Anti-Diabetic Medications to Fight Parkinson's Disease and Lewy Body Dementia

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Anti-Diabetic Medications to Fight Parkinson's Disease and Lewy Body Dementia

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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DPP4	Dipeptidyl Peptidase-4
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SGLT2	Sodium Glucose Cotransporter 2
SOP	Standard Operating Procedure

Study Summary

Title	Anti-Diabetic Medications to Fight Parkinson's Disease and Lewy Body Dementia
Protocol Number	23-008183
Phase	Other
Methodology	Aim 1 is a pilot clinical trial Randomized, blinded, approximately 4-week therapy with: a) SGLT2 inhibitor therapy (dapagliflozin 10mg daily), b) DPP4 inhibitor therapy (sitagliptin 100mg daily), or c) placebo Aim 2 includes analysis of deidentified biobank data (phenome wide association study and gene burden)
Overall Study Duration	4 Weeks +/- 10 days between study days 1 and 2 Screening can occur at the same visit as study day 1 or prior to this.
Single or Multi-Site	Single Site
Objectives	Parkinson's disease is a progressive neurodegenerative disease with increasing prevalence. This proposal aims to evaluate the genetic and pharmacologic target of newer anti-diabetic medications in humans to fight this disease.
Number of Subjects	12 total, not including drop-outs. Number of subjects projected for the entire study (e.g. not for simply one site, rather for entire study, all sites combined)
Diagnosis and Main Inclusion Criteria	We will recruit individuals from Mayo Clinic with Parkinson's disease or Lewy Body Dementia who are on a stable therapy for the past three months. We will prioritize individuals with glucose intolerance or mild diabetes not on anti-diabetic agents. We will not study individuals taking insulin, high dose glucocorticoids, or anti-diabetes medications other than metformin. We will not study individuals who have contraindications to taking a DPP4 inhibitor or SGLT2 inhibitor (including significant renal impairment, pancreatitis, history of allergy to these medications, etc) or to study participation.
Study Product, Dose, Route, Regimen	SGLT2 inhibitor therapy (dapagliflozin 10mg daily), DPP4 inhibitor therapy (sitagliptin 100mg daily), placebo
Duration of Administration	4 Weeks +/- 10 days

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Both Parkinson's and related Lewy Body Dementia are chronic, progressive, and debilitating diseases, with no cure. Parkinson's disease is the most common neurodegenerative movement disorder (11). It is estimated that by 2030, over 1.2 million Americans will have Parkinson's disease (12). Mechanisms underlying Parkinson's disease and Lewy Body Dementia include alpha synuclein toxicity, impaired mitochondrial function, neuroinflammation/ oxidative stress, and impaired insulin signaling (13, 14). Patients with type 2 diabetes are more likely to develop Parkinson's disease and are at higher risk of motor dysfunction and more severe progression (15, 16). It has been estimated that up to 50-80% of patients with Parkinson's disease have impaired glucose tolerance (17). The majority of cases of Parkinson's disease are sporadic and likely have a combination of genetic and environmental causes (18).

Dipeptidyl peptidase-4 (DPP4) inhibitors and sodium glucose cotransporter-2 (SGLT2) inhibitors have neuroprotective effects (19, 20). Both medication classes are commonly prescribed for the treatment of type 2 diabetes, are well-tolerated, and are not associated with hypoglycemia. Recently the FDA also approved SGLT2 inhibitors for use in non-diabetics to reduce the risk of heart failure and for renal protection. DPP4 inhibitors and SGLT2 inhibitors have shown promise in animal models to be a therapeutic target for Parkinson's disease and possibly related Lewy Body Disorders (21-23), but there are no prospective studies in humans. This study aims to address this critical knowledge gap and leverage genetics and pharmacologic inhibition to better understand how these pathways can fight Parkinson's disease and Lewy Body Disease.

1.2 Investigational Agent

The following will be in tablet form to be taken orally, once daily:
Sitagliptin 100mg
Dapagliflozin 10mg
Placebo

1.3 Preclinical Data

See section 1.4 below which includes a summary of clinical and preclinical data.

1.4 Clinical Data to Date

DPP4 inhibitors

In animal models of Parkinson's disease, DPP4 inhibitors have shown benefit in motor scores and pathways to reduce apoptosis of dopaminergic neurons (22, 23). Retrospective and case control studies in humans have shown a decreased incidence of Parkinson's disease and improved motor outcomes among patients taking DPP4 inhibitors (24-26). A case report of a

patient with Lewy Body Dementia also showed autonomic and dementia improvement during DPP4 inhibition therapy (10). Despite these beneficial findings, there are currently no prospective clinical trials investigating the use of DPP4 inhibitors to fight Parkinson's disease or related Lewy Body Dementia.

DPP4 inhibitors are FDA approved and commonly prescribed for the treatment of type 2 diabetes (6). DPP4 is a ubiquitously found enzyme (in transmembrane form on endothelial cells, soluble form in the circulation, and is CD26 on lymphocytes) that rapidly degrades several peptides within minutes (7, 27). The most well-known of these are the incretin hormones glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), that are released in response to food intake and improve glucose without causing hypoglycemia (7). Pharmacologic inhibition of DPP4 increases availability of the active form of these hormones to improve glucose control (7) and therapy with this class of medications is well-tolerated (6).

In addition to peripheral effects, GLP-1 receptors are located on neurons in the brain (frontal cortex, hypothalamus, thalamus, hippocampus, cerebellum, and substantia nigra) as well as astrocytes and glial cells (14). GLP-1 receptor stimulation improved dopamine metabolism in a rodent model of Parkinson's disease (28) and in humans, (prospectively) the GLP-1 agonist exenatide has been shown to improve motor score off medication (MDS-UPDRS part 3) (29). This class of medication however, is available in injection and associated with more gastrointestinal side effects and weight loss compared to DPP4 inhibitors which are oral, better tolerated, and increase activity of endogenous GLP-1 (30). This is particularly relevant in Parkinson's and Lewy Body Disorders as the disease itself or its therapy can cause gastrointestinal dysfunction (31).

The study investigator has extensive experience investigating off-target effects of DPP4 inhibitors in individuals with type 2 diabetes as well as healthy subjects and women with polycystic ovarian syndrome (1-5). In a prior study, subjects during DPP4 inhibition had increased catecholamine release compared to placebo when also taking an angiotensin converting enzyme inhibitor (ACE-inhibitor) or angiotensin receptor blocker (versus calcium channel blocker) (3, 4). Increased catecholamine release may be a helpful off-target effect though in Parkinson's disease and Lewy Body Dementia, as individuals can have inappropriate norepinephrine release, lowered blood pressure (particularly if on dopamine agonists), or orthostatic hypotension (9). To this point, in a published a case report, a woman with Lewy Body Dementia had improvement in autonomic function, with reduction in postprandial and orthostatic hypotension, and improvement in Mini Mental Statue Examination score after treatment with the DPP4 inhibitor, sitagliptin (10).

SGLT2 inhibitors

SGLT2 inhibitors are a class of anti-diabetic medications that inhibit glucose reabsorption from the kidney. Similar to DPP4 inhibitors, they have a low risk of causing hypoglycemia (32). They decrease oxidative stress (including mitochondrial) and decrease apoptosis (33, 34). SGLT2 inhibitors have been FDA approved in non-diabetic patients to improve cardiovascular (heart failure) and renal outcomes (32).

SGLT2 receptors are expressed throughout the central nervous system and SGLT2 inhibitors have neuroprotective effects (19). SGLT2 inhibitor use in animal models of Parkinson's disease

has shown a reduction in oxidative stress, less neuronal apoptosis, and improvement in motor outcomes (21). In retrospective studies in humans, SGLT2 inhibitors have been associated with decreased risk of dementia (35) and show promise in Parkinson's disease, Lewy Body Dementia, and neuroprotection (36). In addition to improving glucose levels, SGLT2 inhibitors inhibit acetylcholinesterase (to improve cognition) and increase brain derived neurotropic factor (BDNF), a hormone implicated in neuroplasticity (37). Furthermore, SGLT2 inhibitors can increase ketones, which have been proposed as a treatment for neurodegenerative disease (38, 39). Although studies are underway to evaluate the effectiveness of SGLT2 inhibitors in individuals with Alzheimer's disease, there are none in Parkinson's disease or Lewy Body Dementia.

1.5 Dose Rationale

The doses that we will use in this protocol are the standard doses in humans. Specifically, dapagliflozin 10mg is FDA approved for heart failure with reduced ejection fraction or chronic kidney disease (both regardless of type 2 diabetes status) as well as the treatment of type 2 diabetes. Sitagliptin 100mg is approved for the treatment of type 2 diabetes. We have also used sitagliptin 100mg daily in prior research studies in non-diabetics. It is well tolerated.

1.6 Risks and Benefits

1) Blood draw may cause bleeding, bruising, or infection.
2) Blood draws can lead to anemia.
3) Fasting may cause lightheadedness, hunger.
4) The electrocardiogram (adhesive) may cause skin irritation.
5) Risks related to sitagliptin include nausea, allergic or hypersensitivity reaction, peripheral edema, nasopharyngitis, upper respiratory infection, pancreatitis, and joint pain. Risk of hypoglycemia is low.
6) Risks related to dapagliflozin include urinary tract or genital yeast infections, allergic or hypersensitivity reaction, nasopharyngitis, nausea, dyslipidemia, hypoglycemia, and constipation. There are rare reports of euglycemic ketoacidosis. Risk of volume depletion or low blood pressure/ orthostasis is low.

Potential risks are described in further detail below:

<u>Risks associated with blood draws (uncommon):</u>
Occasionally there are risks associated with blood draws such as bruising, swelling, black and blue marks, fainting and/or infection at the site. Subjects may also experience a decrease in hemoglobin and hematocrit (red blood cell number, called anemia) from having blood drawn frequently. At most, 6 tablespoons of blood (less than half a cup) or less will be drawn for research purposes during this research study on one day.

Benefits include informing the design of a future larger study to evaluate the potential benefits of taking such medications to treat Parkinson's Disease and related Lewy Body Dementia.

2 Study Objectives

Aim 1: Test the hypothesis that prospective intervention with a DPP4 inhibitor or SGLT2 inhibitor is tolerated well and potentially improves Parkinson's disease and Lewy Body Dementia related biomarkers compared to placebo.
We will study individuals with Parkinson's disease or Lewy Body Dementia in a small pilot clinical trial randomized to approximately 4-week therapy with one of the following: SGLT2 inhibitor therapy, DPP4 inhibitor therapy, or placebo. We assess tolerability and will measure pertinent biomarkers before and after intervention.

Aim 2: Test the hypotheses that genetically reduced DPP4 and SGLT2 (loss of function variants of genes DPP4 and SLC5A2) confer metabolic and neurological benefit.
We will work with the biobank teams at Mayo Clinic including Mayo Biobank and Tapestry to perform an analysis of ICD9/10 codes (phenome wide association study) among individuals with loss of function variants of these genes and measure biomarkers of interest in available stored samples. We will utilize existing Parkinson's disease and dementia cohorts (including cases and controls) at Mayo to assess for possible benefit of loss of function variants of these genes. We hypothesize that loss of function variants of DPP4 and SLC5A2 (SGLT2 gene) will be protective and more common in individuals without Parkinson's disease and Lewy Body Dementia.

These data are essential to determining the next best steps for future clinical investigation and grant submission.

3 Study Design

Aim 1 is a prospective randomized blinded parallel study design with three groups. There will be approximately 4-week therapy with: a) SGLT2 inhibitor therapy (dapagliflozin 10mg daily), b) DPP4 inhibitor therapy (sitagliptin 100mg daily), or c) placebo. We will test the hypothesis that DPP4 and SGLT2 inhibition are well tolerated and have beneficial neurological effects. Primary outcomes will include adverse event assessment and neurological examination including motor scores [Movement Disorder Society- Unified Parkinson's Disease Rating Scale (MDS-UPDRS)] and Mini Mental State Examination. Secondary biomarkers of interest include plasma biomarkers such as: GLP-1, glucose, and ketones. We will measure blood pressure including supine and standing.

Aim 2 is a phenome-wide association study and gene burden analysis with existing data in biobanks at Mayo Clinic. We will obtain approval from the respective biobanks prior to such analyses. Participants of the biobanks have consented to such de-identified data analyses.

The description of subjects and endpoints etc. below pertains primarily to Aim 1.

General Description

3.1 Number of Subjects

12 total not including drop-outs (4 per group, 1:1:1 sitagliptin: dapagliflozin: placebo) at Mayo Clinic Florida.

3.2 Duration of Participation

Subjects will have study days at baseline and approximately 4 weeks. To increase participation and subject retention, we will allow some flexibility of scheduling the follow up study day at +/- 10 days. Based on pharmacokinetic data, both will achieve steady state within 1 week.

3.3 Primary Study Endpoints

Primary outcomes will include tolerability, safety, and clinical examination [including Movement Disorder Society- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Mini Mental State Examination].

3.4 Secondary Study Endpoints

Secondary biomarkers of interest include plasma: GLP-1, glucose, and ketones. We will measure blood pressure including supine and standing.

3.5 Primary Safety Endpoints

We will measure baseline metabolic panel, lipids, blood counts, A1C, and electrocardiogram. We will measure follow up metabolic panel and lipids. Due to the study duration we will not repeat A1C, however, we will have follow up glucose data collected as part of the metabolic panel. A1C measurements are typically only repeated every three months. We do not anticipate a decline in blood counts as part of the study, but will have baseline levels collected for comparison if necessary. If someone has these data available within the past 3 months, we can use such clinical results in lieu of a repeat laboratory collection for the baseline/ screening.

The risk of orthostasis with dapagliflozin is small, but we will obtain blood pressure and heart rate measurements at baseline (study day 1) and during intervention (study day 2) as well as supine and standing (or seated if the subject cannot safely stand).

3.6 Identification of Source Data

We will record data in a case report form and in RedCAP. Case Report Form (CRF) data will include vital signs, any adverse events/ concerns, and data collected at screening including height, weight, etc.

The following source data will not be directly collected in the CRF but will be captured in supportive documentation (study source documents, electronic health data): laboratory results and clinical interpretation of the values, records and clinical significance of observations (when applicable).

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

- Adults age 45 years and older
- Parkinson's disease or Lewy Body Dementia (diagnosis confirmed by neurologist at Mayo Clinic) with stable neurological treatment in the past approximately three months
- Glucose intolerance or mild diabetes
    - The American Diabetes Association criteria for pre-diabetes/ glucose intolerance includes fasting glucose 100-125, random glucose 140-199, or hemoglobin A1C 5.7-6.4% and diabetes is > 125 mg/dL, >200 mg/dL, and 6.5% or greater, respectively (40). It has been previously reported that 50-80% of individuals with Parkinson's disease have abnormal glucose tolerance (17), so this should not limit recruitment.

4.2 Exclusion Criteria

- Use of insulin or other anti-diabetes medications other than metformin.
- Contraindication to taking a DPP4 inhibitor or SGLT2 inhibitor including: allergy, history of angioedema, pancreatitis, active gallbladder disease, renal impairment with EGFR < 45)
- Bleeding disorder, use of anticoagulants, thrombocytopenia, or severe anemia
- Use of high dose steroids
- Current systemic chemotherapy
- Pregnancy or breastfeeding
- Recent (within 30 days) or recurrent (defined as more than one in the past 12 months) urinary tract infection or yeast infection
- Other contraindication that would make study participation unsafe or make study related data unable to be interpreted.

4.3 Subject Recruitment, Enrollment and Screening

We will recruit individuals primarily from Mayo Clinic Neurology clinics and the Mayo Biobank and Tapestry. Participants of the Mayo Clinic Biobank and Tapestry Biobank and Mayo have consented to be re-contacted to participate in future research. If needed to improve recruitment numbers, we may also post advertisements at approved locations at Mayo Clinic. We will provide potential individuals who may qualify with contact information to learn more about the study. We will use the electronic health record to screen for individuals who may qualify.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

A subject may be withdrawn from the study prior to that subject completing all study related procedures. Some reasons may include:

- Subject safety issues
- Failure of subject to adhere to protocol requirements
- Disease progression
- Subject decision to withdraw from the study (withdrawal of consent)

Subjects who are withdrawn will be replaced. We will collect pertinent safety information from subjects who are withdrawn due to safety concerns including clinical laboratory data and examination. In general, we will not have long-term follow up as part of this study, given the short duration of intervention. The exception would be if a subject had an adverse event.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Even though a subject has withdrawn from the study, it may be important to collect follow-up or survival data throughout the protocol defined follow-up period. Such data are important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug. If a subject withdraws consent to participate in the study, for subject safety reasons, attempts will be made to obtain permission to collect follow up information whenever possible.

5 Study Drug

5.1 Description

Sitagliptin 100mg: Sitagliptin is an oral tablet. It is a dipeptidyl peptidase 4 (DPP4) inhibitor. Sitagliptin is FDA approved for the treatment of type 2 diabetes mellitus.

Dapagliflozin 10mg: Dapagliflozin is an oral tablet. It is a sodium glucose cotransporter 2 (SGLT2) inhibitor. Dapagliflozin is FDA approved for the treatment of type 2 diabetes mellitus, heart failure (regardless of diabetes status), and chronic renal failure (regardless of diabetes status).

Placebo: The Mayo Clinic Investigational Drug Service will compound or purchase a safe placebo for oral administration made from an inert material such as cellulose or similar that meets necessary quality/ purity standards.

5.2 Treatment Regimen

Participants are randomized to one of the following study drugs for the approximately 4-week treatment period:
Sitagliptin 100mg once daily, oral
Dapagliflozin 10mg once daily, oral
Placebo, once daily, oral

5.3 Method for Assigning Subjects to Treatment Groups

Subjects will be randomized in a 1:1:1 design to the two study drug groups and placebo group. A randomization table will be provided by a biostatistician not affiliated with the analysis and given to Mayo Clinic Investigational Drug Service for subject assignment and dispensing.

5.4 Preparation and Administration of Study Drug

Study drugs will be ordered and prepared for packaging by the Investigational Drug Service (IDS). Each is to be administered orally. The subject will take the study drug once daily in the morning at home (approximately 4 weeks total) and on study day 2. Sitagliptin and dapagliflozin are FDA approved medications that are available. The placebo study drug will be made by IDS.

5.5 Subject Compliance Monitoring

Subjects will be instructed to bring in their study drug container for a pill count at study day 2. If it is clear that a subject has not been compliant with the instructions, we will make note of this and if significant, the subject may be removed from the study (after review by the investigator). Any adverse events or protocol deviations will be reported.

5.6 Prior and Concomitant Therapy

Subjects who are taking anticoagulation or diabetes therapy other than metformin may not participate in the study (see exclusion criteria).

5.7 Packaging

Study drugs will be dispensed in a container that does not list the name or contents of the drug on the package (blinded). These will be provided to the subject directly in person (for example at study day 1). In rare circumstances, we will have the option to mail study drug if it is not available at the time of study day 1, and if so, we will use tracking and temperature safe packaging.

5.8 Masking/Blinding of Study

To minimize bias in the study, we will have a placebo group and Mayo Clinic Investigational Drug Service will provide blinded sitagliptin 100mg, dapagliflozin 10mg, and placebo for this study. Neither the study subject nor investigator will be provided with treatment assignment during the study.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Study drugs will be obtained by Mayo Clinic Investigational Drug Service (IDS). This includes: sitagliptin 100mg, dapagliflozin 10mg, and placebo. IDS will perform inventory and logs for the drugs. These will be blinded and dispensed to the study team to give to subjects who consent and qualify for participation. Study drug allocation per group will be in a randomized manner.

5.9.2 Storage

Study drugs will be stored at the research pharmacy, Mayo Clinic Investigational Drug Service until dispensed to the subject. They will be kept stored in a dry shelf away from direct sunlight and in room temperature.

5.9.3 Dispensing of Study Drug

Study drug assignment will be per Mayo Clinic Investigational Drug Service using a randomization table. Sufficient doses will be dispensed to complete the treatment period. (Each is administered once daily.) Dispensing date and quantity will be logged by the study team. A study team member will also perform a pill count at study day 2 (end of study).

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged, with any discrepancies noted. Unused drug will be provided to Investigational Drug Services or disposed of by the study team in an appropriate manner.

6 Study Procedures

Aim 1 is a prospective randomized blinded parallel study design with three groups. There will be approximately 4-week therapy with: a) SGLT2 inhibitor therapy (dapagliflozin 10mg daily), b) DPP4 inhibitor therapy (sitagliptin 100mg daily), or c) placebo.

6.1 Screening

Prior to undergoing any study related procedures, the subject will review and sign the informed consent form. A copy will be provided. Key study personnel will review the study in detail with the subject. The screening visit and study day 1 can occur at the same day or separate visits depending on the subject's availability and for convenience. This is to increase recruitment/ retention in the study.

Baseline Assessments

- Vital signs, weight, waist/ hip measurements, and height will be collected for all participants.
- Medical history, medications, social history, and family history will be obtained.
- We will obtain an electrocardiogram (ECG).
- We will collect a lipid panel, metabolic panel (including renal function, glucose, etc), hemoglobin A1C, and complete blood count. If the subject has results for clinical labs within the past three months, the investigator may choose to skip collection of the test(s) at the study day.
- In women of childbearing potential, we will check a urine pregnancy test to confirm this is negative. Pregnancy is exclusionary.

6.2 Visit 1 - Baseline

Subjects will present to the clinical research center fasting for study day 1.

Blood collection(s)
We will collect clinical labs and baseline biomarkers for processing and storage (Biorepository aka BAP). Examples include GLP-1, glucose, ketones, and catecholamines.
There will also be an optional blood collection at baseline only for DNA analysis.

Hemodynamic measurements
At baseline, resting for at least 10 minutes supine, three blood pressure and heart rate measurements will be collected by an automated oscillometric device (blood pressure cuff). These will be collected approximately 3 minutes apart.
Next, in subjects who are able (not a high fall risk for example), they will be asked to stand for 15 to minutes. If they are unable to do so due to risk, this will be documented and they can remain seated. For subjects able to stand, we will collect blood pressures and heart rate every 3 minutes.

Subjects will be provided with study drug for the approximately 4-week treatment period to start after study visit 1 is completed.

6.3 Visit 2 – Week 4

Subjects will present to the clinical research center fasting for study day 2.

We will confirm that the subject has taken the final dose of study drug prior to the visit or at the start of the visit (within 12-24 hours minimum).

Blood collection(s)
We will collect the same biomarkers for processing and storage as visit 1 (Biorepository aka BAP). We will also collect additional safety labs such as metabolic panel and lipid panel.

Hemodynamic measurements
These will be the same as for visit 1. At baseline, resting for at least 10 minutes supine, three blood pressure and heart rate measurements will be collected by an automated oscillometric device (blood pressure cuff). These will be collected approximately 3 minutes apart.
Next, in subjects who are able (not a high fall risk for example), they will be asked to stand for 15 to minutes. If they are unable to do so due to risk, this will be documented and they can remain seated. For subjects able to stand, we will collect blood pressures and heart rate every 3 minutes.

Schedule of Events			
Study Activity	Screening (Day 0)	Visit 1 - Baseline (Day 1)	Visit 2 – Week 4 (Day 28 +/- 10 days)
Informed consent	X		
History	X		
Concurrent meds	X		
Hemodynamic measurements (BP, HR)	X	X	X
Electrocardiogram (ECG)	X		
Physical exam (Height, Weight, Anthropomorphic measurements, Vital signs)	X		
Neurological Examination and assessment		X	X
Clinical safety labs (comprehensive metabolic panel and lipid panel) [a]At screening only, complete blood count, A1C, and urine pregnancy test will also be collected	X[a]	X	X
Assay collection (blood draws) for research labs		X	X
Optional DNA Collection		X	
Study Agent(s) Sitagliptin, dapagliflozin, placebo		X	X
Adverse event evaluation		X	X
Blood pressure (BP), Heart rate (HR), Hemoglobin A1C (A1C)			

7 Statistical Plan

7.1 Sample Size Determination

We are limited to a sample size of 12 not including drop-outs due to grant funding and timeline. Funding is through the internal grant, the Mayo Clinic Innovation in Aging Award. This is a pilot study to help inform future clinical research directions and future grant submissions to fund a larger, well-powered study.

7.2 Statistical Methods

Descriptive Statistics

Given the pilot nature of the study and the corresponding small sample size, formal statistical tests will not be performed. Instead, emphasis will be placed on descriptive summaries such as mean, median, standard deviation, and interquartile range, along with graphical examination, in the separate treatment groups in order to inform future larger and more definitive studies.

Handling of Missing Data

We will check for outliers, any missing data, and data quality prior to data analyses.

Multiplicity

We acknowledge that we are underpowered for multiple variable comparison, but due to the pilot nature of the study, this is still quite valuable for future directions.

Primary Hypothesis:

Aim 1: We hypothesize that subjects will tolerate study drugs well and have stable or improved motor scores/ clinical examination [Movement Disorder Society- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Mini Mental State Examination] from baseline (study day 1) to study day 2, with sitagliptin or dapagliflozin compared to placebo. Based on prior data, we expect these medications to be well tolerated in this population. This study will inform future clinical research and the design of a larger well-powered study.

Secondary Hypothesis 1

Aim 2: We hypothesize that loss of function variants of DPP4 or SGLT2 will be protective against neurological disease such as Parkinson's and Lewy Body Dementia (based on biobank data).

Interim Analysis

We will not have an interim analysis. The duration of the trial is short and with a low number of subjects as it is a pilot study.

7.3 Subject Population(s) for Analysis

This is a pilot study and we will replace drop-outs. We will perform analyses with the following populations and compare results:

- Protocol-compliant population: Any subject who was randomized and received the protocol required study drug exposure and required protocol processing
- All-completed population: Only subjects who completed ALL study related procedures and follow-up will be included

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death

- life threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity
- substantial disruption of the ability to conduct normal life functions
- birth defect/congenital anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, will be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as the day of consent to study day 2 (end of study).

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting 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.

Post-study Adverse Event
All unresolved adverse events will be followed until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the study investigator or key personnel will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if it is deemed related to study drug.

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

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event 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 for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF) or in a separate adverse event worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

This section is written with the intent that a specifically designed adverse event worksheet will be completed for any SAE. The information on that worksheet will be reported to the IRB in a de-identified manner. IRB requirements reflect the guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) in early 2007 and are respectively entitled “Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events” and “Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection.”

The investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.
According to Mayo IRB Policy any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO must be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

Information collected on the adverse event worksheet (and entered in the research database):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

The relationship of an AE to the Investigational Drug is a clinical decision by the investigator based on all available information at the time of the completion of the CRF and is graded as follows:

1. Not related: a reaction for which sufficient information exists to indicate the etiology is unrelated to the study drug; the subject did not receive the study medication or the temporal sequence of the AE onset relative to administration of the study medication is not reasonable or the event is c1early related to other factors such as the subject' s clinical state, therapeutic intervention or concomitant therapy.

2. Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

3. Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but which could also be explained by concurrent disease or other drugs or chemicals; information on drug withdrawals may be lacking are unclear.

4. Probable: a clinical event including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (de-challenge): re-challenge information is not required to fulfill this definition.

5. Definite: a reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure (re-challenge).

The maximum intensity of an AE during a single day should be graded according to the definitions below and recorded in details as indicated on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates.

1. Mild: AEs are usually transient, requiring no special treatment, and do not interfere with patient's daily activities.

2. Moderate: AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities but are usually ameliorated by simple therapeutic measures.

3. Severe: AEs interrupt a patient's usual daily activity and traditionally require systemic drug therapy or other treatment.

8.3.2 Sponsor-Investigator reporting: Notifying the FDA

This protocol is being conducted under a FDA IND exemption.

The investigator will report to the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

The investigator must also notify the FDA in a safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under § 312.32(c)(1)(i)-(iv).

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

8.4 Unmasking/Unblinding Procedures

Safety of the subject always comes first. We will consider unmasking/ unblinding the study therapy if necessary to ensure a subject's safety. We will plan to unmask/ unblind in the case of a serious adverse event that is likely related to study drug. We will work with the Mayo Clinic Investigational Drug Service to do so and document unmasking/unblinding in the subject's source document. We will use a similar timeline as requirements for reporting of SAEs.

8.5 Stopping Rules

In the case of a serious adverse event related to study participation, the investigator may choose to stop the pilot study if appropriate.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Internal Data and Safety Monitoring Board

We do not plan to have a separate DSMB. All data and safety monitoring will be led by the primary investigator who is a board-certified endocrinologist with expertise prescribing the study drugs.

8.6.2 Independent Data and Safety Monitoring Board

We will not have a DSMB, however, we will have an independent safety monitor. This physician will review any adverse events along with the primary investigator. The primary investigator will be responsible for reporting (as above).

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the 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". All entries should be printed legibly in ink. If any entry error has been made, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

We will record data on case report forms and use an institutionally secured and managed device or server to store data and the Research Electronic Data Capture (REDCap) system. Charts containing case report forms, signed informed consent documentation, and subject identifiers

such as name will be kept in a locked cabinet or uploaded to a secure folder on the Mayo hard drive that is password protected. Only key study personnel will have access to the locked cabinet. All investigators and key study personnel have completed CITI related training including responsible conduct of research and good clinical practice training and will keep training up to date. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Data Processing

We will have a single study site. For Aim 1, we will de-identify data for statistical analyses.

For Aim 2, data will already be de-identified for these analyses. We will work with the respective biobank teams at Mayo Clinic.

Data Security and Confidentiality

A unique identification case number will be used to protect the confidentiality of the study participants. Only case numbers will be included in spreadsheets used for the statistical analyses.

Data Quality Assurance

We will use RedCAP electronic data collection forms when possible. Data will be input into a protected, web-based form that allows for direct data entry by investigators and is designed to minimize errors and erroneous values. Expected ranges are pre-specified to prevent errors such as the shifting of decimal points. The program includes a computerized audit trail so that the identity of individuals entering or changing data and, in the case of changes, both original and revised data are saved. Data are backed up daily. Clinical data including clinical laboratory results will be entered by the research nurse, key study personnel, or investigator. Research laboratory data will be entered by a research nurse, key study personnel, or investigator.

Data Clarification Process

The investigator and study team will document resolution of data queries when applicable.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. Data will be retained and archived for at least five years, and then records may be shredded.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The Investigator will allocate adequate time for such monitoring activities. The investigator will also ensure the monitor or other compliance or quality assurance reviewer has access to all study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Data and safety monitoring provides a clinical investigation with a system for appropriate oversight and attention to the protection of human subjects by the investigator and research team. Members of the team include board-certified endocrinologist (investigator) with clinical expertise in the treatment of pre-diabetes and diabetes (with extensive experience using study drugs sitagliptin and dapagliflozin in clinical practice) and neurologists with clinical expertise in Parkinson's Disease and Lewy Body Dementia (Dr. Wszolek and Dr. Dulski). If a serious adverse event occurs, the investigator and other key personnel will review this and can choose to terminate the study for safety concerns. The study will also include a physician named as the independent safety monitor. The principal investigator will report any adverse events to the safety monitor as well as the IRB as above.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, 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.).

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

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

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. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

We will not enroll children, individuals in prison, or pregnant women.

12 Study Finances

12.1 Funding Source

This project is funded by the Mayo Clinic Innovation in Aging Award (through July 2024).

12.2 Conflict of Interest

No study team members have conflicts of interest with this study.

12.3 Subject Stipends or Payments

Subjects will be compensated with the following:
$50 screening visit, initial labs, medication pick up
$100 study day 1
$100 study day 2

Payments will be in the form of a gift card, check, or comparable payment form.

13 Publication Plan

We plan to publish de-identified data after statistical analyses are completed.
We will register the prospective pilot study on ClinicalTrials.gov prior to subject recruitment/ enrollment and post results of the primary outcome as per policy.

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