/B MRI visit. S3/B MRI will occur up to 2 weeks prior to Baseline; the Tau scan needs to occur 1 or more days before the cognitive visit.

3 Week 1 visit will occur 7 days after the baseline visit.

[4] Subjects who discontinue treatment early (ie, at any time after randomization) will have the early termination visit assessments performed as soon as possible after treatment termination.

[5] All subjects who enroll and subsequently discontinue treatment will be followed up with a phone call during week 78 to assess their medical status and encourage them to come in for a final CDR and neuropsychological assessments and AE reporting.

[6] 7 days after the baseline visit (week 1), day 119 (week 17), and day 392 (week 56), a phone call will be made to all the subjects to assess their medical status and inquire about any adverse events/serious adverse events.

[7] There will be approximately a 20 minute wait time between the immediate recall and delayed recall portion of the ISLT.

[8] The MMSE and the GDS will be administered, in this order, between the immediate recall and delayed recall portion of the ISLT.

[9] A practice BPS-O will be administered at screening visit 1.

[10] MRI/PET scans may be redone if the scan is not technically satisfactory (as judged by the imaging vendor) within 2 weeks of the original scan as long as the radiation exposure is within the limits approved by the IRB.

[11] Previous MRI scans will not be allowed. A baseline for structural imaging will be established using procedures in this protocol.

[12] fMRI will only be performed as an optional procedure at JHU.

[13] Dosing begins the morning after the baseline visit.

[14] Prior medications will only be recorded during the screening phase (S1, S2, S3/B MRI).

### 3.5.2 Study Procedures

The following assessments will take place at the specified study visits.

#### 3.5.2.1 Screening Phase (Day -42 to -7)

The assessments during the screening phase (screening, screening 2, screening 3/baseline MRI) will determine the subjects' eligibility to enter the study and comply with the protocol requirements. Subjects must meet all the criteria during all the screening visits in order to be enrolled in the study.

The following procedures will be performed and recorded during screening phase:

**Screening visit 1 (clinic visit)**

- Informed consent
- Demographic information and medical history
- Eligibility criteria
- Blood sample for serum chemistry, complete blood count (CBC), thyroid panel, and liver function tests
- Electrocardiogram (ECG)
- Physical and neurological exams, and HIS score assessment
- Vital signs and body weight
- Urine sample for urinalysis and urine drug screen (amphetamines, benzodiazepines, cannabinoids, opiates, methadone, and alcohol)
- ISLT, MMSE, GDS, practice BPS-O, CDR score (participant and study partner), Columbia Suicide Severity Rating Scale (C-SSRS), and HIS assessments
- AEs/SAEs and prior medication reporting

**Screening visit 2 (imaging visit)**

- An amyloid-imaging PET scan with Neuroceq (florbetaben), Amyvid (florbetapir), or Vizamyl (flutemetamol) will be performed unless there is documented evidence of an amyloid-positive scan, and it will only be conducted on prospective participants who meet all the other eligibility criteria (see Appendix 8.2).
- AEs/SAEs and prior medication reporting

**Screening visit 3/baseline MRI (imaging visit)**

- Baseline visit will occur on day -1 within 12 days ± 2 days of the S3/B MRI visit. S3/B MRI will occur up to 2 weeks prior to Baseline; the Tau scan needs to occur 1 or more days before the cognitive visit. This MRI is to be conducted prior to the cognitive Baseline visit; up to 2 weeks can occur between S3/B and cognitive Baseline visit.

- A 3T MRI imaging scan will occur and will only be conducted on prospective participants who meet all the other eligibility criteria (see Appendix 8.3).

  3T MRI (structural: magnetization-prepared gradient echo [MP-RAGE] or radiofrequency-spoiled gradient echo [IR-SPGR], fluid attenuation inversion recovery [FLAIR] sequence, T2) (previous MRI scans will not be allowed).

- A 3T task activated fMRI scan will occur during the same MRI session after completing the structural MRI sequences. An in-scanner version of the BPS-O will be used as the fMRI task (*optional procedure at JHU only*).

- AEs/SAEs and prior medication reporting

#### 3.5.2.2 Randomization and Baseline Visit (Day -1 Within 12 Days ± 2 Days of the S3/B MRI Visit)

The following procedures will be performed and recorded during the baseline visit:

- Randomization of treatment assignment
- Study drug dosing (begins the morning after the baseline visit). Subjects will be given their assigned study drug and instructed to take their 1$^{st}$ dose the next morning
- Vital signs and body weight
- Blood sample for ApoE genotyping (all sites) and DNA banking *(optional procedure;* JHU only*)*
- A PET scan after injection with the tau PET marker [$^{18}$F]MK-6240 (*optional procedure)*
- MMSE, GDS, BPS-O task, trail making test (A and B), FAQ, CDR score (participant and study partner), and C-SSRS assessments
- AEs/SAEs and concomitant medication reporting

#### 3.5.2.3 Weeks 1 (Baseline + 7 Days ± 2 Days), 17 (Day 119 ± 5 Days), and 56 (Day 392 ± 5 Days) Phone Call

A phone call will be made to all the subjects to evaluate at weeks 1, 17, and 56 (for Study Day and time window see Table 7):

- Medical status
- C-SSRS assessment
- AEs/SAEs and concomitant medication reporting

#### 3.5.2.4 Weeks 13, 39, and 65 Visits "Clinic Minor" (Baseline + 13, 39, and 65 Weeks ± 5 Days)

The "clinic minor" visits will take approximately 1 hour each and will include a few basic assessments:

- Study drug dispensing
- Physical and neurological exams
- Vital signs and body weight
- C-SSRS assessment
- AEs/SAEs and concomitant medication reporting

#### 3.5.2.5 Weeks 26, 52, and 78 "Clinic Major" (Baseline + 26, 52, and 78 Weeks ± 5 Days)

The "clinic major" visits will take approximately 4 hours each and will include a few additional assessments, including neuropsychological testing and blood draws:

- Study drug dispensing (weeks 26 and 52 only)
- Physical and neurological exams
- Vital signs and body weight
- Blood sample for PK testing, serum chemistry, CBC, thyroid panel, and liver function tests
- Urinalysis
- 3T MRI (structural: MP-RAGE or IR-SPGR) at week 26 (JHU only) and at weeks 52 and 78 (all sites)
- 3T fMRI using scanner version of the BPS-O task at Baseline MRI and week 26 only (*optional procedures at JHU only*)
- ISLT, MMSE, BPS-O task, FAQ, CDR score (participant and study partner), and C-SSRS assessments
- AEs/SAEs and concomitant medication reporting

#### 3.5.2.6 Week 78 Visit (Additional Assessments)

The following additional assessments will be performed during the week 78 visit:

- GDS assessment
- ECG
- Additional blood sample for biomarkers of neurodegeneration

#### 3.5.2.7 Week 78 Visit (Additional Imaging Assessments)

The following additional imaging assessment will be performed during the week 78 visit:

- PET scan after injection with the tau PET marker [$^{18}$F]MK-6240 (*optional procedure*)

### 3.5.3 Early Termination Visit and Early Termination/Follow-up Visit

Subjects who discontinue treatment (ie, at any time after randomization and before the week 78 visit) will have the early termination visit assessments performed as soon as possible after treatment termination. In addition, all subjects who enroll and subsequently discontinue will be followed up with a phone call during week 78 to assess medical status and encourage them to come in to complete the early termination/follow-up visit assessments.

#### 3.5.3.1 Early Termination Visit

- ECG
- Physical and neurological exams
- Vital signs and body weight
- Blood sample for PK testing, serum chemistry, CBC, thyroid panel, liver function tests and for blood-based biomarkers
- Urinalysis
- ISLT, MMSE, GDS, BPS-O task, FAQ, CDS (participant and study partner), and C-SSRS
- AEs/SAEs and concomitant medication reporting

#### 3.5.3.2 Early Termination Follow-up Visit (Week 78)

- Vital signs and body weight
- ISLT, MMSE, GDS, BPS-O task, FAQ, CDR (participant and study partner), and C-SSRS
- AEs/SAEs and concomitant medication reporting

### 3.5.4 Efficacy Assessments

#### 3.5.4.1 Primary Efficacy Assessments

The primary efficacy evaluation will be the change in CDR-SB score from baseline to 78 weeks. This will be measured by asking the subject and their study partner a series of questions to collect information about the subject's memory, orientation, judgment, and problem-solving ability, interest and knowledge of community affairs, home and hobbies, and ability to maintain personal care. In rating each of these domains, the assessment is based on the subject's cognitive ability to function in these areas ("box score"). The change over the course of the treatment will be indicative of the relative efficacy of the test product.

#### 3.5.4.2 Secondary Efficacy Assessments

The gated secondary efficacy assessments will consist of change in cognition/function, as measured by change in FAQ or MMSE from baseline to 78 weeks, and evaluation of

neuronal injury, as measured by change in AGB101 effects on EC thickness from baseline to 78 weeks.

FAQ is a questionnaire administered to an informant who rates each subject's performance over the preceding 4 weeks on 10 separate categories of instrumental activities of daily living: 1) writing checks, paying bills, keeping financial records; 2) assembling tax or business records; 3) shopping alone; 4) playing a game of skill; 5) making coffee or tea; 6) preparing a balanced meal; 7) keeping track of current events; 8) attending to and understanding a television program, book, or magazine; 9) remembering appointments, family occasions, medications; and 10) traveling out of the neighborhood. Performance in each category is rated as follows: 0- normal; 1- has difficulty, but does by self; 2-requires assistance; or 3-dependent (Pfeffer et al. 1982).

MMSE is a sensitive, valid, and reliable 30-point questionnaire that measures and evaluates cognitive function and mental impairment. It involves presenting the subjects with simple questions and/or problems and evaluating their responses (Folstein et al. 1975).

**Other neuropsychological tests:**

- The ISLT is a 12-word, three-trial verbal list-learning test. The lists consist of shopping items selected to be language and regionally commonplace. The presentation of lists and the recording of responses are controlled by a laptop computer. Each list is randomly generated from a pool of 128 words. A different set of 12 words is chosen when a new list is required, with eight different lists without overlap. A trial finishes as soon as no further recall is possible or 90 seconds has elapsed. The ISLT can reliably detect AD-related verbal learning and memory impairment in people from different cultures who read in different languages.
- BPS-O task measures recognition memory by asking subjects to view a series of objects (phase 1) and then recall (phase 2) whether the objects being presented are old (ie, were originally presented in phase 1), new (were not presented in phase 1), or similar to those presented earlier in phase 1. The proportion of responses for each category (new items identified as "new", repeated items identified as "old", similar items identified as "similar", and all incorrect response categories) is calculated.

**Neuroimaging evaluations:**

- EC thickness will be measured by imaging the brain (MRI) at set points throughout the study utilizing ADNI-2 imaging procedures.

MRI measurements of brain structures have been shown to demonstrate brain atrophy correlated with neuronal loss in MCI and increasing rates of brain atrophy as subjects become more impaired. In this MCI study, rates of atrophy of the EC over time are used as a measure of disease progression and possible treatment effect. Structural MRI sequences (MP-RAGE/IR-SPGR) will be used to generate measures of rate of change in

the EC thickness in all study subjects, which will serve as a secondary endpoint for the treatment study. The core MRI protocol will consist of 3 structural MRI scans from every subject at baseline, and weeks 52 and 78 on every MRI vendor system. For the purpose of exclusion, cerebrovascular disease, including white matter lesions and micro bleeds will be assessed using FLAIR and T2 sequences during the baseline assessment.

All structural MRI acquisition methods and quality control procedures employed in this study will follow those employed in the ADNI-2 study to facilitate standardization and comparability (see Appendix 8.3). Summary descriptions of those methods are included below with deviations from the ADNI-2 procedures outlined explicitly.

Hippocampal volume will also be measured with comparable techniques.

**PET Marker for tau protein evaluation:**

[$^{18}$F]MK-6240 (*optional*): is a radiopharmaceutical that binds to tau protein and has been used to monitor the progression of AD. This procedure will be performed at baseline and week 78. A substudy of approximately 56 subjects is planned to have this procedure and evaluation performed to assess the value of this endpoint in future studies.

**fMRI scanning for functional evaluation**

Hippocampal network functioning will be measured by functional imaging (fMRI) at set points throughout the study utilizing published functional imaging procedures. Functional neuroimaging of the hippocampal subregions has been shown to provide a measure of increased activation in MCI associated with episodic memory impairments. In this MCI due to AD study, functional neuroimaging of the hippocampal network is used as a measure of disease progression and possible treatment effect. High-resolution functional neuroimaging methods will be used to measure relative levels of activation in the hippocampal subregions, specifically the DG/CA3 subregion in the context of performance on the BPS-O task. The fMRI protocol will consist of 8 runs of the functional MRI sequence that will be acquired during the MRI at baseline and week 26 visits (*optional at JHU site only*).

### 3.5.5 Safety Assessments

#### 3.5.5.1 Physical Examination

Physical examinations will include examining the general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system. Neurological examinations will include examination of coordination, gait, patellar deep tendon reflexes, sensation, strength and muscle tone, and orientation. An AE form must be completed for all changes identified as clinically noteworthy. Height without shoes will be recorded in inches or meters at screening.

#### 3.5.5.2 Vital Signs and Body Weight

Vital signs will include body temperature (F or C), respiratory rate, supine (optional) and sitting radial pulse rates, and supine (optional) and sitting systolic and diastolic blood pressures (BPs). Supine recordings, if possible, will be made after the subject has been recumbent for 3 minutes. Body weight without shoes will be recorded in pounds or kilograms whenever vital signs are recorded.

#### 3.5.5.3 Electrocardiogram

Standard 12-lead ECGs will be measured at screening, week 78, and ET.

#### 3.5.5.4 Laboratory Parameters

The following clinical laboratory tests will be performed as indicated by the schedule of assessments (see Table 7):

- Hematology: hemoglobin, hematocrit, CBC with differential, platelet count.
- Chemistry: albumin, albumin/globulin ratio, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, B12, bilirubin-direct, bilirubin-indirect, bilirubin-total, blood urea nitrogen, blood urea nitrogen/creatinine ratio, calcium, cholesterol, chloride, creatine kinase, creatinine, gamma-glutamyl transpeptidase, globulin, glucose, lactate dehydrogenase, phosphorus-inorganic, potassium, protein-total, sodium, triglycerides, and uric acid.
- Urinalysis: pH of freshly voided specimen, specific gravity, protein, glucose, ketones, blood, and microscopic examinations of the sediment, and drug screen (amphetamines, benzodiazepines, cannabinoids, opiates, methadone, and alcohol).
- Other: thyroid panel and liver function tests.

Laboratory samples will be analyzed by a central laboratory to ensure consistent interpretation of results. Mailing instructions will be included in the laboratory manual. In the event of an unexplained clinically noteworthy abnormal laboratory test value as assessed by the investigator, the test should be repeated and followed up until the test value has returned to the normal range and/or an adequate explanation of the abnormality is found.

### 3.5.6 Additional Assessments

The long form GDS is a 30-item self-report assessment used to identify depression, specifically in an elderly population. The GDS questions are answered "yes" or "no", instead of a 5-category response set. This simplicity enables the scale to be used with ill or cognitively impaired individuals. A score of 0 to 9 is considered normal, while a score > 9 suggests depression.

C-SSRS is a semi-structured interview designed to assess the severity and intensity of suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior over a

specified time period (eg, lifetime at baseline and since last visit at the additional visits). The assessment is completed by study staff with appropriate clinical training at scheduled visits as shown in the schedule of assessments (Table 7). If, at any visit following the baseline visit, there are any "YES" answers on items 4, 5, or any of the behavioral questions, a risk assessment should be done by a qualified clinician to determine whether it is safe for the subject to continue participation in the study.

The modified HIS is a clinical tool used for screening to differentiate vascular dementia from degenerative forms of the disorder (MCI, AD). Subjects with a score of 7 or higher are more likely to have vascular dementia. A low HIS is less likely to indicate vascular dementia because ischemic lesions severe enough to produce dementia would be expected to be severe enough to cause the accompanying neurologic changes and elevation in the index (Hachinski et al. 1975).

Trail making test is a neuropsychological test of visual attention and task switching. For part A, subjects connect a set of 25 sequentially numbered dots in order as fast as possible while still maintaining accuracy. For part B, subjects are asked to follow the same instructions but alternate between letters and numbers keeping each set in order. This will be conducted at baseline only.

The additional blood draw at ET/week 78 visit will be used to provide samples for assessment of blood-based biomarkers that may reflect neurodegeneration. Markers to be measured may include A-beta 1-40, A-beta 1-42, total tau, pTau 181, pTau 217 and neurofilament light chain (nfl).

### 3.5.7 Pharmacokinetic Assessments

A total of 3 samples will be collected for PK analysis at weeks 26, 52, and 78. In addition, approximately 40 mL of blood will be collected for screening and the end-of-study clinical laboratory evaluations. The total volume of blood collected will not exceed 300 mL.

Blood samples (1 mL x 4 mL) will be collected in Vacutainer tubes containing dipotassium ethylenediaminetetraacetic acid as a preservative at 4 hours to 7 hours after dosing with AGB101 or placebo. The time and date of collection for each sample will be recorded.

Blood samples will be centrifuged at approximately 3000 revolutions per minute (rpm) for 10 minutes at 4ºC. The resulting plasma samples will be harvested and transferred into approximately equal portions into 2 appropriately labeled polypropylene screw-cap tubes labeled "A" and "B". PK samples will be placed in a freezer at -20ºC or lower within 60 minutes of the blood draw.

Procedures for storage and shipment of the PK samples are provided in the PK Manual.

### 3.5.8 Appropriateness of Measurements

All assessments that will be used in this study are commonly used, standard measurements frequently employed in studies investigating MCI and AD.

# 4 ADVERSE EVENT REPORTING

Throughout the course of the study, all AEs will be monitored and recorded on an AE eCRF, including the AE's description, start and end date, outcome, seriousness, severity, action taken, and relationship to the study drug. If AEs occur, the first concern is the safety of the study subjects. All AEs will be followed until resolved or stable and the outcome documented on the eCRF.

## 4.1 Definitions and Criteria

### 4.1.1 Adverse Events

Per International Conference on Harmonisation (ICH) E2A: An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events meeting the definition of an AE **include**:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication

Clinically significant abnormal findings (laboratory test results, vital signs, physical examination findings, ECGs, radiologic exams, or other studies) should be recorded as AEs. A "clinically significant" finding is one that affects clinical management, including additional visits, monitoring or referrals, diagnostic tests or alteration of treatment, or that is considered clinically significant by the investigator. A clinically significant finding may be a change in a test that has previously been abnormal but now requires additional action.

When a medical or surgical procedure is performed, the condition that leads to the procedure should be recorded as the AE.

Events that **do not** meet the definition of an AE include:

- Anticipated day-to-day fluctuations or expected progression of pre-existing disease(s) or condition(s) present or detected at the start of the study unless

judged by an investigator to be more severe than expected for the subject's underlying condition

- Abnormal laboratory, ECG, or vital sign measurements that are not labelled clinically significant (see definition above)
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Pregnancy
- Overdose in the absence of other AEs will not be reported as an AE in its own right

Changes in C-SSRS during the course of the study indicating worsening should be evaluated by the investigator for clinical significance, and if clinically significant (eg, alteration in medical care or intervention is required), an associated AE should be recorded, if present. The AE should be the primary underlying clinical manifestation assessed as clinically significant, and not the change in score itself.

Change in cognitive functioning (improvement or worsening) is also not considered to be an AE, since it is related to the underlying disease and the condition under study.

### 4.1.2 Serious Adverse Events

An SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization, with the exception of:
    - Visits to the emergency room or hospital department that do not result in an overnight hospital admission
    - Elective surgery for a pre-existing condition that has not worsened
    - Routine health assessments requiring admission not associated with any deterioration in condition
    - Social admission (lack of housing, family circumstances, etc.)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (eg, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, development of drug dependency or drug abuse, or malignancy tumors [histologically different from the primary tumor])

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. An SAE is not necessarily severe, eg, a hospitalization for a diagnostic procedure must be reported as an SAE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea of several hours’ duration may be rated as severe but may not be considered serious.

### 4.1.3 Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction (ADR) is a reaction for which the nature or severity is not consistent with the applicable product information (see current Investigator’s Brochure). Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected.” Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

Guidance on reporting AEs and SAEs is described in Section 4.2.

### 4.1.4 Assessing Intensity and Relationship

All AEs will be assessed on 2 descriptive parameters: intensity and relationship to the study drug:

1. Intensity refers to the severity of an event and references the impact on a subject’s functioning.
2. Relationship refers to the likelihood that the event being assessed was caused by the study drug.

**Intensity**

Each AE will be classified according to the following criteria:

| | |
|---|---|
| Mild: | The AE does not interfere in a significant manner with the subject’s normal level of functioning. |

| | |
|---|---|
| Moderate: | The AE produces some impairment of functioning but is not hazardous to the subject's health. |
| Severe: | The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health. |

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over a number of days, those changes should be recorded separately (with distinct onset dates).

**Relationship**

Each AE will be assessed as to its relationship to the study drug based on the following criteria. Although the attribution by the investigator will be collected for reported events, for analytic purposes a temporal association with the use of the study drug will be assumed sufficient for at least plausible association.

| | |
|---|---|
| Not related: | No causal relationship exists between the study drug and the AE, but an obvious alternative cause exists, eg, the subject's underlying medical condition or concomitant therapy. |
| Related: | There is a reasonable/plausible possibility that the AE may have been caused by the study drug. |

When assessing the relationship to the study drug, the following criteria will be considered:

- Temporal relationship
- Positive rechallenge
- Positive dechallenge (resolution upon stopping the study drug, in absence of other intervention or treatment)
- Known class effect
- Biological plausibility
- Lack of alternative explanation—concomitant drug or disease

## 4.2 Reporting Procedures and Requirements

### 4.2.1 Adverse Events

AE recording will begin at the first screening visit. Thereafter, AEs will be ascertained by asking the subject (and study partner) how he/she has been since the last visit. Any

AEs/SAEs occurring before the start of treatment (ie, before the first dose of the study drug) will be recorded and reported as such.

Also, the sign, symptom, or disease present before starting the treatment period are only considered AEs if they worsen after starting the treatment period.

If the investigator detects an AE in a study subject within 1 month of the last scheduled follow-up visit and considers the event possibly related or related to prior study treatment, the investigator should report it to WCT.

The investigator should report all information about AEs on the AE/SAE section of the electronic data capture (EDC) system. Whenever possible, an AE will be reported using a diagnostic term (eg, “common cold” or “upper respiratory infection” rather than “runny nose, cough, mild fever”) and should be described with the attributes described in Section 4.1.4.

### 4.2.2 Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (Section 4.1.2). If the AE is considered serious, the investigator should report this event to WCT as outlined below and also to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) according to its standard operating procedures.

All information about SAEs will be collected and reported by entering the SAE information in the AE/SAE section of the EDC system. The investigator should send the initial report to WCT within 24 hours of becoming aware of the SAE and followed by follow-up reports as soon as possible, whether the events are deemed related to the study drug or not. The information provided in the EDC system should be as complete as possible, but minimally it must contain the following:

- Subject number
- Brief description of the SAE (diagnosis or signs/symptoms)
- Serious criteria
- Causality assessment
- Assessment of the intensity of the event

WCT Drug Safety will receive notification of the initial SAE *via* an e-mail alert generated from the EDC system. In the event of any temporary disruption of the EDC system, an alternative SAE reporting mechanism will be available to site personnel; in this instance, a paper SAE report form will be available. Site personnel will complete the paper SAE report form, scan and e-mail it within 24 hours to the following address: drugsafety@wwctrials.com.

Site personnel must complete the AE/SAE section with the SAE information as soon as the EDC system becomes available. SAEs that are ongoing should be followed until resolved or stabilized to a level acceptable to the investigator.

The investigator is obliged to provide additional information as requested by the medical monitor or pharmacovigilance physician. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. In the case of a subject death, a summary of available autopsy findings, if performed, must be submitted as soon as possible to the contract research organization. However, any supporting information provided should not reveal a subject's identity beyond the agreed study identifier. The investigator should ensure that information reported is accurate and consistent.

Information not available at the time of the initial report (eg, an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented on a follow-up form. All follow-up information must be reported in the same timelines as initial information.

Any SAEs considered related to the study drug and discovered by the investigator at any interval after the study must also be reported to the sponsor within 24 hours following knowledge of the event.

### 4.3 Procedures for Documenting Pregnancy During Study

Females of childbearing potential are to be excluded from this study. If a female sexual partner of a male subject becomes pregnant during the study, the investigator must notify WCT immediately of becoming aware of the pregnancy and will complete the pregnancy eCRF page. The investigator will also follow the progress of the pregnancy to term or termination and document the outcome of the pregnancy (health of the infant up to 8 weeks of age). Male subjects should be instructed to notify the investigator if their female sexual partner becomes pregnant either during the treatment period of the study or within 3 months after the last dose of study drug. Although the pregnancy is not considered to be an AE or SAE, any pregnancy complications should be recorded as AEs or SAEs (if applicable). Any pregnancy should be followed through delivery for the observation of any SAE. Therefore, regardless of whether or not a pregnancy is actually considered an SAE, a pregnancy should be reported in the EDC. A paper CRF will be used as backup only.

All data related to pregnancy, pregnancy outcome, and SAEs associated with pregnancy will be recorded in a safety database maintained by personnel responsible for pharmacovigilance at WCT.

## 4.4 Sponsor Reporting of Suspected Unexpected Adverse Reactions to Regulatory Authorities

SUSARs are AEs that are believed to be related to an investigational medicinal product and are both unexpected (ie, the nature or severity is not expected from the information provided in the Investigator's Brochure) and serious. As stated in the European Union (EU) 'CT-3' Communication from the Commission (2011/C 172/01) and the US Code of Federal Regulations (21 CFR 312.32), for there to be a reasonable possibility of a causal relationship between the event and the study drug, there must be facts (evidence) or arguments to suggest a causal relationship. Final assessment of expectedness for purposes of regulatory reporting is the responsibility of the sponsor.

It is the responsibility of the sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify regulatory authority and investigators.

Requirements and unblinding procedures for SUSAR reporting are described below. All SUSAR reporting, whether determined following unblinding during study conduct or apparent only after the study has ended, will adhere to European Directives 2001/20/EC, 21 CFR 312.32 of the US CFR, Health Canada Food and Drug Regulation C.05.014, and other regions as applicable.

### 4.4.1 Unblinding Treatment Allocation

Generally, only SUSARs for which the treatment allocation of the subject is unblinded should be reported by the sponsor to the pertinent regulatory authorities.

When an event may be a SUSAR, the blind should be broken only for that specific subject, and only if knowledge of the study drug assignment is material to the medical management of the AE (see Section 3.4.4). When unblinded to assist in the medical management, the blind for that subject should be maintained for individuals responsible for the ongoing conduct of the study (eg, management, monitors, and investigators) and those responsible for data analysis and interpretation of results at the conclusion of the study (eg, biometrics personnel).

Unblinded information should only be accessible to those who need to be involved in the safety reporting to pertinent regulatory authorities, independent ethics committees/independent review boards (IECs/IRBs) and DSMBs, or individuals performing ongoing safety evaluations during the study.

### 4.4.2 Fatal or Life-Threatening Serious Unexpected Adverse Reactions

It is the responsibility of the sponsor to report fatal or life-threatening SUSARs to the pertinent regulatory authorities as soon as possible, but no later than 7 calendar days (or earlier, if locally mandated). These will be reported to the DSMB in parallel.

### 4.4.3 Other Serious Unexpected Adverse Reactions

It is the responsibility of the sponsor to report other SUSARs to the pertinent regulatory authorities as soon as possible, but no later than 15 calendar days (or earlier if locally mandated). These will be reported to the DSMB in parallel.

## 4.5 Reporting to Institutional Review Board and Independent Ethics Committee

The IEC/IRB will be notified of any SUSARs according to local regulations and within the designated timeframe.

The investigator (or prospectively agreed to designee) is required to notify the IEC/IRB of any fatal SUSAR as soon as possible but no later than 7 calendar days after he/she first became aware of the reaction (or earlier if locally mandated).

The investigator (or prospectively agreed to designee) is required to notify the IEC/IRB of any other SUSAR as soon as possible but no later than 15 calendar days after he/she first became aware of the reaction (or earlier if locally mandated).

# 5 DATA MANAGEMENT AND STATISTICAL ANALYSIS

## 5.1 Data Management Considerations

An EDC system will be utilized in this study. The database will be designed, reviewed, and tested for user acceptance prior to the first study visit. Once data entry is completed at the site, WCT data management will review and check the data for completeness. Queries will be raised for inconsistencies found during the exhaustive process checking performed both electronically and by manual review. The statistical analysis of these data will be performed by the sponsor or its representative. All AEs will be coded using the latest version of the Medical Dictionary for Regulated Activities (MedDRA). Concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary. Data management activities, dates, and responsibilities will be outlined in the data management plan, which will be finalized prior to when the database goes live.

## 5.2 Statistical Considerations

The statistical analysis will be undertaken by WCT in collaboration with AgeneBio, Inc. Dr. Michael Rosenblum will conduct the primary analysis.

A detailed Statistical Analysis Plan (SAP) will be finalized and signed before the database lock, before the code for all subjects is broken, and before analysis of the study data are carried out. Any deviations from the analyses described below will be included in the SAP, which will be included in the clinical study report.

### 5.2.1 Analysis Populations

The **enrolled set** includes all subjects screened into the study who signed an Informed Consent Form (ICF) and who participated in screening activities, irrespective of whether they were randomized to treatment.

The **full analysis set** includes all randomized subjects. All analyses of efficacy will be performed on the full analysis set, and these analyses will be considered the primary analyses of efficacy. In analyses based on the full analysis set, subjects will be analyzed as randomized. The reason the focus is on the full analysis set is to follow the intention-to-treat (ITT) principle.

The **safety analysis set** includes all subjects who took at least one dose of the study drug following randomization. Safety will be analyzed using the safety analysis set. In analyses based upon the safety analysis set, subjects will be analyzed as treated.

The **per-protocol analysis set** includes a subset of the full analysis set consisting of subjects who satisfy all of the inclusion/exclusion criteria, who correctly receive the treatment to which they are randomized, and who have completed all the visits up to and including the week 78 visit. In addition, significant protocol deviations defined in

Section 5.2.2 will be removed from the per-protocol analysis set. Analyses of efficacy based on the per-protocol analysis set will be considered secondary analyses of efficacy. Prior to the database lock, subject evaluability will be reviewed by the sponsor and detailed in the signed analysis population document. All subjects excluded from the per-protocol population and the reason for their exclusion will be listed.

**Assessing the Impact of COVID-19 on trial results:**

We will assess the impact of the four factors listed below on the trial results, following the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency Guidance for Industry, Investigators, and Institutional Review Boards (FDA 2020):

1) Discontinuations due to COVID-19

2) Study visits missed due to COVID-19

Laboratory safety assessments that are unable to be done due to COVID-19 restrictions will not be required for the subject to continue in study due to the long safety record of marketed levetiracetam. The site PI should conduct a careful interview with the participant and study partner to determine whether there have been any adverse events or change in the participants clinical condition. If no AEs or clinical concerns are present the PI should then document that the subject has no clinical symptoms of concern. Safety labs should be obtained at the earliest time permitted by COVID-19 restrictions or be obtained at next routine site visit if not a part of that assessment.

3) Assessments that were conducted remotely rather than in person due to COVID-19

4) Visits that were performed out of window due to COVID-19

### 5.2.2 Protocol Deviations

All protocol deviations will be assessed and documented on a case-by-case basis prior to the database lock. The following deviations will be summarized for the full analysis set:

- Failure to meet the study entry criteria.
- Treatment administration errors including improper administration of the study drug not supported by randomization; deviations from permitted dosage and regimen with the study drug.
- Noncompliance with the study drug over the treatment period is defined as subjects who took < 80% or > 120% of the prescribed study drug, taking into account the number of days since the last study drug had been dispensed. The investigator may use clinical judgement in evaluating noncompliance with the study drug as a reason for early termination from the study. Subjects who discontinue treatment will not be automatically discontinued from the study.

Every effort should be made to bring subjects back for study visits unless the subject withdraws consent.

- Significant noncompliance with the timing of the study visits, outside of a visit window.
- Ingestion of prohibited medications after randomization.

In addition, the following types of protocol deviations due to COVID-19 will be assessed, documented, and summarized:

1) Discontinuations due to COVID-19

2) Study visits missed due to COVID-19

3) Assessments that were conducted remotely rather than in person due to COVID-19

4) Visits that were performed out of window due to COVID-19

### 5.2.3 Subject Disposition

Subject disposition will be summarized using the full analysis set. The number of subjects in each analysis population, the number of subjects present at each scheduled visit, and the reason for the early discontinuation will also be summarized by treatment group.

### 5.2.4 Demographic and Baseline Characteristics

The comparability of treatment groups with respect to subject demographics and baseline assessments will be summarized in a descriptive manner. Formal statistical testing will not be performed. The baseline data will be summarized using the full analysis set.

### 5.2.5 Measurement of Treatment Compliance

Study drug containers must be returned at each visit, as compliance will be assessed by tablet counts. Noncompliance is defined as taking < 80% or > 120% of the study drug during any outpatient evaluation period (visit to visit).

### 5.2.6 Efficacy Analyses

#### 5.2.6.1 Primary Efficacy Endpoint

The primary endpoint is defined as the difference between the CDR-SB score measured at baseline and the week 78 visit. This is referred to as the CDR-SB change score. Following the ITT principle, the data analyzed are from the full analysis set. The primary goal of the study is to estimate the **average treatment effect**, **defined as the difference between the population mean outcome of the primary endpoint under treatment and control**. The primary null hypothesis is that the average treatment effect is zero.

#### 5.2.6.2 Secondary Efficacy Endpoints

The two cognitive/functional secondary endpoints below will be tested using a fixed sequence procedure with Type I error controlled as described below.

- Secondary endpoints: cognitive/functional
    - Change in FAQ score from baseline to 78 weeks
    - Change in MMSE score from baseline to 78 weeks
- Secondary endpoints: neuronal injury
    - Change in EC thickness on MRI from baseline to 78 weeks
- Additional secondary efficacy endpoints:
    - Change in CDR global score from baseline to 78 weeks
    - Change in CDR memory box score from baseline to 78 weeks
    - Change in BPS-O task score from baseline to 78 weeks
    - Change in ISLT score from baseline to 78 weeks
    - Change in EC volume on MRI from baseline to 78 weeks
    - Change in hippocampal volume on MRI from baseline to 78 weeks
    - Change in [$^{18}$F]MK-6240 in the brain from baseline at week 78

An overall false-positive ($\alpha$) rate of 5% level for the key secondary efficacy endpoints will be maintained, in that no significance of key secondary endpoints will be claimed unless the primary statistical analysis is significant at the 5% level. In addition, the testing of the key secondary endpoints will be conducted in a hierarchical fashion, in that once a null hypothesis is not rejected, all subsequent key secondary hypothesis tests will be considered exploratory. The hierarchical ordering of the secondary endpoints will be specified in the SAP prior to study unblinding.

#### 5.2.6.3 Sensitivity Analysis to Missing Data and to Treatment Noncompliance

A sensitivity analysis will be performed on the missing data at random assumption, based on the repeated measures pattern mixture model approach of Section 4 of the National Research Council, 2010. Specifically, for each arm, a sensitivity parameter will be suggested that represents the difference between the mean primary endpoint for those who drop out and those who do not at a given analysis time, conditional on the variables observed prior to that analysis time. The analysis times and variables used in the primary analysis will be restricted. The average treatment effect and *p*-value will be estimated for each pair of sensitivity parameters in a fine grid. The result will show how much of a deviation from the missing at random assumption is required to change the result from significant to non-significant.

Also, analyses will be conducted to estimate the average effect of assignment to the treatment versus control arms under perfect compliance with the study protocol (including treatment compliance and attending all visits). The analysis method (targeted maximum likelihood estimation) is the same as for the principal analysis described above except that there will be an indicator for treatment compliance at each visit and participants will be censored at the first visit at which they are either lost to follow-up or they are noncompliant with the study protocol. This analysis requires stronger assumptions than the principal analysis, and these assumptions will be clearly stated along with the results of this analysis.

### 5.2.7 Safety Analyses

#### 5.2.7.1 Extent of Exposure

Extent of exposure will be described by the number of days of exposure (last date of dosing minus first day of dosing plus 1), and the number of days of exposure to each dose of the study drug (last date of dosing minus first date of dosing plus 1 summed over each period of time where the subject receives the same dose) will be summarized. No allowance will be made for breaks in therapy for the calculation of the total number of days of exposure. If the date of last dosing is completely missing, then the date of last dosing will be taken for analysis purposes as the date the relevant medication was last dispensed. If only the month of the last dose is recorded, the first day of the month will be assumed as the last dosing date.

#### 5.2.7.2 Adverse Events

AEs will be summarized by treatment group and by maximum dose, latest dose received prior to the onset of the AE, by visit and treatment period.

A TEAE is defined as any AE that has an onset on or after the first dose of study drug, or any pre-existing condition that has worsened on or after the first dose of study drug, regardless of the causal relationship to the study drug. TEAEs will be attributed to a treatment using the following rules:

All analyses of AEs will be performed by the study period, so that it is possible to identify AEs that may be related to withdrawal from study treatment. The summaries of AEs will be limited to TEAEs. For summaries of TEAEs, a TEAE will be assigned to a given period if the date of onset of the TEAE is on or after the date of the first visit during the period but before the date of the first visit of the next period.

If the relationship of the AE to study drug is missing, it will be assumed to be related to the study drug for analysis purposes.

The incidence of subjects reporting TEAEs, treatment-emergent SAEs, TEAEs related to study treatment, treatment-emergent SAEs related to study treatment, and TEAEs leading

to study discontinuation will be summarized using counts and percentages. The total number of TEAEs, treatment-emergent SAEs, TEAEs related to study treatment, treatment-emergent SAEs related to study treatment, and TEAEs leading to study discontinuation will also be summarized.

AEs will be coded using MedDRA. The incidence of TEAEs and treatment-emergent SAEs will be summarized at the subject level by MedDRA primary system organ class and preferred term using counts and percentages.

The incidence of TEAEs and treatment-related TEAEs will also be summarized by maximum severity and by closest relationship to study drug by MedDRA primary system organ class and preferred term. The summary will include the total number and percentage of subjects reporting a particular event. In counting the number of events reported, a continuous event, ie, an event reported more than once and which did not cease, will be counted only once; non-continuous TEAEs reported several times by the same subject will be counted as multiple events.

The incidence of TEAEs resulting in dose reduction will be summarized by the latest dose received and also by treatment group.

Withdrawal-related events will be tabulated separately.

Narratives of deaths, SAEs, and other significant AEs will be provided in the relevant section of the study report.

A complete subject listing of all AEs will be provided in the study report. This listing will include treatment, AE verbatim term, MedDRA primary system organ class and preferred term, the time of onset and cessation of the event relative to the first dose of study drug, duration of the AE, whether serious or not, severity, relationship to study drug, action taken, and outcome.

#### 5.2.7.3 Electrocardiographic Data

A list of subjects with abnormal 12-lead ECG parameters at screening will be presented. Baseline ECG parameters (heart rate, cardiac rhythm, PR interval, QRS interval, QT interval, and QT interval corrected for heart rate) will be summarized for the final visit/early termination visit time point. For exploratory purposes, analyses of QT, QT interval corrected for heart rate using Fridericia's formula, and QT interval corrected for heart rate using Bazett's formula will be completed using accepted definitions for outliers (eg, frequency counts of interval changes from baselines $\geq$ 30 msec and $\geq$ 60 msec) as well as analyses of central tendency of active drug versus placebo and active dose versus placebo.

#### 5.2.7.4 Laboratory Data

Mean changes from baseline at each post-baseline time point for each laboratory variable will be presented. In addition, each reading will be classified as below, within, or above the normal range, based on ranges supplied by the laboratory used. Shift tables for the baseline and follow-up measurements will be presented and clinically significant changes will be summarized.

Potentially clinically significant ranges will be defined in the SAP for selected parameters, and the number and percent of subjects meeting these criteria summarized. Tabular summaries will include only those subjects in whom the values represent a treatment-emergent worsening.

Listings of laboratory parameters will be presented. Listings will flag results above and below the normal range as well as those that meet criteria for being potentially clinically significant (whether or not a treatment-emergent worsening). Separate listings for each hematology, chemistry, and urinalysis parameter will show results that meet criteria for being potentially clinically significant. In addition, for subjects who have one or more results that meet criteria, all laboratory results will be displayed.

#### 5.2.7.5 Vital Signs

Summary statistics for the absolute vital sign value and the changes from baseline will be presented by treatment group for each visit.

The number and percentage of subjects reporting potentially clinically meaningful observations will be summarized:

- Systolic BP: supine $\leq$ 80 mmHg or $\geq$ 140 mmHg
- Diastolic BP: supine $\leq$ 40 mmHg or $\geq$ 90 mmHg
- Pulse rate: supine $\leq$ 50 bpm or $\geq$ 100 bpm
- Respiration rate: $<$ 8 or $>$ 20 breaths per minute

In addition, shift tables from baseline to each post-baseline visit in relation to the clinically meaningful ranges specified above will be presented for each of these vital sign parameters.

#### 5.2.7.6 Other Variables Related to Safety

Change from baseline in C-SSRS is another endpoint related to safety. Changes in C-SSRS during the course of the study indicating worsening should be evaluated by the investigator for clinical significance, and, if clinically significant (eg, alteration in medical care or intervention is required), an associated AE should be recorded, if present. The AE should be the primary underlying clinical manifestation assessed as clinically significant, and not the change in score itself.

Changes from baseline in physical and neurological examinations are additional endpoints related to safety that will also be evaluated by the investigator for clinical significance, and, if clinically significant (eg, alteration in medical care or intervention is required), an associated AE should be recorded.

### 5.3 Pharmacokinetic Analysis

A total of 3 samples will be collected for PK analysis at 26, 52, and 78 weeks. In addition, approximately 40 mL of blood will be collected for screening and month 18 visit clinical laboratory evaluations. The total volume of blood collected will not exceed 300 mL. Plasma levetiracetam concentrations will be reviewed to assess treatment compliance during the outpatient evaluation period, as described in Section 5.2.5.

# 6 STUDY MANAGEMENT

## 6.1 Ethics and Consent

### 6.1.1 Regulations and Guidelines

The study will be performed in accordance with this protocol, US IND 21 CFR 312 or local national laws (as applicable), ICH guidelines for Good Clinical Practice (GCP), and the most recent guidelines of the Declaration of Helsinki. These guidelines are on file at WCT.

### 6.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IRB or IEC. Approval is required for the study protocol, Investigator's Brochure, protocol amendments, ICFs, subject information sheets, and advertising materials. No study drug will be shipped to a site until the sponsor or its representative has received written IRB/IEC authorization.

### 6.1.3 Informed Consent

For each study subject, a written ICF will be obtained before any protocol-related activities. Within this ICF, subjects will provide consent to all study-related procedures and the optional tau PET scan. A separate study partner ICF will be obtained at all sites. As part of this procedure, the investigator or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study drug in such a manner that the subject and (if applicable) appointed guardian are aware of the potential risks, inconveniences, or AEs that may occur. Subjects should be informed that they may withdraw from the study at any time. They will receive all the information that is required by local regulations and ICH guidelines. The investigator or a designated representative will provide the sponsor or its representative with a copy of the IRB/IEC-approved ICF before the start of the study.

## 6.2 Indemnification

The sponsor's indemnification of the investigator and institution during the conduct of this study is addressed in a letter of indemnification provided as a separate document. Other indemnification or insurance will be provided as necessary under local regulations.

## 6.3 Discontinuation of the Study by the Sponsor

The sponsor reserves the right to discontinue the study at a site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the sponsor or its representative.

### 6.4 Study Documentation

By signing a copy of Food and Drug Administration (FDA) Form 1572 or other country-specific regulatory forms, the investigator acknowledges that he/she has received a copy of the Investigator's Brochure on AGB101 and assures the sponsor that he/she will comply with the protocol and the provisions stated in FDA Form 1572 and other country-specific forms. No changes in this protocol can be made without the sponsor's written approval.

### 6.5 Study Monitoring and Auditing

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to the protocol, standard operating procedures, guidelines of GCP, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. On-site review of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject. Note that a variety of original documents, data, and records will be considered as source documents in this study.

Medical advisors and clinical research associates or assistants may request to witness subject evaluations occurring as part of this protocol. The investigator and appropriate personnel will be periodically requested to attend meetings/workshops organized by the sponsor to assure acceptable protocol execution. The study may be subject to audit by the sponsor or by regulatory authorities. If such an audit occurs, the investigator must agree to allow access to required subject records. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

### 6.6 Data Safety and Monitoring Board

The DSMB will meet periodically to review all the safety study data (AEs and clinical labs) by group, with the groups identified only as group A and group B (ie, DSMB members will be blinded to the treatment assignment). The DSMB will not see any efficacy data. If, during the course of the data review, the DSMB observes a separation of the two groups on any safety measure that suggests a pattern of AEs, the DSMB can request information on group assignment from the sponsor. If there is a difference between groups on some important safety finding, the DSMB can request information on group assignment. If no such difference emerges between groups, the DSMB will remain blinded to the treatment assignment until the last subject visit. A description of the

DSMB composition, its charter, and methods of analyses and communication will be provided in a companion document.

### 6.7 Retention of Records

The investigator must arrange for retention of study records at the site. The nature of the records and the duration of the retention period (minimum 3 years) must meet the requirements of the relevant regulatory authority. In addition, because this is an international study, the retention period must meet the requirements of the most stringent authority. The investigator should take measures to prevent accidental or premature destruction of these documents.

### 6.8 Use of Study Findings

By signing the study protocol, the investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the sponsor or its representative.

### 6.9 Publications

As a multicenter study, the sponsor intends to publish clinical data from all centers participating in the investigation. A publication committee selected by the sponsor will submit draft manuscripts to all participating investigators for their comments. In conformity with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published by the International Committee of Medical Journal Editors (see discussion in Kassirer & Angell 1991), investigators whose contribution consists solely in the collection of data will not be named individually as authors. Rather, those investigators will receive a collective authorship as the "AGB101 Study Group" and will be identified in a note.

Individual investigators and/or their associates may subsequently publish additional findings of this study in scientific journals or present them at scientific meetings, provided that the sponsor is given ample opportunity to review any proposed abstract, manuscript, or slide presentation before its submission. This review is required to ensure that the sponsor is aware of all written and oral presentations of the data and does not imply any editorial review or restriction of the contents of the presentation or use.

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# 8 APPENDICES

## 8.1 Accepted and Excluded Medications

The list included below is not exhaustive, but rather it provides examples in each drug class. For drugs not included on this list, inquire with the medical monitor. The medical monitor may grant exceptions in the use of otherwise excluded medications for infrequent or as needed use, provided they do not confound the safety and efficacy assessments.

**1. Acceptable: dose must be stable for 3 months prior to screening and maintained throughout the study**

**Alzheimer's**

Aricept (donepezil)
Exelon (rivastigmine)
Namenda (memantine)
Namzaric (donepezil/memantine)
Razadyne (galantamine)
Vitamin E (4-week stable)
Ginkgo biloba (4-week stable)
Estrogen and estrogen-like drugs

**Antidepressants and anxiolytics (SSRIs, SNRIs, 5-HT1A inhibitors)**

Buspar (buspirone)
Celexa (citalopram hydrobromide)
Cymbalta (duloxetine)
Effexor (venlafaxine HCl)
Emsam (selegiline)
Fluvoxamine maleate
Lexapro (escitalopram hydrobromide)
Marplan (isocarboxazid)
Nefazodone HCl
Parnate (tranylcypromine sulfate)
Paxil (paroxetine HCl)
Pexeva (paroxetine mesylate)
Prozac (fluoxetine HCl)
Sarafem (fluoxetine HCl)
Wellbutrin, Zyban (bupropion HCl)
Zoloft (sertraline HCl)

**Non-sedating antihistamines**

Claritin (loratadine)
Zyrtec (cetirizine)
Allegra (fexofenadine)

**Antipsychotics (second-generation; limit to low doses)**

Abilify (aripiprazole)
Geodon (ziprasidone)
Risperdal (risperidone)
Zyprexa (olanzapine)

**Incontinence drugs (limit to low doses; avoid if possible)**

Detrol (tolterodinel)
Ditropan XL (oxybutynin)
Enablex (darifenacin)
Gelnique (oxybutynin)
Oxytro (oxybutynin)
Sanctura (atrospium)
Vesicare (solifenacin)

**2. May be acceptable: for short-term use (<1 week; not within 2 weeks of screening, baseline, or major clinic visits)**

**Antianxiety drugs (benzodiazepines)**

Ativan (lorazepam)
Dalmane (flurazepam)
Doral (quazepam)
Halcion (triazolam)
Klonopin (clonazepam)
Librium (chlordiazepoxide)
Restoril (temazepam)
Serax (oxazepam)
Valium (diazepam)
Versed (midazolam)
Xanax (alprazolam)

**Sleeping aids (sedative-hypnotics)**

Ambien, Ambien CR (zolpidem tartrate)
Belsomra (suvorexant)
Butisol sodium (butabarbital sodium)
Carbtrital (pentobarbital and carbromal)
Dalmane (flurazepam hydrochloride)
Doral (quazepam)
Edluar (zolpidem tartrate)
Halcion (triazolam)
Intermezzo (zolpidem)
Lunesta (eszopiclone)
Placidyl (ethchlorvynol)
Prosom (estazolam)
Restoril (temazepam)

Rozerem (ramelteon)
Seconal (secobarbital sodium)
Silenor (doxepin hydrochloride)
Sonata (zaleplon)
Zolpimist (zolpidem tartrate)

**Opioid analgesics**

Astramorph (morphine)
Avinza (morphine)
Exalgo (hydromorphone)
Dilaudid (hydromorphone)
Duragesic (fentanyl,
Norco (hydrocodone)
Opana (oxymorphone)
OxyContin (oxycodone)
Percocet (oxycodone)
Vicodin (hydrocodone)

**Motion Sickness / vertigo / nausea / intestinal motility / IBS (anticholinergics)**

Antivert (meclizine)
Bentyl (dicyclomine)
Bonine (meclizine)
Compazine (prochlorperazine)
Lomotil (diphenoxylate with atropine)
Tigan (trimethobenzamide)

**3. Excluded: not allowed within 3 months of screening or during the study**

**Antiepileptic drugs**

Banzel (rufinamide)
Depakote (valproic acid)
Diamox (acetazolamide)
Keppra (levetiracetam) – non-study medications
Lamictal (lamotrigine)
Lyrica (pregabalin)
Neurontin (gabapentin)
Potiga (ezogabine)
Tegretol (carbamazepine)
Topamax (topiramate)
Trileptal (oxcarbazepine)
Zonegran (zonisamide)

**Antidepressant (tricyclic antidepressants) and antipsychotic drugs**

Anafranil (clomipramine)
Asendin (amoxapine)
Aventyl (nortriptyline)

Elavil (amitriptyline)
Etrafon (perphenazine/amitriptyline)
Limbitrol (chlordiazepoxide/amitriptyline)
Ludiomil (maprotiline)
Pamelor (nortriptyline)
Nardil (phenelzine sulfate)
Norpramin (desipramine HCl)
Remeron (mirtazapine)
Seroquel (quetiapine)
Sinequan (doxepin)
Surmontil (trimipramine)
Symbyax (olanzapine/fluoxetine)
Tofranil (imipramine)
Tofranil-PM (imipramine pamoate)
Triavil (perphenazine/amitriptyline)
Vivactil (protriptyline)

**Parkinson's disease drugs (dopamine agonists)**

Apokyn (apomorphine)
Duopa (carbidopa/levodopa)
Mirapex (pramipexole)
Neupro (rotigotine)
Parcopa (carbidopa/levodopa)
Requip (ropinirole)
Rytary (carbidopa/levodopa)
Sinemet (carbidopa/levodopa)
Stalevo (carbidopa/levodopa/entacapone)

**Parkinson's disease drugs (anticholinergics)**

Artane (trihexyphenidyl)
Cogentin (benztropine)
Levsin (Hyoscyamine)
Symmetrel (amantadine)

**Antihistamines (first generation; used prn)**

Atarax (hydroxyzine)
Benadryl (diphenhydramine)
Chlor-Trimeton (chlorpheniramine)
Clistin (carbinoxamine)
Dimetane (brompheniramine)
Priactin (cyproheptadine)
Tavits (clemastine)
Sominex (diphenhydramine)
Vistaril (hydroxyzine)

**Antipsychotics (first generation)**
Etrafon (perphazine)
Haldol (haloperidol)
Loxitane (loxapine)
Mellaril (thioridazine)
Navane (thiotixene)
Prolixin (fluphenazine)
Thorazine (chlorpromazine)
Trilafon (perphenzaine)
Stelazine (trifluoperazine)

**Antipsychotics (second generation with anticholinergic effects or sedation)**
Clozaril (clozapine)
Seroquel (quetiapine)

**Antihypertensive with CNS side effects**
Catapres (clonidine)

CNS=central nervous system; IBS=irritable bowel syndrome; prn=as needed; SNRIs=serotonin-norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors.

## 8.2 Amyloid PET: Dosage, Administration, and PET Scan Acquisition Guidelines

*Neuroceq (florbetaben) Dosage and Administration*

- Recommended activity for florbetaben is 300 megabecquerels (MBq; 8.1 millicuries [mCi] ± 20%), maximum 30 µg mass dose, administered as a single intravenous bolus in a total volume of ≤ 10 mL through a short catheter (max ≤ 1.5 inches or less). Follow the injection with an intravenous flush of 0.9% sterile sodium chloride.
- Inspect the radiopharmaceutical dose solution prior to administration and do not use it if it contains particulate matter or is discolored.
- Use aseptic technique and radiation shielding to withdraw florbetaben solution.
- Assay the dose in a suitable dose calibrator prior to administration.
- Inject florbetaben through a short intravenous catheter (approximately ≤ 1.5 inches) to minimize the potential for adsorption of the drug to the catheter. Portions of the florbetaben dose may adhere to longer catheters.

*Neuroceq (florbetaben) PET Scan Acquisition Guidelines*

- A 20-minute PET image, acquired as 4, 5-minute frames, should be acquired starting 90 minutes after florbetaben intravenous injection. The subject should be

supine and the head positioned to center the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed. Image reconstruction should include attenuation correction with resulting trans-axial pixel sizes between 2 mm and 3 mm. Images are to be read according to florbetaben reading methodology.

*Amyvid (florbetapir) Dosage and Administration*

- The recommended dose for florbetapir is 370 MBq (10 mCi), maximum 50 μg mass dose, administered as a single intravenous bolus in a total volume of 10 mL or less.
- Follow the injection with an intravenous flush of 0.9% sterile sodium chloride.
- Inspect the radiopharmaceutical dose solution prior to administration and do not use it if it contains particulate matter or is discolored. Use aseptic technique and radiation shielding to withdraw florbetapir solution.
- Assay the dose in a suitable dose calibrator prior to administration.
- Inject florbetapir through a short intravenous catheter (approximately 1.5 inches or less) to minimize the potential for adsorption of the drug to the catheter. Portions of the florbetapir dose may adhere to longer catheters.

*Amyvid (florbetapir) PET Scan Acquisition Guidelines*

- A 10-minute PET image should be acquired starting 30 to 50 minutes after florbetapir intravenous injection. The subject should be supine and the head positioned to center the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed. Image reconstruction should include attenuation correction with resulting transaxial pixel sizes between 2 and 3 mm.
- Amyvid images should be interpreted only by readers who successfully complete a special training program. Training is provided by the manufacturer using either an in-person tutorial or an electronic process.
- The objective of florbetapir image interpretation is to provide an estimate of the brain β-amyloid neuritic plaque density, not to make a clinical diagnosis. Image interpretation is performed independently of a patient's clinical features and relies upon the recognition of unique image features.

*Vizamyl (flutemetamol) Dosage and Administration*

- The recommended dose for flutemetamol is 185 MBq (5 mCi) in a maximum dose volume of 10 mL, administered as a single intravenous bolus within 40

seconds. The maximum mass dose is 20 micrograms. Follow the injection with an intravenous flush of 5 to 15 mL of 0.9% sterile sodium chloride injection.

- Use aseptic technique and radiation shielding to withdraw and administer flutemetamol solution.
- Calculate the necessary volume to administer based on calibration time and dose using a suitably calibrated instrument.
- Visually inspect flutemetamol for particulate matter and discoloration prior to administration. Do not administer flutemetamol if it contains particulate matter or is discolored.
- Do not dilute flutemetamol.

*Vizamyl (flutemetamol) PET Scan Acquisition Guidelines*

- The recommended PET scan start time is 60 to 120 minutes after flutemetamol injection, using a PET scanner in 3-D mode with appropriate data corrections. A scan duration of 10 to 20 minutes is recommended. The time of initiation and the duration of the scan may vary depending on dose, imaging acquisition, and reconstruction parameters.
- Position the patient supine with the brain (including the cerebellum) within a single field of view. The patient's head should be tilted so that the anterior commissure-posterior commissure (AC-PC) plane is at right angles to the bore-axis of the PET scanner, with the head positioned in a suitable head support. Reducing head movement with tape or other flexible head restraints may be employed. Iterative or filtered back-projection reconstruction is recommended with a slice thickness of 2 to 4 mm, matrix size of 128 x 128 with pixel sizes of approximately 2 mm. Where a post-smoothing filter is applied, a full width half maximum (FWHM) of not more than 5 mm is recommended; filter FWHM should be chosen to optimize the signal-to-noise ratio while preserving the sharpness of the reconstructed image.
- Flutemetamol images should be interpreted only by readers who successfully complete the electronic or in-person training program provided by the manufacturer. The objective of flutemetamol image interpretation is to provide an estimate of the brain β-amyloid neuritic plaque density, not to make a clinical diagnosis. Image interpretation is performed independently of a subject's clinical features and relies upon recognition of image features in certain brain regions.
- Image interpretation is based upon the distribution of radioactive signal within the brain; clinical information is not a component of image assessment. Images are designated as positive or negative either by comparing radioactivity in cortical grey matter with activity in adjacent white matter, or based on the intensity in the

five regions mentioned above. Signal uptake in the cerebellum does not contribute to scan interpretation (for example, a positive scan may show retained cerebellar grey-white contrast even when the cortical grey-white contrast is lost). Images should be viewed with the minimum image intensity set to zero and the maximum set such that the signal level in the easily identifiable pons is at 90% of maximum.

- Negative scans show more radioactivity in white matter than in grey matter, creating clear grey-white matter contrast.

## 8.3 MRI Scanning Procedures

### 8.3.1 MRI Subject Pre-Scan Procedures

a. All subjects should be screened by the study coordinator for standard MRI contraindications during screening and immediately prior to each MRI session. Contraindications include, but are not limited to, non-removable ferrous metal objects, aneurysm clips, pacemakers, and any other implanted medical or other devices, such as defibrillators, etc.
b. Sedation will not be offered for the baseline MRI scan in this study. Subjects who experience significant claustrophobia or are otherwise uncomfortable with MRI scans should not participate in this study. When necessary to obtain a follow-up scan, sedation will be offered.
c. Universal MRI safety precautions and local standard practice for monitoring subjects during the scan should be followed. This may include devices to monitor pulse and oxygen levels.
d. Proper positioning of subjects into the scanner will be crucial for successful data acquisition, and each subject should be positioned in the same manner for each MRI scan.

Subject should remove all upper-body clothing with metallic trim, zippers, buttons, or embroideries that may cause artifacts. A stereotactic marker (either vitamin E or fish oil capsule) should be placed on the subject's right temple. Subjects should be provided with hearing protections and should be positioned without rotation in either plane. After positioning, the head should be immobilized using a Velcro strap across the forehead, or padding along the sides of the head, to reduce the possibility of motion. Align the center of the table by positioning cross-hairs on the subject's nasion at every scanning session. Ensure subjects are high enough in the coil to prevent signal loss at the inferior aspect of the brain. Subjects should be reminded frequently throughout the scanning session to hold as still as possible.

### 8.3.2 MRI Subject Scan Protocol

All image sequence protocols for each scanner vendor will be provided electronically and should be loaded by the MRI support engineer. Scans acquired using a different sequence

definition will not be accepted. All scans will be performed in the straight axial or sagittal plane. No manual adjustments should be made. The following scans will be performed in the following order:

a. Localizer scan
b. Calibration/reference scan (if applicable)
c. Accelerated sagittal MP-RAGE/IR-SPGR
d. Repeated accelerated sagittal MP-RAGE/IR-SPGR
e. FLAIR (baseline only)
f. T2 (baseline only)
g. Functional MRI scans (***optional procedure performed only at JHU***)

*a. Localizer scan*

A brief acquisition in 3 orthogonal planes for anatomical orientation. Multiple slices are acquired in the middle of each of the 3 planes. The head should be centered laterally along the inter-hemispheric fissure and centered on the thalamus for the anterior/posterior and superior/inferior planes. Sample images will be provided to ensure the subject is positioned correctly.

Scans are only acquired in straight orthogonal planes. The head should be positioned as straight as possible in all 3 views. Oblique scans are not permitted. If the subject is not positioned correctly, positioning should be adjusted and a localizer scan repeated.

*b. Calibration/Reference Scan*

The MRI scanner should provide automated adjustment procedures for calibration and RF coil tuning and frequency adjustments after a subject is positioned in the scanner bore. Standard procedures provided by the manufacturer should be followed.

*c. Accelerated Sagittal 3D MP-RAGE/IR-SPGR*

The 3D MP-RAGE sequence will be utilized on the Siemens and Philips vendor systems, and the IR-SPRGR sequence will be used on the GE vendor system.

The accelerated sagittal structural scan will be oriented as a straight sagittal scan with slice prescription from left to right. Acquisition should not be oblique to compensate for subject's head tilt. The full head and skull should be included in the acquisition. The skull must be fully included superiorly and laterally. The entire cerebellum should be included inferiorly. The nose should be included in the anterior/posterior plane to avoid image fold over. The accelerated sagittal structural scan will be repeated to complete 2 identical structural scans.

*d. FLAIR and T2*

FLAIR and T2 scans will be completed during the baseline MRI. Orientation should be planned as a straight axial scan with slice prescription from inferior to superior. Scans

should not be oblique to adjust for the head tilt. Scans should be positioned on the mid-sagittal slice from the tri-planar scout. The full brain must be covered. The slices should be placed to cover the cerebellum fully, as well as the full extent of the brain in the lateral and the anterior to posterior planes. If additional transverse slices are required to achieve full brain coverage, those slices should be added and acquired.

### 8.3.3 MRI Subject Scan Procedures

If a subject elects to discontinue the MRI procedure, every effort should be made to alleviate the source of discomfort and complete the MRI session. This includes making adjustments to the table, head coil, and padding. However, if the subject is still unable to complete the scan, then the MRI session should be terminated and recorded as incomplete with a description of the reasons for terminating the session.

## 8.4 PET Scanning Procedures for[$^{18}$F]MK-6240 (*Optional*)

*[$^{18}$F]MK-6240 Administration*: Participants will receive a single intravenous bolus injection of 185 MBq (5 mCi) ± 10% of not more than 10 mL total volume followed by a 10 mL normal saline (0.9% NaCl) flush.

*Scan Acquisition*: The following procedure will be used for obtaining the [$^{18}$F]MK-6240 PET imaging scans:

Subjects will receive the [$^{18}$F]MK-6240 injection and should make themselves as comfortable as possible and should be encouraged to void frequently, walk, eat, and drink in an uptake room. At 90 minutes (acceptable starting range 90 to 110 minutes) following the injection, participants will undergo a continuous 30-minute brain scan consisting of 6 × 300 sec frames to achieve a minimum of 10 minutes of artifact-free data.

## 8.5 Site Qualification

Each site must be qualified for MRI/PET acquisition by the imaging vendor. Phantom scans will be used for MRI/PET site qualification.

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