COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: Pilot Study to investigate the safety and feasibility of Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (SToMP-AD)

NCT number: NCT04063124

IRB Approval Date: 08/12/2021

Unique Protocol ID: HSC20190222H

Pilot Study to investigate the safety and feasibility of **S**enolytic **T**herapy t**o** **M**odulate the **P**rogression of **A**lzheimer's **D**isease (**STOMP-AD**)

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Study Product: *Dasatinib (SPRYCEL®, Bristol Myers Squibb) and Quercetin (Thorne Research) in combination*

Protocol #: *HSC20190222H*

IND Number: 143945

NCT#: 04063124

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List of Abbreviations

CSF – cerebrospinal fluid
AD – Alzheimer's disease
D – dasatinib
Q – quercetin
D+Q or DQ, combination therapy with D and Q
HPLC/MS/MS – High Performance Liquid Chromatography-Mass Spectrometry
MoCA – Montreal Cognitive Assessment
CDR – Clinical Dementia Rating
WMS-IV – Wechsler Memory Scale
CNS – Central nervous system
NFT – neurofibrillary tangles

Study Summary

Title	**S**enolytic **T**herapy t**o** **M**odulate the **P**rogression of **A**lzheimer's **D**isease (SToMP-AD)
Protocol Number	HSC20190222H
Phase	2
Methodology	Open label pilot
Study Duration	Between 20-24 weeks
Study Center(s)	Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases and UT Health San Antonio Medical Arts and Research Center (MARC)
Objective	To evaluate dasatinib and quercetin (D+Q) brain penetrance in older adults with early Alzheimer's disease (AD) and investigate changes in senescent and AD-related markers as initial proof-of-concept for a larger phase 2 clinical trial
Number of Subjects	Screen up to 40 with intent for 5 completers. Additional subjects may be enrolled if attrition exceeds the anticipated rate (~25%).
Inclusion Criteria	1) Both genders and all ethnic groups 2) Age 65 years and above 3) Clinical diagnosis of AD (MoCA 7-23 and Clinical Dementia Rating [CDR global] = 1 and memory domain ≥1) on a stable dose of cholinesterase inhibitors for at least three months 4) Labs: Normal blood cell counts without clinically significant excursions; liver and renal function; total cholesterol (<240 mg/dl),), and glucose control (HbA1c ≤ 7%). PT/PTT/INR within normal limits 5) A Legally Authorized Representative (LAR) designated to sign informed consent and to provide study partner reported outcomes at all remaining visits must accompany participants. 6) Participants must have no travel plans that would interfere with scheduling visits following consent over the 4-5 months of study duration
Exclusion Criteria	1) Hearing, vision, or motor deficits despite corrective devices 2) Alcohol or drug abuse 3) MRI contraindications 4) Myocardial infarction, angina, stroke or transient ischemic attack in the past 6 months; QT interval >440 on screening ECG will be excluded. Chronic heart failure is exclusionary. 5) Coagulation disorders are exclusionary. 6) Neurologic, musculoskeletal, or other condition that limits subject's ability to complete study physical assessments 7) Uncontrolled diabetes (HbA1c > 7% or the current use of insulin) 8) Current or chronic history of liver disease, or known hepatic or biliary abnormalities (>2x normal values) 9) Use of anti-arrhythmic medications known to cause QTc prolongation, anti-platelet or anti-coagulant medication 10) Current use of quinolone antibiotics, hydroxychloroquine or chloroquine 11) Use of systemic steroids within 6 months prior to screening and throughout the study duration 12) Poorly controlled blood pressure (2 or more readings of systolic BP>160, diastolic BP>90 mmHg) 13) Active inflammatory, COVID-19, autoimmune, infectious, hepatic, gastrointestinal, malignant, and psychiatric disease 14) History of, or positive CT or MRI image with any space occupying lesion, including mass effect or abnormal intracranial pressure, which would indicate contraindication to lumbar puncture.

Study Product, Dose, Route, Regimen	D is given as (1) 100mg capsule daily for 2 consecutive days (Sprycel®, Bristol Myers Squibb). Q will be given as (4) 250 mg capsules daily (total 1000 mg daily) for the same 2 consecutive days (Thorne Research). Both are administered orally.
Duration of administration	D+Q will be administered once daily (1st dose of each cycle will be given, supervised, at the clinic visit; the 2nd dose will be taken at home) for 2 consecutive days followed by a 13-day (+/- 2 day) no-drug period for 12 consecutive weeks for 6 rounds of administration.
Statistical Methodology	Similar to an early phase 2 trial, we are seeking preliminary evidence of safety and tolerability and the objective is to estimate the pre/post differences in pertinent laboratory values and adverse event reporting. 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 underlying processes driving chronic neurodegeneration in Alzheimer's disease (AD) and related neurodegenerative disorders are largely unknown. Moreover, individuals with AD suffer from significantly more co-morbid conditions than demographically matched older adults. Treatments that target systemic pathologies associated with advanced aging may provide benefit to the AD patient demographic. Toward this end, we have identified cellular senescence as a relevant target for intervention. Cellular senescence is a complex stress response involving aberrant cell cycle activity, adaptations to maintain survival, cellular remodeling, and metabolic dysfunction. Simultaneously, senescent cells secrete toxic molecules that induce chronic cell death. Senescent cells accumulate in many tissues with aging, and their clearance improves tissue from individuals with AD. With the use of AD transgenic mouse models and postmortem human brain tissue, we identified tau protein accumulation as the cause of senescence in the brain. Preclinical studies using dasatinib and quercetin (D+Q) cleared senescent cells, and decreased tau accumulation, ventricle enlargement, white matter hyperintensities and rescued aberrant cerebral blood flow(1). Clinical studies with this drug combination are underway in individuals with a separate chronic age-associated health conditions, idiopathic pulmonary fibrosis (IPF); the study retention rate is 100% with no DQ discontinuation(2). In the 14 completed study participants, non-serious events were primarily mild-moderate in severity and reversible including respiratory symptoms, skin irritation/bruising, and gastrointestinal discomfort. One serious event was reported following completion of the intervention – possible bacterial pneumonia and pulmonary edema superimposed on IPF (the study trial disease condition). The subject was temporarily hospitalized and subsequently released with complete resolution. Of note, the dosing strategy we are employing is less frequent (2 out of every 15 days instead of 3 out of every 7 days), reducing toxicity. We are well positioned to test intermittent senolytic treatment in individuals with AD to evaluate blood brain barrier penetrance of D and Q, and begin collecting initial data on target engagement and AD-relevant outcomes for future trials.

1.2. Innovation

Treatment with senolytics to measure the concentration of D+Q that reaches the cerebrospinal fluid and crosses the blood-brain barrier is a novel approach to help identify targeted therapy and dosing for clearing cellular senescence and tau accumulation known to be present in Alzheimer's disease.

1.3. Preliminary data

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects over 5.6 million Americans and has no curative treatment. Recent evidence suggests that AD pathophysiology begins decades prior to symptoms(3). A poor understanding of mediators that drive disease onset and progression during the long prodromal, asymptomatic stages presents a large barrier for developing effective therapeutic strategies.

The cellular senescence stress response is the quintessence of latent, chronic tissue destruction. Effects of a toxic insult may lay dormant for years or decades. Using gene expression derived from postmortem human brain tissue from individuals with AD, we found neurons with NFTs (neurofibrillary tangles) upregulate signaling pathways consistent with cellular senescence (**Fig. 1a**)(1). These include upregulation of pro-survival and inflammatory pathways and down regulation of cell death pathways. Predicted upstream regulators of these gene expression profiles were also consistent with senescence in human AD and transgenic AD mouse models recapitulated these gene expression patterns (**Fig.**

1b, c).

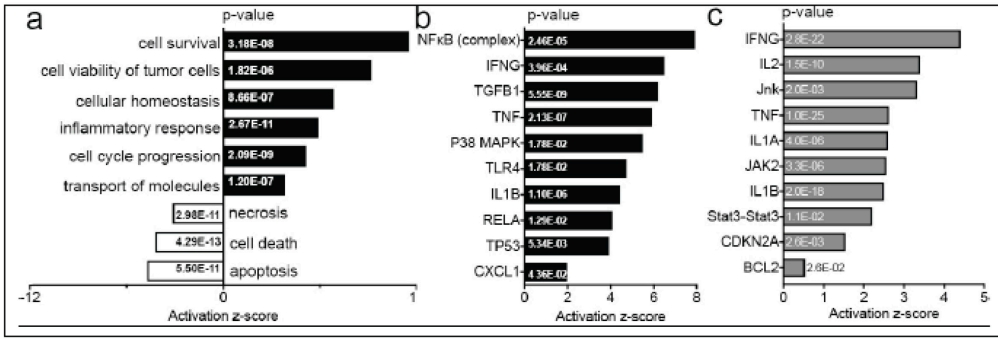

Figure 1. Senescence-associa genes and pathways upregulated in Alzheimer's disea (a) IPA gene expression profiles f postmortem human AD brain re that neurons with NFTs transcriptionally similar to senes cells. (b) Predicted upstr regulators of human AD incl senescence-associated cell cycle inflammatory regulators and are recapitulated in AD transgenic mice

Pharmacological agents targeting senescent cells, termed senolytics, have successfully decreased a variety of age-associated pathologies in model organisms(4-6). The intervention consists of brief and intermittent dosing, which allows for the clearance of senescent cells thereby eliminating a source of inflammation and toxicity. One of the best-characterized senolytic treatments is dasatinib and quercetin (D+Q or DQ). D, a tyrosine kinase inhibitor with blood brain barrier penetrance, decreased microgliosis and exerted neuroprotective effects in AD pre-clinical models(7-9). Q, a naturally occurring flavonoid, reduced AD-associated protein accumulation and inflammation in transgenic AD mice(10). Recently we treated AD mice with DQ combination therapy and found a significant improvement in multiple AD-relevant phenotypes including reduced ventricle volume, aberrant cerebral blood flow, and white matter hyperintensity (WMH) pathology (Fig. 2a, b)(1). These significant differences occurred concomitant with clearing 35 percent of pro-inflammatory senescent NFT-containing neurons (Fig. 2c). In these old mice, clinically relevant outcomes were improved after only 6 single oral doses of DQ spanning 12 weeks. The dose, 5 mg/kg D and 50 mg/kg Q, are similar to dosages used in humans. These results demonstrate the feasibility of selectively ablating senescent cells in vivo and the efficacy of these drugs for alleviating AD-associated deficits in brain structure and function. Since D and Q have been used in patients for other indications, and improve AD-relevant outcomes in pre-clinical studies, we propose to pilot this drug combination in older adults with early stage AD.

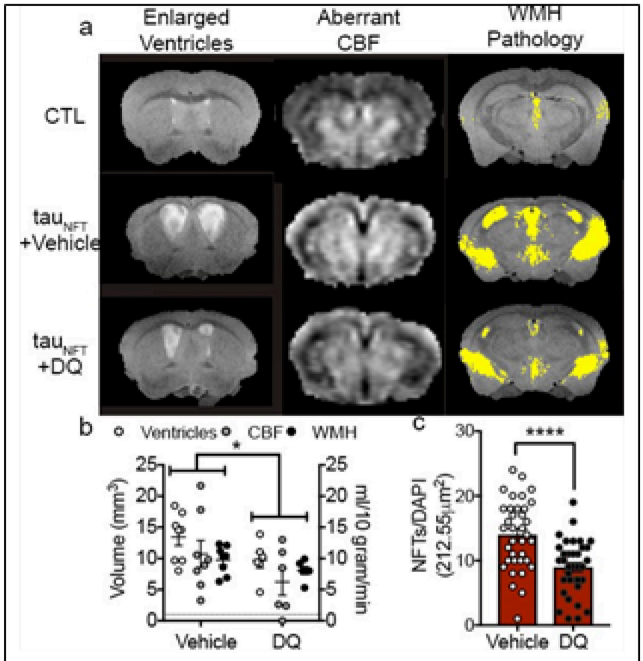

Figure 2. Senescent cell removal with D+Q improved brain structure and function in AD mice. (a) MRI on advanced aged control (CTL) and AD transgenic mice (tau_{NFT}) revealed anatomical (ventricles), cerebral blood flow (CBF) and white matter hyperintensity (WMH) pathologies.
b) Treatment with DQ mitigated these pathologies. Two-way ANOVA, significant treatment effect $p < 0.05$. (c) Quantification of the number of senescence neurons with neurofibrillary tangles (NFTs) between vehicle and DQ treated mice. Two-tailed t-test, **** $p < 0.0001$.

1.4. Dose Rationale and Risk/Benefits

Eligible participants will be treated with 100 mg of dasatinib (D) daily for 2 consecutive days plus quercetin (Q) for the same 2 consecutive days with (4) 250 mg capsules daily (total 1000 mg daily: 2 in AM and 2 in PM), followed by a 13-day (+/- 2 day) no-drug period to complete a single cycle. We will repeat until completing 6 cycles in approximately 12 consecutive weeks to achieve a time period in which cognitive

changes may be detectable. The small sample and objectives would be consistent with a Phase II study (i.e., we need to know what the D and Q drug levels would be in the CSF during this same duration). The risk profile is described in detail in Section 3.4.

The study will consist of a screening/baseline period of up to 30 days pre-medication, with an 84-day treatment period, and a post-intervention visit for study outcomes on day 85 (up to +10 days). The study duration is not expected to exceed 24 weeks for subjects.

2. Study Objective

The objective of the study is to test intermittent senolytic treatment in 5 individuals with early AD to determine levels of drug that reach the central nervous system (CNS) by collecting cerebral spinal fluid (CSF), and begin collecting initial data on target engagement of senescent cells, 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 intermittent D+Q to measure its target engagement in CSF and blood, and to establish the feasibility and safety of D+Q treatment in older adults with early stage AD as initial proof-of-concept for a larger Phase 2 clinical trial.

Aim 1: To assess the degree of drug brain penetration by assessing cerebrospinal fluid (CSF). D and Q are rapidly metabolized and cleared from the systemic circulation; however, less information is known on brain penetration and metabolism. Lumbar punctures will be performed pre-treatment and after the final D+Q dose to assess CSF D and Q levels after a 12-week intermittent treatment regimen. D and Q and their metabolites will be measured by HPLC/MS chromatography.

Aim 2: To investigate target engagement of D+Q treatment in early Alzheimer's disease with CSF and blood markers and MRI measures. Pre- and post- measures will include brain MRI-derived traditional markers of white matter damage (primary: white matter hyperintensities; secondary: covert brain infarcts, cerebral microbleeds, enlarged perivascular spaces) as well as novel indices (functional connectivity, peak skeletonized mean diffusivity, cerebral blood flow, free-water fractional anisotropy). We will also analyze levels of relevant AD markers (i.e., total tau, phosphorylated tau, Aβ40 and Aβ42, neurofilament light, and glial fibrillary acidic protein), senescence (i.e., p16, IL-6, PAI-1, ICAM-1) and lipid (through shotgun lipidomics) markers in the CSF and/or plasma.

Aim 3: To evaluate change from baseline in cognition and functional status after 12 weeks of D+Q treatment. Cognitive changes will be evaluated with a detailed neuropsychological battery with measures of global cognition, verbal and visual memory, attention, processing speed, executive function, visuospatial function, language, and mood/behavioral symptoms. Functional status will be evaluated with questionnaires, interview, grip strength and electronic gait mapping.

Aim 4: To establish the safety and tolerability of 12-week D+Q treatment in older adults with early symptomatic Alzheimer's disease. At three, five, seven, nine, and twelve weeks, safety evaluations will be conducted including assessment for adverse events, compliance to study drug regimen, physical examination, vital signs, and laboratory assessment (CBC, CMP, plasma D+Q levels).

3.2. Study Endpoints

a) **Primary outcome: To determine blood brain barrier penetrance of D and Q in older adults with early symptomatic Alzheimer's disease.** Lumbar punctures will be performed before and after the final D+Q dose, to assess CSF D and Q levels after a 12-week intermittent treatment regimen. D and Q and their metabolites will be measured by HPLC/MS chromatography.

Secondary outcomes:

b) **To assess target engagement of D+Q.** Target engagement of D+Q will be assessed by pre- and post-measurements of blood and/or CSF by analyzing plasma and/or CSF levels of relevant AD markers (i.e., t-tau, p-tau, Aβ40, Aβ42, NFL, GFAP), senescence markers (i.e., p16, IL-6, PAI-1, ICAM-1), and lipid species prior to beginning D+Q treatment and after the final D+Q dose 12 weeks later.

c) **To establish the safety and tolerability of 12-week D+Q treatment in older adults with early symptomatic Alzheimer's disease.** At three, six, nine, and twelve weeks, safety evaluations will be conducted including assessment for adverse events, study compliance, physical examination, vital signs, and laboratory assessment (CBC, CMP, plasma D+Q levels).

d) **To assess changes in cognition, functional status, and physical performance** - Change from baseline in gait, grip, cognitive exams (MoCA, WMS-IV Logical Memory, Benson Figure, California Verbal Learning Test II Short Form, Trail Making Test Parts A&B, Number Span Test, Category Fluency, Phonemic Fluency, Boston Naming Test, Digit Symbol Substitution Test), and questionnaires (Lawton ADL/IADL, Neuropsychiatric Inventory)

e) **To assess changes in MRI-derived markers of brain structure and function -** Change from baseline in brain MRI measures including WMH, covert brain infarcts, cerebral microbleeds, enlarged perivascular spaces, functional connectivity, peak skeletonized mean diffusivity, cerebral blood flow, free-water fractional anisotropy.

3.3. Potential Risks to Subject Safety

a) **Drug Administration.**

Dasatinib (SPRYCEL®) is indicated for use in chronic myeloid leukemia and acute lymphoblastic leukemia. In cancer trials the most frequently reported adverse event is fluid retention(11). Also common are rash and gastrointestinal effects (**Please refer to Attachment D, Full Prescribing Information**). Dasatinib treatment may result in mild hypoglycemia, especially in uncontrolled type II diabetics(12, 13).

QTc prolongation may occur. Dasatinib may increase the risk of prolongation of QTc in patients including those with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking antiarrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Correct hypokalemia or hypomagnesemia prior to and during dasatinib administration.

The most serious side effects are cardiac adverse events including rare fatal myocardial infarction(14). Many side-effects are alleviated in intermittent D administration(15).

For more detail, please refer to Attachment D, Full Prescribing Information, including:

- *Most common adverse reactions* (≥15%) in patients receiving SPRYCEL® (dasatinib) as single-agent therapy:
    - Myelosuppression
    - Fluid retention events

- Diarrhea
- Headache
- Skin rash
- Hemorrhage
- Dyspnea
- Fatigue
- Nausea
- Musculoskeletal pain.

- *Drug Interactions:*
  - Strong CYP3A4 Inhibitors: Dose reduction may be necessary.
  - Strong CYP3A4 Inducers: Dose increase may be necessary.
  - Antacids: Avoid simultaneous administration.
  - H2 Antagonists and Proton Pump Inhibitors: Avoid co-administration.

Quercetin is a flavonoid present in many fruits, vegetables, and grains and is also used as an ingredient in supplements, beverages, or various types of foods. Q administered as an oral supplement at doses similar to those described in the present trial is used as an anti-inflammatory and antineoplastic, and is indicated for cancer, cardiovascular disease, inflammation, lipid effects, platelet aggregation, prostatitis, and viral infection, though data is inconclusive for several of these conditions. Quercetin is generally safe and well-tolerated. However, mild and temporary side effects such as headaches, extremity tingling, and stomach discomfort have been reported, along with kidney toxicity. It is also possible that quercetin may interact with antihypertensive drugs to lower blood pressure.

D+Q: In a recent open label pilot of 14 subjects with idiopathic pulmonary fibrosis, a multi-site study used this combination intermittently for 3 days on, 4 days off over 3 consecutive weeks to total 9 doses (Justice et al., 2019, EbioMedicine, https://doi.org/10.1016/j.ebiom.2018.12.052). In their pilot, the most common adverse experiences were respiratory symptoms (16 reports), skin irritation/bruising (14 reports), and gastrointestinal discomfort (12 reports). Two severe headache events occurred. One serious adverse event was reported following completion of DQ intervention (possible pneumonia and pulmonary edema with underlying idiopathic pulmonary fibrosis), which resulted in temporary hospitalization with subsequent complete resolution.

a) **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

b) **Cognitive Assessment.**

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

c) **Brain Imaging.**

- No known harmful side effects associated with temporary exposure to the strong magnetic field used by MRI scanners.
- Anxiety and claustrophobia inside the MRI tube - severe claustrophobia is exclusionary for this study.

d) **Lumbar Puncture.** (To minimize these risks, a qualified provider specifically trained in the procedure will perform the lumbar puncture, and, if clinically indicated may use fluoroscopy.)

- 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.

The lumbar puncture will be completed with fluoroscopy if clinically indicated and at the discretion of the provider or investigator. 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 0.5 times the 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 electronic gait mapping repeating tasks 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

4. Subject Selection and Withdrawal

4.1. Subjects

Up to 40 potential candidates will be pre-screened to identify eligible men and women ages 65 years and over with a clinical diagnosis of early AD. Additional subjects may be enrolled if attrition exceeds the anticipated rate (~25%).

4.2. Inclusion Criteria

1) Age 65 years or above.
2) Clinical diagnosis of AD (MoCA 7-23 and Clinical Dementia Rating Scale/global CDR = 1 and memory domain ≥1) on a stable dose of cholinesterase inhibitors for at least three months
3) Labs: Normal blood cell counts without clinically significant excursions (WBCs: 4,500-10,500

cells/mcL; absolute neutrophil count: 1,800-8,700 cells/mcL; platelets: 140-450 K/uL; hemoglobin 12.0-17.5 grams/dL); liver and renal function (AST 10-40 IU/L, total bilirubin 0.1-1.4 mg/dl); cholesterol (<240 mg/dl), , and glucose control (HbA1c < 7%). PT/PTT/INR within normal limits

4) Participants must be accompanied by a Legally Authorized Representative designated to sign informed consent and to provide study partner reported outcomes at all remaining visits
5) Participants must have no plans to travel over the next 4-5 months that interfere with study visits following consent

4.3. Exclusion Criteria

Subjects will be excluded if they exhibit:

1) Hearing, vision, or motor deficits despite corrective devices;
2) Alcohol or drug abuse;
3) MRI contraindications;
4) Myocardial infarction, angina, stroke or transient ischemic attack in the past 6 months; QT interval >440 on ECG will not be enrolled. Chronic heart failure will be exclusionary;
5) Participants with coagulation disorders;
6) Neurologic, musculoskeletal, or other condition that limits subject's ability to complete study physical assessments;
7) Uncontrolled diabetes (HbA1c > 7% or the current use of insulin);
8) Current or chronic history of liver disease, or known hepatic or biliary abnormalities >2x normal values;
9) Use of anti-arrhythmic medications known to cause QTc prolongation, anti-platelet or anti-coagulant medication;
10) Current use of quinolone antibiotics, hydroxychloroquine or chloroquine.
11) Use of systemic steroids within 6 months prior to screening and throughout the study duration
12) Poorly controlled blood pressure (2 or more readings of systolic BP>160, diastolic BP>90 mmHg).
13) Active inflammatory, COVID-19, autoimmune, infectious, hepatic, gastrointestinal, malignant, and psychiatric disease.
14) History of, or current positive CT or MRI with any space occupying lesion, including mass effect or abnormal intracranial pressure, which would indicate contraindication to lumbar puncture

4.4. Subject Recruitment and Retention

Participants with early AD will be enrolled from the UT Health San Antonio outpatient clinics, adjunct private practice offices and or University Hospital System clinics and hospitals. 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 or sub-investigator 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.

Investigator 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.

Investigator and 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.

5. Study Drug

5.1. Description

Dasatinib. SPRYCEL® is a potent inhibitor of multiple oncogenic kinases, cellular enzymes involved in the transmission of growth signals from the cell membrane to the nucleus. The CAS number for dasatinib monohydrate is 863127-77-9. The molecular formula is C22H26C1N7O2S • H2O, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01.

Dasatinib is a white to off-white powder and has a melting point of 280°–286°C. The drug substance is insoluble in water (0.008 mg/mL) at 24 ± 4°C. The pH of a saturated solution of dasatinib in water is about 6.0. Two basic ionisation constants (pKa) were determined to be 6.8 and 3.1, and one weakly acidic pKa was determined to be 10.8. The solubilities of dasatinib in various solvents at 24 ± 4°C are as follows: slightly soluble in ethanol (USP), methanol, polyethylene glycol 400 and propylene glycol; very slightly soluble in acetone and acetonitrile; and practically insoluble in corn oil. SPRYCEL® film-coated tablets contain the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, hydroxpropyl cellulose and magnesium stearate. The tablet coating contains: hypromellose, titanium dioxide and polyethylene glycol.

Mechanism of Action

Dasatinib inhibits the activity of the BCR-ABL kinase and SRC-family kinases at low nanomolar or subnanomolar concentrations. Dasatinib also inhibits a number of other kinases including c-KIT, the EPHA2 receptor and the PDGFβ receptor. Unlike imatinib, it binds not only to the inactive but also to the active conformation of the BCR-ABL kinase. This suggests a reduced propensity for acquired drug resistance due to the emergence of mutations that promote the adoption of the kinase's active conformation.

Quercetin.

Widely found in the plant kingdom, quercetin is the most abundant of the flavonoid molecules. It is found in numerous foods, including apples, onions, teas, and berries, vegetables of the cabbage family, seeds, and nuts.
Quercetin is most commonly taken by mouth.

Mechanism of Action

Quercetin's best-known mechanism of action involves its ability to stabilize mast cell membranes, which in turn can decrease the release of histamine. In this way, it provides nutritional support for individuals who occasionally suffer from allergies. Other benefits include its cardiovascular support and protection of the gastrointestinal tract. A number of quercetin's beneficial effects appear to be due to its antioxidant activity. Quercetin can scavenge free radicals and inhibit the oxidation of LDL cholesterol. By itself, and when paired with vitamin C, quercetin can reduce the incidence of oxidative damage to skin and nerves caused by glutathione depletion.

For more detailed information, see Protocol Attachment D.

5.2. Treatment Regimen

Administration Protocol.

Study subjects will come to the clinic on the first day of each drug schedule (i.e., day 1 of each drug cycle). At this visit subjects will be given D and Q by study staff. The subjects will be sent home with the PM dose of Q and the day 2 medication (D+Q). This will be followed by the 13-day (+/- 2 day) no-drug holiday, and then repeated (subjects to clinic for day 1 D+Q, home day 2 D+Q, 13-day no drug, etc., etc.,) for 12 weeks totaling 6 rounds of D+Q.

Assigning Subjects
In this pilot, all subjects receive the same treatment, dose and frequency.

5.3. Preparation and Administration of Study Drug

The initial intake of dasatinib and quercetin will be through the Biggs Institute of 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. The study subjects will have the 2-day quantity of D+Q dispensed to them at each cycle on day 1 of study visits (week 1, 3, 5, 7, 9, and 12).

5.4. Subject Compliance Monitoring

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

5.5. Prior and Concomitant Therapy

<u>Exclusionary medications:</u>

Drugs that affect coagulation (i.e., anti-platelet or anti-coagulant medications) and current use of quinolone antibiotics are exclusionary.

Low dose aspirin (81mg) may not be considered exclusionary if used for stroke prevention or other cardiovascular treatment and participant is on stable therapy without adverse reaction for at least 6 months (consult with sponsor before enrolling).

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®), Subjects will be asked to not get the COVID-19 Vaccine injection within 4 days after the second day of a treatment cycle (Day 1 and Day 2 of taking the study medication). Subjects will also be asked to not get the COVID-19 vaccine injection within 3 days prior to beginning a new treatment cycle.

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 resumption of therapy with the IP. A delegated study clinician will have a documented conversation with the participant and/or their LAR regarding scheduling their COVID-19 vaccination in the context of the study dosing schedule.

5.6. Packaging and Product Inventory

Nature and Contents of the Container
Drugs for individual subject use will be clearly labeled and identified as “For Investigational Use only—Not for Resale”.

The Research Pharmacy will:

- Inventory receipt of initial shipment and ensure appropriate temperature control
- Distribute D and Q by labeling each individual subject packet(s) with Subject ID from list provided by PI or Co-PI to the Biggs Institute 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 the Research Pharmacy. The Research Pharmacist will notify the Principal Investigator and the Material Supplier of any damaged study drug.

Special instructions upon receipt
The Research Pharmacy 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

SPRYCEL® (dasatinib) tablets should be stored at 25° C (77° F); excursions permitted between 15°– 30° C (59°–86° F) [see USP Controlled Room Temperature]. For more details, please see also SPRYCEL® (dasatinib) Full Prescribing Information 12-2018, Attachment D, Pharmacy Manual.

5.6.3. Dispensing of Study Drug

Designated staff from the Biggs Institute maintains 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 dasatinib 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.

Procedures for proper handling and disposal of anticancer drugs should be considered. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. SPRYCEL (dasatinib) tablets consist of a core tablet (containing the active drug substance), surrounded by a film coating to prevent exposure of pharmacy and clinical personnel to the active drug substance. However,

if tablets are crushed or broken, pharmacy and clinical personnel should wear disposable chemotherapy gloves. Note: personnel who are pregnant should avoid exposure to crushed and/or broken tablets.

6. 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 and may withdraw the subject from participation in the trial. 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.

3) 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.

5.7. Visit -1 (minus 1), Consent and Screening Visit

5.7.1. Consent Process

The participant is scheduled to come to the designated research area 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 AD. 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 (see Attachment E.).In the event of questions regarding capacity, the research coordinator and/or research nurse practitioner 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.

5.7.2. 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, BMI), medical history, concomitant medication review (participants will be encouraged to bring their medications to the appointment), electrocardiogram (ECG), non-fasting blood measures for safety, including: complete blood count (CBC), comprehensive metabolic panel (CMP) including liver function tests, and lipid

panel, hemoglobin A1c (A1c), urinalysis (UA), and coagulation panel (PT/PTT/INR). Screening cognitive assessments will include Montreal Cognitive Assessment (MoCA) score and Clinical Dementia Rating scale (CDR).

If clinical bloodwork has been obtained within 60 days of the screening visit, and results are available to the investigator through medical records, the values may be recorded for research and not require repeat blood specimen collection. Clinical urinalysis results obtained within 10 days of screening may be recorded for research and not require repeating, unless investigator deems the new specimen collection is clinically indicated. Since bacteriuria is common in the older population, a positive specimen may be sent for culture and sensitivity or the specimen collection may be repeated if investigator deems appropriate.

The screening visit is estimated to require 2.5 hours.

For participants scheduled for Visit 1, research staff will call the study participant and/or LAR/study partner within one business day of Visit 1 to confirm the appointment and provide a reminder about fasting.

5.8. Visit 1 – Baseline Measurements "A" (1-4 weeks after screening).

Within 4 weeks of the Screening visit, enrolled subjects will return to the research site in a fasting state for vital signs, concomitant medication review, adverse event review, research marker urine sample and blood draw, and lumbar puncture to acquire CSF baseline measures of senescence, aging and Alzheimer's disease. A snack will be offered. Researchers will assess study participants' willingness to continue their study participation with direct inquiry to the study participant and LAR. 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 question 2 (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).

The LP Baseline A Visit is estimated to require 1 hour, including processing of specimens shown below and 30 minutes rest following the procedure. Refer to Manual of Operating Procedures for details of the LP procedure.

(i) Lumbar puncture (LP) to acquire CSF (5mL volume, 30 minutes).

- CSF: CSF will be separated into 0.5-1mL aliquots and frozen at -80C. See Analyses below.

(ii) Blood draw 30-40mL volume for inflammatory and senescent markers.

- Blood: Blood will be separated into aliquots for analysis by UTHealth/Biggs Institute and stored, in part, for confirmation by Mayo and/or Wake Forest
- Separated from 20-30mL drawn, will be plasma volume of 10-15mL for inflammatory and senescent markers
- Whole blood volume of 5-10mL for senescent markers

(*iii) Urine*

- Urine will be separated into aliquots and stored by UTHealth/Biggs Institute until analysis phase.

Analyses.

CSF:

CSF will be separated into 1mL aliquots and frozen at -80C. (i) Aliquots will be analyzed by the Pharmacology Core facility (Dr. Marty Javors) using HPLC/MS chromatography; (ii) ELISA or Simoa HD-1 Analyzer for tau and Abeta to be performed by UT Health/Biggs Institute; (iii) lipidomics by the UT Health Lipidomics Core,

Director Dr. Xianlin Han; (iv) metabolomics by UT Health Dr. Kumar Sharma; (v) senescence measures to be confirmed by Mayo Clinic and/or Wake Forest.

Blood/plasma:

Whole Blood: Whole blood will be processed with Magnetic-activated cell sorting (MACS); CD3+T lymphocytes (blood) will be analyzed for senescence-associated markers (such as p16, IL-6 and IL-6R, plasminogen activator inhibitor (PAI) -1 and 2, intracellular adhesion molecule (ICAM)-1 and 2).

Plasma and urine will be separated into 1mL aliquots and frozen at -80C. i) Aliquots of plasma will be analyzed by the Pharmacology Core facility (Dr. Marty Javors) using HPLC/MS chromatography; (ii) ELISA or Simoa HD-1 Analyzer for tau and Abeta to be performed by UT Health/Biggs Institute; (iii) lipidomics by the UT Health Lipidomics Core, Director Dr. Xianlin Han; (iv) metabolomics by UT Health Dr. Kumar Sharma (plasma and urine); (v) senescence measures (plasma and urine) to be confirmed by Mayo and/or Wake Forest Clinic.

Confirm scheduling of Visit 2, Baseline B. Within one to two business days of Visit 2, research staff may call the study participant and/or LAR/study partner to confirm the appointment.

5.9. Visit 2 – Baseline Measurements "B" (within 30 days of Visit 1).

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

(i) Cognitive examination (90 minutes) - note all measures may not be administered depending on researcher discretion):
- Hopkins Verbal Learning Test – Revised (HVLT-R)
- WMS Logical Memory
- Benson Figure
- Number Span Test
- Trail Making Test Parts A&B
- Phonemic Fluency
- Semantic Fluency
- Geriatric Depression Scale – 15-item
- Questionnaires (Lawton ADL/IADL, Neuropsychiatric Inventory)

(ii) Functional and physical performance measure (30 minutes):
- Electronic gait mapping under single and dual-task conditions
- Grip strength

(iii) To establish feasibility of MRI brain imaging for a larger study, we will encourage, but not require, study participants to receive brain imaging including: (45 minutes)
- WMH, covert brain infarcts, cerebral microbleeds, enlarged perivascular spaces, functional connectivity, peak skeletonized mean diffusivity, cerebral blood flow, free-water fractional anisotropy.

Visit 2 is estimated to require 3.0 hours. 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.

5.10. Visit 3 – Cycle 1 - Drug Administration (+3-10 days after Visit 2"B")

The participant and LAR will be asked to come to the research unit for drug dispensing and safety monitoring at Visits 3-8. Participant will undergo reassessment of willingness to participate in the study (as described under Visit 1), vital signs, concomitant medication review, ECG, and:

- AE assessment
- Blood draw (non-fasting) for safety labs: CBC, CMP, plus uric acid and phosphorus levels, prior to drug administration
- Administer, dispense study medication, and schedule further follow up safety monitoring Visits 4-8.

Administration of the 1st dose of medication and dispensing of PM dose of Q and the 2nd dose of D+Q medication (to be taken at home, 24 hours after dose #1). A study staff member calls the subject and/or LAR to verify that the subject has taken the second dose at the designated time.

Visit 3 is estimated to require 2 hour or less. Scheduling of Visit 4: to occur 14 days (± 2 days) after Visit 3. 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.

5.11. Visit 4 – Cycle 2 (14 (± 2) days after Visit 3)

Study subjects will return to the research unit for reassessment of willingness to participate in the study, vital signs, weight/BMI, concomitant medication and adverse event review, non-fasting CBC, D+Q compliance/tolerability, administration of the 3rd dose of study medication (to be taken in the clinic during this visit) and dispensing the PM dose of Q with the 4th dose of D+Q to take at home the following day. A study coordinator calls the subject and/or LAR to verify that the subject has taken the second dose at the designated time.

The estimated duration of this visit is 30-60 minutes. Confirm scheduling of Visit 5. 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.

5.12. Visit 5 – Cycle 3 (14 (± 2) days after Visit 4)

Subjects will return to the research unit for reassessment of willingness to participate in the study, safety labs [complete blood cell count (CBC), comprehensive metabolic panel (CMP)] plus uric acid and phosphorus levels, ECG, vital signs, concomitant medication and adverse event review, D+Q compliance/tolerability, and administration of the 5th dose of study medication (to be taken in the clinic during this visit). Study staff dispenses the PM dose of Q with the 6th dose of D+Q to take at home the following day, and performs a telephone follow up call to verify that the subject has taken the second dose at the designated time.

The estimated duration of this visit is 30-60 minutes. Confirm scheduling of Visit 6. 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.

5.13. Visit 6 – Cycle 4 (14 (± 2) days after Visit 5)

Subjects will return to the research unit for reassessment of willingness to participate in the study, vital signs, weight/BMI, concomitant medication and adverse event review, D+Q compliance/tolerability, and administration of the 7th dose of study medication (to be taken in the clinic during this visit). Study staff dispenses the PM dose of Q with the 8th dose of D+Q to take at home the following day, and performs a

telephone follow up call to verify that the subject has taken the second dose at the designated time.

The estimated duration of this visit is 30-60 minutes. Confirm scheduling of Visit 7. Within one to two business days of Visit 7, research staff may call the study participant and/or LAR/study partner to confirm the appointment.

5.14. Visit 7 – Cycle 5 (14 (± 2) days after Visit 6)

Subjects will return to the research unit for reassessment of willingness to participate in the study, safety labs (CBC. CMP plus uric acid and phosphorus levels, PT/PTT/INR), vital signs and ECG, concomitant medication and adverse event review, D+Q compliance/tolerability, and administration of the 9th dose of study medication (to be taken in the clinic during this visit). Study staff dispenses the PM dose of Q with the 10th dose of D+Q to take at home the following day, and performs a telephone follow up call to verify that the subject has taken the second dose at the designated time.

The estimated duration of this visit is 30-60 minutes. Confirm scheduling of Visit 8.

5.15. Visit 8 – Cycle 6 (14 (± 2) days after Visit 7)

Subjects will return to the research unit for final assessment of D+Q compliance/tolerability, reassessment of willingness to participate in the study, safety labs (CBC, CMP plus uric acid and phosphorus levels, A1c), vital signs, weight/BMI, concomitant medication and adverse event review, and physical exam. Study staff administers the 11th dose of medication and dispenses the PM dose of Q with the 12th dose of D+Q medication (to take at home, 24 hours after dose #11).

Schedule Visit 9 post-treatment LP for the following day (within 4 hours after participant takes dose DQ#12) and provides detailed instructions to the participant and LAR.

The estimated duration of this visit is 30-60 minutes. Confirm scheduling of Visit 9. Research staff will call the study participant and/or LAR/study partner within one business day of Visit 9 to confirm the appointment and provide a reminder about fasting.

5.16. Visit 9 – Cycle 6 (within 4 hours of Dose #12)

A study coordinator calls the subject and/or LAR for D+Q compliance/tolerability, and to confirm that the subject took the second dose at the designated time or plans to bring their second dose to the appointment. Timing of the LP appointment may be adjusted according to the actual timing of morning Dose #12. The participant returns to the designated research unit at the confirmed time.

Examination and activities during this visit include: arrive in the fasting state, reassessment of willingness to participate in the study, vital signs, weight, concomitant medication and adverse event review, and (i) urine sample and blood draw for research labs with (ii) lumbar puncture to acquire CSF. A snack will be offered. Study staff dispenses the final dose of Q for PM home administration.

The estimated duration of this visit is 1.5 hours. Scheduling of Visit 10 for further post-treatment measures and final follow up with disenrollment.

Analyses. (repeat as shown in Visits 1 and 2)

5.17. Visit 10 – End of Study Measures and Disenrollment (3-10 days after Visit 9)

The participant returns to the research unit 3-10 days after the LP to undergo reassessment of willingness to participate in the study and 12-week post-treatment measures, including vitals, weight, ECG,, concomitant

medication and adverse event review as well as:

- Cognitive test battery, including MoCA and CDR plus all assessments shown in Visit 2
- Brain MRI (repeat as shown in Baseline “B” and “C”)
- AE review, instructions for future AD follow up and study staff enters disenrollment note.

The estimated duration of this visit is 3.5 hours.

5.18. Follow Up Visit-Conducted at least 3 Months after the date of Visit 10

The participants will be contacted at least 3 months after they have completed visit 10 regarding a follow up visit to be done either in person or remotely. The process of this follow up will be as follows:

i. Consent

1) The participant and/or their LAR will be contacted and the in-person follow up visit (including risks and discomforts) will be described to them in order to determine if they are willing to return to the Biggs for these measures. If the participant/LAR agrees a visit will be scheduled. They will also be asked to fast for least 8 hours prior to labs being drawn.

2) If the participant/LAR declines to come back to the Biggs Institute for the purpose of the follow up visit or it is not feasible due to health state/relocation, the study staff will ask if they would be agreeable to conducting a visit remotely by phone. IF the participant/LAR declines, no follow up information will be collected.

3) In both situations 1 or 2, the study staff will first get consent from the LAR and, if possible, obtain assent from the participant. Given the situation, assent may be obtained at the time of the visit.

3) If, at the time of follow up it is discovered the participant has passed away, no decedent information will be collected from their LAR/Next of Kin.

ii. Study Follow up Visit-In person.

If a participant and their LAR return to clinic, the visit procedures conducted will be as follows:

1) Obtaining verbal assent from the participant (if not conducted during the initial phone call)

2) Collection of Vital Signs (BP/HR) and Weight.

3) Fasting blood draw for Disease Biomarkers (~35 mL total)

4) Provision of a Snack

5) Update of medical history, concomitant medications, and serious adverse events incurred since visit 10.

6) Neuro-cognitive tests: MoCA, CDR, and the cognitive battery as described in visit 2.

7) Completion of the ADCS-CGIC, GDS-15, Lawton IADL, and the NPI.

iii. Study Follow up Remote Visit

If a participant elects to provide follow up information remotely (i.e. via phone) the visit procedures conducted will be as follows:

1) Obtaining verbal assent from the participant (if not conducted during initial phone call)

2) Update of Medical History, concomitant medications, and serious adverse events incurred since visit 10.

3) Conducting the CDR

4) Completion of the ADCS-CGIC, GDS-15, Lawton IADL, and the NPI. This can be done either over the phone or the assessments can be mailed to the participant/LAR and they can be returned.

5) The participant/LAR will be asked if they've been examined by their PCP or other provider in the

past 2-3 months or if they have any upcoming doctors appoints in the next 2-3 months. If so, they will be asked if they are agreeable to signing a release of information form to allow us to request records in order to obtain a more recent recording of vitals and weight.

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

5.18. Summary Visit Schedule Table

Visit Number	**Visit (-) 1 Consent & Screen**	**Visit 1 Baseline "A"**	**Visit 2 Baseline "B"**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	Follow Up Visit
Visit Window	1- 4wks ā V1"A"	Wk 1, Day 1	V1 + up to 30d	V2 + 3-10d	V3 +14 ±2d	V4 +14 ±2d	V5 +14 ±2d	V6 +14 ±2d	V7 +14 ±2d	V8 +1d	V9 +3-10d	V10+90 days or more
Cycle# (dose#)	---	---	---	Cycle 1 (DQ1-2)	Cycle 2 (DQ3-4)	Cycle 3 (DQ 5-6)	Cycle 4 (DQ 7-8)	Cycle 5 (DQ9-10)	Cycle 6 (DQ11)	Cycle 6 (DQ12)	**Post tx testing and EOS**	
Consent with LAR	X											x
Reassess willingness to participate with LAR		X	X	X	X	X	X	X	X	X	X	
MoCA, CDR	X										X	x
Vitals: BP,HR,T,RR	X	X	X	X	X	X	X	X	X	X	X	X***
Height (V1 only), Weight (BMI)	X		X		X		X		X	X	X	
ECG	X			X		X		X			X	
H & P	X								X			
ConMeds	X	X	X	X	X	X	X	X	X	X	X	x
Safety Labs (not fasting)												
CBC w diff	X			X	X	X		X	X			
CMP w/ liver panel, lipids, (add uric acid, phosphorus V3,5,7,8)	X			X		X		X	X			
Hemoglobin A1c	X								X			
PT/PTT/INR	X							X				

*COVID-19 RT-PCR***				X**								
Clinical Procedures												
MRI			X								X	
*LP for CSF**		X								X		
Blood draw and urine specimen-Research Labs		X								X		X***
HVLT-R			X								X	X***
WMS Logical Mem			X								X	X***
Benson Figure			X								X	X***
Number Span Test			X								X	X***
Trail Making Test A&B			X								X	X***
Phonemic and Semantic Fluency			X								X	X***
Geriatric Depression Scale-15			X								X	X
Lawton IADL			X								X	X
CGIS			X								X	X
Neuropsych inventory			X								X	X
Physical Function Testing												
Electronic gait mapping			X								X	
Grip strength			X								X	
Study Medication												
Administer in clinic				X	X	X	X	X	--	--		
Dispense next dose to home				X	X	X	X	X	X	--		
Schedule Next Visit	X	X	X	X	X	X	X	X	X	X		
Phone Follow up Dose & Tolerability				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	

**may include fluoroscopy, if indicated **May require COVID-19 RT-PCR testing 24-48 hours prior to drug dispensing visit or procedure*

***TO be done at the in-person follow up visit only.

6. Statistical Plan

6.1. 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).

6.2. Statistical Methods

Analytical Approach.

Similar to an early phase 2 trial, we are seeking preliminary evidence of blood brain barrier penetrance, changes in senescence, with secondary evaluation of safety and tolerability to estimate the pre/post differences in pertinent laboratory values and adverse event reporting. 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.

7. Safety and Adverse Events

7.1. 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 <u>any one of the following</u> 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.

7.2. 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.

7.3. 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 a Prompt Report 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 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.

7.3.1. 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: Nicolas Musi, MD UT Health Barshop Institute 210-630-5001 musi@uthscsa.edu

Within the following 48 hours, the PI provides further information on the SAE or UPIRSO in the form of a written narrative. This should include a copy of the completed Prompt Report 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 Metabolism and Endocrinology Products
5901-B Ammendale Road, Beltsville, MD 20705-1266
Phone: (301) 796-2290 Fax: (301) 796-9712

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. To determine whether deviations or violations require prompt reporting or other action, refer to the IRB document entitled "Decision Tree – Evaluating Departures" on the IRB website. Failure to report departures from the protocol according to IRB policy may constitute possible non-compliance, which will require a Prompt Report 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
- For more information , refer to UTHSCSA IRB Policy website: https://research.uthscsa.edu/irb/policy/deviations

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.

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, IDEAS (subject registration with identifiers), or in REDCap (questionnaires answered verbally). 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.

NOTE: Identifiers will not be entered into REDCap, except for the unique study number assigned to each subject. The electronic enrollment key with identifiable information will be created in IDEAS where the unique study number is assigned and stored.

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. **The electronic enrollment key with identifiable information will be created in IDEAS where the unique study number is assigned and stored.**

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 Sponsor-investigator and Principal 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 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 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. Refer to funding agency policies as to whether or not submitting amendments may be required.

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.

12. Study Finances

12.1. Funding Source

This study is financed through an institutional grant from the Center for Biomedical Neuroscience in partnership with Institute for Integration of Medicine and Science. Additional funds have been awarded for analysis of CSF and lipidomics. An RL5 Scholar Award from the Pepper Center will also supplement the funding for this pilot.

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 $625, including the additional $150 if opting in for MRIs, for the study for all visits, or 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	$25
Visit 1	$100
Visit 2	$50 + (opt in MRI $75)
Visit 3, 4, 5, 6, 7, 8	$25 each
Visit 9	$100
Visit 10	$50 + (opt in MRI $75)
Manual Payment (unscheduled visit, lab visit, or AE)	$25

13. Publication Plan

The Institution, IND Sponsor or respective designees may present or publish the results of a scientific investigation involving this Study in accordance with ICJME guidelines and institutional requirements.

14. References

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15. Attachments

A. Agreements
B. Visit schedule
C. Lab protocol
D. Pharmacy and Drug Information
E. Capacity to Consent (Jeste et al, 2007)

SUMMARY OF PROTOCOL CHANGES

Date of Change	Version	Section Modified	Before Change	After Change
03-13-19	1.0 initial to IRB	all	NA	NA
03-25-19	1.0 updated to FDA	5. Study Drug	--	Added quercetin
04-16-19	1.1 admin changes after VPRCTO review	6.9, pg 18 (14) Visit Schedule Summary Table Cover page	Scheduling Visits 10 and 11, missing visit duration for Visits 8 and 9 Missing elements in visit table that are written in the narrative protocol, ie, telephone calls per Font size 11 IND,IRB# pending	Remove Visit 11, added visit duration Added telephone calls to Visit Schedule at Visit 3 Font size 9 Numbers updated
04-17-19	1.1 repeat admin changes	Visits and Visit Schedule	Inconsistencies identified between narrative and table	Consistency check and update
04-18-19	1.1 repeat admin changes	Visit 10 and footer version date	Cycle 6 Drug Compliance & Tolerability	Replaced with new visit title Replaced as Phone FU Dose and Tolerability
04-30-19	1.1 repeat admin changes	Visit table, footer version date	Table missing flexible window @V3-8	Added ±2d window @ V3-8 to be consistent with protocol narrative, ICF
06-19-19	1.2	Cover page Summary Table Inclusion/Exclusion Study Design	Regulatory Sponsor Objectives Objectives and Inclusion/Exclusion	Changed to “Co-PI and IND Sponsor” for Dr. Musi Add “to investigate senescent and AD-related markers’ Add contraindication language for to LP as an exclusion Add “to investigate senescent and AD-related markers’ Add contraindication language for to LP as an exclusion

06-30-19 cont'd	1.2 cont'd	Study Design cont'd Visit Schedule Section 5.4 Section 5.6 Section 6.1 Section 8.3 Section 8.5 Section 9.3 Section 10.1 General document cleanup	 Subjects, section 3 Visits 3, 5, 7, 9 "…bring empty pill bottles…." --drug responsibiltlies Consent process and screening separated PI phone number Re: medical monitoring Data management Data safety Entire document	Moved Subjects to Section 4.1 Added ECG testing upon recommendation by Pepper Center DSMB review of protocol Added "adherence logs" Added Co-PI (MD) to pharmacy information since PhD PI cannot prescribe Added Section 6.1.1. to show consent process details and reassessment at each visit Changed to correct phone number Added Co-PI(MD) to medical monitoring since PI is PhD Added information about IDEAS for identifiers Added Co-PI responsibility for data safety and monitoring Grammatical and formatting edits to clarify and polish
	1.2.1	Section 3.3.a)	Potential risks – paragraph on D+Q, Page 11	Revised paragraph to include reference to JJustice article on the D+Q pilot, consistent with consent form
08-30-19	1.3	Section 3.3, Drug Section 3.3, LP	Risks related to Quercetin Risks related to	Modified per IRB request in response to stipulations Added optional use of

			Lumbar Puncture	fluoroscopy and radiation exposure
11-27-19	1.4	Cover page, versioning Inclusion/Exclusion Criteria Visits/Procedures Summary of Protocol Changes, version 1.4 herein		Add uric acid and phosphorus to Safety Labs at visits 3,5,7,8 Change PT/PTT/INR labs to visit 7 (rather than 8) Remove Clinical Global Impressions of Change scale – add general statement that not all tests (visits 2 and 10) may be given depending on research discretion Change inclusion criteria: Moca 10-20, CDR global of 1, CDR memory domain >1 Exclusion criteria: remove TRGs, add two BP readings, add CT or MRI, specify values for abnormal hepatic or biliary abnormalities Make visits 1 and 9 (LP visits) fasting Move the final ECG from visit 9 to visit 10 Remove SPPB and TUG (visits 2 and 10) Add metabolomics analyzed by Dr. Sharma Add urine to be frozen for research
01-14-2020	1.5	Cover page Study Design, Aims Exclusion criteria and Concomitant Meds prohibited Change fluoroscopy at Visit 1 and 9 to be the default Throughout document	IND# 143495 NCT# pending SPPB in Aims Section 3.3.d. Risk of LP, fluoroscopy "if indicated" Administrative errors	IND# 143945 NCT#04063124 Remove SPPB, TUG, from Aims Added systemic steroid use as exclusionary 6 months prior and during study The lumbar punctures will be performed under fluoroscropy (default). Remove extra spaces, commas
06-05-2020	1.6	Cover page	Versioning	Versioning updated

		Sect 6, Study Visits & Procedures Visit 2 and 9, Lumbar Puncture Exclusion criteria Visit 4	Required update Updated Fluoroscopy as default	Added Barshop Inst. as clinical site Added special considerations related to COVID-19 Fluoroscopy only if clinically indicated Exclude if taking hydroxychloroquine or chloroquine Add non-fasting CBC
08-03-2020	1.7	Section 6, ,Study Visits & Procedures	Updates	Added update for COVID testing
09-15-20	1.8	Throughout document	Study site update	Removed FORU, MARC and BICRC as study sites.
11-19-20	1.9	Inclusion Criteria	MoCA score 10-20	Expanded MoCA score to 7-23
1-15-2021	2.0	Concomitant Therapy	COVID 19 Vaccination	Added dosing guidelines for patient who may undergo COVID-19 vaccination.
1-26-2021	2.1	COVID 19 Considerations	COVID testing	Added that the initial COVID 19 test could be waived if participants have been vaccinated at least one week prior to first dosing.
8-12-2021	2.2	Add 5.18 Follow Up Visit Conducted at least 3 months after the date of Visit 10	Final Follow up data	Added to look at longer term outcomes in patients who completed the study at least 3 months prior. Verbal consent will be obtained for either a fasting in-person visit or to complete assessments over the phone without the additional blood draw.