Icahn School of Medicine at Mount Sinai
Mount Sinai Beth Israel
Mount Sinai Brooklyn
The Mount Sinai Hospital
Mount Sinai Queens
New York Eye and Ear Infirmary
Mount Sinai St. Luke's
Mount Sinai West

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Institutional Review Boards

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NCT01703117
IRB-17-02664
Application

Last approved on 6/18/2020

1. Summary - Title

Protocol Title

Glutamatergic Dysfunction in Cognitive Aging: Riluzole in Mild Alzheimer's Disease

Principal Investigator	Ana Pereira
Primary Department	Neurology
Application Initiated By	Ana Pereira

Lay Summary

Cognitive aging is a major source of disability in an increasingly aging population (1, 2). The paucity of effective treatments for cognitive aging disorders, and most importantly in Alzheimer's disease instigates a need for further research into novel therapeutic possibilities. Alzheimer's disease is the most common neurodegenerative disorder and its prevalence steeply increases (3). Glutamate-mediated toxicity in neuropsychiatric disorders and in particular in Alzheimer's disease has been shown to cause significant cerebral damage (4-6). Furthermore, the release, propagation and toxicity of beta-amyloid and phosphorylated tau, neuropathological hallmarks of Alzheimer's disease, are also dependent on glutamatergic dysfunction. Bringing glutamatergic synapses to more homeostatic levels is a therapeutic opportunity for Alzheimer's disease treatment. Early effective therapeutic intervention in Alzheimer's disease is critical in order to prevent or at least slow down neuropathological progression that will lead to widespread irreversible neuronal loss and significant cognitive dysfunction. Riluzole, a glutamate modulator agent approved for ALS (7) has not yet been used in cognitive aging disorders, will be tested in mild Alzheimer's disease patients. Cognitive functional changes along with two in vivo biomarkers, namely, Fluorodeoxyglucose (18F) positron emission tomography (FDG- PET) and Magnetic Resonance Spectroscopy (MRS) will be evaluated.

IF Number IF2357604

2. Summary - Setup

Funding Has Been Requested / Obtained	Yes
Application Type	Request to Rely on Mount Sinai IRB
Research Involves	Prospective Study ONLY
Consenting Participants	Yes
Requesting Waiver or Alteration of Informed Consent for Any Procedures	No
Humanitarian Use Device (HUD) Used Exclusively in the Course of Medical Practice	No
Use of an Investigational Device to Evaluate Its Safety or Effectiveness	No
Banking Specimens for Future Research	Yes
Cancer Related Research that Requires Approval from the Protocol Review and Monitoring Committee (PRMC).	No

Is this Cancer Related Research? Cancer Related Research is defined as research that has cancer endpoints or has a cancer population as part of or all of its targeted population. This includes protocols studying patients with cancer or those at risk for cancer.

Clinical Trial	Yes

**** A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). * Used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.***

Drugs / Biologics	Yes

**** Drugs / Biologics That Are Not a Part of Standard Practice***
**** Controlled Substances***
**** Drugs / Biologics Supplied by the Research Sponsor or Purchased with Study Funds***

Ionizing Radiation for imaging or therapy, including X-Ray, Fluoroscopy, CT, Nuclear Medicine, PET andor Radiation Therapy:

*** Purely for standard of care:**	No
*** In frequency or intensity that exceeds what is necessary for standard of care:**	Yes
Hazardous Materials	No

Recombinant DNA
**** Viral Vectors***
**** Plasmids***
**** Bacterial Artificial Chromosomes***
**** Toxic Chemicals, Potentially Toxic Medications, Carcinogens***
**** Autologous Cell Lines***

Request Use of Clinical Research Unit Resources No

3. Summary - Background

Objectives

The objectives of the study is to investigate if an improved modulation of the glutamatergic synapse in Alzheimer's patients, which are vulnerable to degeneration in Alzheimer's disease, will impact brain function, evaluated through neuroimaging and neuropsychological measures.

Aims 1 (primary): To measure cerebral levels of glucose metabolism using FDG PET and the neuronal viability marker NAA and glutamate using proton magnetic resonance spectroscopy (1H MRS) and in patients with probable mild AD at baseline and after 24 weeks of treatment with riluzole or with placebo. Hypothesis: Treatment with riluzole for 24 weeks compared to placebo will alleviate glutamatergic and metabolic dysfunction and decrease excitotoxic neurodegeneration in mild AD as revealed by a slowing in the rate of temporal decline of FDG-PET glucose metabolism and cerebral glutamate and other 1H metabolites. Thus, at 24 weeks, the placebo group will show lower PET glucose metabolism and MRS metabolite levels than at baseline relative to the riluzole-treated group.

Aim 2 (secondary): To correlate the neuroimaging outcome measures with neuropsychological measures at baseline and at 24 weeks.
Hypothesis: A subset of cognitive measures (e.g. memory, executive function, functionality cognitive and AD score measures) will more strongly correlate with the neuroimaging outcome measures to be further investigated in larger clinical studies/trials.

Background

Please, see attachment with extensive background, significance and graphs as well.

Cognitive dysfunction is a growing health problem with the aging of the population. The common disorders of cognitive aging in the spectrum from normal cognitive aging, mild cognitive impairment and Alzheimer's disease (AD) will increasingly impair the life of millions of people worldwide (1, 2). Alzheimer's disease is a progressive neurodegenerative disorder that represents a major threat to public health (3). Thus, this scenario imposes the urgency for an effective medication that can ameliorate or slow down the onset of those cognitive aging symptoms in the setting of the current era of an extremely scarce therapeutic armamentarium for those disorders. Glutamate is one of the most important neurotransmitters in the brain.
Excitotoxicity from dysfunctional glutamatergic neural circuits has been implicated in various neurocognitive disorders as an important cause of neuronal damage, and especially in Alzheimer's disease (5, 6). Numerous studies have now shown that while the activation of the synaptic NMDA receptors (the major glutamatergic receptor) is neuroprotective and important for synaptic plasticity, activation of extrasynaptic NMDA receptors will lead to cell death molecular signaling -see review by Hardingham et al. 2010 (8).

Amyloid beta and phosphorylated tau are the neuropathological hallmarkers of AD. Studies have shown that oligomers of amyloid beta disrupt neuronal glutamate uptake (9) which will lead to elevated levels of glutamate that inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NMDA receptors (10). There is also evidence that dysfunctional glutamate levels increases tau phosphorylation (11), tau gene expression (12) and tau propagation (Wu W. Karen Duff 2016). Riluzole (2-amino-6-trifluoromethoxy benzothiazole) is a medication that has been shown to decrease presynaptic glutamate release (13), it facilitates astrocytic

glutamate uptake (14) and increases oxidative metabolism with mitochondrial enhancing properties (15). Riluzole is a neuroprotective agent that has been safely used to treat amyotrophic lateral sclerosis (ALS), with evidence that it is effective in prolonging the median survival of patients with this condition (16). Recent clinical studies suggest riluzole also possesses anti-depressant and anxiolytic effects in patients with depression and anxiety (17, 18). As riluzole increases glutamate reuptake through the enhancement of glial excitatory amino-acid transporter functioning (19), riluzole may rapidly enhance glutamate-glutamine cycling, increasing the surviving promoting synaptic glutamatergic activity (17) while limiting the overflow of glutamate into the extrasynaptic space where it can stimulate extrasynaptic NMDA receptors that promote excitotoxicity and cell death. Riluzole, to our knowledge, has not been yet tested in cognitive aging disorders and in particular and of most interest in Alzheimer's disease. Synaptic density is the strongest pathological correlate of cognitive ability (20). Alzheimer's disease patients develop a robust synaptic degeneration (20). The hippocampal and cortical atrophy visible in AD brains demonstrate the degeneration of brain areas predominated by large glutamatergic pyramidal neurons. Dysfunction of glutamatergic neural circuits and glutamate levels extra-synaptically could lead excitotoxicity, more release, propagation and toxicity of beta-amyloid and tau, pathophysiological hallmark of AD and a cycle of toxicity in AD that culminates in synaptic and neuronal loss. Importantly, as noted before, amyloid beta decreases glutamate uptake which will lead to more spillover of glutamate to extrasynaptic NMDA receptors that promote neuronal death signaling. On the other hand, dysfunctional glutamate increases tau expression and phosphorylation, which are also deleterious, enhancing a toxicity cycle. A medication such as riluzole that modulates the glutamatergic system by enhancing synaptic glutamatergic activity and inhibiting the activation of extrasynaptic NMDA receptor toxic signaling may be beneficial to patients with Alzheimer's disease.

We hypothesize that the use of riluzole, a glutamate modulator agent, at the same dose approved by FDA that has been safely and effectively used for patients with ALS 50mg BID, in subjects with mild Alzheimer's disease can decrease glutamatergic dysfunction, slow down decline of biomarkers of cerebral metabolism and slow down progression of cognitive disability. Notably, the PI has three preclinical publications showing that (1) riluzole rescued age-related cognitive decline through clustering of dendritic spines, which increases neural communication, (2) that riluzole rescues age and AD gene expression profiles (below) and (3) riluzole prevented hippocampal-dependent spatial memory decline in an early-onset aggressive mouse model of AD (5XFAD), reversing many of the gene expression changes in immune pathways:

-Pereira et al. Glutamatergic Regulation Prevents Hippocampal-Dependent Age-Related Cognitive Decline through Dendritic Spine Clustering. PNAS 2014

-Pereira et al. Age and Alzheimer's disease gene expression profiles reversed by the riluzole. Mol. Psych2016

-Okamoto M…., Pereira AC. Riluzole reduces amyloid beta pathology, improves memory, and restores gene expression in a transgenic mouse model of early-onset Alzheimer's disease. Translational Psychiatry. 2018

We will use imaging biomarkers as a primary outcome measure. Cerebral magnetic resonance spectroscopy (MRS) will be used as a biomarker of plasticity changes in the brain. N-acetylaspartate (NAA) is a neuronal viability marker that has been well studied -see review (23). It has been used in MRS studies in ALS, depression, anxiety and several other neurologic and psychiatric disorders (17, 18). A decline in NAA levels occurs in Alzheimer's disease (24). In Alzheimer's disease drug trials changes in ADASCognitive scores strongly correlate with parietal NAA changes during donepezil treatment (25). Glutamate levels can also be measured through MRS as a secondary outcome measure. Our focus of interest in the magnetic resonance spectroscopy analysis is the posterior cingulate cortex (primary) and exploratorily we will evaluate the hippocampus.

Importantly, FDG-PET will be used as the main primary outcome measure biomarker as baseline hypometabolism in posterior cingulate, temporoparietal regions, hippocampus and prefrontal cortex has been validated in several studies in patients with Alzheimer's disease (26); it is a well established biomarker in AD (more validated than MRS for AD) that correlates with disease progression that we will evaluate for changes after riluzole administration. FDG-PET is the golden standard technique to evaluate for cerebral metabolism as it measures regional cerebral glucose use. 18F-FDG is as a glucose analog that is taken up by the neuron and is a reflection of the distribution of glucose uptake. Synaptic and neuronal loss are tightly associated with a decrease in glucose metabolism, a primary energy source in the brain. FDG-PET metabolic changes will be evaluated pre-specified regions of interest (posterior cingulate, precuneus, lateral temporal, inferior parietal, hippocampus and frontal cortex). Neuroimaging changes will be the primary outcome measure in this study.

Primary and Secondary Study Endpoints

The primary outcome measures will be the glucose metabolic changes obtained through 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) in regions of interest and the imaging biomarker N-acetylaspartate (NAA) obtained through magnetic resonance spectroscopy (^{1}H MRS).

The secondary outcome measures will be glutamate obtained through MRS, and the neurocognitive measures obtained through neuropsychological tests for correlation with neuroimaging biomarkers.

Protocol Was Already Approved by the Icahn School of Medicine at Mount Sinai (ISMMS) Institutional Review Board (IRB) Under a Different Principal Investigator No

Protocol Was Previously Submitted to an External(non-ISMMS) IRB Yes

External IRB Name

Rockefeller University IRB for protocol
Weill Cornell Medical Center IRB (for imaging portion of the study)

Protocol Was Approved by the External IRB Yes

External IRB Approval Document RU IRB approval.pdf

4. Research Personnel

Name/Department	Role/Status	CC	Access	Obtaining Consent	Phone	Email
Ana Pereira / Neurology	PI /	Yes	SIGNAUTH	Yes		
Tarah Gustafson / Neurology	Admin (non-FCOI) /		EDIT		212-241-4264	
Emily Lampshire / Psychiatry	Research Nurse /	Yes	EDIT	Yes	212-659-8301	
Florence Lau / Psychiatry	Study Coordinator /		READONL	YYes		
Caroline Meuser/ Psychiatry	Study Coordinator /	Yes	EDIT	Yes		
Hillel Grossman / Psychiatry	Co-Investigator /		READONL	YYes	212-241-6500	
Julie Ciardullo / Neurology	Co-Investigator /		READONL	Y		
Gina Garcia Camilo / Psychiatry	Admin (non-FCOI) /	Yes	EDIT		718-584-9000x1710	
Judith Neugroschl / Psychiatry	Co-Investigator /		SIGNAUTH	Yes	212-241-8329	
Allison Ardolino / Psychiatry	Study Coordinator /		READONL	YYes		
Amy Aloysi / Psychiatry	Co-Investigator /		READONL	Y	2126598751	

Jonathan Greenberg / Psychiatry	Study Coordinator /		READONL	YYes	(212) 659-5621	
Nelly Velasco / Psychiatry	Study Coordinator /		READONL	YYes		
Martin Ljekocevic / Psychiatry	Study Coordinator /		READONL	YYes		
Margaret Sewell / Psychiatry	Faculty Member /		READONL	Y	212-241-0188	
Clara Li / Psychiatry	Faculty Member /		READONL	Y	212-659-8786	
Michael Kinsella / Psychiatry	Admin (non-FCOI) / Staff (non MD)	Yes	SIGNAUTH		212-659-8883	
Kelly Pun / Psychiatry	Study Coordinator /		READONL	YYes		
Caroline Meuser / Psychiatry	Study Coordinator /	Yes	EDIT	Yes		
Chloe Larson / Neurology	Study Coordinator /	Yes	EDIT	Yes		

5. Sites

Site Name	Icahn School of Medicine at Mount Sinai
Other External Site Name	
Contact Details	
Approved	
Approval Document	
Funded By Mount Sinai	
Other IRB	

Site Name	Other External Site
Other External Site Name	Rockefeller University
Contact Details	
Approved	1
Approval Document	RU IRB approval.pdf
Funded By Mount Sinai	0
Reviewed By	Other IRB
Other IRB	Rockefeller University

6. Subjects - Enrollment

Site Name	Icahn School of Medicine at Mount Sinai
Subjects To Be Enrolled	
47	
Site Name	Other External Site
Subjects To Be Enrolled	
23	
Total Number of Subjects to be Enrolled Across All Listed Sites Above (Auto Populated)	70

As per IRB Modification Request – approved 6/18/19 – local enrollment increased from 26 to 47 at Mount Sinai and to 70 across both sites.

7. Subjects - Setting and Resources

Setting of Human Research Other

Specify Other Setting of Human Research

Neurology Research Office and ADRC

Total Number of Subjects Needed To Complete Study 26

Feasibility of Meeting Recruitment Goals

Participants will be referred from Neurology clinic, Center for Cognitive Health, ADRC Dataware house, clinicaltrial.gov, Alzheimer's Association and other related websites which will make recruitment goal feasible. The ADRC has a registry of subjects who have already been characterized and who have expressed interest in clinical trials. This subject population is the most readily available cohort at the ADRC sites and the ADRC physicians are most efficient at recruiting from. The ADRC at Mount Sinai evaluates a total of approximately 5-7 patients a month who have been diagnosed with mild to moderate AD. Active recruitment to the ADRC comes from within Mount Sinai, from outside physicians and other health care professionals, and from efforts to inform the community at large. This recruitment is accomplished through lectures, brochures, and institutional advertising including community and targeted advertising such as the NYC chapter of the Alzheimer 's disease Association newsletter. Special efforts are made to inform the geriatric community through public lectures, health fairs, articles in local papers and drug store magazines. These efforts are organized through the EIT Core, using a large roster of community Senior Centers, and senior organizations. In addition, the MSHS neurological clinic will provide recruitment of participants to the study.

Facilities To Be Used for Conducting Research

Neurology Research Clinic/Office and ADRC

Multi-Center Study Yes

Mount Sinai Principal Investigator is Responsible for All Centers Management of Multi-Center Study Yes

Summary of recruitment:At both Rockefeller University and Mt Sinai sites, we screened a total of 94 subjects, 44 did not pass screening, 50 were randomized and 42 completed the study.

At the Mt Sinai site, a total of 31 subjects were screened, 7 did not pass screening, 24 were randomized and a total of 20 completed the study. At the Rockefeller University site, 63 participants were screened, 37 did not pass screening, 26 were randomized and 22 completed the study.

Community-Based Participant Research Study No

PI must attest to the following.

**** Process is adequately described to ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial related duties and functions.***

8. Subjects - Populations

Inclusion Criteria

1. Male or female; 50-95 years old with mild Alzheimer's disease determined after neurological and neuropsychological evaluation following the National Institute on Aging – Alzheimer's disease Association criteria (30) that recently revisited the NINCDS-ADRDA criteria (29). For mild Alzheimer's disease, Mini Mental State Examination (MMSS) between 19 and 27.

2. Must be on donepezil or rivastigmine or galantamine at a consistent dose for at least 2 months. Patients will be considered for inclusion if they were previously unable to tolerate acetylcholinesterase inhibitors and as a result, are no longer on the medication for at least 2 months.

3. Must be fluent in English

4. The subject will appoint or have previously appointed a health care proxy specifically designated for research consent and that this be documented.

Exclusion Criteria

1. Severe Alzheimer's disease and other dementias as determined by neuropsychological testing and neurological evaluation.

2. Previous riluzole treatment.

3. MRI contra-indication (severe claustrophobia, metal implants, shunts, pacemaker, joint implants, metal valves).

4. Currently taking medications that either have evidence of glutamatergic activity or has previous MRS evidence of effects on brain glutamate levels at the discretion of the PI such as lamotrigine, lithium, opiates, bupropion, psychostimulants such as amphetamines and methylphenidates, tricyclic antidepressants, benzodiazepines and any other drug that the investigators judge might interfere with the study. (subjects on those medications may still be included in the study however only the values of NAA from MRS will be utilized and not the glutamate measurements).

5. Self-reported history or reported by LAR: study participant is a current user of the following illicit drugs: cocaine, MDMA ("ecstasy"), heroin and other opioids (as verified by urine drug test) or has a history of drug or alcohol abuse within the past 5 years.

6. Serum creatinine >1.5 times the upper limit of normal.

7. Abnormal liver function test (greater than 2 times the upper limit of normal for alanine aminotranferase (ALT) or aspartate aminotransferase (AST); or bilirubin >1.5 times the upper limit of normal.

8. History of brain disease including Parkinson's Disease, severe brain trauma, seizures, history of stroke,clinically significant lacunar infarct in a region important for cognition or multiple lacunes or a cortical infarct or focal lesions of clinical significance, multiple sclerosis, mental retardation, normal pressure hydrocephalus, CNS tumor, Huntington's disease, subdural hematoma or other serious neurological disorder.

9. Uncontrolled diabetes mellitus (Hba1c higher than 7) or chronically uncontrolled hypertension.

10. Subject must not be taking Namenda® (memantine) for 6-weeks prior to study entrance.

11. Currently taking any concomitant hepatotoxic drugs such as allopurinol, methyldopa and sulfasalazine.

12. Any unstable serious co-existing medical condition(s) including but not limited to myocardial infarction, coronary artery disease requiring coronary bypass surgery, unstable angina, clinically evident congestive heart failure within 6 months prior to the screening visit.

13. Current smoker or user of nicotine-containing products, such as chewing tobacco, nicotine patch or gum for the past 2 months.

14. Current untreated major depression defined by Geriatric Depression Scale > 20. (40)

15. Participation in any investigational or marketed drug or device trial within 30 days prior to the screening visit.

16. Significant neuropsychiatric illnesses such as bipolar disorder, schizophrenia, moderate- severe anxiety, vascular dementia, Creutzfeldt-Jakob dementia, HIV dementia, and dementia in other specified diseases.

17. Subjects who have been on acetylcholinesterase inhibitor for longer than 5 years.

18. Weight> 300 pounds.

19. Lactose intolerance.

20. Any medical or social condition that, in the opinion of the Investigator, might pose additional risk to the participant or confound the results of the study.

21. Positive Hepatitis Serology (Hep. B antigen+ or Hep. C antibody+)

Other Aspects that Could Increase Subjects Vulnerability

Subjects are patients with mild Alzheimer's disease experiencing cognitive impairment .

Safeguards to protect Subjects rights and welfare

Subjects will undergo a capacity evaluation by a doctor to assess their understanding of the consent form and study procedures. There is also a possibility that participants may be socially or economically disadvantaged. It will be emphasized that their participation is completely voluntary, and clinical care is not dependent on participation.

9. Subjects - Participation

Duration of an Individual Subjects Participation in the Study

8 months

Procedures for Subjects to Request Withdrawal

Subjects are free to withdraw from the study at any time without penalty. If a subject wishes to withdraw, they should contact the PI or study staff.

Procedures for Investigator to Withdraw Subjects

The Principal Investigator may withdraw subjects if they feel the subject's health is at risk, or subject fails to keep appointments and to follow protocol directions or if subject needs treatments not allowed during the course of the study or if the investigator terminates or cancels the research or if the willingness of participation has changed (i.e., a subject revokes consent).

Participants Will Be Recruited	Yes
Recruitment Method(s)	Clinical Practice, Other Website, Physician Referral, Research Match, Other

Specify Other Recruitment Method

ADRC Data warehouse, clinicaltrial.gov, Alzheimer's Association and other related websites, Neurology and Geriatric clinic referrals at MSSM.

How Participants Will Be Identified

This subject population is the most readily available at the MSSM ADRC site. ADRC physicians have a record of efficiency at recruiting. The ADRC at Mount Sinai evaluated a total of approximately 5-7 patients a month who have been diagnosed with mild to moderate AD. Active recruitment to the ADRC comes from within Mount Sinai, from outside physicians and other health care professionals, and from efforts to inform the community at large. This recruitment is accomplished

through lectures, brochures, and institutional advertising including community and targeted advertising such as the NYC chapter of the Alzheimer 's disease Association newsletter. Special efforts are made to inform the geriatric community through public lectures, health fairs, articles in local papers and drug store magazines. These efforts are organized through the EIT Core, using a large roster of community Senior Centers, and senior organizations. In addition, the Center for Cognitive Health Clinic, other Neurology clinic at MSSM will facilitate recruitment of participants to the study.

How Research Will Be Introduced to Participants

PI and staff will discuss research with participants at the time that potential participants are identified, including purpose of the study, evaluations, neuroimaging, blood tests, potential risks and alternatives.

How Participants Will Be Screened

Subjects will be consented in a private office at the study site by the PI or approved PI delegate. Subjects will be given as much time as needed to ask questions and consider the research project.
The standard Mount Sinai Program for the Protection of Human Subjects (PPHS) consent document will be used for this study, ADULT ICF template version for those that are deemed to have capacity and the Incapacitated Adult ICF template version for those without capacity.
Capacity to consent will be determined by an attending level physician. If it is determined that the subject does not have capacity to make the decision whether or not to participate in the research project, the subject's legally authorized representative (LAR) will undergo the informed consent process (using the Incapacitated Adult ICF template version). In such cases that it is determined that the subject does not have capacity to consent, verbal assent will be obtained from the subject as well and will be documented in the research chart and checked the box at the bottom of the incapacitated consent form. At the conclusion of screening procedures, including a neurological evaluation, the PI will review the entire forms and then respond to the Inclusion and Exclusion Criteria Checklists and determine eligibility. Subjects who sign consent but are deemed ineligible for the study or otherwise decline to participate after screening evaluation will be recorded in the research database as screen failures with a reason for failure indicated. Data regarding screen failures including demographics, medical history and laboratory results will be retained in the database and available for analytic comparisons with active study cohort.
Participants that pass screen and are considered eligible for the protocol will be enrolled in the study.

10. Subjects - Risk and Benefits

Risks to Subjects

Risks Related to Treatment with Riluzole. Riluzole has been in the market for over 2 decades for ALS, however, potential new risks should be evaluated for AD population.

Experience in almost 800 ALS patients indicates that about 50% of riluzole-treated patients will experience at least one ALT/SGPT level above the upper limit of normal, about 8% will have elevations > 3 X ULN, and about 2% of patients will have elevations > 5 X ULN. Maximum increases in serum ALT usually occurred within 3 months after the start of riluzole therapy and were usually transient when < 5 times ULN. In trials, if ALT levels were < 5 times ULN, treatment continued and ALT levels usually returned to below 2 times ULN within 2 to 6 months.
Among approximately 4000 patients given riluzole for ALS, there were three cases of marked neutropenia (absolute neutrophil count less than 500/mm3), all seen within the first 2 months of riluzole treatment. In one case, neutrophil counts rose on continued treatment. In a second case, counts rose after therapy was stopped. A third case was more complex, with marked anemia as well as neutropenia and the etiology of both is uncertain. Patients should be warned to report any febrile illness to their physicians. The report of a febrile illness should prompt treating physicians to check white blood cell counts.
The most commonly observed AEs associated with the use of RILUTEK more frequently than placebo treated patients were: asthenia, nausea, dizziness, decreased lung function, diarrhea, abdominal pain, pneumonia, vomiting, vertigo, circumoral paresthesia, anorexia, and somnolence. Asthenia, nausea, dizziness, diarrhea, anorexia, vertigo, somnolence, and circumoral paresthesia were dose related. Riluzole Adverse reactions(source Lexicomp) >10%:
Gastrointestinal: Nausea (16%) Neuromuscular & skeletal: Weakness (19%) 1% to 10%:
Cardiovascular: Hypertension (5%), peripheral edema (3%), tachycardia (3%)
Central nervous system: Dizziness (4%), somnolence (2%), vertigo (2%), malaise (1%)
Dermatologic: Pruritus (4%), eczema (2%), exfoliative dermatitis (1%)
Gastrointestinal: Abdominal pain (5%), vomiting (4%), flatulence (3%), oral moniliasis (1%), stomatitis (1%), tooth caries (1%)
Genitourinary: Urinary tract infection (3%), dysuria (1%)
Hepatic: Liver function tests increased (8% >3 x ULN; 2% >5 x ULN)
Neuromuscular & skeletal: Arthralgia (4%), paresthesia (circumoral; 2%), tremor (1%) Respiratory: Lung function decreased (10%), cough increased (3%)
<1%, postmarketing, and/or case reports (Limited to important or life-threatening): Alkaline phosphatase increased, amblyopia, anaphylactoid reaction, anaphylaxis, angioedema, aplastic anemia, arthrosis, asthma, ataxia, bone necrosis, bradycardia, bundle branch block, cataract, cerebral hemorrhage, deafness, dementia, diabetes mellitus, diabetes insipidus, edema, erythema multiforme, extrapyramidal syndrome, facial paralysis, gastrointestinal hemorrhage, gastrointestinal ulcer, GGT increased, glaucoma, hallucination, heart failure, hematemesis, hematuria, hemoptysis, hepatitis, hypercalcemia, hypokalemia, hypokinesia, hyponatremia, hypotension, hypersensitivity pneumonitis, interstitial lung disease, jaundice, LDH increased, leukocytosis, leukopenia, lymphadenopathy, mania, myoclonus, neutropenia, osteoporosis, pancreatitis, peripheral neuritis, pleural effusion, pseudomembranous colitis, purpura, respiratory acidosis, seizure, subarachnoid hemorrhage, thrombosis, urinary retention, urticaria, uterine hemorrhage, ventricular fibrillation, ventricular tachycardia Respiratory: Bronchitis, cough increased, dyspnea, pharyngitis, pneumonia, sore throat Miscellaneous: Diaphoresis, fungal infection, flu symptoms, wandering
<1%, postmarketing, and/or case reports (limited to important or life-threatening): Abscess, angina, breast fibroadenosis, cardiomegaly, cellulitis, cerebrovascular accident, cholecystitis, conjunctival hemorrhage, conjunctivitis, deep vein thrombosis, diabetes mellitus, diverticulitis, eosinophilia, fibrocystic breast, gastrointestinal ulcer, glaucoma, goiter, heart block, heart failure, hemolytic anemia, hepatitis, hyperglycemia, hypertonia, hypokalemia, hypokinesia, hyponatremia, hypoxia, intracranial hemorrhage, jaundice, LFTs increased, MI, neuroleptic malignant syndrome, pancreatitis, pleurisy, pulmonary collapse, pulmonary congestion, pyelonephritis, renal failure, retinal hemorrhage, SVT, thrombocythemia, thrombocytopenia, tongue edema, transient ischemic attack.

Risk related to Brain Imaging:

-MRI/MRS: The MRS procedure is painless and not uncomfortable. It does, however, require the subject to lie still with the head and part of the body confined in a tunnel-like device for up to an hour which may cause anxiety. There is the potential risk that the MRI scanner attracts metal. Subjects with metal parts in their body will be excluded. There is no evidence for long-term effects of MRI procedures on the body. The Food and Drug Administration (FDA) has set recommendations for

exposure in MRI studies and this study satisfies those criteria. There are no contrast agents used for this study, proposing no risk to participants.
MRI studies might involve unsuspected findings which might or might not be a sign of disease and might lead to further medical work-up.

- PET Scan: Risks to the subject associated with the introduction of catheters into veins in the arm for administration of radiotracers during PET scans include the possibility of minor pain, soreness, light-headedness and/or bruising as a result of the needle entering the skin and less commonly, the formation of a small clot or swelling of the vein and bleeding into the tissues surrounding the puncture site. A rare chance of infection also exists. The risks associated with radiation exposure due to radioisotope administration are very small and the dosimetry calculations for the studies that are proposed are within federal guidelines. The radiation dose to the body subjects will receive will be approximately 10 mSv or 1/5th the annual exposure allowed for workers in radiology. For comparison purposes, the dose from PET scan in this protocol is roughly 3-4 times the amount of radiation received annually from radiation present in the natural environment. At this dose level, there are no known risks and this is not expected to cause any pathological consequences. FDG-PET/CT scans included in this study are employed routinely in the care of patients with medical conditions.

- Risks due to venipuncture: Potential side effects associated with venipuncture include discomfort, pain, bleeding, phlebitis, infection, and/or hematoma at the insertion site, and syncope.

- Risk due to neuropsychological testing: Subjects are at risk of boredom and embarrassment from being confronted by their deficits on neuropsychological testing

Withdrawal criteria and procedures below:

Study subjects whose liver enzymes are > 3 X ULN will have their liver enzymes monitored every one to two weeks until it returns to baseline.
Study drug will be discontinued if ALT levels are equal of greater than 5 X ULN or if clinical jaundice develops. Judith Neugroschl, MD, will be monitoring laboratory safety values including liver enzymes and WBC so that the PI an be maintained blinded.
The study drug will be discontinued if there is evidence of marked neutropenia (absolute neutrophil count less than 500/mm3).

Cases of interstitial lung disease have been very rarely reported in patients treated with riluzole, some of them severe; upon further investigation, many of these cases were hypersensitivity pneumonitis. If respiratory symptoms develop such as dry cough and/or dyspnea, chest radiography will be performed, and in case of findings suggestive of interstitial lung disease or hypersensitivity pneumonitis (e.g., bilateral diffuse lung opacities), riluzole will be discontinued immediately. In the majority of the reported cases, symptoms resolved after drug discontinuation and symptomatic treatment.

Description of Procedures Taken to Lessen the Probability or Magnitude of Risks

-Safety will be assessed through monitoring of all adverse events that occur. Patients will be instructed about possible adverse effects.
-Safety assessments will include monthly laboratory tests (hematology, chemistry) and monthly thorough neurologic evaluation. Full neuropsychological testing performed will take place at baseline, 3 months and 6 months. Since the Principal Investigator will be blind to placebo x experimental subjects, ADRC physician will be responsible for checking results of all laboratory tests, including complete blood count, comprehensive metabolic panel and particularly liver enzymes, which can be more commonly affected.
-Medical records and routine laboratory data will be handled with HIPAA compliance and protected by internal rules and regulations.
-To minimize risks associated with phlebotomy, blood drawing will be performed by experienced phlebotomists under aseptic conditions. Insertion of catheter for PET scan will be performed by experienced medical personnel at Weill Cornell Medicine. Should discomfort occurs, we will provide appropriate treatment.
-Adverse events will be managed by the clinical trial team. They will assess and treat the event as appropriate, including referral to an independent physician or department.
-Safety monitoring will be conducted both internally and by an external data safety monitoring board [DSMB] which will review neuropsychological testing and adverse events as outlined by DSMB.
-In addition, a summary will be produced for each of the following: serious adverse events; events leading to withdrawal from treatment; events judged by the investigator to be related to study drug; all events by severity.

-MRI/MRS: Subjects with metal in the body will be excluded from the study due to potential risk that the MRI scanner attracts metal. The subject will be able to communicate with MRI operator throughout the procedure, in case of anxiety or claustrophobia, the subject will be able to stop it at any time.
-All brain imaging in this study will be read and interpreted by Weill Cornell Medicine Department of Radiology the report will be provided to the Principal Investigator. In case of unsuspected incidental findings
occur, the PI of the study, Dr. Pereira, a neurologist, will share the findings with the subject or a physician the subject may designate.

Toxicity Management and Stopping Rules:
-Study subjects whose liver enzymes are higher than 3 times upper normal limit will have their liver enzymes monitored weekly until it returns to baseline (based on data on ALS patients outlined above). If the liver enzyme levels do not decrease within 2 weeks of follow-up labs, the ADRC physician, who will check all laboratory results to maintain PI blind in the study, will communicate to DSMB and the medication will be stopped.
-Study drug will be immediately discontinued if liver enzymes are equal or higher than five times the upper normal limit or if clinical jaundice develops.
-The study drug will be discontinued if there is evidence of the rare side effect of marked neutropenia (absolute neutrophil could less than 500/mm3).
-Cases of interstitial lung disease have been very rarely reported in patients treated with riluzole; upon further investigation, many of those cases were hypersensitivity pneumonitis. If respiratory symptoms develop such as dry cough and/or dyspnea, chest radiography will be performed, and in case of findings suggestive of interstitial lung disease or hypersensitivity pneumonitis (e.g., bilateral diffuse lung opacities), riluzole will be discontinued immediately. In the majority of reported cases, symptoms resolved after drug discontinuation and symptomatic treatment.

Provisions for Research Related Harm / Injury

If the participants are injured or made sick from taking part in this research study, medical care will be provided. Generally, this medical care will be billed to the subject's health care insurance. In some cases, the costs of this care may be paid by someone else. In the event of injury the PI is contacted.

All forms of medical testing – whether routine or experimental – involve some risk of injury. In spite of all safety measures, the participant might develop medical problems from participating in this study. The participant must report any suspected illness or injury to the study doctor immediately. If such problems take place, Mount Sinai Hospital will provide emergency medical treatment and will assist the participant in getting proper follow-up medical treatment. The Dana Foundation and Alzheimer's Drug Discovery Foundation will not provide compensation for research-related injury.
Incidental findings on MRI of clinical meaning or significance will be reviewed by the PI, a neurologist, with the participant and/or responsible caregiver. If the incidental findings warrant any further clinical attention then the PI will work with patient to find suitable resources (e.g. a conversation with the patient's primary care doctor or a referral to a neurologist – this would depend upon the nature of the finding).

Expected Direct Benefit to Subjects

The subject may receive no benefit from participation.

Subjects may personally benefit from the access to the medical expertise of the doctors conducting this research study, and the medical care they deliver.

If riluzole is shown to have benefit to patients with Alzheimer's disease, some participants could benefit from this study. However, we do not know if riluzole is of benefit and this study will start to answer this question.

Benefit to Society

Benefits to society include the possibility that the study medication may show to be effective in treating patients with Alzheimer's disease. This study will generate further knowledge of glutamatergic dysregulation and the neurobiology of Alzheimer's disease that will be informative for future studies.

Provisions to Protect the Privacy Interests of Subjects

From the time participants are identified for recruitment until they complete study participation, every effort will be made to ensure their privacy. Phone calls made to subjects will be made in the privacy of the study coordinator or investigator's office.

In order to ensure that subjects and their caregiver feel at ease with the research situation in terms of the questions being asked and the procedures being performed, the study staff will make every effort to explain the purpose of any testing conducted, what the test(s) will be like, how long testing will take, and what the day's schedule will be, including when the subject and caregiver may take breaks. After answering any questions, the subject (or study partner), as appropriate and feasible, will be asked to wait outside the test room in the designated waiting area. If the subject will comply only with the caregiver present, the caregiver will be instructed not to provide answers to any neuropsychological testing, and to sit in an area of the room where the subject will not easily turn to him or her for feedback.

It is acceptable and appropriate for the members of the research team to approach the prospective participants about research, because they have completed their IRB trainings, including GCP, human subject protection and HIPAA trainings, and have an adequate knowledge of the study protocol.

Economic Impact on Subjects

There are no costs to participating in this study. Clinical and neurological assessments, neuroimaging, neuropsychological testing and blood tests are free of charges to participants and the subjects' other medical care at Mount Sinai or elsewhere is not contingent upon participation in the study.

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11. Subjects - Adults Without Capacity

There is Anticipated Direct Benefit to the Subjects No

Assent is Required of None of the Subjects

PI must attest that all of the following are true.

* ***The proposed plan for the assessment of the capacity to consent is adequate. * The objectives of the trial cannot be met by means of study of subjects who can give consent personally.***
* ***The foreseeable risks to the subjects are low.***
* ***The negative impact on the subject's well-being is minimized and low.***
* ***The trial is not prohibited by law.***
* ***Subjects have a disease or condition for which the procedures involved in the research are intended.***
* ***Subjects will be particularly closely monitored.***
* ***Subjects will be withdrawn if they appear to be unduly distressed.***
* ***The proposed plan for the assessment of the capacity to consent is adequate (and complies with institutional policy GPP-312).***
* ***The assessment of the capacity to consent will be performed by a qualified attending physician with appropriate training, licensing and certification, with special attention paid to qualifications re: assessing incapacity due to mental illness, mental retardation or developmental disability.***
* ***The proposed plan for the assessment of capacity includes the assessment of the cause and extent of the incapacity and likelihood that the subject will regain capacity.***
* ***The PI has indicated that he/she will document this determination with the above details of the assessment appropriately (eg. In the medical record when applicable and in research record).***
* ***The consent document includes a signature line for a legally authorized representative.***

12. Procedures - Narrative

Description of the Study Design

A double-blinded, randomized, placebo-controlled study will be performed. Forty-eight individuals with a diagnosis of mild Alzheimer's disease between 50-95 years old will complete the study. There will be two cohorts of 50-74 and 75-95 years old that will be age-matched. All forty-eight individuals must be on donepezil or rivastigmine or galantamine at a consistent dose for at least 2 months. Patients will be considered for inclusion if they were previously unable to tolerate acetylcholinesterase inhibitors and as a result, are no longer on the medication for at least 2 months.

Twenty-four mild Alzheimer's disease patients will receive riluzole and another 24 will receive a placebo. All patients will have a neurological evaluation and neuropsychological tests performed to confirm that they meet criteria for probable Alzheimer's disease set out by the National Institute on Aging – Alzheimer's disease Association (29) that recently revisited the NINCDS-ADRDA criteria (30) and to have mild Alzheimer's disease. See full inclusion and exclusion criteria. (see below, protocol was later amended for sample size that at least 40 subjects would have completed the study).

Patients will be imaged at baseline, after 3 months and 6 months of the riluzole/placebo administration with magnetic resonance spectroscopy measures for NAA, glutamate in posterior cingulate and for exploratory analysis the hippocampus. FDG-PET will be obtained at baseline and after 6 months. Neuropsychological testing will be performed at baseline, after 3 and 6 months of the study drug administration as per neuropsychological testing panel described below.

Riluzole will be administered at a dose of 50mg once a day for the first 5 days of treatment to see whether it is well tolerated. This will be followed by twice a day dosing for the remainder of the study. Patients will be advised to take study article 1hr before or 2hrs after meals to avoid decreased absorption. This dose is FDA approved and has been safely used in ALS patients for several years. Because there was not much background information whether combination treatment with acetylcholenesterase inhibitors and riluzole, both neurologically active agents, might interact an impact neuropsychological function, the DSMB reviewed on an ongoing basis the results of mental status and neuropsychiatric testing in real time obtained at the first 4 visits (approximately 3 months) of 10 subjects evenly divided on drug and placebo.

If a potential study subject presents for screening but is currently taking Namenda® (memantine), after informed consent is obtained, they will be asked to voluntarily washout this drug from their system for at least 6-weeks prior to participating in the study if they choose to participate in the study. The PI, Dr. Pereira, will discuss with the subject and their LAR the possible implications of stopping this medication and subject and their physician will make a decision on whether to stop Namenda or not. Of note, memantine is only FDA-approved for moderate-severe Alzheimer's disease as clinical trials have failed to demonstrate any benefit in the early stages of Alzheimer's disease that is aimed for this study population.

Ana Pereira, MD PI on the study moved from Rockefeller to Mount Sinai, therefore, the study will also continue here at Mount Sinai once approved. All neuroimaging for this study is being conducted at Weill Cornell (for Rockefeller enrollees); we plan to continue to use this Neuroimaging center once the study is approved at Mount Sinai. The Weill Cornell site has IRB approval to conduct the neuroimaging for the study. Weill Cornell has submitted an amendment to their IRB to accept Mount Sinai enrollees once the study is approved at Mount Sinai

Description of Procedures Being Performed

All Neuroimaging will be performed at Citigroup Biomedical Imaging Center at Weill Cornell Medicine where the imaging portion of the protocol has an IRB approval.

FDG PET Methods

For each FDG PET scan, 5 mCi of florodeoxyglucose will be administered followed by a 40 minute uptake period during which the participant was in a resting state with eyes and ears open, without activity or audiovisual distraction. Images will be acquired on a Siemens Biograph 64mCT scanner as a series of 4 frames of 5 minutes each. In some initial cases, a full dynamic scan will performed and late timeframes extracted for processing and analysis.

All PET images are inspected for motion or artifact. Using SPM12 (Wellcome Trust), motion correction are performed and frames averaged into a static image. Each 6 month scan are coregistered to the baseline FDG scan, which is co-registered to the participant's T1-weighted MRI scan. MRI scans are segmented into gray, white, and CSF tissue and spatially transformed to a template in MNI space, and the spatial transformations applied to the PET scans. Regions of interest atlases are thresholded with a smoothed gray participant-specific segment and average intensities within each region of interest are measured. A reference region for calculation of Standardized Uptake Value Ratios (SUVRs) is defined based upon preserved voxels in the AD Progression Classifier, most pronounced in the paracentral region. Longitudinal changes in SUVRs using this reference will be compared to SUVRs referenced to (separately) centrum semiovale white matter, cerebellum, pons, and whole brain. While these regions tend to be more variable due to

technical factors (cerebellum, pons), progressive hypometabolism effects (whole brain), or potentially affected by riluzole (cerebellum), consistency in results could help to confirm the robustness of findings. Images will also be evaluated (scored) using the FDG AD Progression classifier.
FGD-PET analysis will be performed by ADM diagnostics, in collaboration with Dawn Matthews.

Rockefeller University/PI contracted with ADMdx to analyze the FDG-PET images. PET scans will be deidentified and coded and sent via mail service to ADMdx.

MRI and ^{1}H MRS methods
All MRS neuroimaging studies will be conducted on a multinuclear 3.0T GE SIGNA HDx or Discovery MR750 system. Each enrolled subject will undergo high resolution axial T_1-, T_2- and spin density-weighted scans. These images will be used to prescribe the voxels of interest for the ^{1}H MRS scans. A T_1-weighted volumetric scan will be acquired using a spoiled gradient-recalled echo sequence (SPGR, TR 12.21 ms, TE 5.18 ms, flip angle = 7, voxels 0.94 x 0.94 x 1.5mm) on the GE HDx system or a magnetization-prepared rapid gradient-echo sequence (MPRAGE, TR 8.34 ms, TE 1.7 ms, flip angle = 7, voxels 0.94 x 0.94 x 1.5mm) on the GE Discovery MR750, along with an axial fast Fluid-Attenuated Inversion Recovery (FLAIR) scan for brain tissue segmentation and use in PET image co-registration and region of interest definition, and to rule out exclusionary focal brain lesions.

In vivo brain levels of glutamate, NAA, tCr and other major metabolites will be obtained using ^{1}H MRS and a 2x2x2-cm^3 Posterior Cingulate Cortex (PC) voxel of interest with TE 30 ms, 129 constant-time increments (t1) of 0.8ms, and TR 1500 ms and a receive-only 8-channel phased-array head coil. The distinguishing feature of CT-PRESS is that it enables MRS measurement of glutamate uncontaminated by glutamine
^{1}H MRS Data Processing and Quantification
The areas of the individual spectral peaks, which are proportional to their respective concentrations, are obtained by frequency-domain fitting each resonance to a Gauss-Lorentz (i.e., pseudo-Voigt) lineshape function using the Levenberg-Marquardt nonlinear least-squares algorithm as implemented in ^{1}H MRS data processing software written in IDL**]** for CT-PRESS and J-edited spectra, respectively. The levels of NAA, glutamate, GABA, Glx and other metabolites are expressed semi-quantitatively as ratios of peak areas relative to that of the unsuppressed water signal (W) from the same voxels.

Neuropsychological tests will be performed at MSSM, by neuropsychologists from ADRC and Neurology Department:
-Mini-Mental State Exam (31)
-Clinical Dementia Rating (32)
-Attention/Psychomotor Speed: WAIS-IV Digit Span forward (33); Trail Making Test Part A (34)
-Memory: Logical Memory subtest (older adult version only)- WMS IV (37)(33) and Benton Visual Retention Test V (38)
-Language: Letter and Category Fluency (36)
-Executive Function/Working Memory: Trail Making Test B (34); WAIS-IV Digit Span Backwards (33) -
Visuospatial: Clock Drawing Test (35)
-Premorbid ability: National Adult Reading Test-Revised (39)
-Behavior/Mood: Neuropsychiatric Inventory (46)
-Alzheimer's disease Assessment Scale - Cognitive Subscale (42, 43)
-ADCS-Activities of Daily Living (ADL) Inventory (41)

Screening Visits Screen Visit #1 (3 hours)

Consent process
Medical History and Neurologic Evaluation
Baseline Laboratory (CBC, comprehensive metabolic, LFT, Hba1c, Cytokines (2 Tubes).

***Subjects will not begin washout of medication until they are informed by the PI, Dr. Pereira of any laboratory result(s) that may exclude them from continuation in the study).

Screening Visit #2 (approx. 2 hours)
After all labs are reviewed and if the subject is considered eligible, he/she will receive a call to have their baseline MRS and PET scan at Citigroup Biomedical Imaging Center at Weill Cornell Medicine.

After MRI is read and reviewed for eligibility, Study Visit #1 will be scheduled.

STUDY VISITS

Study Visit #1 (within 4 weeks after Screening visit #2)

Neuropsychological testing
Randomization to study drug (riluzole) or placebo. First dose to be taken the following morning.
Riluzole (Rilutek) tablets should be taken at least an hour before, or two hours after, a meal to avoid a food-related decrease in bioavailability. Study participant and caregiver will be taught how to self-administer the study drug and how to complete the study drug diary.
Labs: Cytokines (if not previously obtained at screening vs. 1).
(If the study participant is not randomized to study drug the day of neuropsychological testing, the study subject will be brought back for study visit #1-A)

Study Visit 1-A

Randomization to study drug (riluzole) or placebo (If not done during study visit #1). First dose to be taken the following morning.
Riluzole (Rilutek) tablets should be taken at least an hour before, or two hours after, a meal to avoid a food-related decrease in bioavailability. Study participant and caregiver will be taught how to self-administer the study drug and how to complete the study drug diary.
Labs: Cytokines (if not previously obtained at screening vs. 1).

**Once the study medication has begun, the PI, Dr. Pereira is blinded to ALL laboratory results. Dr. Judith Neugroschl will monitor laboratory safety values including liver enzymes and WBC and conduct a clinical evaluation so the PI can maintain study blind.

Study Visit #2 (1 hour)(30 days after study visit #1 or #1A)(+/- 7 days)
Targeted mental status exam as required, adverse event (A/E) assessment, vital sign (VS), weight (Wt).
Labs: CBC, Comprehensive metabolic, liver function test (LFT's), genetic testing for APOE collect
returned bottle of study medication
calculate study drug accountability based on diary and returned tablets

dispense a new bottle of study drug
dispense a new diary
Study Visit #3 (1 hour) (60 days after study visit #1)(+/- 7days) clinical assessment -
Targeted mental status exam as required, A/E assessment, VS, Wt.
Labs: CBC, Comprehensive metabolic, LFT's, genetic testing for APOE (if not obtained at study visit #2).
collect returned bottle of study medication
calculate study drug accountability based on diary and returned tablets
dispense a new bottle of study drug dispense a new diary

Study visit #4 (2-3 hours) (90 days after study visit #1) (+/- 7days) clinical assessment -
Targeted mental status exam as required, A/E assessment, VS, Wt.
Neuropsychological testing (to be done prior to lab tests to avoid stress)
Labs: CBC, Comprehensive metabolic, LFTs, (Labs to be drawn after neuropsychological testing).
collect returned bottle of study medication
calculate study drug accountability based on diary and returned tablets
dispense a new bottle of study drug
dispense a new diary
Imaging: MRS (to be done within two weeks of visit)

Study Visit #5 (1 hour)(120 days after study visit #1) (+/- 7 days) clinical assessment - Targeted mental status exam as required, A/E assessment, VS, Wt. Labs: CBC, Comprehensive metabolic, LFT's collect returned bottle of study medication
calculate study drug accountability based on diary and returned tablets
dispense a new bottle of study drug dispense a new diary

Study Visit #6 (1hour) (150 days after study visit #1)(+/- 7 days) clinical assessment - Targeted mental status exam as required, A/E assessment, VS, Wt. Labs: CBC, Comprehensive metabolic, LFT's collect returned bottle of study medication
dispense a new diary
calculate study drug accountability based on diary and returned tablets
dispense a new bottle of study drug

Study Visit #7 (2-3 hours) (180 days after study visit #1; (+/- 7days) clinical assessment - Targeted mental status exam as required, A/E assessment, VS, Wt. Labs: CBC, Comprehensive metabolic, LFT's, Cytokines (2 tubes)
collect returned bottle of study medication
calculate study drug accountability based on diary and returned tablets
Neuropsychological testing
Imaging: MRS and FDG-PET (to be done within two weeks of visit).

Unscheduled Study Visits:
Study subjects may be asked to return to our research clinic for additional bloodwork to be taken in the event of abnormal or missing labs.

Study subjects whose liver enzymes are > 3 times the ULN, will have their liver enzymes monitored every one to two weeks until it returns to baseline. If the liver enzyme levels do not decrease within 2 weeks of follow-up labs, Dr. Judith Neugroschl, who will check all laboratory results to maintain PI blind in the study, will communicate to DSMB and the medication will be stopped. Study drug will be immediately discontinued if liver enzymes are equal or higher than five times the upper normal limit or if clinical jaundice develops.

Changes to study participants medications should be avoided. Any changes to medications, the participant and their caregiver will be instructed to notify Dr. Pereira of those changes.

Description of the Source Records that Will Be Used to Collect Data About Subjects

Medical records, neurological examination, mini-mental state exam will be evaluated on screening visit to determine eligibility, followed by neuroimaging and neuropsychological testing.

Description of Data that Will Be Collected Including Long-Term Follow-Up

Neuroimaging data for FDG-PET and MRS will be used for quantitative analysis for research purposes as well as neuropsychological data.

Research Requires HIV Testing No

13. Procedures - Genetic Testing

Genetic Testing Will Be Performed Yes

Guidance and Policies > Future Use Data Sharing and Genetic Research

Genetic Testing Will Be Performed for Clinical Purposes No

Genetic test is being done for research purposes only and the following must be present in the consent form:

**** a statement that the sample will be used for future Genetic Tests;***

**** the time period during which the tissue will be stored, or if no time limit is specified, a statement that the tissue will be stored for as long as deemed useful for research purposes;***
**** a description of the policies and procedures to protect patient confidentiality;***
**** a statement of the right to withdraw, at any time, consent to future use of the tissue, and the name of the organization that should be contacted to withdraw consent;***
**** a statement allowing individuals to consent to future contact for any or all purposes, including the following: (i) research purposes; (ii) provision of general information about research findings; and (iii) information about test on their sample that may benefit them or their family members in relation to their choices regarding preventive or clinical care , and***
**** a statement explaining the benefits and risks of consenting to future contact.***

14. Procedures - Details

Surveys or Interviews Yes

Type of Instruments Being Used Standardized

Names of Standardized Instruments

Standardized neuropsychological testing, MRI/MRS and FDG-PET will be performed as described under "Description of Procedures Being Performed".

Neuropsychological tests are standardized instruments routinely used in the ADRC to test cognition (memory and thinking abilities).

Audio / Photo / Video Recording No

Deception No

Results of the Study Will Be Shared with Subjects or Others How the Results Will Be Shared Yes

During participation in the study subjects will have access to their medical records and any study information that is part of that record. MRI structural imaging reading by a radiologist will also be made available to participants.

Research results (genetic testing and cognitive testing) will not be shared with the participant and are considered for research purposes only.

When the Results Will Be Shared

The final results of the study may be shared with the participant after the publication.

At subject's request.

15. Consent - Obtaining Consent

Consent Process Adult Consent, Legally Authorized Representative (LAR) Permission

Where and When Consent Will Be Obtained

Neurology Office and ADRC prior to initiation of any research procedures

Waiting Period for Obtaining Consent

The investigator or investigator's representative will explain the study and review the consent document with the potential subject and study partner. The subjects and study partners will also have the opportunity to read the consent document on their own. Ample time will be given for the participant and study partner to ask any questions pertaining to the study.

SOP HRP-090 Informed Consent Process for Research Is Being Used Yes

PPHS Worksheets, Checklists and SOPs

Process to Document Consent in Writing Will Use Standard Template

Non-English Speaking Participants Will Be Enrolled No

Justification for Not Enrolling Non-English Speaking Participants

To maintain standardization of neuropsychological testing previously performed and previous recruitment at Rockefeller University.

16. Consent - Legally Authorized Representative

Process to Determine Whether an Individual is Capable of Consent

To ensure that the protocol is consistent with the hospital policy regarding research involving incapacitated adults, the study team will comply with Mount Sinai Hospital Policies regarding Incapacity, Policy A3-113 and A3-113.9 revised 6/12. An attending level physician will be determining whether a potential participant does NOT have capacity and authorize a surrogate as appropriate. If participant is found to lack capacity, their legal representative will decide how to proceed. If either the subject or legal representative objects to participation then they will not be enrolled in the study. If the subject and the legal representative wish to proceed, the legal representative will sign the consent form for an incapacitated adult and a verbal assent will be obtained from the subject as well and will be documented in the research chart and checked the box at the bottom of the incapacitated consent form. If at any point during the course of the study the investigator feels that the subject has lost capacity, a capacity assessment will be done. For this capacity assessment, the subject will be asked to reiterate in their own words the purpose of the research, what they will need to do as participants in the study, and what the potential risks, benefits, and alternatives are. If the patient is found to have the capacity to understand and sign the consent form, the subject will sign the consent form. If the subject is found to lack the capacity to understand their participation in the study, the subject's LAR will decide how to proceed.

Prioritized List of Individuals from whom Permission will be Obtained

This study adheres to the HRP-013 SOP regarding legally authorized representatives. The hierarchy of who is able to be considered a legal representative is as follows: i) Court appointed guardian who is specifically given authorization to consent to participation in research. ii) A court appointed guardian who is specifically given authorization to consent to health care. iii) A previously designated health care proxy iv) Spouse, partner or significant other.

Process for Assent of the Subjects

Verbal assent will be obtained for incapacitated subjects.
If the subject is determined to not have capacity at the time of the consent process then the Incapacitated ICF will be used.

For research conducted in New York State, review "SOP HRP-013 Legally Authorized Representatives, Children, and Guardians" to be aware of which individuals in the state meet the DHHS and FDA definition of "legally authorized representative."

For research conducted outside of New York State, obtain consultation from Mount Sinai legal counsel as to the definition of "legally authorized representative" in the jurisdiction(s) where you are performing your research. After receiving consultation with Legal, provide an explanation in this section about which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this Human Research.

17. Consent - Documents

Consent Documents

Type	revised consent Adult
Name	Consent form Adult
Upload	Consent form Adult_30JAN2018.doc
Type	revised consent Incapacitated Adult
Name	Consent form Incapacitated Adult

Upload

Consent form Incapacitated Adult_30JAN2018.docx

Consent Templates

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For research conducted outside of New York State, obtain consultation from Mount Sinai legal counsel as to the definition of "legally authorized representative" in the jurisdiction(s) where you are performing your research. After receiving consultation with Legal, provide an explanation in this section about which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this Human Research.

18. Data - Collection

Health Related Information Will Be Viewed, Recorded, or Generated Yes

Description of Health Information That Will Be Viewed, Recorded, or Generated

Mini Mental State Exam scores, neuropsychological testing and neuroimaging as described in detail under "Description of Procedures Being Performed"

Non-Health Related Information Will Be Viewed or Recorded No

HIV / AIDS Related Information Will Be Viewed or Recorded No

Data That Will Be Viewed, Recorded, or Generated Contains ANY of the Following Directly Identifiable Information Yes

Will Be Viewed	Name, Social Security Number, Medical Record Number, Address by street location, Telephone number, Email Address
Will Be Recorded	Name, Social Security Number, Medical Record Number, Address by street location, Telephone number, All Elements of Dates for Dates Directly Related to an Individual (i.e., Birth Date, Admission Date, Discharge Date), Email Address
Data Collection Sheet	DATA AND SAFETY MONITORING PLAN_Mount Sinai and Rockefeller University.docx
Data Collection Source(s)	Participant, Medical Chart (Paper or Electronic), Data Warehouse, External Site, Other Research Study, Clinical Database

19. Data - HIPAA

Obtaining HIPAA Authorization Yes

How PHI Will Be Protected from Improper Use or Disclosure

PERSONALLY IDENTIFIABLE INFORMATION WILL NEVER BE KEPT WITH HEALTH INFORMATION. ONLY THE STUDY TEAM WILL HAVE ACCESS TO AN ENCRYPTED SPREADSHEET THAT LINKS A PARTICIPANT'S PERSONAL INFORMATION AND THEIR STUDY ID (DE-IDENTIFIER). ALL RESEARCH DATA WILL BE DEIDENTIFIED.

PHI Will Be Destroyed at the Earliest Opportunity Consistent with the Research Yes

When and How PHI Will Be Destroyed

DE-IDENTIFIED RESEARCH DATA WILL BE KEPT LOCALLY FOR 7 YEARS FOLLOWING THE COMPLETION OF THE LAST SUBJECT IN THE TRIAL. NO PHI IS BEING STORED. PERSONALLY IDENTIFIABLE INFORMATION WILL BE DESTROYED ONCE IT IS NO LONGER NEEDED (I.E. WE NO LONGER HAVE A NEED TO CONTACT THAT PATIENT AS A PART OF STUDY PARTICIPATION). PAPER RECORDS WILL BE DESTROYED FOLLOWING ISMMS GUIDELINES USING SENSITIVE DOCUMENT SHREDDING BINS.

PHI Will Be Shared No

PI must attest to the following.

**** I assure that the protected health information (PHI) will not be disclosed to any other person or entity not listed on this form except where required by law or for the authorized oversight of this research project. If at any time I want to reuse this PHI for other purposes or disclose it to other individuals or entities I will seek approval from the IRB.***

20. Data - Storage

Location Where Data Will Be Stored

Data will be stored in a secure location during the course of the study and doubled locked at room A20-02a at Annenberg building. Only investigators in this protocol will have access to the data files.

How will the data be stored?	With a Code That Can Be Linked to the Identity of the Participant
Research Personnel Responsible for:	Ana Pereira
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	Yes
Research Personnel Responsible for:	Tarah Gustafson
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Emily Lampshire, Caroline Meuser
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Florence Lau
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	

Research Personnel Responsible for:	Caroline Meuser
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Hillel Grossman
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Julie Ciardullo
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	

Research Personnel Responsible for:	Gina Garcia Camilo
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Judith Neugroschl
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	Yes
Research Personnel Responsible for:	Allison Ardolino
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Amy Aloysi
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Jonathan Greenberg
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Nelly Velasco
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Martin Ljekocevic
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Margaret Sewell
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Clara Li

Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Michael Kinsella
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Kelly Pun
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Caroline Meuser
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Chloe Larson
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	

Duration Data Will Be Stored

15 years

Steps That Will Be Taken to Secure the Data During Storage, Use, and Transmission

Data will be stored in a secure location during the course of the study and doubled locked at room A20-02a at Annenberg building.
Imaging conducted at Citigroup Bio-imaging at Weill Cornell Medicine will be coded as below and kept secure and double locked on CDs at Dr. Dikoma's Shungu office (PI at Weill Cornell Medicine for Neuroimaging portion of the study)

APE-XXX-101a; APE-XXX-102a, etc., will be used for the first MRS scan. APE-XXX-201a; APE-XXX-202a, etc., will be used for the first PET scan.
If a subject undergoes a second scan (e.g., a second PET scan), they will be coded : APE-XXX-201b, APEXXX-202b, etc.

After completion of the study the data source will be stored in a secure location for a period of 15 years.

Power Analysis/Data Analysis Plan (Including Any Statistical Procedures)

In a previous study (Alexander, 2002- ref 45) using longitudinal FDG-PET to evaluate cerebral metabolic decline in similar subjects, it was concluded that "24 patients with Alzheimer's disease per active treatment and placebo group would be needed to detect a 33% treatment response with p # 0.05 (two- tailed) and 80% power". A previous study of memantine, which affects the glutamatergic system through a different mechanism, suggested that significant treatment-related differences in glucose metabolism measured using FDG PET in posterior cingulate and precuneus could be detected in Alzheimer's disease patients at 80% power, 2-tailed t-test, significance at $P<0.05$ (uncorrected for multiple comparisons), with as few as 16 participants per arm (Wang T, Huang Q et a. J Clin Psychopharmaco

2013). Our primary outcomes will be FDG-PET and NAA results. In (Adalsteinsson, 2000 - ref 24), the observed mean change of NAA concentration over a year was #12%, with a standard deviation (SD) of 15%, compared to no change among the healthy controls with an SD of 8%. Hence, we expect a change of #6% over 6 months with an SD of 10% among controls. If riluzole were able to slow down disease progression, we would expect an SD of 8%. Given that the consequences of type I errors in this pilot study are substantially lower than in a later-stage confirmatory trial, we will accept a level of .20 (two- sided), resulting in a nominal sample size requirement of 21 per group. Subjects who are dropping out will be replaced.

As per IRB Approved Continued Review (dated 11/25/2019), we re-visited power analysis and changed total completed subjects across sites to at least 40 (rather than 48 originally planned).

Analysis plan by ADM dx for FDG PET added to protocol prior to unblinding and approved by IRB on 06/18/2020:

FDG-PET analysis plan from ADMdx prepared by Dawn Matthews

Background

In this exploratory Phase II clinical trial, FDG PET images, measuring cerebral glucose metabolism, have been acquired on patients with a clinical diagnosis of mild Alzheimer's disease before and after 6 months of treatment with riluzole or placebo. Volumetric MRI T1 weighted scans have also been acquired at these timepoints.

Analysis Objectives

The primary analysis objective is to compare the 6-month longitudinal change in regional cerebral glucose metabolism in patients treated with riluzole vs. those treated with placebo.

Secondary objectives are to:

- evaluate relationships between covariates of age, sex, and ApoE4 carrier status to changes in glucose metabolism, and compare longitudinal change in younger vs. older participants
- characterize and stratify patients at baseline with regard to pre-treatment patterns and severity of hypometabolism; compare longitudinal change in placebo vs. treatment within these strata
- compare longitudinal change in regional brain volume between patients treated with riluzole vs. placebo
- correlate baseline glucose metabolism and changes in FDG PET and volumetric measures to clinical endpoints

Image Quality Control and Processing

Prior to unblinding, all scans will be quality controlled and processed. Quality control of FDG PET scans includes verification that all brain anatomy was included in the scan, checks for adequate image signal (counts), qualitative and quantitative evaluation of inter-frame motion, review for potential emission-transmission scan misalignment (asymmetry), and checks for occipital or other artifact. Quality control of volumetric MRI scans includes verification that all brain anatomy was included in the scan, checks for adequate gray/white contrast and resolution, review for motion artifact, and examination for other image artifact that could impact processing.

FDG PET scans will be motion corrected and the timeframes averaged to create a single scan per patient per visit. Six-month visit PET scans will be co-registered to their baseline PET scan, and PET scans will be co-registered to their corresponding volumetric MRI. FDG PET images will be smoothed to a uniform resolution consistent with images from the Alzheimer's Disease Neuroimaging Initiative.

Volumetric MRI scans will be processed using Freesurfer version 7.1, producing segments (binary masks) that define anatomical regions in the native space of the MRI scan.

MRI scans will be spatially transformed to a common template and the transforms applied to the FDG PET scans. FDG PET scans will be intensity normalized to whole brain.

Quantitative Measurement

Prior to unblinding

The anatomical segments derived using Freesurfer will be smoothed and thresholded, and used to measure regional values on the FDG PET scans.

FDG PET scans will also be evaluated using ADMdx's Dementia Differentiation Classifier and AD Progression Classifier. These classifiers compare the scans to previously developed patterns that allow quantitation of the degree to which a scan expresses an Alzheimer's like disease pattern. The AD Progression scores can then be used in statistical analysis.

These steps will produce a set of blinded values.

Following unblinding

Once group designations are available, the spatially normalized, intensity normalized images will be evaluated using ADMdx's multivariate classification software. This allows identification of patterns of glucose metabolism, or in the case of MRI, volumetric measures, that differentiate between classes. Analyses will include the following:

- Comparison of placebo and riluzole treatment groups at baseline
- Two class analyses of placebo group at baseline and 6 months, and riluzole group at baseline and 6 months
- Combined analyses of placebo and riluzole groups at baseline and 6 months
- Subgroup analyses using age, baseline severity, and ApoE4 carrier status as stratification factors

The outputs of the classifier analyses are numeric scores and metabolic patterns of hypometabolism and preservation or hypermetabolism relative to whole brain (for FDG) or a listing of brain volumes contributing to group differentiation with relative weights. The numeric scores reflect pattern expression in each case.

Region of interest values and classifier scores will be evaluated in comparison to clinical endpoints at baseline and with regard to longitudinal change.

Patients who exceed the longitudinal time window by more than one month will be flagged and excluded from these group analyses, but will be then scored against the patterns derived. This will prevent them from influencing the patterns, but will still allow for evaluation.

Statistical Analysis

The FDG PET analysis primary endpoints are:

- Regional SUVRs: hippocampus, posterior cingulate, precuneus, lateral temporal, inferior parietal, and middle frontal

Other endpoints:

- AD Progression score
- Classifier scores from the combined multivariate analysis of placebo and riluzole at baseline and after 6 months

Endpoints will be evaluated using t-tests in JMP version 15.1 (SAS) with adjustment for baseline covariates if these are determined to differ between groups or to be significant in the analyses. Covariates evaluated will be age, sex, baseline endpoint measure, and ApoE4 status. A p-values of 0.05 will be considered significant. Because this is an exploratory study with a limited number of patients, correction for multiple comparisons, though evaluated, will not be used to determine significance.

Data Monitoring Committee Description	DATA AND SAFETY MONITORING PLAN_Mount Sinai and Rockefeller University.docx
DMC Charter Available	Yes
Data Monitoring Committee Charter	DATA AND SAFETY MONITORING PLAN_Mount Sinai and Rockefeller University.docx
Will the Research Include Data Coordinating Center Activities?	No

IRB-17-02664 Initial Application Ana Pereira

21. ***Specimen Banking***

Where the Specimens Will Be Stored

Blood samples in freezers at ADRC and Neurology Department will be stored with participants' codes. No identifiers will be associated with samples in freezers.

Sources are stored in the research office room A20-02A at the Annenberg building under double lock with only access by PI and research coordinator specified for this study.

Imaging conducted at Citigroup Bio-imaging at Weill Cornell Medicine will be coded as below and kept secure and double locked on CDs at Dr. Dikoma's Shungu office (PI at Weill Cornell Medicine for Neuroimaging portion of the study)

APE-XXX-101a; APE-XXX-102a, etc., will be used for the first MRS scan. APE-XXX-201a; APE-XXX-202a, etc., will be used for the first PET scan.
If a subject undergoes a second scan (e.g., a second PET scan), they will be coded : APE-XXX-201b, APEXXX-202b, etc.

Duration Specimens Will Be Stored

15 years

How Researchers Will Gain Access to Specimens

through code identifiers

APE-XXX-001; APE-XXX-002; etc. will be used for lab samples.
APE-XXX-101a; APE-XXX-102a, etc., will be used for the first MRS scan. APE-XXX-201a; APE-XXX-202a, etc., will be used for the first PET scan.
If a subject undergoes a second scan (e.g., a second PET scan), they will be coded : APE-XXX-201b, APEXXX-202b, etc.
All codes will not be linked to any subject identifiers.

Information To Be Stored or Associated with Each Specimen

Each specimen will be associated with a code as above. Stored samples will not be associated with identifiers.

Specimens Will Be Released	No

Funding Source Name	Alzheimers Drug Discovery Foundation
Contact	Niyati Thakker
Funding Category	Foundation
	Meditrack (https://contracts.tractmanager.com/Contracts/Login.aspx)
Grant or Contract Title	Alzheimer's Drug Discovery Foundation: Glutamatergic Dysfunction in Cognitive Aging: Riluzole in Mild Alzheimer's Disease
Grant or Contract Number	20120703; GCO #18-0428
Funding Status	Pending
Project Initiated By	Investigator
Grant / Contract Principal Investigator (PI)	Ana Pereira
Department	Neurology
Department	Neurology
Phone	
Email	Ana.Pereira@mssm.edu
Protocol and Funding Proposal Match	Yes
Identify Substantive Differences Between Protocol and Funding Proposal	

Funding Source Name	Dana (Charles A.) Foundation, Inc.
Contact	Edward Rover
Funding Category	Foundation
	Meditrack (https://contracts.tractmanager.com/Contracts/Login.aspx)
Grant or Contract Title	Dana Foundation grant : Understanding the susceptibility of Glutamatergic Neural Circuits to Alzheimer's Disease: Clinical and Basic Studies
Grant or Contract Number	GCO # 18-0664
Funding Status	Pending
Project Initiated By	Investigator
Grant / Contract Principal Investigator (PI)	Ana Pereira
Department	Neurology
Department	Neurology
Phone	
Email	Ana.Pereira@mssm.edu
Protocol and Funding Proposal Match	Yes
Identify Substantive Differences Between Protocol and Funding Proposal	

22. Radiation Safety

Study protocol involves any of the following Radiological Procedures requiring use of Dosimetry Chart Yes

**** Radiological procedures that are administered in addition to those that the participant would receive as part of standard care (radiation above and beyond standard of care)***
**** Radiological procedures that are administered solely for experimental or research purposes (would NOT be otherwise administered)***
**** Standard of care radiological procedures that are being altered or performed differently for research***
**** Use of radiological procedures that are the subject of the investigation (comparison studies)***

Dosimetry Chart
Please fill out the chart and attach it below.

Dosimetry Chart Copy of AP_Dos Wiz_1.22.2018.xlsx

Study protocol involves any of the following Radiological Procedures Yes

**** Use of an investigational radiopharmaceutical, or use of an approved radiopharmaceutical for an investigational purpose***
**** Use of investigational radiotherapy, or use of approved radiotherapy for an investigational purpose***
**** Use of fluoroscopy***
**** Radiation exposure to children or pregnant women***
**** Radiation exposure to healthy subjects (ADULTS)***
**** Use of an investigational radiologic device (such as an experimental scanner), or use of an approved device for an investigational purpose***

Study protocol involves any of the following Standard of Care Radiological Procedures (including projects where discrete Standard of Care Imaging is acquired in addition to Research Imaging) No

**** CT imaging***
**** Nuclear medicine***
**** Radiography***
**** Fluoroscopy***
**** Radiation-based therapy***
**** PET/CT***

	stored in a secure area and in such a way to restrict access to authorized personnel only as defined in the protocol. Additionally, all associated records will be stored in a restricted area and/or locked.
Justification Why Any of the Above Distribution Criteria Cannot Be Met	

23. Attachments

Type	Name	Version	Status	Filename	Uploaded Date
Approval Document	RU IRB approval.pdf	1	approved	RU IRB approval.pdf	10/04/2017
Approval Document	WCMC IRB approval.pdf	1	approved	WCMC IRB approval.pdf	10/04/2017
Other - Other IRB Correspondance	Rockefeller study application	1	approved	PDF_iRIS2Study Application_.pdf	10/23/2017
External IRB Approval Document	RU IRB approval.pdf	1	approved	RU IRB approval.pdf	10/23/2017
Data Monitoring Committee Description	DATA AND SAFETY MONITORING PLAN_Mount Sinai and Rockefeller University.docx	1	approved	DATA AND SAFETY MONITORING PLAN_Mount Sinai and Rockefeller University.docx	10/23/2017
Other - Other IRB Correspondance	General Rational and Graphs_Specific Aims	1	approved	Scan_20171026 (3).pdf	10/26/2017
FDA - FDA Approval of Drug or IND Determination	IND exempt letter	1	approved	Scan_20171026 (2).pdf	10/26/2017
FDA - Package Insert for Approved Drug	Study medication insert	1	approved	Riluzole_Prescription Insert.pdf	10/26/2017
Data Collection Sheet	DATA AND SAFETY MONITORING PLAN_Mount Sinai and Rockefeller University.docx	1	approved	DATA AND SAFETY MONITORING PLAN_Mount Sinai and Rockefeller University.docx	10/27/2017
Data Monitoring Committee Charter	DATA AND SAFETY MONITORING PLAN_Mount Sinai and Rockefeller University.docx	1	approved	DATA AND SAFETY MONITORING PLAN_Mount Sinai and Rockefeller University.docx	10/30/2017
Funding Proposal / Grant Application	NOA_ADDF copy.pdf	1	approved	NOA_ADDF copy.pdf	10/30/2017
Contractual Scope of Work	NOA_ADDF copy.pdf	1	approved	NOA_ADDF copy.pdf	10/30/2017
Funding Proposal / Grant Application	NOA_Dana Foundation copy.pdf	1	approved	NOA_Dana Foundation copy.pdf	10/30/2017
Contractual Scope of Work	NOA_Dana Foundation copy.pdf	1	approved	NOA_Dana Foundation copy.pdf	10/30/2017
Funding Proposal / Grant Application	Seed.docx	1	approved	Seed.docx	10/30/2017
Contractual Scope of Work	Seed.docx	1	approved	Seed.docx	10/30/2017
Written Communication from the FDA Documenting the IND Number	47.pdf	1	approved	47.pdf	10/30/2017

Other - Other IRB Correspondance	Rockefeller University ICF	1	approved	Rockefeller University ICF.pdf	11/19/2017
Other - Other IRB Correspondance	Weill Cornell ICF Neuroimaging	1	approved	Weill Cornell ICF Neuroimaging.pdf	11/19/2017
Dosimetry Chart	Copy of AP_Dos Wiz_1.22.2018.xlsx	1	approved	Copy of AP_Dos Wiz_1.22.2018.xlsx	01/22/2018

Type	Name	Version	Status	Filename	Uploaded Date
Other - Other IRB Correspondance	Riluzole General Rational and Specific aims_Grant	1	approved	General Rational and Specific Aims.pdf	10/19/2018
Other - Other IRB Correspondance	DATA AND SAFETY MONITORING PLAN_Mount Sinai and Rockefeller University.docx	1	approved	DATA AND SAFETY MONITORING PLAN_Mount Sinai and Rockefeller University.docx	10/19/2018
FDA - FDA Approval of Drug or IND Determination	IND acknowledgement.pd	1 f	approved	IND acknowledgement.pd	10/19/2018 f
Other - Other IRB Correspondance	Rockefeller University IRB Continued Review approval letter	1	approved	IRB approval 6.25.18.pdf	10/22/2018
Other - Other IRB Correspondance	Cornell University IRB Continued Review approval letter	1	approved	WCMC IRB approval 4.20.18.pdf	10/22/2018
Other - Other IRB Correspondance	Memo regarding sample storage and future use	1	approved	Questions from IRB analyst review 29NOV2018_due 07DEC2018_GP Edits_Final2.docx	12/05/2018
Other - Other IRB Correspondance	Radiation Dosimetry wizard excel sheet	1	approved	MKinsella_Copy of AP_Dos Wiz_1.22.2018.xlsx	01/08/2019
Advertisement Flyers	Recruitment flyer MSSM	1	Deactiva	edFlyer_01.11.2018.doc	01/19/2018
Consent Documents	Consent form Adult 22JAN2018.doc	1	Deactiva	edConsent form Adult_30JAN2018.do	01/30/2018 c
Consent Documents	Consent form Incapacitated Adult 22JAN2018.docx	1	Deactiva	edConsent form Incapacitated Adult_30JAN2018.do	01/30/2018 cx
Consent - Consent Document	Consent form Adult 25JAN2018.doc	1	Deactiva	edConsent form Adult 25JAN2018.doc	01/25/2018
Consent - Consent Document	Consent form Adult marked up_25JAN2018.doc	1	Deactiva	edConsent form Adult marked up_30JAN2018.doc	01/30/2018
Consent - Consent Document	Consent form Incapacitated Adult 25JAN2018.docx	1	Deactiva	edConsent form Incapacitated Adult marked up_30JAN2018.docx	01/30/2018

Consent - Consent Document	Consent form Incapacitated Adult marked up_25JAN2018.docx	1	Deactiva	edConsent form Incapacitated Adult marked up_25JAN2018.docx	01/25/2018
Advertisement Other Advertising Material	Riluzole blurb	1	Deactiva	edriluzole blurb.docx	07/09/2018
Advertisement Flyers	Riluzole flyer	1	Deactiva	edADRC Riluzole Flyer 10AUG2018.docx	08/10/2018
Advertisement Other Advertising Material	Riluzole Brochure	1	Deactiva	edADRC Riluzole brochure_01AUG201 (2).docx	08/10/2018
Consent - Consent Document	Consent form Adult CLEAN Riluzole 27JUN2018	1	Deactiva	ed132.doc	07/09/2018
Consent - Consent Document	Consent form Incapacitated Adult	1	Deactiva	ed134.docx	07/09/2018
Type	**Name**	**Version**	**Status**	**Filename**	**Uploaded Date**
	CLEAN Riluzole 27JUN2018				
Consent - Consent Document	Incapacitated Adult Consent Form Clean Riluzole 27JUN2018	1	Deactiva	edConsent form Incapacitated JW Edits.docx	01/15/2019
Consent - Consent Document	Adult Consent Form Clean Riluzole 27JUN2018	1	Deactiva	edConsent form Adult Clean_19DEC2018(2	01/11/2019).doc
Advertisement Flyers	Riluzole Flyer v. 10AUG2018	1	Deactiva	edRiluzole Flyer 05DEC2018.docx	12/05/2018
Advertisement Other Advertising Material	Riluzole Brochure	1	Deactiva	edRiluzole brochure_05DEC201	12/05/2018 8.docx
Advertisement Other Advertising Material	Riluzole Blurb	1	Deactiva	edriluzole blurb.docx	12/05/2018
Consent - Consent Document	Consnet form Adult 23APR2019	1	Deactiva	edConsent form Adult Clean_23APR2019.d	04/25/2019 oc
Consent - Consent Document	Consent form Incapacitated Adult 23APR2019	1	Deactiva	edConsent form Incapacitated Clean_23APR2019.d	04/25/2019 ocx
Other - Other IRB Correspondance	Riluzole Analysis Plan v.1_ 03JUN2020.docx	1	approved	Riluzole Analysis Plan v.1_ 03JUN2020.docx	06/04/2020