COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: Cognition, Age, and RaPamycin Effectiveness – DownregulatIon of thE mTor pathway (CARPE DIEM)

NCT number: NCT04200911

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Unique Protocol ID: HSC20190850H

Cognition, **A**ge, and **R**a**P**amycin **E**ffectiveness – **D**ownregulat**I**on of th**E** **m**Tor pathway
(**CARPE DIEM**)

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Study Product: *Sirolimus (Rapamune®, Greenstone LLC)*

Protocol #: HSC20190850H

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List of Abbreviations

AD – Alzheimer's disease
MCI – Mild Cognitive Impairment
CSF – Cerebrospinal Fluid
RAPA – Sirolimus (Rapamune®)
S6K1-P - Ribosomal protein S6 Kinase Beta-1
HPLC/MS/MS – High Performance Liquid Chromatography-Mass Spectrometry
MMSE– Mini Mental State Examination (MMSE)
MoCA - Montreal Cognitive Assessment
CDR – Clinical Dementia Rating
MINT - Multilingual Naming Test
HVLT-R – Hopkins Verbal Learning Test-Revised
CVLT-III – California Verbal Learning Test III
NPI – Neuropsychiatric Inventory
FAQ – Functional Activities Questionnaire
GDS – Geriatric Depression Scale

Study Summary

Title	**C**ognition, **A**ge, and **R**a**P**amycin **E**ffectiveness – **D**ownregulat**I**on of th**E** **m**Tor pathway (**CARPE DIEM**)
Protocol Number	20190850H
Phase	2
Methodology	Open label
Study Duration	Between 12-18 weeks
Study Center(s)	UTHSA McDermott (Biggs, RII)
Objective	To evaluate central nervous system penetration of orally administered RAPA in older adults with Mild Cognitive Impairment (MCI) or early Alzheimer's disease (AD) and investigate associated safety, tolerability, target engagement, cognition, and functional status as initial proof-of-concept for a larger phase 2 clinical trial
Number of Subjects	Screen up to 60 with intent for 10 completers. Additional subjects may be enrolled if attrition exceeds the anticipated rate (~25%).
Inclusion Criteria	1) Both genders and all ethnic groups 2) Ages 55 to 85 years 3) Diagnosis of MCI or AD with a Clinical Dementia Rating Scale (CDR) score = 0.5 – 1; 4) Labs: Normal blood cell counts without clinically significant excursions; normal liver and renal function; and glucose control (HbA1c < 6.5%). Lipid panel and PT/PTT/INR within normal limits 5) A Legally Authorized Representative (LAR) designated to sign informed consent (if necessary) for Visit 1 6) An available LAR or other study partner for reported outcomes must accompany participants to all study visits. 7) Participants must have no travel plans over the three to four months following enrollment that would interfere with scheduling visits following consent 8) Stable dose of AD medications (Donepezil, rivastigmine, Memantine, galantamine) for at least three months prior to baseline (visit 2) is allowed

Exclusion Criteria	1) Diabetes (HBA1c≥6.5% or antidiabetic medications) 2) History of skin ulcers or poor wound healing 3) Current tobacco or illicit drug use or alcohol abuse 4) Use of anti-platelet or anti-coagulant medications other than aspirin 5) Current medications that affect cytochrome P450 3A4 (see section 4.3); current or recent medications for hypertriglyceridemia (eg, Gemfibrozil) 6) Hypersensitivity or history of allergy to Rapamycin 7) Immunosuppressant therapy within the last year; current treatment with hydroxychloroquine and chloroquine (requires "washout period" of 14 days) 8) Chemotherapy or radiation treatment within the last year 9) Current or chronic history of liver disease or known hepatic or biliary abnormalities 10) History of primary hypertriglyceridemia. Abnormal triglycerides >200 or LDL cholesterol >193, or other abnormal labs deemed clinically significant upon investigator review 11) Current or chronic history of pulmonary disease or abnormal pulse oximetry (<90%) 12) Chronic heart failure 13) Pregnancy 14) Recent history (past six months) of myocardial infarction, active coronary artery disease, intestinal disorders, stroke, or transient ischemic attack 15) Significant neurological conditions other than AD 16) Poorly controlled blood pressure (systolic BP>160, diastolic BP>90 mmHG - two readings) 17) Active inflammatory, COVID-19, autoimmune, infectious, hepatic, gastrointestinal, malignant, and/or psychiatric disease 18) History of, or MRI, or CT positive for, any space occupying lesion, including mass effect or abnormal intracranial pressure, which would indicate contraindications to lumbar puncture 19) Organ transplant recipients
Study Product, Dose, Route, Regimen	RAPA (Sirolimus, Rapamune®) will be administered orally as (1) 1mg capsule daily
Duration of administration	RAPA will be administered once daily for 8 consecutive weeks.
Statistical Methodology	Similar to an early phase 2 trial, we are seeking preliminary evidence of the degree of central nervous system penetration of orally administered RAPA in older adults with MCI and early AD and investigate associated safety, tolerability, target engagement, cognition, and functional status as initial proof-of-concept for a larger phase 2 clinical trial. We will report the change in post intervention laboratory values relative to baseline with the 95% confidence interval. Experimental results will be expressed as means ± SE.

1. Introduction

This document is a protocol for a human research study. This study will be conducted according to Good Clinical Practice guidelines as adopted by FDA, applicable government regulations, and within Institutional research policies and procedures.

1.1. Background

The mechanistic (formerly mammalian) target of rapamycin (mTOR) signaling pathway is crucial for cell metabolism and its dysregulation contributes to age-related chronic medical conditions. RAPA (rapamycin, sirolimus), an FDA-approved immunosuppressant, effectively inhibits the mTOR pathway and thus manifests a wide variety of effects. In preclinical trials, orally administered RAPA extends longevity and mitigates the development of chronic diseases[1,2]. Moreover, growing research suggests that RAPA can alter the cellular and biological processes underlying the development of Alzheimer's disease (AD), including abnormal protein accumulation, diminished autophagy, and attenuated cerebral blood flow[3-6]. Specifically, the mTOR pathway exerts a strong influence on amyloid beta (aβ) and tau deposition consistent with upregulated mTOR signaling as observed in postmortem brain tissue from individuals with AD[7]. In multiple mouse models, orally administered RAPA dampens mTOR signaling, reduces cerebral aβ levels by approximately 40-50%, and diminishes tau aggregation[5,6], remediating cognitive deficits[4]. Suppression of the mTOR gene similarly diminishes aβ deposition[8], directly implicating mTOR inhibition as the mechanism mediating RAPA's effect on neuropathological protein accumulation. In addition to exerting direct influence on aβ and tau accumulation, mTOR activity has been shown to accelerate abnormal protein accumulation by suppressing autophagy[5,6]. In contrast, RAPA-treated mice with pharmacologically increased autophagy demonstrate a three-fold increase in lysosomal aβ levels[9], implicating the drug's ability to upregulate autophagy in neuropathological protein clearance.

RAPA has also been shown to restore cerebrovascular function[4], which evidences early alterations in AD including chronic reductions in cerebral perfusion[10], impaired endothelium-dependent vasodilation[11], and increased blood-brain barrier permeability[12]. RAPA increases nitric oxide production through the phosphorylation of endothelial nitric oxide synthase, inducing cortical vasodilation[4]. In mice, RAPA treatment restored cerebral blood flow levels and increased cerebral blood vessel density[4]. These changes were coupled with diminished aβ deposition in the blood vessels, reduced aβ plaques, and lower incidence of cerebral microbleeds[4]. Finally, RAPA dramatically dampened microglial activation,[3] a hallmark pathological feature of AD[13]. Activated microglial cells release pro-inflammatory cytokines and reactive oxygen species[14], inducing neuronal damage. In transgenic AD mouse models, RAPA diminished microglial activation, subsequently reducing interleukin 1-β, enhancing N-methyl-D-aspartate (NDMA) activity, and facilitating memory[3].

1.2. Innovation

Treatment with RAPA to measure the concentration of the drug that reaches the cerebrospinal fluid and crosses the blood-brain barrier is a novel approach to help identify targeted therapy for MCI and Alzheimer's disease.

1.3. Preliminary data

While human clinical trials of RAPA in AD have not yet been conducted, trials for other conditions have provided preliminary support for the cognitive benefits of RAPA treatment. In a sample of heart transplant recipients, four-week RAPA treatment (everolimus) improved performance on measures of memory, attention, and executive function, as well as enhanced mood[15]. To evaluate safety and tolerability in older adults, we recently conducted a randomized, placebo-controlled trial of eight-week RAPA treatment (1 mg/day) in individuals ages 70-95 years old[16]. No serious adverse events occurred. The reported adverse events were limited to facial rash (N=1), stomatitis (N=2, 1 placebo and 1 RAPA treated), and gastrointestinal distress

(N=2). Statistically, but not clinically significant, decrements were observed in multiple erythrocyte parameters (i.e. hemoglobin, hematocrit, red blood cell count).

	PLACEBO (n=14)				RAPA (n=11)				Group Difference	
	Pre	Post	P value	Difference (95% CI)	Pre	Post	P value	Difference (95% CI)	P value	Difference (95% CI)
HgB	13.81± 1.53	13.98± 1.63	0.33	0.16 [-0.19, 0.51]	13.94 ± 1.35	13.12 ± 1.22	0.003	-0.82 [-1.29, -0.35]	0.001	0.98 [0.43, 1.54]
HCT	41.29 ± 4.13	41.96 ± 4.54	0.21	0.67 [-0.42, 1.76]	41.57 ± 3.79	39.24 ± 3.75	0.002	-2.34 [-3.57, -1.1]	<0.001	3.01 [1.45, 4.56]

HgB=hemoglobin HCT=hematocrit

[16] *Ellen Kraig, et al. Table 4*

Measures of cognition and physical functioning were unchanged, although several informants reported anecdotal observations of improved cognition. A subset of individuals underwent assessment of cutaneous vasodilation, a measure of nitric oxide-dependent endothelial function, and displayed a strong trend towards post-treatment improvement (p=0.052). In light of the compelling preclinical data demonstrating that RAPA restores cognition in AD by exerting influence on multiple pathophysiological pathways[4-6,9], coupled with data on safety and possible cognitive benefits derived from human trials, we are now well-positioned to conduct the first clinical trial of RAPA in individuals with symptomatic MCI and AD.

1.4. Dose Rationale and Risk/Benefits

Eligible participants will be treated with 1 mg of RAPA daily for 8 consecutive weeks. The most common adverse events include mucositis, stomatitis, diarrhea, nausea, and acneiform rash. Pneumonitis, the most serious potential adverse event, occurs in ≤1-5% of cases, typically after prolonged drug exposure (≥six months). In our recent clinical trial of elderly adults receiving 1mg RAPA daily, the same dosage to be used in this proposal, no serious adverse events occurred[16]. The reported adverse events were limited to facial rash (N=1), stomatitis (N=1; 1 on placebo and 1 on RAPA), and gastrointestinal distress (N=2).

The study will consist of a screening/baseline period of up to 30 days pre-study drug, with a 56-day (±3 day) treatment period, and a post-intervention visit for study outcomes on final day of dosing and up to +14 days. The study duration is not expected to exceed 18 weeks for participants.

2. Study Objective

The objective of the study is to assess the degree of central nervous system penetration of orally administered RAPA treatment using collecting cerebral spinal fluid (CSF), and begin collecting initial data on safety, tolerability, target engagement, AD-related markers, and AD-relevant outcomes for future trials.

3. Study Design

3.1. General Design

This study is an open-label pilot study of orally administered RAPA to measure its target engagement in CSF and blood, and to establish the feasibility and safety of RAPA treatment in older adults with MCI and early stage AD as initial proof-of-concept for a larger Phase 2 clinical trial.

Aim 1: To assess the degree of central nervous system penetration and drug clearance with 8-week RAPA treatment. Lumbar punctures will be performed before treatment and after the final RAPA dose 8 weeks later to assess CSF levels of the drug. Quantification will be completed with HPLC/MS/MS chromatography.

Aim 2: To assess the safety and tolerability of 8-week RAPA treatment in older adults with MCI and AD. At three timepoints across the 8-week intervention, safety evaluations will be conducted including monitoring for adverse events, study compliance, vital signs, and laboratory assessment (CBC, comprehensive metabolic panel (CMP)

Aim 3: To investigate target engagement of RAPA treatment for AD pathology. We will evaluate levels of relevant AD biomarkers (e.g., total tau, phosphorylated tau, Aβ40 and Aβ42, neurofilament light, and glial fibrillary acidic protein), inflammatory (e.g., IL-6, PAI-1, soluble ICAM-1) and other relevant analytes in the CSF and/or blood at time points prior to RAPA treatment and after 8 weeks on the drug.

Aim 4: To evaluate changes from baseline in cognition, functional status, and physical functioning after 8 weeks of RAPA treatment. Pre- and post-treatment changes in cognition, disease severity, functional status, mood, and physical functioning will be assessed using a battery of tests appropriate for use with AD populations.

3.2. Study Endpoints

a) **Primary outcome: To determine blood brain barrier penetrance of RAPA in older adults with mild cognitive impairment or early symptomatic Alzheimer's disease.** Lumbar punctures will be performed at baseline and after the final RAPA dose, to assess CSF levels of the drug. Quantification will be completed with HPLC/MS/MS chromatography.

Secondary outcomes:

b) **To assess the safety and tolerability of 8-week RAPA treatment in older adults with AD.** At three timepoints across the 8-week intervention, safety evaluations will be conducted including monitoring for adverse events, study compliance, vital signs, and laboratory assessment (CBC, comprehensive metabolic panel (CMP), blood RAPA levels).

c) **To investigate target engagement of RAPA treatment in AD.** We will evaluate levels of relevant AD biomarkers (e.g., total tau, phosphorylated tau, Aβ40 and Aβ42, neurofilament light, and glial fibrillary acidic protein), inflammatory (e.g., IL-6, PAI-1, soluble ICAM-1) and other relevant analytes in the CSF and/or blood at time points prior to RAPA treatment and after 8 weeks on the drug.

d) **To evaluate changes from baseline in cognition, functional status, and physical functioning after 8 weeks of RAPA treatment** Pre-intervention to post-intervention change in cognitive tests (MoCA, HVLT-R, Craft Stories, Benson Figure Copy and Delayed Recall, Trail Making Test Parts A&B, Number Span Test, Semantic Fluency, Phonemic Fluency, MINT, Hayling), physical functioning assessment (electronic gait mapping under single and dual-task conditions, grip strength), and questionnaires/semi-structured interviews (CDR, GDS, NPI, FAQ,).

3.3. Potential Risks to Subject Safety

a) **Drug Administration.**

RAPA and its functional homologs (i.e. everolimus (Afinitor, Novartis)) are FDA-approved drugs with well-established pharmacology and safety profiles[17]. Clinical trials are ongoing for several neurological conditions including amyotrophic lateral sclerosis[18], recurrent glioblastoma[19], and tuberous sclerosis complex[20]. The most common adverse events include mucositis, stomatitis, diarrhea, nausea, and acneiform rash. Pneumonitis, the most serious potential adverse event, occurs in <1-5% of cases, typically after prolonged drug exposure (≥six months), and blood levels ≥ 10ng/ml. Many side effects are alleviated with lower dosing and shorter durations of exposure. In our recent clinical trial of elderly adults receiving 1mg RAPA daily, the same dosage to be used in this proposal, no serious adverse events occurred[16]. The reported adverse events were limited to facial rash (N=1), stomatitis (N=1; 1 on placebo and 1 on RAPA), and gastrointestinal distress (N=2).

Rapamycin and rapalogs "exhibit little or minimal nephrotoxicity" (Ma, 2018). In rare cases involving transplant patients changed from calcinuria inhibitors to rapamycin, decreased creatinine clearance and increased proteinuria have been reported. We will monitor creatinine clearance and proteinuria by safety labs including urinalysis.

For more detail, please refer to the package insert included in this submission, Full Prescribing Information, including:

- *Most common adverse reactions* (≥15%)
    - Mucositis and stomatitis (inflammation of the mouth and tongue)
    - Mouth scores
    - Acne like rash
    - Hyperlipidemia (increased triglycerides and fat in the blood)
    - Increased blood sugar
    - Peripheral edema (swelling in the arms, legs, hands, feet)
    - Hypertension (high blood pressure)
    - Constipation
    - Diarrhea
    - Headache
    - Fever
    - Anemia (low red blood cell count or hemoglobin)
    - Nausea
    - Arthralgias (pain in the joints)
    - Pain
- *Drug Interactions:*
    - Strong CYP3A4 and/or P-gp Inhibitors: Avoid co-administration.
        - Bromocriptine, cimetidine, cisapride, clotrimazole, danazol, diltiazem, fluconazole, protease inhibitors (e.g. HIV and hepatitis C that include drugs such as ritonavir, indinavir, boceprevir, and telaprevir), metoclopramide, nicardipine, verapamil
    - Strong CYP3A4 Inducers: Avoid co-administration

- Carbamazepine, phenobarbital, phenytoin, rifapentine, St. John's Wort (*Hypericum perforatum*)

- Live vaccinations: Avoid co-administration

b) **Blood withdrawal.** (To minimize these risks a qualified phlebotomist will perform venipunctures.)

- Pain, bleeding, bruising, or swelling at the site of the needle stick
- Hematoma
- Nerve damage
- Infection
- Fainting or light-headedness

This study may include genetic testing. Genetic information is unique to each individual and could potentially be used to discover possible changes in a person's future health status or life expectancy, or that of his/her children and family members. Even though the results of genetic testing cannot be linked to an individual, it is possible that people of specific ethnic backgrounds may be found to be at more risk for certain diseases based on future genetic research and this information might harm the individual in the future as a member of the group.

c) **Cognitive Assessment and Semi-structured Interviews/Questionnaires**

- Psychosocial - embarrassment, discomfort or anxiety upon testing memory and thinking
- Patient or Study Partner-Reported Outcomes include questionnaires related to AD symptoms, cognition, sleep, and mood scales.

d) **Lumbar Puncture.** (To minimize these risks, a qualified provider specifically trained in the procedure will perform the lumbar puncture.)

- Temporary pain and discomfort in the back.
- Headache.
- Persistent low-pressure headache due to leakage of CSF. If this headache persists, it may require additional treatment. Uncommonly, a blood patch (injection of some of participant blood into the lumbar puncture site to patch the CSF leak) may be required.
- Infection
- Damage to nerves in the back
- Bleeding into the CSF space
- Allergic reaction to the local anesthetic (lidocaine) used for the lumbar puncture, such as swelling or rash at the puncture site.

If clinically indicated due to obesity, arthritis, scoliosis or any other condition that makes it difficult to identify the correct insertion point on the lumbar spine, the lumbar puncture will be completed with fluoroscopy. Fluoroscopy involves exposure to radiation. The amount of radiation exposure received from the procedure is equivalent to a uniform whole-body dose of 300 mrem (a unit of radiation exposure) which is approximately 50% of the average amount of environmental radiation exposure (620 mrem dose) that each member of the general public receives per year. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (abnormal cells) or cancer. However, the probability of harm from such risk associated with the amount of radiation exposure received from fluoroscopy is considered

to be low when compared to other everyday risks each member of the general public receives each year, depending on the amount of radiation each participant has personally been exposed to in the past, particularly in the previous year.

e) **Physical Function Assessment**.

- Brief, temporary fatigue with timed short distance walking and/or using handheld dynamometer to measure grip strength
- Psychosocial - heightened awareness of physical limitations may cause anxiety or embarrassment during testing, which will be mitigated by ensuring privacy

Subject Selection and Withdrawal

4.1. Subjects

Up to 60 potential candidates will be pre-screened to identify eligible men and women, ages 55 to 85 years old, with a clinical diagnosis of MCI or early AD. Additional subjects may be enrolled if attrition exceeds the anticipated rate (~25%).

4.2. Inclusion Criteria

1) Both genders and all ethnic groups
2) Age 55 to 85 years old
3) Diagnosis of MCI or AD with a Clinical Dementia Rating Scale score (CDR) = 0.5 – 1;
4) Labs: Normal blood cell counts without clinically significant excursions (WBCs: 3500-10,500 cells/ uL; absolute neutrophil count: 1,800-8,700 cells/ uL; platelets: 140-450 K/uL; hemoglobin 11.0-17.5 grams/dL); liver and renal function (AST 10-40 IU/L, total bilirubin 0.1-1.4 mg/dl, creatinine clearance within normal limits); and glucose control (HbA1c < 6.5%). Lipid panel and PT/PTT/INR within normal limits
5) A Legally Authorized Representative (LAR) designated to sign informed consent (if necessary) must provide accompaniment at Visit 1
6) An available LAR or other study partner for reported outcomes must accompany participants to all study visits.
7) Participants must have no travel plans over the three to four months following enrollment that would interfere with scheduling visits following consent
8) Stable dose of AD medications (Donepezil, rivastigmine, Memantine, galantamine) for at least three months prior to baseline (visit 2) is allowed

4.3. Exclusion Criteria

Subjects will be excluded if they exhibit:

1) Diabetes (hbA1c≥6.5% or antidiabetic medications)
2) History of skin ulcers or poor wound healing
3) Current tobacco or illicit drug use or alcohol abuse
4) Use of anti-platelet or anti-coagulant medications other than aspirin
5) Current medications that affect cytochrome P450 3A4); current or recent medications for hypertriglyceridemia (eg, Gemfibrozil)
6) Hypersensitivity or history of allergy to Rapamycin

7) Immunosuppressant therapy within the last year; current treatment with hydroxychloroquine or chloroquine (requires "washout period" of 2 weeks)
8) Chemotherapy or radiation treatment within the last year
9) Current or chronic history of liver disease or known hepatic or biliary abnormalities
10) History of primary hypertriglyceridemia. Abnormal triglycerides >200 or LDL cholesterol >193, or other abnormal labs deemed clinically significant upon investigator
11) Current or chronic history of pulmonary disease or abnormal pulse oximetry (<90%)
12) Chronic heart failure
13) Pregnancy
14) Recent history (past six months) of myocardial infarction, active coronary artery disease, intestinal disorders, stroke, or transient ischemic attack
15) Significant neurological conditions other than AD.
16) Poorly controlled blood pressure (systolic BP>160, diastolic BP>90 mmHg with two readings)
17) Active inflammatory, COVID-19, autoimmune, infectious, hepatic, gastrointestinal, malignant, and/or psychiatric disease
18) History of, or MRI or CT positive for, any space occupying lesion, including mass effect and/or abnormal intracranial pressure, which would indicate contraindication to lumbar puncture.
19) Organ transplant Recipients

4.4. Subject Recruitment and Retention

Participants with MCI and early AD will be enrolled from UT Health San Antonio, local clinics, and the community. Recruitment methods may include electronic medical record queries, posting study fliers in medical offices or senior centers, community engagement activities, and/or newspaper or web-based advertisements including social media. A UT Health website to present the project to the public will be published online and could be referenced by other institutional websites. The study will be published on clinicaltrials.gov. All these strategies will be considered, made available and implemented/adapted according to the local policies and regulations.

Telephone pre-screening prior to the clinic screening visit may be employed to ensure potential candidates will meet inclusion and exclusion criteria for enrollment.

Transportation, parking and/or meal vouchers may be provided to participants according to local policies.

4.5. Early Withdrawal of Subjects

4.5.1. When and How to Withdraw Subjects

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation including any follow-up in person, by phone, through third parties including relatives or friends, via discussion with other treating physicians, and by use of medical records; subject data up to withdrawal of full consent will be included in the analysis of the study. Any subject may withdraw full consent to participate in the study at any time during the study. The Principal

Investigator, co-Principal Investigator, or other trained study staff will discuss with the subject appropriate procedures for withdrawal from the study.

4.5.2. Data Collection and Follow-up for Withdrawn Subjects

If subjects are withdrawn prematurely from the study, appropriately designated research staff will make efforts to collect at least survival data upon last contact that subject.

Investigators will consult with Study Statistician with regard to any incomplete data set as compared to the full data set that fully supports the analysis. If a subject withdraws consent to participate in the study, attempts will be made to obtain permission to record survival data up to the protocol-described end of subject follow-up period.

Investigators and/or designated research staff make it a high priority to obtain survival data on all subjects lost to follow up. Lost to follow up will be defined as a subject missing 2 or more consecutive visits, not answering or responding to 3 follow up phone calls to subject or emergency contacts or returned receipt of 1 certified letter.

4. Study Drug

The study drug is the FDA approved formulation of Rapamune® 1mg oral tablets.

5.1. Description

Rapamune® (sirolimus) is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2.

Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile. The inactive ingredients in Rapamune® Tablets include sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000, glyceryl monooleate, carnauba wax, *dl*-alpha tocopherol, and other ingredients.

Mechanism of Action

Sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The sirolimus:FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mechanistic Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G_1 to the S phase of the cell cycle.

Detailed information is supplied on the Rapamune® package insert.

5.2. Treatment Regimen

Administration Protocol.

Study subjects will come to the clinic on the first day of study drug administration (Visit 4) and will receive enough study medications for consecutive daily administration (+two extra pills) until the next scheduled clinic visit (Visit 5). At Visit 5, subjects will receive enough study medications for consecutive daily administration (+two extra pills) until

the next scheduled clinic visit (Visit 6). At Visit 6, subjects will receive enough study medications for consecutive daily administration (+two extra pills) until the next scheduled clinic visit (Visit 7).

Assigning Subjects
In this open label early phase 2 study, all subjects receive the same treatment dose of 1mg of RAPA once a day.

5.3. Preparation and Administration of Study Drug

RAPA will be dispensed through the Biggs Institute at UT Health San Antonio located in the McDermott Building. They will receive the drugs packaged for individual subject use from the Research Pharmacy. Once appropriately labeled, the study drugs will be dispensed to the designated study staff for administration to the study participant. At study Visits 4, 5, and 6, study subjects will receive enough study medications for consecutive daily administration (+two extra pills) until their next scheduled clinic visit.

5.4. Subject Compliance Monitoring

Participants and/or their study partner will be encouraged to bring pill bottles and adherence logs to each visit for review by the study team. The study coordinator will complete medication reconciliation at each visit.

5.5. Prior and Concomitant Therapy

COVID-19 Vaccinations:
In the event study participants are given the opportunity to receive a vaccination (injection) for COVID-19 prophylaxis (either Tozinameran® or mRNA-1273®), they will be instructed to cease therapy with the IP (RAPA/Placebo) for a period of four days prior to each injection of the vaccine and three days afterwards. Subjects will be asked to notify study staff of their plans to be vaccinated so they can be re-educated on this requirement.

5.5. Prior to the patient resuming therapy with the IP, they will be contacted by the study staff to confirm no changes in status have occurred that would contraindicate immunosuppressive therapy (e.g. active infection). Any subject who experiences a treatment interruption due to COVID-19 vaccination may have their time in the double blind portion of the study extended by the investigators depending on the number of days the IP was not taken.

<u>Exclusionary medications:</u>

- Anti-platelet or anti-coagulant medications other than aspirin are exclusionary.
- Medications that affect cytochrome P450 3A4
- Additionally, immunotherapy, chemotherapy, and/or radiation therapy within one year of study enrollment.
- Current treatment with hydroxychloroquine or chloroquine (requires "washout period" of 2 weeks)

5.6. Packaging and Product Inventory

Nature and Contents of the Container
Drugs for individual subject use will be clearly labeled and identified as “Caution: New Drug –Limited by Federal (or United States) law to investigational use” per 21CFR312.6.

Designated staff at the Biggs Institute will:

- Inventory receipt of initial shipment and ensure appropriate temperature control
- Distribute RAPA by labeling each individual subject packet(s) with Subject ID from list provided by PI or Co-PI to pharmacy prior to receipt of inventory

5.6.1. Receipt of Drug Supplies

Any damaged or unusable study drug in a given shipment will be documented by designated staff and investigators at the Biggs Institute . They will notify the Principal Investigator and the Material Supplier of any damaged study drug.

Special instructions upon receipt
Designated staff at the Biggs Institute reconciles inventory received per local standard operating procedure and makes copies of any accompanying shipping documentation enclosed provides and copies to IND sponsor.

5.6.2. Storage

Rapamune® Tablets should be stored at 20° to 25°C (USP Controlled Room Temperature) (68° to 77°F). Use cartons to protect blister cards and strips from light. Dispense in a tight, light-resistant container.

5.6.3. Dispensing of Study Drug

Designated staff from the Biggs Institute maintain the Drug Inventory and Dispensing Logs to track how, when and to whom the investigational drug was dispensed and assigned to subjects. Study clinical staff will document administration in research records regarding dosing, unused drug, drug damaged, or wasted. Study subjects are instructed to swallow RAPA whole, and not to chew or crush medication when administered.

5.6.4. Return or Destruction of Study Drug

The procedures for final reconciliation of the site's drug supply at the end of the study will be in accordance with local site Pharmacy standard operating procedures. Since Rapamune is not absorbed through the skin, there are no special precautions for destruction. However, if direct contact with the skin or mucous membranes occurs, wash thoroughly with soap and water; rinse eyes with plain water.

5. Study Visits and Procedures

Special Considerations related to COVID-19

1) Potential participants will be screened by telephone 1-2 business days in advance of study visits to assess for signs or symptoms of COVID-19 and for reports of recent exposure to people known to be infected with the virus. Upon arrival to the visit and before entering the research unit building, participants will be surveyed again, body temperature documented, and receive a mask if they need one.

2) For added safety, approximately 1-2 business days before starting the drug intervention, enrolled participants will be tested for SARS CoV-2 with a nasopharyngeal swab for rRT-PCR (Real-time reverse transcriptase–polymerase chain reaction) analysis. Research funds will pay for the testing. If a participant tests positive, the investigator will refer the subject to their primary care physician for medical care.
3) If a participant provides the researchers documentation of completed vaccination for COVID-19 (e.g. vaccination card) that took place at least one week prior to their first dosing, the rRT-PCR test may be waived

with study physician approval. Phone pre-screening(s) and temperature checks will be done on all participants regardless of vaccination status.

4) If a participant develops COVID-19 signs or symptoms at any time during the study, the investigators will arrange for testing and if indicated, will refer the participant to their PCP for medical care. During the 6-month study drug treatment, participants testing positive for COVID-19 will be withdrawn from treatment and their study participation will stop. Participants testing positive for COVID-19 during the pre- or post-treatment study periods will be required to wait until their symptoms resolve and they receive a negative COVID-19 test before continuing their study participation.

6.1. Visit 1, Consent and Screening Visit

6.1.1. Consent Process

The participant is scheduled to come to the designated research area in a non-fasting state, and will be accompanied by a Legally Authorized Representative (LAR) for the consenting process.

In line with recommendations put forth by the Global Alliance for Genomics and Health, Aging, and Dementia Task Team, researchers will first attempt to seek consent from the study participant with cognitive impairment. In order to have appropriate safeguards, decision-making capacity specific to participation in the research study (i.e., understanding the purpose, procedures, risks and benefits of study participation) will be evaluated using a standardized instrument for assessing capacity to consent developed by Jeste et al, 2007[21] and tailored to the study. In the event of questions regarding capacity, the research study will consult with the PI or other qualified study team members. If the study participant is found to lack capacity to consent, researchers will obtain consent from a legally authorized representative (LAR) who will be instructed to respect the will and preferences of the study participant. When a LAR is necessary, the researchers will still include the study participant in the consent process and will seek to obtain assent for study participation.

6.1.2. Screening and eligibility

After the informed consent process is completed, subjects will be screened for eligibility.

Screening will include vital signs, and physical examination with anthropomorphic measurements (height, weight), medical history, concomitant medication review, non-fasting blood measures for safety, including: complete blood count (CBC), comprehensive metabolic panel (CMP), hemoglobin A1c (A1c), routine urinalysis, and coagulation panel (PT/PTT/INR). Screening cognitive assessments will include the MMSE, CDR, and CVLT-II.

The screening visit is estimated to require 2.5 hours.

After receiving all test results (including laboratory data), the study investigators will make a determination regarding eligibility.

Investigators may repeat any labs found to be outside the normal ranges to confirm reliability of results and eligibility throughout the duration of the study.
Investigators or research staff will call the study participant and/or LAR/study partner to inform of eligibility status and schedule Visit 2 (if applicable). For participants scheduled for Visit 2, research staff will call the study participant and/or LAR/study partner within one business day of Visit 2 to confirm the appointment and provide a reminder about fasting and complete COVID-19 symptom and exposure telephone assessment.

6.2. Visit 2 – Baseline Measurements Part I (within 30 days after Visit 1).

Within 4 weeks of the Screening visit, enrolled subjects will return to the research site in a fasting state (nothing to eat/drink, except water, for at least eight (8) hours before visit) for vital signs, concomitant medication review,

adverse event review, fasting safety (CMP, lipid panel) and research labs, and lumbar puncture to acquire CSF baseline measures of RAPA, as well as markers of AD (e.g. total tau, phosphorylated tau, Aβ40 and Aβ42, NFL, and GFAP), pro-inflammatory markers (e.g. IL-6, PAI-1, soluble ICAM-1), and other relevant analytes. A snack will be offered immediately following the lumbar puncture.

Research labs (blood and CSF) will also be banked for future analyses, including possible genetic analyses. Before all study procedures, researchers will assess study participants' willingness to continue their study participation with direct inquiry to the study participant and LAR (if applicable). If there is any indication of diminished capacity or significant cognitive changes (i.e. observed by research staff or reported by family members), the researchers will evaluate the participant's current capacity to consent using a standardized instrument as described under Visit 1 (if the participant originally was deemed to have capacity to consent) or evaluate assent and surrogate consent (if the participant originally was deemed to lack capacity to consent).

Visit 2 is estimated to require up to 3 hours, including at least 30 minutes rest following the procedure. If indicated due to obesity, arthritis, scoliosis or any other condition that makes it difficult to identify the correct insertion point on the lumbar spine, the lumbar puncture will be completed with fluoroscopy. This procedure will occur in room RII 1.326 using a c-arm machine that has been inspected by the UT Radiation Safety Office. This room is shielded, and the procedure will be conducted by a board certified neuroradiologist who has received extensive training in the use of fluoroscopy for LPs. Refer to Standard Operating Procedures for more details about the lumbar puncture procedure.

(i) Lumbar puncture (LP) to acquire CSF (up to 30m volume)

- CSF: CSF will be separated into aliquots and frozen. See Analyses below.

(ii) Blood draw 60mL volume for RAPA/S6k1-P levels, AD markers, proinflammatory and other relevant analytes.

- Blood: Blood will be separated into aliquots for analysis by UTHealth Biggs Institute and Department of Cell Systems and Anatomy as follows:
  - 40ml volume of whole blood, separated into 8 vials
  - 2ml volume of whole blood, separated into three aliquots
  - Separated from 18 of whole blood, 8-12ml of serum (0.2-0.5ml aliquots) and 6-8ml of plasma (0.2-.0.5ml aliquots)

Analyses.

CSF:

CSF will be separated into aliquots and frozen. (i) Aliquots will be analyzed by the Pharmacology Core facility using HPLC/MS chromatography; (ii) ELISA or Simoa HD-1 Analyzer for AD and pro-inflammatory markers to be performed by UT Health (Biggs Institute and Department of Cell Systems and Anatomy).

Blood:

Blood, apportioned as described above, will separated into aliquots and frozen. i) Aliquots will be analyzed by the Pharmacology Core facility using HPLC/MS chromatography; (ii) ELISA, Luminex-based assays, and/or

Simoa HD-1 Analyzer for AD and pro-inflammatory markers performed by UT Health (Biggs Institute and Department of Cell Systems and Anatomy).
Confirm scheduling of Visit 3. Within one to two business days of Visit 3, research staff may call the study participant and/or LAR/study partner to confirm the appointment and complete COVID-19 symptom and exposure telephone assessment.

6.3. Visit 3a – Baseline Measurements Part II (within 30 days of Visit 2) and Visit 3b - COVID-19 testing (within 72 hrs of Visit 4).

Within 30 days of the Visit 2, enrolled subjects will be asked to return to the research unit with LAR for Visit 3a. Examination and activities during this visit include reassessment of willingness to participate in the study (as described under Visit 1), vital signs, concomitant medication, and adverse event review, with the following measures:

(i) Cognitive examination (1.5 hours):

- Montreal Cognitive Assessment (MoCA)
- Hopkins Verbal Learning Test Revised (HVLT-R)
- Craft Stories
- Benson Figure Copy and Delayed Recall
- Number Span Test
- Trail Making Test Parts A&B
- Phonemic Fluency
- Semantic Fluency
- Multilingual Naming Test (MINT)
- Hayling

(ii) Participant-Reported (GDS) and Informant-Reported (FAQ, NPI)

(iii)Functional and physical performance measure (1 hour):

- Electronic gait mapping under single and dual-task conditions
- grip strength

For added safety, approximately 1-2 business days before starting the drug intervention (Visit 4), participants will be asked to return for Visit 3b and tested for SARS CoV-2 with a nasopharyngeal swab for rRT-PCR (Real-time reverse transcriptase–polymerase chain reaction) analysis. Research funds will pay for the testing.. If a participant tests positive, the investigator will refer the subject to their primary care physician for medical care. Visit 3b is estimated to require 30 minutes.

Visit 3a is estimated to require 3 hours. Confirm scheduling of Visit 4. Within one to two business days of Visit 4, research staff may call the study participant and/or LAR/study partner to confirm the appointment. The COVID-19 symptom and exposure telephone assessment may be completed either at Visit 3a or at time of Visit 4 scheduling confirmation, within one-two business days of Visit 4.

6.4. Visit 4 – Study Drug Dispensing & Monitoring (within 15 days of Visit 3)

The participant and LAR/study partner will visit the research unit for drug dispensing and safety monitoring. Participant will arrive in a fasting state (nothing to eat/drink, except water, for at least eight (8) hours before visit), undergo reassessment of willingness to participate in the study (as described under Visit 2), vital signs,

weight, concomitant medication review, and:

- Administration of the CDR (If Visit 1 was conducted more than 60 days prior to visit 4)
- AE assessment
- Blood draw (fasting) for safety labs: CBC, CMP, lipid panel, HbA1c, and urinalysis
- Dispense study medication and schedule further follow up safety monitoring (Visits 5 - 8).

Dispensing of enough study medications for consecutive daily administration (+2 extra pills) until the next scheduled clinic visit (Visit 5).
Visit 4 is estimated to require 1.5 hours or less. Scheduling of Visit 5: to occur four weeks (± 2 days) after Visit 4. Within one to two business days of Visit 5, research staff may call the study participant and/or LAR/study partner to confirm the appointment and complete COVID-19 symptom and exposure telephone assessment.

6.5. Visit 5 – Study Drug Dispensing & Monitoring (4 weeks(± 2 days) of Visit 4)

The participant and LAR/study partner return to the research unit for drug dispensing and safety monitoring. Participant will arrive fasting (nothing to eat/drink, except water, for at least eight (8) hours before visit), undergo reassessment of willingness to participate in the study (as described under Visit 2), vital signs, weight, concomitant medication review, and:

- AE assessment
- Compliance review
- Blood draw (fasting) for safety labs: CBC, CMP, and lipid panel
- Dispense study medication and confirm further follow up safety monitoring (Visit 6).

Dispensing of enough study medications for consecutive daily administration (+two extra pills) until the next scheduled clinic visit (Visit 6).
Visit 5 is estimated to require 1 hour or less. Scheduling of Visit 6: to occur three weeks (± 2 days) after Visit 5. Within one to two business days of Visit 6, research staff may call the study participant and/or LAR/study partner to confirm the appointment and complete COVID-19 symptom and exposure telephone assessment.

6.6. Visit 6 – Study Drug Accountability & Monitoring (3 weeks(± 2 days) of Visit 5)

The participant and LAR/study partner return to the research unit for drug accountability and safety monitoring. Participant will arrive fasting (nothing to eat/drink, except water, for at least eight (8) hours before visit), undergo reassessment of willingness to participate in the study (as described under Visit 2), vital signs, weight, concomitant medication review, and:

- AE assessment
- Compliance review
- Blood draw (fasting) for safety labs: CBC, CMP, lipid panel, urinalysis and coagulation panel (PT/PTT/INR)
- Re-dispense study medication and confirm further follow up safety monitoring (Visit 7).

Confirm participant has enough study medications for consecutive daily administration (+two extra pills) until the next scheduled clinic visit (Visit 7).

Visit 6 is estimated to require 1 hour or less. Scheduling of Visit 7: to occur one week (± 2 days) after Visit 6. Within 24 hours of Visit 7, research staff will call the study participant and/or LAR/study partner to confirm the

appointment, complete COVID-19 symptom and exposure telephone assessment, and provide a reminder about fasting and provision of the final study medication dose in clinic.

*6.7. Visit 7 – Lumbar Puncture, Blood Draw, **Final Drug Accountability** & Monitoring (1 week (± 2 days) of Visit 6)*

The participant will be asked to arrive fasting (nothing to eat/drink, except water, for at least eight (8) hours before visit), accompanied by LAR/study partner, to return to the research unit in the morning before taking his/her final dose of RAPA. Examination and activities during this visit include: reassessment of willingness to participate in the study, administration of the final dose of RAPA, vital signs, concomitant medication, compliance and adverse event review, fasting blood draw for safety and research labs with lumbar puncture to acquire CSF (as described under Visit 2), followed by provision of a snack (optional).

At Visit 7 study staff should collect all remaining supply of RAPA from the participant for a final drug accountability check.

Visit 7 is estimated to require 3 hours or less. Scheduling of Visit 8: to occur 7-14 after Visit 8. Within one to two business days of Visit 8, research staff will call the study participant and/or LAR/study partner to confirm the appointment and complete COVID-19 symptom and exposure telephone assessment.

6.8. +69+ – End of Study Measures and Disenrollment (7 to 14 days after Visit 7)

The participant and LAR/study partner returns to the research unit, in a fasting state (nothing to eat/drink, except water, for at least eight (8) hours before visit), 7-14 days after the LP to undergo reassessment of willingness to participate in the study and 12-week post-treatment measures, including vitals, weight, concomitant medication, history and physical, fasting safety labs (CBC, CMP, lipid panel, HbA1c, and urinalysis)) as well as:

- Provision of a snack
- Cognitive test battery & Questionnaires, including CDR plus all assessments listed in Visit 3
- Physical functional performance (same as Visit 3)
- Final AE review, instructions for future AD follow up and study staff enters disenrollment note.

The estimated duration of this visit is 3.5 hours.

A Summary Visit Schedule Table is shown on the following page(s).

6.9. Summary Visit Schedule Table

Visit Number	**Visit 1 MCD**	**Visit 2 MCD**	**Visit 3a MCD**	**Visit 3b MCD**	**Visit 4 MCD**	**Visit 5 MCD**	**Visit 6 MCD**	**Visit 7 MCD**	**Visit 8 MCD**
Visit Window		V1 + up to 30d	V2 + up to 30d	w/in 24-72 hrs of Visit 4	V3 + up to 15d	V4 +4w ±2d	V5 +3w ±2d	V6 +1w ±2d	V7+7-14d

Consent	X								
Reassess willingness to participate		X	X		X	X	X	X	X
CDR	X				X***				X
Vitals: BP,HR,T,RR, Pulse Oximetry	X	X	X		X	X	X	X	X
Height	X								
Weight	X				X	X	X		X
Has & P	X								X
ConMeds	X	X	X		X	X	X	X	X
AE Review		X	X		X	X	X	X	X
Blood Draws, Labs, and Lumbar Punctures									
*COVID-19 RT-PCR swab***				X					
Fasting Blood Draw		X			X	X	X	X	X
Non-fasting Blood Draw	X								
CBC w diff	X				X	X	X		X
CMP with lipid panel	X	X			X	X	X	X	X
Hemoglobin A1c	X				X				X
PT/PTT/INR	X						X		
Routine Urinalysis	X				X		X		X
Research Labs		X						X	
Lumbar Puncture (potentially with Fluoroscopy)		X						X	

Cognitive, Physical, and Sensory Assessments									
Snack Provision (optional)		X						X	X
MoCA			X						X
HVLT-R			X						X
Craft Stories			X						X
Benson Figure			X						X
Number Span Test			X						X
Trail Making Test A&B			X						X
Phonemic and Semantic Fluency			X						X
MINT			X						X
Hayling			X						X
GDS			X						X
FAQ			X						X
NPI			X						X
Electronic Gait Mapping			X						X
Grip strength			X						X
Study Medication									
Compliance Review						X	X	X	
Administer in clinic								X*	
Dispense Study Drug					X	X			

Schedule/Confirm Next Visit	X	X	X		X	X	X	X	
**COVID-19 symptom and exposure telephone assessment	X	X	X	X	X	X	X	X	
	End of Study								
Final AE review									X
Final Forms Review									X
Follow up instruction									X
Disenrollment Note									X

**COVID testing 24-72 hours prior to drug dispensing visit; COVID symptom and exposure assessment 24-72 hours prior to study visits; COVID testing may be repeated in event participant shows signs or symptoms of COVID-19 or, if positive, until a negative test is achieved
*At visit 7, all remaining supply of RAPA should be returned to the study staff for a final drug accountability check.
***CDR will only be repeated at visit 4 if visit 1 was conducted more than 60 days prior.

7. Statistical Plan

7.1. Sample Size Determination

This is a pilot study to collect data on brain penetrance of a study medication. The sample size was determined as what would be feasible given the time and budget constraints of the pilot (i.e., one-year and $50K).

7.2. Statistical Methods

Analytical Approach.

Similar to an early phase 2 trial, we seek preliminary evidence of drug safety and tolerability with estimation of pre/post differences in a pertinent laboratory values and adverse event occurrences. We will report changes in post-intervention laboratory values relative baseline with the 95% confidence interval. Experimental results will be expressed as means ± SE. Comparisons of means between pre/post evaluations will be done by regression using the intent to treat principle defined above. Given the small sample size, there are no plans for interim analyses.

8. Safety and Adverse Events

8.1. Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRSO)

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event (AE)

In general, AE is used very broadly and encompasses physical and psychological harms and includes:

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as up to 2 weeks following the last administration of study treatment or procedures.

Pre-existing Condition

A preexisting condition is one that is present at the start of the study. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition.
- Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2. Recording of Adverse Events

At each contact with the subject, the investigator or study staff will seek information about adverse events by specific questioning and, if appropriate, by examination. Information on all AEs will be recorded immediately in the source document, and in the appropriate AE section of the case report form (CRF). AEs will be tracked using the HSC IRB AE tracking form or REDCap data management tool (See Section 9.3) to be reviewed by Site Investigator and IND Sponsor on a monthly and ad hoc basis, depending on severity and expected/unexpected nature of the event.

All AEs occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. SAEs that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported per Institutional policy and according to FDA requirements.

8.3. Reporting of Serious Adverse Events and Unanticipated Problems

Any incidents, experiences, and outcomes reported or discovered during clinic or telephone assessment that meet AE criteria will be documented. Any AE reported as serious (SAE) requires submitting an institutional Prompt Response Form to the IRB with a copy of the SAE or UPIRSO prompt report submitted to the Pepper DSMB for review as well as the funding agency Program Officer within 24 hours of notification to PI. All AE that are not serious nor UPIRSO will be summarized annually and submitted at continuing review to the IRB, FDA (if applicable) or other pertinent research committees with oversight of the study.

SAE and or UPIRSO will be reported per institutional IRB policy and procedure. Events that do not involve AE or SAE (non-AE UPIRSO), and which are a result of study participation may also require prompt reporting to the IRB per local policy. The report will include a description of the event, when and how it was reported, as well as any official chart records or documentation to corroborate the event or the reporting of the event. All AE will be graded as mild, moderate, or severe. Any action resulting in a temporary or permanent suspension of this study (e.g. local site IRB actions) will be reported per funding agency, DSMB, and IRB stipulations.

Serious adverse events (SAE) still ongoing at the end of the study period will be followed up to determine the final outcome and or referred to participant's primary care provider. Any SAE that occurs after the study period that is considered to be possibly related to the study treatment or study participation will be recorded and reported per Institutional policy and according to FDA requirements.

8.3.1. Investigator responsibilities - The PI or Co-PI (MD) is responsible for:

- Reviewing all incidents, experiences, and outcomes that may represent UPIRSO.
- Determining whether event represents a possible UPIRSO
- Promptly reporting to IRB per local policy
- Contacting institutions involved
- Implementing actions necessary to eliminate immediate hazard
- Submitting follow up reports to IRB
- Submitting amendments to IRB, if applicable or stipulated

Report SAE and UPIRSO immediately by phone and or secure email to:

PI: Mitzi Gonzales, PhD Assistant Professor, Biggs Institute 323-273-2107 Gonzalesm20@uthscsa.edu	AND	Co-PI/IND Sponsor: Dean Kellogg, MD, PhD Barshop Institute & VA Hospital 210-617-5197 kelloggd@uthscsa.edu

Within the following 48 hours, the PI or co-PI provides further information on the SAE or UPIRSO in the form of a written narrative. This should include a copy of the completed Institutional Prompt Response Form and any other diagnostic information that will assist the IRB to understand of the event. A copy of the SAE or UPIRSO prompt report is submitted to the Pepper DSMB for review as well as the funding agency or Program Officer.

For further special reporting requirements, please refer to the DSMP document approved by the funding agency or Program Officer.

Additional reporting requirements

The site investigator reports to the regulatory sponsor of the study. The IND sponsor (or sponsor-investigator if investigator initiated) is responsible for reporting to FDA when applicable, according to 21 CFR 312 regulations. Contact FDA for guidance

8.4. Reporting Process

SAE may be submitted on FDA Form 3500A or in a narrative format. The contact information for submitting safety reports is noted below:

Food and Drug Administration, Center for Drug Evaluation and Research
Division of Neurology Products
10903 New Hampshire Avenue, Silver Spring, MD 20993
Building 22, Suite 4346
Phone: (301) 796-2250
Fax: (301) 796-9842

8.5. Medical Monitoring

The PI and Co-PI initiating the study will review the safety and progress of this study on a frequent basis or when needed if protocol deviations/violations, SAE or SAE-UPIRSO occurs. The Pepper Center DSMB shall serve in a monitoring capacity and receive notification of SAE or SAE-UPIRSO. (See Section 10.1)

The PI and or Co-PI will review source documentation in the research record and or medical record when study coordinator provides an electronic alert or secure email to review.

8.5.1. Investigator reporting of Protocol Deviations/Violations

Departures during the conduct of a research study constitute a protocol deviation, violation or exception and as such must be reported to the UTHSCSA IRB.

Tracking and reporting of protocol deviations and violations to the IRB is the responsibility of the PI. Determination of whether deviations or violations require prompt reporting or other action will be made according to IRB and institutional policies Failure to report departures from the protocol according to IRB policy may constitute possible non-compliance, which will require a prompt response form and possible FDA reporting by IRB.

Deviations and violations may be identified in a number of ways including:

- A report by an individual can be made directly to the IRB Office.
- The IRB may learn of event through its continuing review of ongoing research.
- Compliance reviews (audits) conducted by the Office of Regulatory Affairs and Compliance or one of the HSC affiliated institutional compliance offices.
- A report by an individual can be made directly to the Office of Regulatory Affairs and Compliance (Hotline) or one of the HSC affiliated institutional compliance offices.
- A report by another committee, department, institution, or official.
- An audit or report from the study sponsor or sponsor's monitoring entity.

8.5.2. Definitions of Protocol Deviations/Violations

- Protocol deviations
- Protocol violations
- Emergency violations
- Refer to UT Health San Antonio IRB Policy website for more information

8.6. Stopping Rules

In the unlikely event that a study-related death or SAE occurs, the decision to stop the trial, either temporarily or permanently, will be the responsibility of the MSM or Pepper Center DSMB in collaboration with the Sponsor Investigator.

There are several reasons why the researchers may need to end the subject's participation in the study.

Some reasons are:

- The researcher believes that it is not in the subject's best interest to stay in the study

- Adverse drug reaction that does not resolve by dosing titration or if reaction is severe
- Subject becomes ineligible to participate due to concomitant use of an exclusionary medication
- Subject's health condition changes and needs treatment that is not allowed while participating in the study
- Subject does not follow instructions from the research team.
- The study is stopped

In the unlikely event that a study-related death or SAE occurs, the decision to stop the trial, either temporarily or permanently, will be the responsibility of the Designated Safety Officer in collaboration with the Sponsor Investigator.

The research team will discuss options for medical care with the subject when participation in the study ends.

9. Data Handling and Record Keeping

9.1. Confidentiality

Information learned about all subjects will be kept confidential. All data and protected health information in paper form will be kept confidential by assigned anonymous identifier and kept secured (password protected and/or double locked). Subjects will not be identified in any way in any publication.

9.2. Source Documents

Source data will be originated both electronically and on paper. Electronic data may be originated in either the medical record or in REDCap (. The study team will maintain a list of forms to identify where source data are generated for this protocol.

Print all entries legibly in black ink. Erasures and white-out material are prohibited. If any entry error has been made on paper, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.2.1. Research Electronic Data Capture (REDCap) and origination of electronic source data

Contemporaneous medical histories, physical exams, concomitant medications, checklists of consent processing, and documentation of eligibility criteria may be originated electronically in REDCap with date and time stamp and e-signed by the study team member obtaining the data. Then REDCap forms will be downloaded in PDF format containing saved source data and printed to file in the paper participant record at the research site. Other electronically originated data in REDCap include: adverse event (AE) assessments and AE logs, enrollment logs, protocol deviation logs, and other study management checklists. Other electronic medical record data (UT Health EPIC, UHS Sunrise) including pre-existing history, exams, medication lists, and such may be accepted as source data.

All missing data will be routinely queried, corrected, and or explained. If a space on the Case Report Form (CRF) is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

9.2.2. Paper source data

Paper source data will be collected from handwritten subject diaries, pharmacy logs, then entered into the REDCap database. All missing data will be routinely queried, corrected, and or explained. If a space is left blank on paper because the procedure was not done or the question was not asked, write "N/D", initialed and dated by the staff member. If the item is not applicable to the individual case, write "N/A".

- Lab reports originating from medical records will be printed and filed in paper participant files to facilitate investigator review. Lab data will be entered into REDCap to facilitate analysis.

- Questionnaires and assessments (e.g., cognitive assessments verbally administered according to purchased test booklets and copyrighted material) may be originated electronically in REDCap. Otherwise, it may be necessary to originate survey data on a paper source and transfer the data elements to REDCap for calculation, data management and analysis. Paper sources will be filed in paper subject records.
- Supervising physician investigators will sign and date paper records upon review.

9.2.3. Handwritten entries

All handwritten entries will be created contemporaneously to the visit or phone call, and legibly in blue or black ink. Erasures and white-out material are prohibited. If any entry error has been made on paper, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.3. Data Management

Database Management Software: All data collection for this project will be maintained using the UT Health San Antonio REDCap platform which is managed by the Department of Epidemiology and Biostatistics.

Data System: REDCap is a computing environment developed by Vanderbilt University consisting of a collection of instruments, under the management of UT Health San Antonio's Information Management systems, policies, and procedures that govern its informatics operations. Data projects are designed to be end-user oriented and constructed to optimize workflow and minimize errors.
All data will be input using a web front-end interface. All users are individually assigned authorization for access to specific components of the database application. Information that is input is checked for logical and range consistency and mandatory data fields must be entered in order to input a record.

9.4. Records Retention

The Principal Investigator and co-Investigator are responsible for maintaining study essential documents for at least 3 years after the funding grant period ends or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, whichever is longer.

These documents should be retained for a longer period if required by a funding agency, the FDA or other institutional retention policy. In such an instance, it is the responsibility of the sponsor or Principal Investigator to inform the institution as to when these documents no longer need to be retained.

10. Study Monitoring, Auditing, and Inspecting

10.1. Data and Safety Monitoring Plan (DSMP)

The Principal Investigator (PI) and Co-PI (MD) will be responsible for ensuring the timely monitoring of the data integrity and safety of study participants. The PI and/or Co-PI will communicate on a per visit basis with other members of the study staff to review adverse events and protocol compliance within 5-7 calendar days of the most recent study visit or phone encounter.

The (PI) and Co-PI (MD) assign a staff member to conduct periodic quality assessments on consent processes and on collected data to ensure data integrity, security and control for quality assurance, which is also reviewed on an annual basis by the regulatory coordinator and PI and Co-PI when preparing continuing review documentation for IRB submission.

This study may choose to utilize one of two options for objective monitoring: 1) appointment of a Medical Safety Monitor to review the study after the first subject is completed and again before the last subject is completed; or 2) the Older Americans Independence Center (OAIC) Pepper Center Data and Safety Monitoring

Board (Pepper DSMB) at appropriate intervals determined by the Board following initial protocol review and based on relative risk. The Pepper Center DSMB meets 2-3 times a year, by teleconference call, to review study progress of designated studies and assesses participants' safety.

10.2. Auditing and Inspecting

The Principal Investigator will permit study-related monitoring, audits, and inspections by the IRB, the funding sponsor, the Pepper DSMB, government regulatory bodies, and University compliance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

The Principal Investigator will ensure that the designated regulatory coordinator or other quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct study monitoring visits as assigned.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11. Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312) applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to the Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. Funding agency policies will be referenced regarding the potential requirement of an amendment submission.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. In line with recommendations put forth by the Global Alliance for Genomics and Health, Aging, and Dementia Task Team, researchers will first attempt to seek consent from the study participant with cognitive impairment. In order to have appropriate safeguards, decision-making capacity specific to participation in the research study (i.e., understanding the purpose, procedures, risks and benefits of study participation) will be evaluated using a standardized instrument for assessing capacity to consent developed by Jeste et al, 2007 and tailored to the study . In the event of questions regarding capacity, the research study will consult with the PI or other qualified study team members. If the study participant is found to lack capacity to consent, researchers will obtain consent from a legally authorized representative (LAR) who will be instructed to respect the will and preferences of the study participant. When a LAR is necessary, the researchers will still include the study participant in the consent process and will seek to obtain assent for study participation

12. Study Finances

12.1. Funding Source

This study is financed through an institutional grant from the Institute for Integration of Medicine and Science/Clinical Translational Science Award.

12.2. Conflict of Interest

UT Investigators are required to submit Conflict of Interest disclosures with every new study submitted for review by UTHealth San Antonio IRB.

12.3. Subject Stipends or Payments

This study will reimburse subjects for time and transportation. A schedule of payments is shown below. The total potential reimbursement to a subject is $435 for the study for all visits. Payments may be prorated to

include the last visit completed if study participation is terminated early. Manual payments for additional visits, if necessary, will be handled on an ad-hoc basis with prior approval from the funding sponsor.

Table 2. Participant Compensation

Study Visit	Compensation Amount
Visit 1: Screening and Consent	$35
Visit 2	$75
Visit 3	$75
Visit 4, 5, 6	$25 each
Visit 7	$100
Visit 8	$75
Manual Payment (unscheduled visit, lab visit, or AE)	$25

13. Publication Plan

The Institution, Sponsor or respective designees may review results prior to presenting or publishing the results of a scientific investigation involving this Study in accordance with ICJME guidelines and institutional requirements.

14. References

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SUMMARY OF PROTOCOL CHANGES TABLE

Date of Change	Version	Section Modified	Before Change	After Change
10-22-19	IND (should have been 1.0)	N/A	Clinical Protocol for FDA by OCR	Submitted 11-05-19
11-25-19	Updated to 1.1	Cover Page Clinical Site Summary of Protocol Changes Table	IND Number: VA Clinical Research Unit None	Exempt UT MARC Added table on Page 29 to track future changes
02-10-20	Updated to v1.2	Multiple	From v1.1	Changed to v1.2 during IRB review process
04-30-20	Updated to v1.3	Cover page and headers Inclusion criteria, Study Summary and Section 4.2 Section 6, Visits Section 8.6, Stopping Rules	v1.2 2-20-20 Cholesterol >240 Safety labs Fundamental statement Recruitment- at phone screening and Exclusion criteria Section 4.3	Versioning updated v1.3 04-09-20 Removed cholesterol as an inclusion criterion Added lipid panel to safety labs at Visit 2,4,5,6,7,8 Clarified stopping rules Added exclusion language about history of triglyceridemia
06-05-20	Updated to v1.4	Cover page and headers Section 6, Visits	V1.3 or 1.3.1 No introductory statement about COVID screening and testing Visit window and Drug dispensing …weeks +3days	Versioning updated to v1.4 05-26-20 Added paragraphs about COVID screening and testing pre-drug intervention Changed to +2 days to = monthly dispensed amount to 30/bottle

06-30-20	Updated to v1.5	Exclusion criteria	See v1.4**	Added "Hypersensitivity or history of allergy to Rapamycin"
08-03-20	Updated to v1.6	Multiple	List of Abbrev. Inclusion Criteria Secondary Outcomes Fitbit Monitoring Optional OCT/OCTA Study Visits & Procedures Summary Visit Schedule Table Source Documentation	Updated Updated lab info for Dx of MCI or AD Revised lab info and testing batteries Removed from protocol Removed from protocol Revised COVID info and cognitive exams Required updates Removed IDEAS
09-15-20	Updated to v1.7	Multiple	Study Site Update	Removed MARC, FORU & BICRC as study sites.
10-16-20	1.7.1	6.3 6.6, Visit 6 6.8, Visit 8 6.9, Summary Visit Schedule Table	Removed Geneus Lab for COVID testing Corrected safety labs to fasting specified tests to be performed, added optional snack Added optional snack at Visit 8	Require update Required correction Added for clarity Required correction
12-21-20	1.7.2	5.5	Added guidance for dosing interruption(s) in the event a participant may	Per internal discussion of changing medical situation(s)

01-21-2021		5-special considerations for COVID	receive a COVID-19 Vaccination. Criteria by which COVID-19 PCR test can be waived	
2-5-2021		4.2 inclusion criteria	Change CVLT-III cut off ≤	Per PI to develop more consistent set of IC/EC with the other alzheimers association funded trials.
2-5-2021		6.6 and 6.7	Language clarification of drug dispensing.	Clarifying that no new drug will be dispensed at visit 6 and all study drug should be returned at visit 7.
4-12-2021		4.2	Modification of inclusion criteria 3	Change of inclusion criteria to make the diagnosis of AD/MCI based on the CDR Rating exclusively. After further review of literature removal of the other two assessments will not make a significant difference in population.
4-12-2021		6.4	Adding CDR assessment to Visit 4	Repeat of the CDR prior to drug dispensation for confirmation purposes.
21-May-2021		4.2	Modification of Inclusion Criteria # 8.	Clarification that participants must be on stable dosage(s) of Alzheimer's medications for 3 months prior to baseline (visit 2)
18-JUN-2021		6.4 and 6.9	Change to Schedule of procedures	Clarify that CDR will only be done at visit 4 if the visit is done 60 or more days after Visit 1.

**v1.4 changes included with v1.5 changes and submitted together for IRB approval (amendment dated 7-01-2020)