TITLE: A Phase 2a, Randomized, Double-Blinded, Placebo-Controlled, Crossover Study of the Efficacy of Levetiracetam to Treat Alzheimer's Disease-Associated Neural Network Hyperexcitability

PROTOCOL NO.: LEV-AD-001

INVESTIGATIONAL DRUG: Levetiracetam

DOSAGE FORM: Oral, capsules

INVESTIGATOR & SPONSORS:

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DATE OF VERSION: August 8, 2015

VERSION: 3

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PROTOCOL SIGNATURE SHEET

The undersigned has reviewed the format and content of this protocol and has approved Protocol No. LEV-AD-001 for issuance.

8/26/15
Date

Keith Vossel, M.D., M.Sc.
Investigator Sponsors
University of California, San Francisco (UCSF)
Memory and Aging Center
Gladstone Institute of Neurological Disease

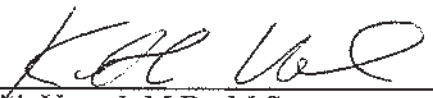
INVESTIGATOR SIGNATURE SHEET

I have read the attached protocol and agree that it contains all the necessary details for performing the study.

I will provide copies of the protocol and of the preclinical and clinical information on the study drug to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the study drug and the conduct of the study.

Once the protocol has been approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), I will not modify this protocol without obtaining the prior approval of the IRB/IEC, except when necessary to protect the safety, rights, or welfare of subjects. I will submit the protocol modifications and/or any informed consent form (ICF) modifications to the IRB/IEC, and approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (GCP) [current International Conference of Harmonisation (ICH) guidelines], and the Declaration of Helsinki (1964) including all amendments up to and including the 2008 revision.



8/26/15

Keith Vossel, M.D., M.Sc.
Investigator Sponsors UCSF
Memory and Aging Center,
Gladstone Institute of
Neurological Disease

Date

LIST OF ABBREVIATIONS

Aβ	Amyloid-beta
AD	Alzheimer's disease
AD-PCA	Alzheimer's disease - posterior cortical atrophy subgroup
ADAS-cog	Alzheimer's Disease Assessment Scale-cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale
ADCS-CGIC	Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change
AE	adverse event
AED	antiepileptic drug
aMCI	amnestic mild cognitive impairment
ANOVA	analysis of variance
b.i.d.	twice a day
CBC diff	complete blood count with differential
CCRC	Clinical Translational Science Institute – Clinical Research Center
CDR-SOB	Clinical Dementia Rating-Sum of Boxes
CFR	Code of Federal Regulations
CNS	central nervous system
CSF	cerebrospinal fluid
CTSI	Clinical Translational Science Institute
DLB	dementia with Lewy bodies
EXAMINER	Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research
FDA	Food and Drug Administration
FTLD	frontotemporal lobar degeneration
GCP	Good Clinical Practice
hAPP	human amyloid precursor protein
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
IEC	Independent Ethics Committee
IND	Investigational New Drug application
INR	International Normalized Ratio
IRB	Institutional Review Board
LEV	levetiracetam
MCI	mild cognitive impairment
MEG	magnetoencephalography
MEG-I	magnetoencephalographic imaging
M/EEG	magnetoencephalography with simultaneous electroencephalography
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NCRU	Neuroscience Clinical Research Unit
NIH	National Institutes of Health
NPI	neuropsychiatric inventory
PET	positron emission tomography
PHI	protected health information
PT	prothrombin time
PTT	partial thromboplastin time
SAE	serious adverse event
TSH	thyroid stimulating hormone
UCSF	University of California, San Francisco

PROTOCOL SYNOPSIS

Name of Sponsor:	Keith Vossel, M.D., M.Sc.
Name of Finished Product:	Levetiracetam oral capsule
Name of Active Ingredient:	Levetiracetam
Title of Study:	A Phase 2a, Randomized, Double-Blinded, Placebo-Controlled, Crossover Study of the Efficacy of Levetiracetam to Treat Alzheimer's Disease-Associated Neural Network Hyperexcitability
Protocol No.:	LEV-AD-001
Number of Study Centers:	Single-center (UCSF Memory and Aging Center, San Francisco, CA)
Phase of Development:	Phase 2a
Study Period:	36 months (first subject enrolled to last subject completed)
Summary of Modifications in Version 2	• Inclusion criteria: added patients with one or more unprovoked seizures or epileptiform activity within 5 years of enrollment. *Rationale:* to improve rate of enrollment. • Study period: lengthened from 24 to 27 months. *Rationale:* to allow more time to meet enrollment goal. • Exploratory measures: removed 5-hour word recall trial from ADAS-cog word recall task and 40-min recall from Virtual Route Learning Test and changed time of Virtual Route delayed recall from a 5 hours to 4 hours. *Rationale:* to shorten the visit time.

Summary of Modifications in Version 3	• Inclusion criteria: added patients without known seizures or epileptiform activity and increased enrollment age from "symptom onset < age 70" to "age ≤ 80 years at time of screening." *Rationale:* to improve rate of enrollment. AD subjects without clinical signs of neuronal hyperexcitability could have aberrant neuronal activity that is below the level of detection of surface EEG and M/EEG, and they could respond favorably to LEV. • Screening visit: modified to use a single consent form that covers entire study and referred inclusion criteria to date of screening. *Rationale:* to simplify consent process and to enable subjects to meet inclusion criteria at date of screening (all subjects enrolled to date have met these criteria). • Study period lengthened from 27 to 36 months. *Rationale:* to allow more time to meet enrollment goal. • Exploratory objectives: added the following subgroups for analysis of the effects of LEV: - AD subjects with seizures or epileptiform activity, - AD subjects without seizures or epileptiform activity, - Early-onset AD (symptom onset < 65 years of age), and - Late-onset AD (symptom onset ≥ 65 years of age). *Rationale:* to explore hypothesis that patients with clinical signs of neuronal hyperexcitability and with early-onset AD will be more likely to respond favorably to LEV. • Exploratory objectives: added 45-min word recall to the word recall task of the ADAS-cog, and MEG neural activity during cognitive stimulation. *Rationale:* to add a long-term measure of verbal memory and explore novel MEG protocols. • Study Design: added overnight video-EEG to the screening visit, added baseline M/EEG exam to study day 1, and removed requirement that epileptologists are blinded to diagnosis. *Rationale:* the combination of overnight EEG and 1-hour M/EEG is more sensitive to detect epileptiform activity than either measure alone. Blinding to diagnosis is not necessary because all subjects in the trial have AD. • Statistics: changed to one-tailed analysis to test whether LEV reduces epileptiform activity on M/EEG. *Rationale:* with new enrollment criteria, only a subgroup of subjects will have epileptiform activity on M/EEG, and we will be underpowered to perform a two-tailed analysis.

Objectives:	**Primary Objective** To determine the efficacy of levetiracetam (LEV) versus placebo to improve executive function evaluated using the Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research battery (NIH EXAMINER), in patients with Alzheimer's disease (AD). **Secondary Objectives** The secondary objectives are as follows: 1. To determine the efficacy of LEV versus placebo to suppress epileptiform activity in those who have epileptiform activity on their baseline M/EEGs. 2. To determine the efficacy of LEV versus placebo to improve cognitive function for the following tasks: a. Stroop interference naming (number correct), and b. Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). 3. To determine the effects of LEV versus placebo on degree of disability and behavior using the following measures: a. Clinical Dementia Rating-Sum of Boxes (CDR-SOB), b. Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL), c. ADCS-clinical global impression of change (ADCS-CGIC), and d. neuropsychiatric inventory (NPI). **Exploratory Objectives** The exploratory objectives are as follows: 1. To explore the effects of LEV versus placebo on learning and memory using a computerized Virtual Route Learning Test. 2. To explore the effects of LEV versus placebo on Stroop color naming correct, Stroop color naming errors (uncorrected and self-corrected), and Stroop interference naming errors (uncorrected and self-corrected), and subcomponents of the ADAS-cog (learning and memory, language, constructional praxis, ideational praxis, and orientation). 3. To explore the effects of LEV versus placebo on clinical fluctuations using two standardized scales (Walker et al. 2000). 4. To explore the effect of LEV versus placebo on MEG power spectrum measures during rest and neural activity during cognitive stimulation. 5. To explore the effect of LEV versus placebo on MEG functional connectivity measures in brain regions that correlate with performance on NIH EXAMINER (composite and each component), ADAS-cog (composite and each component), Stroop Test, Virtual Route Learning Test with 4-hour recall, Clinician Assessment of Fluctuation, One Day Fluctuation Assessment, CDR-SOB, ADCS-ADL, ADCS-CGIC, and NPI (composite and each component). 6. To explore the effect of LEV versus placebo on blood serum prolactin levels. 7. To explore the effects of LEV versus placebo on all primary, secondary, and exploratory measures listed above in the following subgroups of subjects: a. AD subjects with seizures or epileptiform activity, b. AD subjects without seizures or epileptiform activity, c. Early-onset AD (symptom onset < 65 years of age), d. Late-onset AD (symptom onset ≥ 65 years of age), e. AD-language (Gorno-Tempini et al. 2011), f. AD-PCA (Mendez et al. 2002), g. AD patients not classified as AD-language or AD-PCA, h. Very mild AD (MMSE of 24 and above), i. Mild to moderate AD (MMSE of 18 to 23), j. Subjects taking memantine, k. Subjects not taking memantine, g. Carriers the apolipoprotein E4 allele, and h. Noncarriers the apolipoprotein E4 allele

Methodology:	**Overall study design** This is a phase 2a, single-center, randomized, double-blinded, placebo-controlled, crossover study of the efficacy of LEV in patients with AD. We will enroll 36 subjects. Each subject will undergo a screening assessment, including a neuropsychological battery, caregiver interview, an overnight video-EEG including hyperventilation, a 1-hr magnetoencephalography with simultaneous EEG (M/EEG) including hyperventilation, and blood test. For patients with known seizures or subclinical epileptiform activity, the screening video-EEG and M/EEG will be optional. Cerebrospinal fluid (CSF) will be obtained to assess beta-amyloid (Aβ) peptide and tau protein levels in subjects in whom positron emission tomography (PET) amyloid imaging is not already completed or scheduled. Subjects who are consented to enroll in the treatment trial will be randomized into two groups and treated in a double-blinded design. One group will receive low-dose LEV treatment (125 mg b.i.d.) for 4 weeks, followed by washout for 4 weeks, and then placebo treatment (b.i.d) for 4 weeks, while the other group will receive these treatments in reverse sequence. At weeks 0, 4, 8, and 12, participants will undergo a 1-hr M/EEG including hyperventilation, a neuropsychological battery and caregiver interview, and serum LEV and prolactin levels.
Number of Subjects (planned):	36 subjects

Diagnosis and Main Criteria for Inclusion and Exclusion:	**Inclusion Criteria:** Subjects must meet all of the following inclusion criteria to be enrolled in this trial: 1. Ability to obtain written informed consent from the patient or caregiver as a surrogate; 2. Meets National Institute on Aging-Alzheimer's Association Workgroups criteria for probable AD dementia (McKhann et al. 2011); 3. Age ≤ 80 years at time of screening; 4. Willing and able caregiver who has daily contact with the subject; 5. Mini-Mental State Examination (MMSE) score ≥ 18 and/or Clinical Dementia Rating (CDR) < 2 at the initial screening assessment; 6. Subjects and caregivers must be able to comply with prescribed regimen of study treatment throughout the course of the study, and meet the required time commitment of four days of in-person visits; 7. Any concurrent treatment for AD approved by the Food and Drug Administration (FDA), such as donepezil, galantamine, or rivastigmine, and memantine, must be stable for at least 30 days prior to screening and at least 60 days prior to study day 1. Other medications (except those listed under exclusion criteria) are allowed as long as the dose is stable for 30 days prior to screening. **Exclusion Criteria:** Subjects meeting any of the following exclusion criteria will be excluded from the trial: 1. Any conditions that could account for cognitive deficits in addition to AD, including but not limited to Vitamin B12 or folate deficiency, abnormal thyroid function, posttraumatic conditions, syphilis, multiple sclerosis or another neuroinflammatory disorder, Parkinson's disease, vascular or multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, central nervous system (CNS) tumor, progressive supranuclear palsy, subdural hematoma, etc.; 2. Previous history of a seizure disorder, excepting cases where the first seizure or detection of epileptiform activity was within 5 years of screening and the patient is not prescribed an anticonvulsant; 3. Significant systemic medical illnesses; 4. Use of medications likely to affect CNS functions (e.g., benzodiazepines, narcotics) 5. Severe renal dysfunction with creatinine clearance < 30 mL/min, which would affect serum LEV levels; 6. Any other medical condition which is determined by the investigators to potentially create an undue risk for an adverse effect (AE); 7. Prior biomarker evidence unsupportive of a diagnosis of AD; 8. Participation in another AD clinical trial within 3 months of screening, or any AD clinical trial, such as a vaccine, that has potential long-term effects; 9. Treatment with another study drug or investigational drug within 30 days of screening; 10. Pregnant or lactating.

Test Product, Dose, and Mode of Administration:	**Active Pharmaceutical Ingredient** The study drug is levetiracetam (LEV). LEV is an antiepileptic drug (AED) belonging to the 'racetam' class of drugs that share a pyrrolidone nucleus. The chemical name of levetiracetam, is (-)-(S)-a-ethyl-2-oxo-1-pyrrolidine acetamide. LEV has a molecular weight of 170.21 and a molecular formula of $C_8H_{14}N_2O_2$. **Drug Products** The dosage form of the study drug product is an oral capsule. The inactive ingredients for both the active drug and the placebo are corn starch, croscarmellose sodium, hypromellose, magnesium stearate, polyethylene glycol, povidone, and titanium dioxide. A single dosage (125 mg) of LEV will be used for this trial. **Dose and Mode of Administration** All doses of study drug, placebo or active, will be administered by the subject or caregiver. Subjects will be instructed not to drive or operate machinery or do other dangerous activities for at least two doses when starting a 4-week treatment period, or until they know how the drug affects them. They will be provided a list of the most common side effects of LEV in the consent form and also in the package insert.
Duration of Treatment:	The total duration of the trial is 12 weeks. One group will receive low-dose LEV treatment (125 mg b.i.d.) for 4 weeks, followed by washout for 4 weeks, and then placebo treatment (b.i.d) for 4 weeks, while the other group will receive these treatments in reverse sequence.

Criteria for Evaluation:	**Primary Endpoints** The efficacy of LEV to improve executive function (NIH EXAMINER) in patients with AD is the primary endpoint for this trial. **Secondary Endpoint** The efficacy of LEV to suppress epileptiform activity (M/EEG), to improve cognitive function (Stroop interference naming and ADAS-cog), and to improve the degree of disability (CDR-SOB, ADCS-ADL, and ADCS-CGIC) and behavior (NPI) in patients with AD are the secondary endpoints for this trial. **Exploratory Endpoints** We have the following exploratory endpoints for patients with AD: 1. Effects of LEV on learning and memory using a computerized Virtual Route Learning Test. 2. Effects of LEV on Stroop color naming correct, Stroop color naming errors (uncorrected and self-corrected), and Stroop interference naming errors (uncorrected and self-corrected), and subcomponents of the ADAS-cog (learning and memory, language, constructional praxis, ideational praxis, and orientation). 3. Effect of LEV on clinical fluctuations using two standardized scales (Walker et al. 2000). 4. Effect of LEV on MEG power spectrum (delta, theta, alpha, beta and gamma activity) measures during rest and neural activity during cognitive stimulation. 5. Effect of LEV on MEG functional connectivity measures in brain regions that correlate with performance on NIH EXAMINER (composite and each component), ADAS-cog (composite and each component), Stroop Test, Virtual Route Learning Test with 4-hour recall, Clinician Assessment of Fluctuation, One Day Fluctuation Assessment, CDR-SOB, ADCS-ADL, ADCS-CGIC, and NPI (composite and each component). 6. Effect of LEV on serum prolactin levels. 7. Effects of LEV on all primary, secondary, and exploratory endpoints listed above in the following subgroups: a. AD subjects with seizures or epileptiform activity, b. AD subjects without seizures or epileptiform activity, c. Early-onset AD (symptom onset < 65 years of age), d. Late-onset AD (symptom onset ≥ 65 years of age), e. AD-language (Gorno-Tempini et al. 2011), f. AD-PCA (Mendez et al. 2002), g. AD patients not classified as AD-language or AD-PCA, h. Very mild AD (MMSE of 24 and above), i. Mild to moderate AD (MMSE of 18 to 23), j. Subjects taking memantine, i. Subjects not taking memantine, j. Carriers the apolipoprotein E4 allele, and k. Noncarriers of the apolipoprotein E4 allele
Safety Analysis	All adverse events will be tabulated by system organ class, preferred term, and treatment. Any significant findings related to patient safety, including but not limited to lab results, M/EEG results, and neuropsychological testing data, will be recorded. Throughout the course of the study team will meet weekly to review recently collected data.

Statistical Methods:	**Efficacy** Data from all subjects who complete at least the first 4 weeks of the study drug (placebo or active) will be included in the efficacy analysis. Subjects whose biomarkers (CSF or amyloid PET) are found to be unsupportive of AD after they enroll in the trial will be excluded from the efficacy analysis. Subjects who decline to have CSF or amyloid-PET imaging will not be excluded from the efficacy analysis. Cognitive, behavioral and functional measures, as well as M/EEG epileptiform activity, power spectral density for different frequency bands, and MEG-I functional connectivity at study days 1, 29, 57, and 85 will be recorded and summarized. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Each treatment effect will be tested for the assumption of normality. If the data are not normally distributed, we will investigate transforming data so they are normally distributed or nonparametric options. If we choose parametric tests, significance testing will be performed using analysis of variance (ANOVA) for repeated measures with drug treatment (LEV or placebo) as the independent variable. Prior to this analysis, ANOVA will be used to analyze the effect of drug-placebo sequence and to compare group demographics and severity of dementia at baseline (MMSE and CDR-SOB); if any of these factors confound the relationship between the study drug and the outcome measure, then they will be included as covariates in the ANOVA model. If factors arise that limit the appropriateness of the repeated-measures ANOVA model, such as a large dropout rate or varying data collection time points causing imbalance of longitudinal data, we will substitute a linear mixed effects regression model to better fit the longitudinal data without the intrinsic constraints of the repeated-measures ANOVA framework (Fitzmaurice et al. 2004, Finucane et al. 2007). If a drug carryover effect is observed on an outcome measure between weeks 4 and 8, then we will analyze the initial 4 weeks of the study separately for this outcome measure. Analyses will be two-tailed except for analysis of epileptiform activity, which will be one-tailed based on our expectation that LEV will reduce epileptiform activity (Sanchez et al. 2012, Mintz et al. 2009). For all analyses, the null hypotheses will be rejected at $p < 0.05$. For the exploratory whole-brain MEG-I functional connectivity analyses, corrections for multiple comparisons will be performed using a cluster correction with a cutoff level of 20 voxels, and p values thresholded to 0.01.If no significant voxels are found at this threshold, we will use a less stringent threshold of $p < 0.05$. A hierarchical validation analysis will be used to account for multiple cognitive, behavioral, and functional tests.

STUDY PROTOCOL

1. BACKGROUND

1.1 Seizures and Epileptiform Activity in Alzheimer's Disease

Alzheimer's disease (AD) is the leading cause of neurodegenerative dementia worldwide. Early symptoms of AD include short-term memory loss, word-finding difficulties, and visuospatial dysfunction. In addition to cognitive decline, AD carries an increased risk of seizures. An estimated 10–22% of patients with AD develop unprovoked seizures, with much higher rates in familial and early-onset cases (Mendez and Lim 2003; Palop and Mucke 2009). These estimates are based primarily on convulsive seizures that occur in the later stages of AD. Recent evidence from our center suggests that epileptic activity is much more common and occurs even in the early stages of AD, escaping detection because it is nonconvulsive or subclinical in nature (Vossel et al. 2013). In a prospective study utilizing prolonged electroencephalography (EEG) and magnetoencephalography (MEG) monitoring, we have observed subclinical epileptiform activity in about 40% of the patients with mild, early-onset AD (symptom onset < age 65). Patients with AD and epileptiform activity appeared to have a faster decline in global cognitive function and executive function than those without epileptiform activity (unpublished data). Others have also reported that patients with AD and seizure disorders have greater cognitive impairment (McAreavey et al. 1992), faster progression of symptoms (Volicer et al. 1995) and more severe neuronal loss at autopsy (Förstl et al. 1992) than those without seizures.

Transgenic mouse models that overexpress mutant human amyloid precursor protein (hAPP) (e.g., J20-hAPP mice) have pathologically elevated levels of amyloid-β (Aβ) peptides in brain and simulate key aspects of AD, including cognitive and synaptic deficits. hAPP mice have silent epileptic activity characterized by nonconvulsive seizures and interictal epileptiform discharges (Palop et al. 2007). Interventions that suppress epileptic activity in hAPP mice also prevent cognitive deficits, suggesting aberrant network activity as a potentially reversible cause of cognitive dysfunction in AD (Sanchez et al. 2012). The strong association between cognitive dysfunction in AD and network hyperexcitability raises a new opportunity for therapeutic approaches to AD.

1.2 Levetiracetam

Levetiracetam (LEV) is an FDA-approved AED indicated as adjunctive therapy in the treatment of partial-onset seizures, myoclonic seizures, and primary generalized tonic-clonic seizures. In a double-blind trial, LEV was also shown to be effective as a first-line monotherapy for partial-onset seizures (Brodie et al. 2007), and LEV is commonly used as monotherapy in clinical practice. While many mechanisms of action for LEV have been proposed, its most unique mechanism is modulation of synaptic neurotransmitter release through binding to the synaptic vesicle protein SV2A in the brain (Lynch et al. 2004).

LEV Pharmacology: As reviewed by Abou-Khalil 2008, LEV has an excellent clinical profile with low side effects, no drug interactions, and broad efficacy for epilepsy subtypes. LEV is well

absorbed after oral intake, and food does not reduce its bioavailability (Patsalos 2003). LEV is predominantly excreted unchanged through the kidneys, and about 27% is metabolized into an inactive product (Radtke 2001). LEV has an immediate onset and an elimination half-life of 6-8 hours. No dose adjustment is needed when the creatinine clearance is above 30 mL/min. With little protein binding (< 10%) and no dependence on the liver cytochrome P450 enzyme for metabolism, LEV has no clinically relevant pharmacokinetic interactions (Nicolas et al 1999). The low dosage of LEV used in this trial will not require gradual titration or weaning.

Side effects are minimal for LEV compared to most other AEDs. The following side effects have been experienced by adult patients with seizure disorders in clinical trials of LEV, as outlined the Micromedex database:

1. Common Side Effects
    a. Dermatologic: Erythema multiforme
    b. Gastrointestinal: Diarrhea, nausea, loss of appetite, pancreatitis
    c. Hematologic: Decreased erythrocyte production, decreased white blood cell count, neutropenia, platelet dysfunction due to drugs
    d. Immunologic: Acquiring an infectious disease, influenza
    e. Neurologic: Asthenia, somnolence, insomnia, tremor, vertigo, coordination problem, ataxia, amnesia, confusion, parasthesia, dizziness, headache
    f. Ophthalmic: Blurred vision
    g. Psychiatric: Abnormal Behavior (such as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, mood swings, hostility, irritability, nervousness), hallucinations, psychotic disorders
    h. Respiratory: Rhinitis, cough, nasal congestion, nasopharyngitis, pharyngitis, sinusitis
    i. Other: Fatigue, pain, decreased bone mineral density

2. Rare but Serious Side Effects
    a. Dermatologic: Stevens-Johnson syndrome, toxic epidermal necrolysis due to drug
    b. Hematologic: Pancytopenia, thrombocytopenia
    c. Hepatic: Liver failure
    d. Psychiatric: Suicidal thoughts or intent, suicide

Rationale: In preclinical investigations, we screened numerous FDA-approved AEDs in J20-hAPP mice (AD mouse model). LEV emerged as the only AED that effectively blocked epileptiform activity. LEV also improved hAPP/Aβ-induced network, synaptic, cognitive and behavioral dysfunction (Sanchez et al. 2012). Therapeutic blood levels of LEV in the mice were 4 μg/ml, the exact levels that were achieved with low dosing of LEV (125 mg b.i.d) in a clinical trial for people with amnestic mild cognitive impairment (aMCI) (Bakker et al. 2012). LEV suppressed task-based hippocampal hyperactivity and modestly improved performance in a hippocampus-dependent pattern separation task in these aMCI patients, but did not improve other neuropsychological measures (Bakker et al. 2012) Whether task-based hippocampal hyperactivity and resting-state epileptic activity are related phenomena in AD patients, is unknown. Levetiracetam is well tolerated and effective as a monotherapy at suppressing seizures in patients with Alzheimer's disease and seizure disorders, often at low doses (Cumbo and Ligori

2010, Vossel et al. 2013). No cognitive side effects were noted in AD patients with seizures taking LEV (Cumbo and Ligori 2010). Based on the above evidence, we have a strong indication to evaluate the efficacy of LEV improve cognitive function in AD. We will explore whether AD subjects with seizures or epileptiform activity, and whether AD subjects with early-onset disease who have a higher risk for epilepsy, respond better to LEV than AD subjects without these biomarkers of neuronal hyperexcitability. AD subjects without these clinical signs of neuronal hyperexcitability are also included in this study because they could have aberrant neuronal activity that is below the level of detection of surface EEG and M/EEG, and they could also respond favorably to LEV.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this trial is to determine the efficacy of levetiracetam (LEV) versus placebo to improve executive function (NIH EXAMINER) in patients with Alzheimer's disease (AD).

2.2 Secondary Objectives

The secondary objectives of this trial are as follows:

1. To determine the efficacy of LEV versus placebo to suppress epileptiform activity in those who have epileptiform activity on their baseline M/EEGs.

2. To determine the efficacy of LEV versus placebo to improve cognitive function for the following tasks:
   a. Stroop interference naming (number correct), and
   b. Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog).

3. To determine the effects of LEV versus placebo on degree of disability and behavior using the following measures:
   a. Clinical Dementia Rating-Sum of Boxes (CDR-SOB),
   b. Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL),
   c. ADCS-clinical global impression of change (ADCS-CGIC), and
   d. neuropsychiatric inventory (NPI).

2.3 Exploratory Objectives

The exploratory objectives of this trial for patients with AD and seizures or epileptiform activity are as follows:

1. To explore the effects of LEV versus placebo on learning and memory using a computerized Virtual Route Learning Test.

2. To explore the effects of LEV versus placebo on the following outcomes measures:
   a. Stroop color naming correct,
   b. Stroop color naming errors (uncorrected and self-corrected),
   c. Stroop interference naming errors (uncorrected and self-corrected), and
   d. subcomponents of the ADAS-cog (learning and memory, language, constructional praxis, ideational praxis, and orientation).

3. To explore the effects of LEV versus placebo on clinical fluctuations using two standardized

scales (Walker et al. 2000):
   a. Clinician Assessment of Fluctuation, and
   b. One Day Fluctuation Assessment.

4. To explore the effect of LEV versus placebo on the following MEG power spectrum measures during rest and neural activity during cognitive stimulation:
   a. Delta band activity
   b. Theta band activity
   c. Alpha band activity
   d. Beta band activity
   e. Gamma band activity

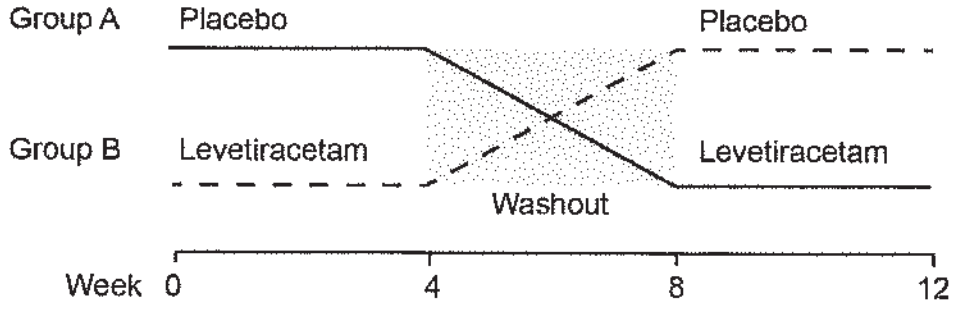
5. To explore the effect of LEV versus placebo on the following magnetoencephalographic-imaging (MEG-I) functional connectivity measures in brain regions that correlate with performance on the following tasks:
   a. NIH EXAMINER composite score
   b. NIH EXAMINER – antisaccade
   c. NIH EXAMINER – set shifting
   d. NIH EXAMINER – flanker task
   e. NIH EXAMINER – dot counting
   f. NIH EXAMINER – spatial 1-back
   g. NIH EXAMINER – category fluency
   h. NIH EXAMINER – letter fluency
   i. ADAS-cog composite score
   j. ADAS-cog learning and memory
   k. ADAS-cog language
   l. ADAS-cog constructional praxis (visuospatial measure)
   m. ADAS-cog ideational praxis
   n. ADAS-cog orientation
   o. ADAS-cog 45-min word recall
   p. Stroop color naming correct
   q. Stroop color naming errors (uncorrected and self-corrected)
   r. Stroop interference naming correct
   s. Stroop interference naming errors (uncorrected and self-corrected)
   t. Virtual Route Learning Test
   u. Virtual Route 4-hour recall
   v. Clinician Assessment of Fluctuation
   w. One Day Fluctuation Assessment
   x. CDR-SOB
   y. ADCS-ADL
   z. ADCS-CGI
   aa. NPI

6. To explore the effect of LEV versus placebo on serum prolactin levels.

7. To explore the effects of LEV versus placebo on all primary, secondary, and exploratory measures listed above in the following subgroups:
    a. AD subjects with clinical signs of neuronal hyperexcitability including one or more of the following:
        a. One or more unprovoked seizures within 5 years of screening,
        b. Epileptiform activity within 5 years of screening,
        c. Epileptiform activity on their initial overnight EEG or M/EEG, or
        d. Epileptiform activity on either of their baseline M/EEGs (study days 1 and 57)
    b. AD subjects without clinical signs of neuronal hyperexcitability listed in (a)
    c. Early-onset AD (symptom onset < 65 years of age)
    d. Late-onset AD (symptom onset ≥ 65 years of age)
    e. AD with predominant language impairment (AD-language) (Gorno-Tempini et al. 2011)
    f. AD with predominant posterior cortical atrophy (AD-PCA) (Mendez et al. 2002)
    g. AD patients not classified as AD-language or AD-PCA
    h. Very mild AD (MMSE of 24 and above)
    i. Mild to moderate AD (MMSE of 18 to 23)
    j. Subjects taking memantine
    k. Subjects not taking memantine
    l. Carriers the apolipoprotein E4 allele (obtained through umbrella projects)
    m. Noncarriers the apolipoprotein E4 allele.

3. STUDY DESIGN

This is a phase 2a, single-center, randomized, double-blinded, placebo-controlled, crossover study of the efficacy of LEV in patients with AD. We will enroll 36 subjects. Each subject will undergo a screening assessment, including a neuropsychological battery, caregiver interview, an overnight video-EEG including hyperventilation, a 1-hr magnetoencephalography with simultaneous EEG (M/EEG) including hyperventilation, and blood test. For patients with known seizures or subclinical epileptiform activity, the video-EEG and M/EEG will be optional. Cerebrospinal fluid (CSF) will be obtained to assess beta-amyloid (Aβ) peptide and tau protein levels in subjects in whom positron emission tomography (PET) amyloid imaging is not already completed or scheduled. Subjects who are consented to enroll in the treatment trial will be randomized into two groups and treated in a double-blinded design. One group will receive low-dose LEV treatment (125 mg b.i.d.) for 4 weeks, followed by washout for 4 weeks, and then placebo treatment (b.i.d) for 4 weeks, while the other group will receive these treatments in reverse sequence. At weeks 0, 4, 8, and 12, participants will undergo a 1-hr M/EEG including hyperventilation, a neuropsychological battery and caregiver interview, and serum LEV and prolactin levels.



4. ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

A subject may be included in this study if he or she meets **all** of the following criteria:

1. Ability to obtain written informed consent from the patient or caregiver as a surrogate;

2. Meets National Institute on Aging-Alzheimer's Association Workgroups criteria for probable AD dementia (McKhann et al. 2011);

3. Age $\leq$ 80 years at time of screening;

4. Willing and able caregiver who has daily contact with the subject;

5. Mini-Mental State Examination (MMSE) score $\geq$ 18 and/or Clinical Dementia Rating (CDR) < 2 at the initial screening assessment;

6. Subjects and caregivers must be able to comply with prescribed regimen of study treatment throughout the course of the study, and meet the required time commitment of four days of in-person visits;

7. Any concurrent FDA-approved treatment for AD (such as donepezil, galantamine, or rivastigmine, and memantine) must be stable for at least 30 days prior to screening and at least 60 days prior to study day 1. Other medications (except those listed under exclusion criteria) are allowed as long as the dose is stable for 30 days prior to screening.

4.2 Exclusion Criteria

A subject will be excluded from this study if he or she meets **any** of the following criteria:

1. Any conditions that could account for cognitive deficits in addition to AD, including but not limited to Vitamin B12 or folate deficiency, abnormal thyroid function, posttraumatic conditions, syphilis, multiple sclerosis or another neuroinflammatory disorder, Parkinson's disease, vascular or multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, CNS tumor, progressive supranuclear palsy, subdural hematoma, etc.;

2. Previous history of a seizure disorder, excepting cases where the first seizure or detection of epileptiform activity was within 5 years of screening and the patient is not prescribed an anticonvulsant;

3. Significant systemic medical illnesses;

4. Use of medications likely to affect CNS functions (e.g. benzodiazepines, narcotics);

5. Severe renal dysfunction with creatinine clearance < 30 ml/min, which would affect serum LEV levels;

6. Any other medical condition which is determined by the investigators to potentially create an undue risk for an adverse effect;

7. Prior biomarker evidence unsupportive of a diagnosis of AD;

8. Participation in another AD clinical trial within 3 months of screening, or any AD clinical trial, such as a vaccine, that has potential long-term effects;

9. Treatment with another study drug or investigational drug within 30 days of screening;

10. Pregnant or lactating.

4.3 Withdrawal of Subjects

A subject may choose to withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled.

A subject will be withdrawn from this study if one or more of the following events occur:

1. Subject requests to be withdrawn from study;

2. AE that in the judgment of the Investigator poses unacceptable risk to the subject;

3. Intercurrent illness, including seizure, that requires treatment that is not consistent with the protocol requirements, or intercurrent illness or the associated treatment that in the judgment of the Investigator poses a significant risk to the subject for continued participation in the study;

4. Pregnant or suspected of being pregnant;

5. Use of prohibited medication (listed in Section 5.7) that in the judgment of the Investigator will interfere with the interpretation of the results of this study;

6. Significant protocol violation or noncompliance on the part of the subject or the Investigator;

7. Investigator terminates the study;

8. Any other reason that in the judgment of Investigator poses unacceptable risk to the subject.

If a subject is withdrawn from the study, the date and reason will be recorded in the source documents, and final study visit evaluations will be performed if feasible. Any subject withdrawn due to a suspected study drug-related adverse event (AE) would be followed until resolution or

stabilization of the event.

If subject becomes pregnant or is suspected of being pregnant, study drug will be discontinued immediately, and the subject will be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. The subject will be followed until delivery or other termination of pregnancy for outcome.

Subjects may choose to withdraw authorization to use and disclose their Protected Health Information (PHI) as defined by the Health Insurance Portability and Accountability Act (HIPAA) of 1996 or foreign equivalent where appropriate. Such withdrawal of authorization must be made to the Investigator in writing. Any PHI collected by the Investigator prior to the date of such withdrawal will continue to be used and disclosed.

4.4 Replacement of Subjects

Subjects who are withdrawn from the study for reasons other than suspected study drug-related AEs may be replaced at the Investigator's discretion.

4.5 Termination of Trial

The Investigator has the right to terminate this study at any time, and will notify the IRB/IEC of premature termination in writing.

Events that may trigger premature termination of the study include, but are not limited to non-compliance with the protocol, slow recruitment, or change in development plans for the study drug.

5. STUDY DRUG

5.1 Description of Study Drug

5.1.1 Active Pharmaceutical Ingredient

The study drug is levetiracetam (LEV). LEV is an antiepileptic drug belonging to the 'racetam' class of drugs that share a pyrrolidone nucleus. The chemical name of levetiracetam, is (-)-(S)-a-ethyl-2-oxo-1-pyrrolidine acetamide. LEV has a molecular weight of 170.21 and a molecular formula of $C_8H_{14}N_2O_2$.

5.1.2 Drug Product

The dosage form of the study drug product is an oral capsule. The inactive ingredients for both the active drug and the placebo are corn starch, croscarmellose sodium, hypromellose, magnesium stearate, polyethylene glycol, povidone, and titanium dioxide. A single dosage (125 mg) of LEV will be used for this trial.

5.1.3 Packaging and Labeling

Teva will supply the study drug for this trial. The Investigational Site pharmacists will not be blinded to the study drug. The study drug (active or placebo) will be packaged into 4-week supply blister packs that indicate twice-a-day dosing. The blister packs will look equivalent between active drug and placebo. Each 4-week supply will be labeled to indicate the participant and the phase of the cross-over study for which they are designated.

5.1.4 Storage and Handling

At the Investigational Site, the investigational study drug will be stored in a locked, secure area to prevent unauthorized access. The study drug will be stored in the provided packaging out of direct sunlight and at controlled room temperature (65 to 77°F; 18 to 25°C).

5.2 Randomization

This is a randomized, double-blinded, placebo-controlled crossover study. Subjects will be assigned to a treatment sequence (Group A or B) according to a randomization process. Only subjects that meet all eligibility criteria at the initial screening will be randomized to treatment. Randomization will take place on Day 1 after completion of screening.

A computer-generated randomization schedule will be used for assigning the sequence in which subjects are assigned to treatment sequence (Group A or B). Randomization will be performed four participants at a time to ensure relatively equal distributions of participants into the two groups at all phases of the trial and in case the trial is terminated prior to reaching goal enrollment. The Investigational Site pharmacist will be responsible for generating and maintaining the

randomization schedule, and will assign a randomization code to each subject upon enrollment.

5.3 Preparation and Administration of Study Drug

The Investigational Site pharmacists in the UCSF Drug Product Services Laboratory will compound LEV tablets into 125 mg oral capsules. Placebo capsules will be prepared in the same way, using the inactive ingredients of the LEV tablets. All doses of study drug (placebo and active) will be self-administered by the participant or administered by the participant's caregiver.

All subjects will take the study drug (placebo or active) twice a day for 4 weeks, followed by a 4-week washout period during which time they will not take any study medications, followed by a second 4-week treatment period during which they will take whichever study drug (placebo or active) was not taken during the first treatment phase.

5.4 Measuring Subject Compliance

Investigational Site staff will ascertain compliance through weekly contact with the study participants during treatment phases, and by checking for empty blister packs at the end of each treatment phase. Blood LEV levels will be collected at study days 1, 29, 57, and 85 and sent to Quest Diagnostics. The LEV levels will not be disclosed to the study investigators during the active trial, but will be reviewed at the end of the study to determine drug compliance for each participant.

5.5 Drug Accountability

In accordance with current Good Clinical Practice (GCP), the Investigational Site will account for all study drug supplies. Details of receipt, storage, administration, and return or destruction will be recorded in the study drug accountability record according to the standard operating procedure of the Investigational Site.

Study drug will only be dispensed to subjects randomized to treatment under this protocol, and only as directed by this protocol. Administration of study drug will be accurately recorded in each subject's source documents.

5.6 Concomitant Medications

All medications (or treatments) other than study drug taken or received by the subject at any time during the study from the first dose of study drug through the final study visit assessment will be considered concomitant medications. Use of all concomitant medications, including any change in therapy, must be recorded and updated in the source documentation.

Subjects are not to take any other study drugs or investigational drugs beginning 30 days prior to the first dose of study drug and continuing until completion of the study (final study visit).

FDA-approved AD medications are allowed as long as the dose is stable for at least 30 days prior

to screening and at least 60 days prior to study day 1. Other medications (except those listed above) are allowed as long as the dose is stable for 30 days prior to screening. All drugs taken during the two months prior to screening, as well as between screening and baseline (Day 1) should be recorded.

All intercurrent medical conditions will be treated at the discretion of the Investigator according to acceptable community standards of medical care.

6. SCHEDULE OF EVENTS

The schedule of events is provided in tabular format in Appendix B and is summarized below by study visit.

6.1 Screening

Subjects will initially be screened for any previous or current history of the following exclusion criteria:

1. Korsakoff's syndrome
2. Alcohol or substance abuse preceding dementia symptoms & still present within 5 years of onset
3. Head trauma with persistent deficits
4. CNS lesions deemed to be clinically significant
5. Epilepsy/seizure disorder developing > 5 years before onset of cognitive symptoms
6. Hydrocephalus
7. Intracerebral hemorrhage
8. Ischemic vascular dementia
9. Multiple sclerosis or other demyelinating disease
10. Encephalitis or meningitis
11. Untreated B12 deficiency
12. Untreated hypothyroidism
13. Untreated syphilis
14. Positive HIV status
15. Renal insufficiency requiring dialysis
16. Symptomatic liver disease
17. Severe periventricular white matter disease or greater than grade 4 white matter lesions
18. Lacunar infarcts deemed to be clinically significant.
19. Cortical stroke
20. Respiratory condition requiring oxygen
21. Significant systemic medical illness such as cancer requiring chemotherapy or endstage cardiac insufficiency

Each subject will be provided with an informed consent form (ICF) describing the study and will have any questions answered. Subjects that consent to participate in the study will undergo the following assessments:

1. Blood test for vitamin B12, thyroid stimulating hormone (TSH), complete blood count with differential (CBC diff), chemistry-7, coagulation tests [prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR)], and prolactin. Vitamin B12 and TSH may be excluded if recorded in the previous year, and CBC diff and coagulation tests if recorded in previous 90 days.

2. Mini mental state exam (MMSE). The MMSE (Folstein et al. 1975) will be used to evaluate the

cognitive function of subjects. Refer to the referenced publication for details regarding the exam.

3. Clinical Dementia Rating.

4. Lumbar puncture for subjects in whom amyloid positron emission tomography (PET) imaging is not already completed or scheduled. Cerebral spinal fluid (CSF) will be collected for measurement of cell count with differential, glucose, total protein, and CSF biomarkers of AD. This CSF test will not be a requirement for enrollment in the treatment study.

5. Clinician Assessment of Fluctuation and One Day Fluctuation Assessment.

6. Overnight video-EEG, including 3 minutes of hyperventilation and 7 minutes of post-hyperventilation resting-state activity, and 60-minute resting-state M/EEG comprised of 50 minutes of resting-state activity, 3 minutes of hyperventilation, and 7 minutes of post-hyperventilation resting-state activity. The EEG and M/EEG will be read by epileptologists who will note whether there is any epileptiform activity (spikes and sharp waves) and identify the spikes and sharp waves for quantitation.

6.2 Sharing of experimental research test results with subjects or their care providers

Written reports of the overnight video-EEG or M/EEG will be faxed or mailed to the subject's primary care provider in all cases where epileptiform activity is detected and in other cases where clinical follow-up is warranted. The purpose of sending these reports is to alert their health care provider to any abnormal results that could prompt further medical workup. The significance of any abnormal findings will be explained in a letter, written by Dr. Vossel, or by phone. Also, Dr. Vossel will contact primary care physicians when the results of the study indicate the need for expedited medical workup. There are currently no clinical guidelines on whether to treat subclinical epileptiform activity with antiepileptic medications. However, the subject and their care provider will be given an opportunity to consider whether to start a medication for subclinical epileptiform activity in lieu of participating in this clinical treatment trial.

6.3 Study Day 1

Eligible subjects will return to clinic on the morning of Day 1. Prior to enrollment, to confirm that the subject continues to meet eligibility criteria, subjects will be asked to provide an updated medical history and to list any new medications taken since initial screening visit.

Subjects that continue to meet all eligibility requirements after the above baseline assessments will be enrolled in the study. The subjects will then undergo the following assessments:

1. Obtain vital signs
2. NIH EXAMINER
3. Stroop Test

4. ADAS-cog
5. Virtual Route Learning Test
6. ADCS-ADLs
7. ADCS-CGIC baseline assessment
8. CDR-SOB
9. NPI
10. Clinician Assessment of Fluctuation
11. One Day Fluctuation Assessment
12. 60-minute resting M/EEG, including 3 minutes of hyperventilation and 7 minutes of post-hyperventilation resting activity
13. 30-minute M/EEG to measure neural activity during cognitive stimulation
14. Virtual Route, 4-hour recall

At the end of the day, subjects will be randomized to treatment. Subjects will be given a month's supply of the study drug (placebo or active) in a blister pack with daily dividers and provided instructions on drug dosing. A packet insert and Frequently Asked Questions guide about LEV will be provided. The subjects will be instructed to begin the first dose that evening. Subjects will be given a diary to record any adverse events (AEs) or concomitant medications taken between visits.

Subjects or informants will be contacted weekly between study day 1 and 29 for general safety assessments.

6.4 Study Day 29

On the morning of study day 29, subjects will return to clinic for the following assessments:

1. Obtain vital signs
2. Review of diary for any recorded AEs or concomitant medications taken between visits.
3. Review of medication blister pack to count and verify number of pills taken since the previous visit
4. Collection of blood samples for determination of LEV and prolactin levels
5. NIH EXAMINER
6. Stroop Test
7. ADAS-cog
8. Virtual Route Learning Test
9. ADCS-ADLs
10. ADCS-CGIC
11. CDR-SOB
12. NPI
13. Clinician Assessment of Fluctuation
14. One Day Fluctuation Assessment
15. 60-minute resting M/EEG, including 3 minutes of hyperventilation and 7 minutes of post-hyperventilation resting activity
16. 30-minute M/EEG to measure neural activity during cognitive stimulation

17. Virtual Route, 4-hour recall

At the end of the day, the subjects will be instructed to begin a four-week break period (washout) during which time they will take no study medications.

6.5 Study day 57

On the morning of study day 57, subjects will return to clinic for the following assessments:

1. Obtain vital signs
2. Review of diary for any recorded AEs or concomitant medications taken between visits.
3. Collection of blood samples for determination of LEV and prolactin levels
4. NIH EXAMINER
5. Stroop Test
6. ADAS-cog
7. Virtual Route Learning Test
8. ADCS-ADLs
9. ADCS-CGIC (new baseline assessment)
10. CDR-SOB
11. NPI
12. Clinician Assessment of Fluctuation
13. One Day Fluctuation Assessment
14. 60-minute resting M/EEG, including 3 minutes of hyperventilation and 7 minutes of post-hyperventilation resting activity
15. 30-minute M/EEG to measure neural activity during cognitive stimulation
16. Virtual Route, 4-hour recall

At the end of the day, subjects will be given a month's supply of the study drug in a blister pack with daily dividers and provided instructions on drug dosing. The subjects will be instructed to begin the first dose that evening.

Subjects or informants will be contacted weekly between study day 57 and 85 for general safety assessments.

6.6 Study day 85

On the morning of study day 85, subjects will return to clinic for the following assessments:

1. Obtain vital signs
2. Review of diary for any recorded AEs or concomitant medications taken between visits.
3. Review of blister pack to count and verify number of pills taken since the previous visit
4. Collection of blood samples for determination of LEV and prolactin levels

5. NIH EXAMINER
6. Stroop Test
7. ADAS-cog
8. Virtual Route Learning Test
9. ADCS-ADLs
10. ADCS-CGIC
11. CDR-SOB
12. NPI
13. Clinician Assessment of Fluctuation
14. One Day Fluctuation Assessment
15. 60-minute resting M/EEG, including 3 minutes of hyperventilation and 7 minutes of post-hyperventilation resting activity
16. 30-minute M/EEG to measure neural activity during cognitive stimulation
17. Virtual Route, 4-hour recall

6.7 Duration of Participation

The total duration of participation for subjects in this study will be up to 18 weeks (first screening visit through final follow-up visit).

6.8 Location of Study Activities

Initial screening and overnight video-EEG recordings will take place at the Clinical and Translational Science Institute (CTSI) Clinical Research Center (CCRC), located at Moffitt Hospital, 505 Parnassus Ave., 12th floor. M/EEG recordings will take place at the Biomagnetic Imaging Laboratory, located at 513 Parnassus Ave, Room S-362. Blood draws will occur at the CCRC or at the Neurosciences Clinical Research Unit (NCRU) of the Sandler Neurosciences Center, located at 675 Nelson Rising Lane Suite 130. All other assessments will occur at the NCRU. All sites have private rooms for consenting and evaluations.

7. ASSESSMENT OF SAFETY

LEV is an FDA-approved medication, and an investigational new drug (IND) exemption was obtained for this study from the FDA (IND 120562) in accordance with IND regulations 21 CFR 312.2(b)(4). Safety will be assessed primarily based on adverse events (AEs). Secondary safety assessments will include ADAS-cog, ADCS-ADL, and NPI.

7.1 Safety Reporting and Adverse Events

7.1.1 Definitions

7.1.1.1 Adverse Event

An AE is defined in 21 Code of Federal Regulations (CFR) 312.32(a) as follows:

> Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
>
> An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

7.1.1.2 Serious Adverse Event

A serious adverse event (SAE) is defined in 21 CFR 312.32(a) as follows:

> An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
>
> - death
> - a life-threatening AE
> - inpatient hospitalization or prolongation of existing hospitalization
> - a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
> - a congenital anomaly/birth defect
>
> Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood

dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.1.2 Severity of Adverse Events

The severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. A copy of CTCAE version 4.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

The severity of AEs not classified by the above referenced toxicity grading scale will be categorized using the following definitions:

Mild (Grade 1):	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2):	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
Severe (Grade 3):	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Life-threatening (Grade 4):	Life-threatening consequences; urgent intervention indicated
Death (Grade 5):	Death related to AE

7.1.3 Relationship of Adverse Events to the Study Drug

The relationship of AEs to the study drug will be classified as one of the following:

1. **Adverse reaction**: Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

2. **Suspected adverse reaction**: Any AE for which there is a reasonable possibility that the

drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Examples of the types of evidence that would suggest a causal relationship between the drug and the AE are as follows:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

3. **Unrelated**: AE for which there is evidence that the AE definitely has an etiology other than the drug.

7.1.4 Expectedness of Adverse Events

An unexpected AE is defined in 21 CFR 312.32(a) as follows:

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

The LEV package insert will serve as the investigator brochure for this study.

7.1.5 Monitoring of Adverse Events

AEs will be monitored continuously during the study. Subjects will be instructed to report all AEs experienced during the study, and subjects will be assessed for the occurrence of AEs throughout the study. Subjects will be given a diary to record any AEs between visits. During the treatment period study staff will be available by telephone in case of unexpected adverse events. Subjects will be contacted by telephone by the study staff once a week during the treatment phases to

review any AEs, and the diary will be reviewed for any recorded AEs on study days 29, 57, and 85.

In order to avoid bias in eliciting AEs, subjects will be asked general, non-leading questions such as "How are you feeling?"

All AEs will be followed until resolution or stabilization of the event. This may require additional clinical assessments and laboratory tests.

7.1.6 Routine Reporting of Adverse Events

AEs, whether or not associated with study drug administration, will be recorded in the source documents.

Follow-up assessments should be repeated to document return of any abnormalities to normal, or to document other outcome of the AE.

7.1.7 Reporting of Serious Adverse Events, Including Death

SAEs, including death due to any cause, which occur during this study or within 30 days following the last dose of the study drugs, whether or not related to the administration of study drugs, will be recorded in the source documents, and on an SAE report. The SAE report will include the following information:

1. Subject identification including subject number, initials, and date of birth;
2. Randomization number;
3. Date of first dose of study drug and details of administration, including study drug name (including labeled strength and manufacturer), lot number, expiration date, and dose;
4. Date of last dose of study drug (i.e., prior to onset of SAE) and details of administration, including study drug name (including labeled strength and manufacturer), lot number, expiration date, and dose;
5. Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event);
6. Date of onset of the event;
7. Date of resolution of the event (or confirmation ongoing);
8. Severity of the event according to criteria in Section 7.1.2;

9. Assessment of the attributability of the event to the study drug according to the definitions in Section 7.1.3;

10. Why event is considered serious per the definition in Section 7.1.1.2;

11. Whether the event is expected per the definition in Section 7.1.4;

12. Action taken in treating the event and/or change in study drug administration or dose (including concomitant medications or therapies administered, whether hospitalization or prolongation of hospitalization was required, diagnostic procedures performed, and whether the subject was discontinued from the study);

13. All concomitant medications (including doses, routes, regimens, and indications);

14. Pertinent laboratory data;

15. Medical history.

The Investigator will review each SAE report and evaluate the relationship of the adverse experience to study drug and to underlying disease. Based on the Investigator's assessment of the adverse experience, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of subjects participating in the clinical trial. If the discovery of a new adverse experience related to the study drug raises concern over the safety of continued administration of study drug, the Investigator will take immediate steps to notify the regulatory authorities. Further action that may be required includes the following:

1. Alteration of existing research by modification of the protocol;

2. Discontinuation or suspension of the study;

3. Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings;

4. Modification of previously identified expected adverse experiences to include adverse experiences newly identified as study drug-related.

7.2 ADAS-cog

The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) rating instrument (Rosen et al. 1984) will be used to evaluate global cognitive functioning, and thus AD severity. The ADAS-cog will serve a dual function as both a safety measure and an efficacy endpoint. Refer to the referenced publication for details regarding the administration and scoring of the ADAS-cog.

7.3 ADCS-ADL

The ADCS-ADL rating instrument (Galasko et al. 1997) will be used to evaluate functional capacity. The ADCS-ADL will serve a dual function as both a safety measure and an efficacy endpoint. Refer to the referenced publication for details regarding the administration and scoring of the ADCS-ADL.

7.4 NPI

The neuropsychiatric inventory (NPI) (Cummings et al. 1994) will be used to evaluate behavioral symptoms, including agitation and irritability, which are possible side effects of LEV. The NPI will serve a dual function as both a safety measure and an efficacy endpoint. Refer to the referenced publication for details regarding the administration and scoring of the NPI.

8. ASSESSMENT OF LEV BLOOD LEVELS

The steady state blood levels of LEV will be obtained for each subject on study days 1, 29, 57, and 85.

8.1 Blood Collection

Blood samples will be taken by direct venipuncture. The blood sample volume at each collection time point will be 18 mL. The samples will be collected in three 6 mL tubes coated in silica clot activator. One tube will be processed to serum and sent to Quest Diagnostics to assess serum levels of LEV and prolactin. The remaining 2 tubes will be processed to serum and stored at the UCSF Neuroscience Clinical Research Unit (NCRU) lab for future analyses.

8.2 Blood Processing, Labeling, and Shipment

Blood samples intended for Quest Diagnostics LEV and prolactin serum levels (one 6 mL tube) will be processed in the following manner, as outlined in the Quest Diagnostics lab manual. The whole blood will be allowed to clot for 60 minutes and centrifuged at 2200 – 2500 RPM for at least 15 minutes. The resulting serum will be split into 2 cryovials which will be stored at -20°C and immediately shipped for external assessment of LEV and prolactin levels. Detailed labeling and shipping instructions will be specified by Quest Diagnostics.

Blood samples intended for local storage (two 6 mL tubes) will be processed to serum in an identical manner. Each serum sample will be split into 4 – 6 cryovials (1 mL/vial) to serve as back-up samples. The serum samples will be stored at approximately -80°C until analyzed. The back-up samples will be reserved for retesting if required.

8.3 Bioanalytical Methods

The concentration of LEV in serum will be measured using validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) methods.

9. ASSESSMENT OF EFFICACY

The efficacy endpoints for this trial include changes in epileptiform activity, cognition, degree of disability, and behavior. The exploratory endpoints for this trial include changes in cognition (novel tasks and subcomponents of established standardized tasks), clinical fluctuations, MEG power spectrum, MEG-I functional connectivity, blood prolactin levels, and subgroup analysis of all efficacy measures.

9.1 NIH EXAMINER

The NIH EXAMINER (Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research – http://examiner.ucsf.edu) will be used to measure executive function. The NIH EXAMINER battery of tests has psychometrically robust scales generated using item-response theory and provides strong predictors of real-world executive behavior (Possin et al. 2013). The NIH EXAMINER tasks will include antisaccade, set shifting, flanker task, dot counting, spatial 1-back, category fluency, and letter fluency. Four alternative forms will be used.

9.2 Epileptiform activity

Epileptiform activity will be measured using an overnight video-EEG and a 1-hr resting magnetoencephalography with simultaneous EEG (M/EEG). MEG-compatible EEG electrodes will be fixed to the scalp using a standard international 10-20 electrode placement. During the screening visit, each subject will undergo an overnight video-EEG, including a 3-min session of hyperventilation followed by 7 minutes of post-hyperventilation resting state activity. At the screening visit and each study visit (study days 1, 29, 57, and 85), subjects will undergo an M/EEG. The M/EEG will be recorded on a whole-head MEG system (MISL, Coquitlam, British Columbia, Canada) consisting of 275 axial gradiometers (sampling rate = 600 Hz). Three fiducial coils including the nasion and the left/right pre-auricular points will be placed to localize the position of the head relative to the sensor array. These points will later be co-registered to a T1-weighted structural magnetic resonance image (MRI) to generate a head shape. MRI scans will be acquired on a 3 Tesla Siemens MRI scanner at the UCSF Neuroscience Imaging Center. Data collection will be optimized to minimize within-session head movements to not exceed 0.5 cm. Sixty minutes of continuous EEG and MEG recording will be collected from each subject lying supine and with eyes closed. The last 10 minutes will include 3 minutes of hyperventilation followed by 7 minutes of post-hyperventilation resting state activity. Hyperventilation is a provocative maneuver that can help elicit epileptiform activity.

The overnight EEG recordings will be read by an epileptologist and the M/EEG recordings will be read by an epileptologist with specialized training in MEG. The readings will note whether there is any epileptiform activity (spikes and sharp waves), and quantify the total number of spikes and sharp waves present during the recording. The M/EEG readings will note wither epileptiform activity is present on MEG, EEG, or both. M/EEG often detects spikes not detected by EEG (Kirsch et al. 2007).

9.3 ADAS-cog

The ADAS-cog rating instrument (Rosen et al. 1984) will be used to evaluate the global cognitive functioning, and thus AD severity. The ADAS-cog is a 70-point scale that includes an assessment of verbal memory, language, orientation, reasoning, and praxis. Four alternative forms will be used. Refer to the referenced publication for details regarding the administration and scoring of the ADAS-cog. We added a 45-min recall trial to the word recall task as an exploratory measure.

9.4 Stroop Test

The Stroop Test (Stroop 1992) will be used to assess executive functions including selective attention, cognitive flexibility and processing speed. Subtasks include Stroop color naming and Stroop interference naming, and each subtask is restricted to 1 minute. Measures include color naming correct, color naming errors (uncorrected and self-corrected), interference naming correct, and interference naming errors (uncorrected and self-corrected). Subjects who are color blind will be excluded from this task.

9.5 Virtual Route Learning Test

The Virtual Route Learning Test will be used to assess navigation learning. Subjects learn a pre-determined route comprised of 15 turns through a virtual neighborhood by trial and error over a maximum of 15 trials, responding via a driving simulator. Four alternate forms with different neighborhoods and routes will be used. In each form, there is a single building repeated many times, and unique cues (e.g., distinct buildings, a bush, grass, palm trees, hot dog stand, school bus, etc.). Performance is measured by accuracy summed across trials 2 through 15 (max score = 210) and by accuracy at the delay trials (max score = 15) Additional performance metrics will be explored as described in section 10.2.

9.6 Fluctuation questionnaire

Two standardized methods will be used to quantitate fluctuations of dementia symptoms: The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale (Walker et al. 2000). These scales consist of a series of questions addressed to the caregiver/informant. The Clinical Assessment of Fluctuations (range 0-12) quantifies fluctuations in confusion or consciousness over the previous month. The One Day Fluctuation Assessment Scale (range 0-21) focuses on fluctuating confusion over the day prior to the assessment and includes the following seven items: falls, fluctuations, drowsiness, attention, disorganized thinking, altered level of consciousness, and communication.

9.7 CDR-SOB

The Clinical Dementia Rating (CDR) will be used to as a global measure of dementia severity (Morris 1993). The CDR consists of questions addressed to the caregiver/informant and includes the following domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Scores in each domain include 0 (no impairment), 0.5 (questionable

impairment), 1 (mild impairment), 2 (moderate impairment), and 3 (severe impairment). Refer to the referenced publication for details regarding the CDR scoring rules. The CDR sum of boxes (CDR SOB) summates the severity score for all domains and provides a higher range of values for tracking changes over time (range 0-18).

9.8 ADCS-ADL

The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) rating instrument (Galasko et al. 1997) will be used to evaluate functional capacity. The ADCS-ADL is a caregiver rated questionnaire of 23 items. Possible scores range from 0-78, where 78 implies full functioning with no impairment. Refer to the referenced publication for details regarding the administration and scoring of the ADCS-ADL.

9.9 ADCS-CGIC

ADCS-clinical global impression of change (ADCS-CGIC) is a seven-point scale that gives a global rating of change from baseline (Schneider et al. 1997). The baseline and follow up assessments are based on interviews with the subject and the informant. Refer to the referenced publication for details regarding the administration and scoring of the ADCS-CGIC.

9.10 NPI

The neuropsychiatric inventory (NPI) (Cummings et al. 1994) will be used to evaluate behavioral symptoms. The informant is asked about the presence and severity of the following neuropsychiatric abnormalities: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, and appetite/eating. Refer to the referenced publication for details regarding the administration and scoring of the NPI.

9.11 MEG spectral analysis

The power spectral density for different frequency bands will be measured via resting-state magnetoencephalography (MEG). A 60-second artifact-free recording segment from the first 10 minutes of recording (prior to sleep onset) will be manually selected for analysis. For each subject, power spectrograms of this 60-second epoch of sensor data will be generated using the power spectral density estimation based on Welch's averaged modified periodogram method of Matlab signal processing toolbox (sampling rate of 600 Hz). In subjects who are able to complete additional tests, we will measure dynamics of neural responses during cognitive tasks such as speech preparation and execution.

9.12 MEG-I

Whole-brain alpha-band functional connectivity will be derived from MEG-imaging (MEG-I) using the 60-second artifact-free recording epoch that is selected for the MEG spectral analysis. MEG-I uses MEG sensor data with millisecond precision and applies source reconstruction algorithms to

overlay cortical oscillatory activity onto structural brain images. Source-space MEG-I reconstructions and functional connectivity metrics will be computed with the NUTMEG software suite (http://nutmeg.berkeley.edu). We will compute imaginary coherence, which is a reliable metric for functional connectivity with MEG reconstruction. Functional connectivity will measure the strength of coherence between a given region and the rest of the brain. We will perform an unbiased search for MEGI-functional connectivity deficits that correlate with specific cognitive, behavioral, and functional deficits. Refer to the referenced publication for details of the methodology (Hinkley et al. 2011).

9.13 Prolactin levels

Blood samples intended for Quest Diagnostics LEV and prolactin serum levels (one 6 mL tube) will be processed in the following manner, as outlined in the Quest Diagnostics lab manual. The whole blood will be allowed to clot for 60 minutes and centrifuged at 2200 – 2500 RPM for at least 15 minutes. The resulting serum will be split into 2 cryovials which will be stored at -20°C and immediately shipped for external assessment of LEV and prolactin levels. Prolactin will be assessed via immunoassay.

Blood prolactin levels have been reported to be elevated in epileptic patients with interictal epileptiform discharges during awake states compared to nonepileptic control subjects (Molaie et al. 1986). We will explore whether prolactin levels correlate with epileptiform activity in our subjects and whether prolactin levels are reduced by LEV administration compared to placebo.

10. STATISTICS

10.1 Sample Size Considerations

We based sample-size estimates on our hypotheses that LEV will improve cognitive performance to an extent that is clinically meaningful, compared to placebo. Standard sample-size calculations for repeated measures analysis of variance (ANOVA) (Cohen 1988) show that F tests could detect an effect size of 0.356 with power greater than 0.8 with our sample sizes, allowing for a 10% dropout rate.

For the M/EEG exams, if we observe epileptiform activity in 12 of our subjects (33%), as predicted by our preliminary data, we should be powered to detect small reductions in epileptiform activity during LEV treatment compared to placebo. As a reference, 10 hAPP mice provided robust power to detect a 40% reduction ($p<0.0005$) in spike frequency with chronic LEV administration compared to baseline (Sanchez et al. 2012).

10.2 Statistical Analysis of Efficacy Data

Data from all subjects who complete at least the first 4 weeks of the study drug (placebo or active) will be included in the efficacy analysis. Subjects whose biomarkers (CSF or amyloid PET) are found to be unsupportive of AD after they enroll in the trial will be excluded from the efficacy analysis.

Cognitive, behavioral and functional measures, as well as M/EEG epileptiform activity, power spectral density for different frequency bands, neural activity during cognitive tasks, and MEG-I functional connectivity at study days 1, 29, 57, and 85 will be recorded and summarized. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data).

Each treatment effect will be tested for the assumption of normality. If the data are not normally distributed, we will investigate transforming data so they are normally distributed or nonparametric options. If we choose parametric tests, significance testing will be performed using ANOVA for repeated measures with drug treatment (LEV or placebo) as the independent variable. Prior to this analysis, ANOVA will be used to analyze the effect of drug-placebo sequence and to compare group demographics and severity of dementia at baseline (MMSE and CDR-SOB); if any of these factors confound the relationship between the study drug and the outcome measure, then they will be included as covariates in the ANOVA model. If factors arise that limit the appropriateness of the repeated-measures ANOVA model, such as a large dropout rate or varying data collection time points causing imbalance of longitudinal data, we will substitute a linear mixed effects regression model to better fit the longitudinal data without the intrinsic constraints of the repeated-measures ANOVA framework (Fitzmaurice et al. 2004, Finucane et al. 2007). If a drug carryover effect is observed on an outcome measure between weeks 4 and 8, then we will analyze the initial 4 weeks of the study separately for this outcome measure. Analyses will be two-tailed except for analysis of epileptiform activity, which will be one-tailed based on our expectation that LEV will reduce

epileptiform activity (Sanchez et al. 2012, Mintz et al. 2009). For all analyses, the null hypotheses will be rejected at $p < 0.05$.

For the Virtual Route Learning Task, we will measure total accuracy summed across trials 2 through 15 (max score = 210) and accuracy at the delay trials (max score = 15). We will also explore the trial-by-trial accuracy, error rates, learning rates and asymptotes. The preliminary data suggest a 2 parameter exponential model will provide a good fit for the learning data. We will compare estimated learning rates and asymptotes parameters using ANOVA for repeated measures with drug treatment (LEV or placebo) as the independent variable. However, if additional data collection suggests that simple slopes better summarize the data, then we will use linear mixed effects models. If we use linear mixed effects models and residuals are not normally distributed, we will use bootstrapping techniques to produce reliable standard errors.

For the whole-brain MEG-I functional connectivity analyses, neuropsychological, behavioral, and functional measures from each subject will be correlated with global connectivity values at each voxel using the Pearson's correlation. Corrections for multiple comparisons will be performed using a cluster correction with a cutoff level of 20 voxels, and p values thresholded to 0.01. If no significant voxels are found at this threshold, we will use a less stringent threshold of $p< 0.05$. A hierarchical validation analysis will be used to account for multiple cognitive, behavioral, and functional tests.

11. ACCESS TO SOURCE DOCUMENTS AND RETENTION OF RECORDS

The Investigator will make the source documents for this trial available for monitoring by regulatory authorities or health authority inspectors.

Subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, and the IRB/IEC. The Investigator will retain all study documents for at least 2 years after the Investigation is discontinued and regulatory authorities have been notified.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Data Collection

All data required by the study protocol will be recorded onto source documents.

Only authorized Investigational Site personnel will record data on the documents. Any corrections to data recorded on the documents will be made in such a way that the original entry is not obscured. The date of the correction and the initials of the person making the correction will be documented.

The source documents will be kept up-to-date by the Investigator and the research staff at the Investigational Site.

12.2 Data Management

All source document data will be entered into a validated database and an electronic audit trial of edits maintained. Data may be imported to the database electronically.
The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures completed.

12.3 Inspection by Regulatory Authorities

At some point during the study, a regulatory authority may visit the Investigator to conduct an inspection of the study. The Investigator and staff will cooperate with the inspectors and allow access to all source documents and other study-related documents.

13. ETHICS

13.1 Declaration of Helsinki

This study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the 2008 revision, as described in Appendix C.

13.2 Good Clinical Practice and Regulatory Compliance

This study will be conducted in accordance with the principles of GCP (current ICH guideline) and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

13.3 Institutional Review Board/Independent Ethics Committee

The protocol, ICF, and any materials (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) for this study will be reviewed and approved by a duly constituted IRB/IEC.

The Investigator will ensure that all aspects of the IRB/IEC review are conducted in accordance with current institutional, local, and national regulations. The study will not be initiated until the Investigator receives a letter documenting IRB/IEC approval.

Amendments to the protocol will be subject to the same requirements as the original protocol. Implementation of the changes described in the protocol amendment will not be initiated until the Investigator receives a letter documenting IRB/IEC approval.
Revisions to the ICF will be reviewed and approved by the IRB/IEC prior to use in the study.
The Investigator will inform the IRB/IEC of all reportable AEs and all periodic reports and updates that the IRB/IEC may require.

13.4 Informed Consent

No study related procedures, including screening evaluations, will be performed until the subject has given written informed consent.

The ICF will clearly describe the nature, scope, and potential risks and benefits of the study, in a language that the subject understands. The ICF will conform to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50) and any additional elements required by the Investigator's institution or local regulatory authorities. The Investigator will submit the ICF to the IRB/IEC for review, and will not proceed with initiation of the study until the IRB/IEC provides a letter documenting approval.

The IRB/IEC approved ICF will be given to each prospective participant. The subjects will be given adequate time to discuss the study with the Investigator or site staff and to decide whether or not to participate. Each subject who agrees to participate in the trial and who signs the ICF will

be given a copy of the signed, dated, and witnessed document. The original signed ICF will be retained by the Investigator in the study files.

The Investigator will also obtain authorization from the subject to use and/or disclose PHI in compliance with HIPAA or equivalent. Written HIPAA authorization may be obtained as part of the informed consent process.

If a protocol amendment substantially alters the study design or increases the potential risk to the subject, or the known risks of the study drug change over the course of the study, the ICF will be revised and submitted to the IRB/IEC for review and approval. The revised approved ICF must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment and to obtain consent from new subjects prior to enrollment.

13.5 Emergency Departure from Protocol

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that subject. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Investigator/IND Sponsor immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the subject (for whom the departure from protocol was effected) is to continue in the study. The source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB/IEC will be notified in writing of such departure from protocol.

14. PUBLICATION POLICY

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, HIPAA or equivalent.

15. PROTOCOL AMENDMENTS AND MODIFICATIONS

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. The Investigator will not modify the protocol without first receiving IRB/IEC authorization to do so, except in those cases intended to reduce immediate risk of the subjects. The Investigator/IND Sponsor is responsible for submitting protocol amendments to the appropriate IRB/IEC and government regulatory authorities.

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APPENDICES

APPENDIX A: NATIONAL INSTITUTE ON AGING-ALZHEIMER'S ASSOCIATION WORKGROUPS RECOMMENDATIONS ON DIAGNOSTIC GUIDELINES FOR ALZHEIMER'S DISEASE (MCKHANN ET AL. 2011)

Subjects enrolled in this trial must be diagnosed with probable AD dementia per the criteria recommended by the National Institute on Aging-Alzheimer's Association Workgroups (McKhann et al. 2011) as outlined below.

Criteria for all-cause dementia: Core clinical criteria

Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and

2. Represent a decline from previous levels of functioning and performing; and

3. Are not explained by delirium or major psychiatric disorder;

4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.

5. The cognitive or behavioral impairment involves a minimum of two of the following domains:

   a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.

   b. Impaired reasoning and handling of complex tasks, poor judgment— symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, or inability to plan complex or sequential activities.

   c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.

d. Impaired language functions (speaking, reading, or writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.

e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

Probable AD dementia: Core clinical criteria

Probable AD dementia is diagnosed when the patient:

1. Meets criteria for dementia described above (i.e., criteria for all-cause dementia), and in addition, has the following characteristics:

   A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

   B. Clear-cut history of worsening of cognition by report or observation; and

   C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

      a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.

      b. Nonamnestic presentations:

         - Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.

         - Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.

         - Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

D. The diagnosis of probable AD dementia ***should not*** be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

APPENDIX B: SCHEDULE OF EVENTS FOR RANDOMIZED, PLACEBO-CONTROLLED, CROSSOVER STUDY

	Screening	Treatment and Washout Periods			
		Day 1	Day 29	Day 57	Day 85
Informed consent form	X				
Record demographic data	X				
Medical and surgical history	X	X			
Screening labs[a]	X				
Lumbar puncture[b]	X				
Efficacy labs[c]		X	X	X	X
Assessment of concomitant medications		X	X	X	X
MMSE	X				
CDR-SOB	X	X	X	X	X
Overnight video-EEG	X				
Resting M/EEG[d]	X	X	X	X	X
NIH EXAMINER		X	X	X	X
ADAS-cog		X	X	X	X
Stroop Test		X	X	X	X
Virtual Route Learning Test		X	X	X	X
ADCS-ADLs		X	X	X	X
ADCS-CGIC baseline		X		X	
ADCS-CGIC follow-up			X		X
NPI		X	X	X	X
Clinician Assessment of Fluctuation	X	X	X	X	X
One Day Fluctuation Assessment Scale	X	X	X	X	X
Virtual Route, 4-hour recall		X	X	X	X
Diary[e]			X	X	X
Review of medication blister pack			X		X

ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; ADCS-ADLs = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale; ADCS-CGIC = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; M/EEG = magnetoencephalography with simultaneous EEG; MMSE = Mini Mental State Exam; Clinical Dementia Rating -Sum of Boxes; NIH EXAMINER = National Institutes of Health Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research; NPI = neuropsychiatric inventory

a. Blood levels of vitamin B12, thyroid stimulating hormone, complete blood count with differential, chemistry-7, coagulation, prolactin, and levetiracetam
b. Collection of cerebrospinal fluid for measure of cell count with differential, glucose, total protein, and biomarkers of Alzheimer's disease.
c. Blood levels of levetiracetam and prolactin
d. 60 minutes of resting-state activity; the final 10 minutes include 3 minutes of hyperventilation and 7 minutes of post-hyperventilation resting-state activity.
e. Subjects will record any adverse events or concomitant medications taken between visits in their diary. The diary will be reviewed at each visit.

APPENDIX C: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the

causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

15. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, and other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed

as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of

interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their

research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.