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Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (SToMP-AD): A Pilot Clinical Trial

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Abstract

Preclinical studies indicate an age-associated accumulation of senescent cells across multiple organ systems. Emerging evidence suggests that tau protein accumulation, which closely correlates with cognitive decline in Alzheimer's disease and other tauopathies, drives cellular senescence in the brain. Pharmacologically clearing senescent cells in mouse models of tauopathy reduced brain pathogenesis. Compared to vehicle treated mice, intermittent senolytic administration reduced tau accumulation and neuroinflammation, preserved neuronal and synaptic density, restored aberrant cerebral blood flow, and reduced ventricular enlargement. Intermittent dosing of the senolytics, dasatinib plus quercetin, has shown an acceptable safety profile in clinical studies for other senescence-associated conditions. With these data, we proposed and herein describe the objectives and methods for a clinical vanguard study. This initial open-label clinical trial pilots an intermittent senolytic combination therapy of dasatinib plus quercetin in five older adults with early-stage Alzheimer's disease. The primary objective is to evaluate the central nervous system penetration of dasatinib and quercetin through analysis of cerebrospinal fluid collected at baseline and after 12 weeks of treatment. Further, through a series of secondary outcome measures to assess target engagement of the senolytic compounds and Alzheimer's disease-relevant cognitive, functional, and physical outcomes, we will collect preliminary data on safety, feasibility, and efficacy. The results of this study will be used to inform the development of a randomized, double-blind, placebo-controlled multicenter phase II trial to further explore of the safety, feasibility, and efficacy of senolytics for modulating the progression of Alzheimer's disease. Clinicaltrials.gov registration number and date: NCT04063124 (08/21/2019).

Key words: Clinical trial, Alzheimer's disease, tau, cellular senescence, senolytic therapy.

Introduction

Preventive and curative interventions for prevalent causes of mortality have extended the human lifespan (1). An unintended consequence of the growing aging demographic is increased incidence of Alzheimer's disease (AD) and related dementias (2). Among the top ten causes of mortality in the United States, AD is the only condition without a conclusively proven disease modifying therapy (3). An incomplete understanding of the causal pathways underlying AD has stymied progress in novel treatment discovery (4). While hypertension, diabetes, physical inactivity, and lower educational attainment all increase the likelihood of developing AD (5), aging is the single most robust risk factor of developing AD (6). The risk of mortality due to AD increases approximately 700-fold between the ages of 55 and 85 years (7, 8). The strong association between aging and AD suggests overlapping molecular and cellular processes (9), which may serve as viable treatment targets to prevent or alleviate neurodegenerative diseases.

Cellular senescence is a hallmark feature of aging and contributes to numerous age-related chronic medical conditions including AD (10-19). Cellular senescence is a dynamic molecular process induced by stressors such as DNA and mitochondrial damage, telomere shortening, protein accumulation and metabolic dysfunction (17, 20). In response to a stressor, the cells undergo pronounced morphological and functional changes including alterations in chromatin, metabolism, and DNA damage signaling (20), culminating as a cell fate change. Cell cycle arrest is governed by complex interactions across p53, p21, and p16 tumor suppressive pathways (21). Through dysregulation of p38 mitogen-activated protein kinases (p38MAPK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), NOTCH, and mammalian target of rapamycin (mTOR) signaling, senescent cells can develop a senescence-associated secretory phenotype

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(SASP) (22, 23). The SASP consists of a noxious secretome comprised of pro-inflammatory cytokines, proteases, chemokines, and extracellular matrix degrading proteins (24-27). The SASP triggers immune cells to clear senescent cells, which is beneficial; however as senescent cells accumulate, the SASP exerts paracrine effects on adjacent cells, becoming the precipitant for broader cellular conversion to the senescent phenotype (17, 20). In murine models, transplantation of senescent cells at a ratio of one to 10,000 with healthy cells was sufficient to engender frailty, physical disability, and premature mortality (18). Senescent cells accumulate with advancing age throughout multiple organ systems, including the brain (17, 28). This cell specific loss-of-function and toxic SASP gain-of-function contributes to disease and dysfunction.

The burden of senescent cells in the brain increases with advanced chronological age and neurodegenerative diseases, and occurs across cell types including neurons, microglia, astrocytes, oligodendrocyte precursor cells, and endothelial cells (28-32). Previous work by our team identified that cellular senescence in the brain is associated with tau-containing neurofibrillary tangles (NFTs), a hallmark feature of AD that closely correlates with cognitive decline (29). Transcriptomic analyses of neurons with or without NFTs in postmortem human brain tissue of individuals with AD revealed upregulation of genes associated with cellular senescence in NFT-bearing neurons. These included increased expression of genes related to cell survival and inflammation, as well as downregulation of genes implicated in apoptosis and cellular death. NF-κB was the strongest upstream regulator of the NFT-associated gene expression profile. Overlapping expression of pathways implicated in senescence were common across tau-transgenic mice and human brain tissue with NFTs. These included tumor necrosis factor (TNF), interleukin 1β (IL-1β), and interferon gamma (IFN-γ), suggesting that these cells may accelerate neurodegeneration through release of toxic SASP factors. Pathogenic tau propagates neuroinflammation through activation of microglia and astrocytes (33). Microglia and astrocytes can acquire a senescent phenotype themselves (28, 31, 32), promoting further diffusion of the SASP and the conversion of healthy cells to the senescent phenotype. Collectively, preclinical research has provided strong proof-of-concept data that tau-induced cellular senescence may be a novel therapeutic target for AD (29, 32).

Efforts are underway to identify and develop senolytic agents, drugs that selectively ablate senescent cells (17-19). Using RNA and protein expression profiles, five senescent-cell anti-apoptotic pathways (SCAPs) were discovered. Drugs predicted to interfere with the SCAP pathways were shown to cause death of senescent cells, while leaving healthy cells unaffected. The best characterized senolytic agents are dasatinib (D) plus quercetin (Q) (D+Q) (32). D+Q target multiple senescent cell types; the combination of the two agents has been demonstrated to effectively clear senescent cells and alleviate numerous chronic medical conditions in preclinical models, including physical frailty, muscle weakness, vascular stiffness, osteoporosis, and hepatic stenosis (12-15, 18, 34). D was originally identified through a screen for proto-oncogene kinase inhibitors, and utilized as a chemotherapeutic agent that through inhibition of multiple Src kinases, interferes with anti-apoptotic cellular survival pathways in senescent adipocyte progenitor cells (35, 36). D is FDA-approved for chronic myeloid and acute lymphoblastic leukemia (37). Q, a naturally derived plant flavonoid with anti-inflammatory, antioxidant, and antineoplastic properties (38), also targets various protein kinases (39) and inhibits B-cell lymphoma 2 family proteins that mediate cell survival in senescent endothelial progenitor cells (20, 36). Importantly, D+Q have been well tolerated and demonstrated benefits in first-in-human clinical trials of other conditions (i.e., idiopathic pulmonary fibrosis (40) followed by diabetic kidney disease (34).

Both D and Q have demonstrated blood-brain barrier penetrance in rodent models with some supportive data in clinical studies of individuals undergoing cancer treatment (41, 42). Preclinical research by our team and others has demonstrated the efficacy of senolytic agents for neurodegenerative disease (28-30, 32). Musi et al. treated tau transgenic mice with late-stage pathology (equivalent to 70-year-old humans with advanced AD). The mice received senolytics on two consecutive days every other week, which totaled six rounds of treatment spanning 12 weeks (29). Histopathological analyses revealed 35% lower NFT density in senolytic treated mice (29). Brain MRI indicated that senolytic treatment mitigated pathogenic ventricular enlargement, aberrant blood flow, and the SASP. An independent study conducted by Zhang et al. validated the finding of D+Q clearance of senescent cells in the brain of an β-amyloid model of AD pathology (30). To date, research conducted across six transgenic AD mouse models has demonstrated that orally administered senolytic drugs ablate senescent cells in the brain and alleviate AD-relevant pathogenesis (28-30, 32).

Senescent cell accumulation has been broadly linked to age-related diseases, which has motivated clinical trials of senolytic therapy for a multitude of chronic medical conditions (17, 34, 40). As senescent cells do not divide and slowly accumulate over a period of weeks to months, senolytic agents do not need to be administered continuously to be effective (20, 29, 43). Intermittent dosing regimens have the benefit of reducing the risk of associated medication side effects, which could include D-associated myelosuppression, fluid retention, hemorrhage, difficulty breathing, and myocardial dysfunction (44). The first clinical trial of senolytic treatment, published in 2019, showed D+Q was generally well tolerated and suggested improvements in physical function in an open-label trial for individuals with idiopathic pulmonary fibrosis, a fatal disease, providing encouraging first evidence for further clinical

testing (40). Similarly, in an open-label trial of D+Q for diabetic kidney disease, short-term treatment effectively reduced senescent cell burden in adipose tissue and attenuated plasma levels of key SASP factors, including IL-2 and IL-6 (34). Given the compelling evidence from preclinical studies implicating cellular senescence in the pathogenesis of neurodegenerative disease, coupled with the safety data from previous clinical studies, we are conducting an open-label pilot clinical trial of senolytic treatment in individuals with early-stage dementia due to AD.

Methods

Study Aims

The primary aim is to:

1. Determine blood brain barrier penetrance of D+Q in older adults with early symptomatic AD.

Secondary aims include the following:

2. Assess target engagement of D+Q.
3. Establish the safety and tolerability of 12-week D+Q treatment in older adults with early symptomatic AD.
4. Assess changes in cognition, functional status, and physical performance.
5. Evaluate changes in MRI-derived neuroimaging markers of brain structure and function.

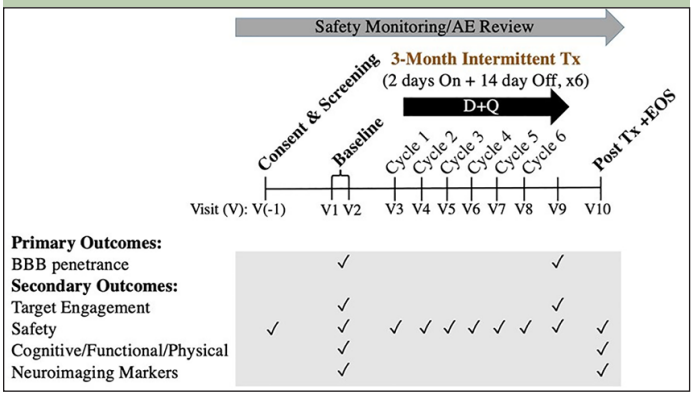
Study Design

This is an open-label pilot study of intermittent D+Q to measure target engagement in cerebrospinal fluid (CSF) and blood and to establish the feasibility and safety in older adults with early-stage AD, as an initial proof-of-concept for a larger phase II multisite clinical trial, anticipated to begin enrollment in October 2021 (NCT04685590). Adults aged 65 years and older with diagnosed early-stage AD will be considered for inclusion. All participants must adhere to the inclusion and exclusion criteria presented in Table 1. A total of five eligible participants will be enrolled and will complete 10 scheduled visits across a study period not to exceed 24 weeks. Relevant safety measures will be collected throughout the study, while neuroimaging, cognitive and physical function assessment visits will be conducted both pre- and post-treatment (Figure 1). All study visits will be conducted at the University of Texas Health Science Center at San Antonio Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases.

Study Intervention

As an open-label trial, all participants will receive the study drugs. Eligible participants will be administered 100 mg of D (one 100 mg capsule, Sprycel, Bristol Myers Squibb) and 1000 mg of Q (four 250 mg capsules, Thorne Research) daily for two consecutive days followed by a 14-day (+/- 2 day) no-drug period to complete a single cycle. Six cycles will be completed across 12 consecutive weeks. The study drugs will be taken orally. D+Q are administered under IND# 143945 (N. Musi).

Figure 1. Outline of study timeline and major measures collected at each visit



Primary and secondary outcomes are indicated by black checkmarks under each relevant visit where their collection falls. Outcomes, relevant to safety monitory measures are indicated by the gray arrow across the top, and will be assessed at every study visit (V(-1)-V10). BBB= blood brain barrier, Tx = Treatment, EOS= End of Study.

Study Schedule

Prior to randomization, participants will complete a screening visit to assess eligibility for study participation. Procedures to assess eligibility include physical and neurological examination, cognitive screening assessments, vital sign assessment, anthropomorphic measurements (height, weight, body mass index), medical history, concomitant medication review, electrocardiogram (ECG), and blood draw.

Within four weeks of the screening visit, eligible participants will complete two baseline visits. At the first baseline visit, participants will undergo pre-treatment lumbar puncture and blood draw for research labs. The second baseline visit will include assessments of cognition, physical functioning, and neuroimaging via brain MRI. Within 10 days of the second baseline assessment, participants will begin the 12-week study drug regimen. On the first day of each 2-week drug cycle, participants will present to the study site for safety assessments and drug dispensing (weeks 1, 3, 5, 7, 9, 11). Following the 12-week treatment period, participants will complete post-treatment assessments matching those conducted at each baseline visit. Table 2 displays the timeline of all study procedures.

Primary Outcome Measures

1. CSF D+Q Concentrations: 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

Table 1. Inclusion and exclusion criteria for the SToMP-AD pilot trial

Inclusion Criteria	Exclusion Criteria
Age 65 years and older at study entry	Hearing, vision, or motor deficits despite corrective devices
Clinical diagnosis of early AD defined by MoCA = 7-23, and CDR Global = 1, with memory domain ≥ 1	Active or history of alcohol or substance abuse
FDA-approved medications for AD (e.g., donepezil, rivastigmine, galantamine) are permitted if a stable dose has been maintained for ≥ 3 months prior to study entry	MRI contraindications
Normal blood cell counts, coagulation panel, liver and renal function without clinically significant excursions	Myocardial infarction, angina, stroke, or transient ischemic attack in the past 6 months; chronic heart failure or QTc > 450 msec on screening ECG
A LAR designated to sign informed consent and to provide study partner reported outcomes at all study visits	Coagulation disorders
Absence of travel plans that would interfere with scheduled visits over the 20–24-week study duration	Significant neurologic, musculoskeletal, or other condition that limits subject's ability to complete study physical assessments
	Uncontrolled diabetes (HbA1c > 7%, or current use of insulin)
	Current or chronic history of liver disease, or known hepatic or biliary abnormalities (>2x normal values)
	Current or chronic history of liver disease, or known hepatic or biliary abnormalities (> 2x normal values)
	Use of anti-arrhythmic medications known to cause QTc prolongation, anti-platelet or anti-coagulant medication
	Current use of systemic steroids, quinolone antibiotics, hydroxychloroquine or chloroquine within 6 months prior to screening and throughout the study duration
	Poorly controlled BP (systolic BP > 160, diastolic BP > 90 mmHg)
	Active inflammatory, COVID-19, autoimmune, infectious, hepatic, gastrointestinal, malignant, and psychiatric disease
	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
	Medications that are strong CPY3A4 inhibitors or inducers, or that that induce cellular senescence (i.e. alkylating agents, anthracyclines, platins, other chemotherapy)

AD = Alzheimer's disease; BP = blood pressure; CDR = Clinical Dementia Rating scale; CT = Computed Tomography; CYP = cytochrome P; ECG = electrocardiography; FDA = Food and Drug Administration; HbA1c = hemoglobin A1c; LAR = Legally Authorized Representative; MoCA = Montreal Cognitive Assessment; MRI = Magnetic Resonance Imaging; QTc = corrected QT interval

metabolites will be measured by high-performance liquid chromatography or mass spectrometry by the San Antonio Nathan Shock Center Analytic Pharmacology and Drug Evaluation Core.

Secondary Outcome Measures

2. CSF AD and Cellular Senescence Markers: CSF collected from lumbar punctures performed pre- and post-treatment will be assayed for established AD biomarkers including total tau, phosphorylated tau, and β-amyloid measured using the Simoa HD-1 Analyzer (Quanterix). In addition, single or multiplex immunoassays will be performed to assess changes in markers of cellular senescence and SASP such as IL-6, IL-9, IL-1α, IL-2, IL-1β, and matrix metalloproteinases.
3. Safety Parameters: We will track occurrence of adverse events (AEs) and serious adverse events (SAEs) from the screening visit to the end of the study. For safety monitoring, participants will routinely complete measures of vital signs, physical assessment, ECG, and laboratory values (biochemistry, hematology, liver and renal function; see Table 2 for details). Participant reported abnormalities can also be reported during scheduled or unscheduled telephone visits. Incidence of AEs and SAEs will be reviewed by the UTHSCSA Data Safety Monitoring Board (DSMB). AEs and SAEs will be defined according to the International Conference on Harmonization Guidance for Clinical Safety Data Management.
4. Cognition and Physical Functioning: The main cognitive outcomes are pre- and post-treatment changes on the Montreal Cognitive Assessment (MoCA) and the Clinical Dementia Rating Scale Sum of Boxes. Additional cognitive assessments include Weschler Memory Scale Fourth Edition (WMS-IV) Logical Memory, Benson Figure, Trail Making Test Parts A&B, Number Span Test, Category Fluency, Phonemic Fluency, Boston Naming Test, and the Hopkins Verbal Learning Test Revised (HVLT-R). The

Table 2. Study design timeline

Phase	Screen	Baseline		Treatment							Post-Treatment
Visit Number	(-) 1	1	2	3	4	5	6	7	8	9	10
Week				1	3	5	7	9	11		
Visit Window		V (-) 1 + 7-28d	V1 + ≤ 30d	V2 + 3-10d	V3 + 14d (±2d)	V4 + 14d (±2d)	V5 + 14d (±2d)	V6 + 14d (±2d)	V7 + 14d (±2d)	V8 + 1d	V9 + 3-10d
Cycle (dose)				1 (D+Q 1-2)	2 (D+Q 3-4)	3 (D+Q 5-6)	4 (D+Q 7-8)	5 (D+Q 9-10)	6 (D+Q 11)	6 (D+Q 12)	
Consent with LAR	X										
Reassess willingness to participate with LAR		X	X	X	X	X	X	X	X	X	X
CDR, MoCA	X										X
Vitals: BP, HR, T, RR	X	X	X	X	X	X	X	X	X	X	X
Height (V (-) 1 only), weight (BMI)	X		X		X		X		X	X	X
ECG	X			X		X		X			X
H & P	X								X		
Concomitant med and AE review	X	X	X	X	X	X	X	X	X	X	X
CBC w differential	X			X	X	X		X	X		
CMP w/ liver panel, lipids, uric acid, phosphorus	X			X		X		X	X		
Hemoglobin A1c	X								X		
PT/PTT/INR	X							X			
COVID-19 RT-PCR*				X							
Brain MRI			X†								X†
Lumbar puncture for CSF*		X‡								X‡	
Research labs- blood and urine		X								X	
Cognitive assessments			X								X
Physical function assessments			X								X
Administer IP in clinic				X	X	X	X	X	X		
Dispense next dose to home				X	X	X	X	X	X		
Phone follow-up visit				X	X	X	X	X	X	X	

*May require COVID-19 RT-PCR testing 24-48 hours prior to first drug dispensing visit; †may include fluoroscopic guidance, if indicated; ‡Encouraged but optional; AE = Adverse Events; BP = blood pressure; BMI = Body Mass Index; CBC = Complete Blood Count; CDR = Clinical Dementia Rating scale; CMP = Comprehensive Metabolic Panel; CSF = cerebrospinal fluid; d = day; D+Q = dasatinib plus quercetin; ECG = electrocardiogram; H & P = history and physical; HR = heart rate; IP = Investigational Product; LAR = Legally Authorized Representative; MoCA = Montreal Cognitive Assessment; MRI = Magnetic Resonance Imaging; PE/NE = Physical Exam/Neurological Exam; PT/PTT/INR = Prothrombin Time and International Normalized Ratio; S = Screening; T = temperature; V = Visit

primary physical outcome is gait speed collected on an electronic gait map under both single and dual-task conditions (45). Grip strength will also be assessed pre- and post-treatment using a handheld dynamometer.

5. Neuroimaging: Pre- and post-treatment changes in neuroimaging outcomes will be examined including hippocampal volumetry and white matter hyperintensities. Comparisons will be made from images derived from anatomical T1 images using Freesurfer (46), default mode connectivity will be examined with resting state BOLD.

Data Collection, Retention, and Management

Data required by the protocol will be collected on the official case report forms and entered into a validated data management system that is compliant with all regulatory requirements. Database lock and subsequent data analyses will be conducted after the completion of enrollment, all participant data entry, and data verification.

Ethics

The study will be conducted in accordance with the Declaration of Helsinki and will be approved by the

University of Texas Health Science Center at San Antonio Institutional Review Board. All participants will provide written informed consent prior to enrollment with appropriate legal representation for individuals lacking capacity to provide informed consent on their own behalf (47).

Statistical Analyses

Similar to an early phase II 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. Comparisons of means between pre/post evaluations will be examined.

Discussion

Despite great efforts made to identify pharmacologic interventions for the treatment of AD, the disease remains the only top contributor to mortality without a disease modifying intervention (3), aside from the recently, and controversially, FDA-approved Aducanumab (Aduhelm). Our pilot study evaluating a novel therapeutic agent for AD is a direct follow-up to the preclinical studies and clinical trials utilizing D+Q for other age-related conditions, which demonstrated an encouraging safety profile coupled with modest but promising therapeutic outcomes (18, 34, 40-42). As a first step in translating senolytics to AD, the SToMP-AD vanguard is focused on study drug penetration within the central nervous system. While it has been shown that D and/or Q can cross the blood barrier in rodent models and individuals undergoing cancer treatment, the central nervous system drug penetrance in individuals with AD remains unknown (41, 42). As blood brain barrier dysfunction occurs early in the underlying neurodegenerative disease cascade (48), the study medications may be more readily absorbed in our target study population relative to neurologically healthy adults.

Though there are several senolytic compounds which have been identified and are being further studied (e.g., fisetin and other flavonoids) for their associations with improvements in cognition and reductions in AD-relevant pathology (36, 49-52), D+Q was selected for use in this first AD relevant trial as it is the most well established. Indeed, testing these first generation senolytics in early AD is a necessary and critical step in carefully moving this field forward. Though there are obvious benefits to being able to repurpose a FDA approved chemotherapeutic medication, D, with a well-established side effect profile (53), there is a need to carefully evaluate safety and the equipoise of treatment in our vulnerable target population, especially as D+Q are utilized in combination to achieve broader targeting of senescent cell survival mechanisms (19). As senolytic drug discovery continues to advance, we anticipate the possibility of tissue- or cell-type specific agents. In future studies, more target-specific senolytics could be tested against broad acting agents (such as D+Q) to elucidate which may be most efficacious with the most acceptable and tolerable adverse side-effects.

A unique feature of our trial design that may contribute to the mitigation of some adverse events typically associated with these compounds, is the intermittent dosing strategy being utilized. The intermittent administration of senolytics in other study populations has been shown to attenuate side effects and effectively circumvent potential off-target effects induced by continuous receptor occupancy. Justification for this approach is provided by data demonstrating that senolytic target engagement does not require continuous receptor binding, enzyme activity modification, or persistent modulation of biochemical pathways. Instead, their mechanism of action is to temporarily disrupt anti-apoptotic pathways utilized by senescent cells for their survival (19, 43). Our preclinical research demonstrated that senescent cells in the brain accumulate over a period of two to four weeks (29). Moreover, disease-modifying effects were observed with a partial (35%) decrease in NFTs, which was consistent with preclinical studies of senolytic treatment for other models of aging and disease (10-16, 18, 19, 30, 54-56). A prior phase I clinical trial reported that three doses of D+Q administered across eleven days was sufficient to clear senescent cells (34). Therefore, we anticipate that the SToMP-AD pilot trial length with intermittent administration over 12 weeks will be suitable for ablating senescent cells. The 12-week treatment period was further selected to enable the collection of safety, feasibility and efficacy data, as well to inform the design of larger studies. We hypothesize that longer trials may be necessary to observe potential changes in cognitive trajectories and other AD biomarkers. As such, an extended multi-center randomized, placebo-controlled phase II study is in development (NCT04685590).

One of the major challenges to our trial and related studies as this field moves forward is the lack of a universally accepted definition and biomarkers of cellular senescence (57). Preclinical and clinical trials have identified various cellular and molecular features of cellular senescence (58). The characterization of cellular senescence in our trial was informed by our transcriptomic analyses conducted on human AD brain tissue and AD mouse models (29). NFTs derived from both species have overlapping expression of pathways implicated in senescence, providing converging evidence of core senescence markers. In addition, our trial will examine changes in SASP utilizing a composite score that was validated in a phase I clinical trial of intermittent D+Q (34). The senescence markers included in the secondary aim were selected a priori based on

the literature. However, as no clinical trials of aMCI and early-stage AD have examined cellular senescence, it is possible that the treatment regimen will affect various cellular and molecular senescence markers, which will be determined though exploratory analyses of a broader panel of senescence markers.

Our preclinical research demonstrated that pathological tau accumulation is closely coupled to cellular senescence (29). Senolytic treated mice had lower tau deposition, which correlated with favorable clinically relevant outcomes. Utilizing mouse models, studies by our research team are underway to tease apart the mechanism by which senolytics reduce tau load, either by active clearance of NFTs, and/or prevention of the formation of new tangles. To gather preliminary data on target engagement, our clinical trial will examine treatment-related changes in CSF total and phosphorylated tau levels as a secondary outcome. CSF tau levels demonstrate elevation prior to tau PET imaging, suggesting that it may be a sensitive marker of early change (59). However, future studies incorporating tau PET imaging will be needed for examining regional changes in tau deposition across the cortex (60) and further informing our understanding of mechanisms of action and anticipated treatment effects. Beyond tau, our study will obtain preliminary data on other established AD biomarkers, including measures of CSF β-amyloid levels and hippocampal atrophy, which will further elucidate potential drug mechanisms.

In summary, this vanguard study will provide preliminary data on the safety, feasibility, and efficacy of a leading combination senolytic agent, for indication in early AD. Based on preclinical and first-in-human data, we hypothesize that senolytics will be well tolerated, and will cross the blood-brain-barrier. We further anticipate to collect data on target engagement and efficacy relevant to future studies focused on additional aspects of senescent cell behavior, including the time course of their re-emergence after clearance. Beyond D+Q, research teams are actively pursuing the potential of other senolytic (e.g., fisetin) (36, 61) and senomorphic agents (62) as alternative senescence-associated therapeutic candidates for the treatment of AD. Collectively the field aims to identify the senotherapeutic with the most favorable safety and efficacy profile that simultaneously improves aging and AD-relevant outcomes. If the link demonstrated between senescence and AD pathology is as significant as the rapidly mounting preclinical evidence suggests (29, 30, 63, 64) our pilot and planned phase II clinical trials may foster the discovery of novel therapeutic pathways. Increasing evidence suggests that effectively treating complex, progressive and highly debilitating AD and related dementias will likely necessitate a broad arsenal of treatment approaches. As such, the SToMP-AD vanguard is critical in that it will provide the first proof-of-concept AD-relevant data utilizing a senescence-associated pharmacotherapy.

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