4. PROTOCOL SYNOPSIS

Name of Sponsor/Company: The Michael J. Fox Foundation for Parkinson's Research
Title and Phase of Master Protocol: Path to Prevention (P2P) Platform Trial: A Phase 2A, Randomized, Double Blind, Placebo Controlled Study to Evaluate Investigational Interventions in Early-Stage Neuronal Alpha-Synuclein Disease (NSD)
Master Protocol Design: The Path to Prevention (P2P) Platform Trial is a perpetual multi-center, multi-regimen proof of concept Phase 2A randomized clinical trial evaluating the safety and early efficacy of investigational products for the treatment of Early-Stage Neuronal Alpha-Synuclein Disease (NSD) populations. Early-stage NSD includes participants with alpha-synuclein pathology, presence of dopamine dysfunction, motor, and non-motor clinical manifestations but lack of related functional impairment (see Table 3). These participants were previously defined as prodromal Parkinson's disease (PD), and/or prodromal Dementia with Lewy Bodies (DLB). The trial is designed as a perpetual platform trial. This means that there is a single Master Protocol dictating the conduct of the trial. The Master Protocol describes the overall framework of the platform trial, including the target population, inclusion and exclusion criteria, intervention assignment and randomization schemes, Master Protocol endpoints, schedule of activities (SOA), trial design, the mechanism for adding and removing interventions, and the statistical methodology and prespecified statistical methods for evaluating interventions. Each investigational product is tested in a trial regimen, which is described in its own Regimen Specific Sub Protocol (RSSP) that is to be read in combination with the Master Protocol.
Master Protocol Objectives: Assess the impact of putative NSD therapies in participants with Early-Stage NSD on Dopamine Transporter Single-photon emission computed Tomography (DAT SPECT) imaging, clinical measures of symptom worsening**,** feasibility, safety, and tolerability. Additional analyses will examine many other exploratory clinical outcome measures and biomarkers.
Multiple Primary Endpoints: 1. DAT SPECT imaging as measured by the rate of progression in the mean putamen Specific Binding Ratio (SBR) from baseline through follow-up. 2. Clinical outcome as defined by the rate of progression in the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score from baseline through end of follow-up or the initiation of dopaminergic treatment. **Safety Endpoint:** 1. Safety as measured by all treatment emergent adverse events (TEAEs), and serious adverse events (SAEs) for the active treatment arm versus placebo controls in each RSSP.

Secondary Endpoints:

1. Feasibility as defined by ability to recruit, retain participants, and complete Master Protocol activities as per SOA.
2. Tolerability as measured by ability to complete an RSSP on the assigned dose and treatment arm (active versus placebo controls)

Key Exploratory Endpoints (to be included in Final RSSP Study Reports):

1. The number of participants who progress from NSD Stage 2B to NSD Stage 3 or higher.
2. Clinical outcome as defined by the rate of progression in MDS-UPDRS Total from baseline through follow-up or the initiation of dopaminergic treatment and rate of progression in Part I & II subscores from baseline through follow-up.
3. Change in cognition as defined by the number of participants developing new syndromes of mild cognitive impairment (MCI) or dementia.
4. Change in functional status as measured by Penn Parkinson's Daily Activities Questionnaire-27 (PDAQ-27) from baseline through follow-up.
5. Time to progression milestones as defined by Brumm et al[1]

Target Population

Stage 2B NSD (see Table 3).

Main Inclusion Criteria:

Participants will be eligible for inclusion in this Master Protocol if they meet the following criteria:

1. Enrollment in the Parkinson Progression Marker Initiative (PPMI) study
2. Age 60 years or older at Screening Visit
3. Able to provide informed consent
4. NSD based on research diagnostic criteria[2] (i.e., defined by presence of a validated biomarker of disease specific neuronal alpha-synuclein pathology)
5. NSD Stage 2B based on staging anchors criteria[3] (see Table 3)
6. Female participants of childbearing potential and male participants must agree to use contraception as detailed in the RSSP
7. Meet any additional inclusion criteria and none of the exclusion criteria that are accessible at the time of screening (if applicable) for at least one active RSSP

Main Exclusion Criteria

Participants fulfilling any of the following criteria are not eligible for inclusion in this Master Protocol:

1. Clinical diagnosis of PD, DLB, dementia or other neurodegenerative disease at Screening
2. Received any of the drugs associated with drug induced parkinsonism within 6 months of the Baseline Visit (see Appendix 2)
3. Received dopaminergic therapy for PD or cholinesterase inhibitors for PD/DLB within 90 days of the Baseline Visit

4. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the site investigator (SI) might preclude Master Protocol participation
5. Individuals taking any of the drugs that might interfere with the DaTscan read out unless they are willing and medically able to hold the medication for at least five half-lives before DAT SPECT imaging (see Appendix 1)
6. Current treatment with anticoagulants (e.g., coumadin, heparin, other) that might preclude safe completion of the lumbar puncture
7. Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia
8. Women who are pregnant, lactating or planning pregnancy
9. Participation in other investigational drug studies less than 30 days (or five half-lives, if longer) prior to screening and for the duration of participation in the RSSP (unless specified otherwise in the RSSP)
    a. Participants that are enrolled in other PPMI sub-studies that do not involve investigational interventions, such as experimental radiopharmaceuticals, may remain enrolled in those sub-studies while in P2P-013
10. History or current diagnosis of electrocardiogram (ECG) or cardiac abnormalities indicating significant risk of safety for participants such as:
    a. Myocardial infarction, unstable angina pectoris, transient ischemic attack, stent placement or coronary artery bypass graft, any of those within 6 months of Screening
    b. Cardiac failure [New York Heart Association (NYHA) functional class II-IV], stroke or clinically significant uncontrolled arterial hypertension
    c. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II- and third-degree AV block)
    d. Resting QTcF >450 ms (in males) or >460 ms (in females) and < 300 ms (regardless of sex) at Screening or inability to determine the QTcF interval
    e. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
11. Score “yes” on item 4 or item 5 of the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale (C-SSRS), if this ideation occurred in the past 6 months, or “yes” on any item of the Suicidal Behavior section if this behavior occurred in the past 2 years, except for the “Non-Suicidal-Self Injurious Behavior” (item also included in the Suicidal Behavior section)
12. Study participant has a current history of alcohol or drug use disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders: DSM-5-TR, within the previous 5 years before Screening
13. Clinically significant abnormalities in laboratory test results at the screening visit, including hepatic and renal panels, complete blood count, chemistry panel and urinalysis as determined by SI
14. Presence of human immunodeficiency virus (HIV) infection based on either history or testing

15. Any of the following:
    a. Presence of hepatitis B surface antigen or positive hepatitis B virus (HBV) Deoxyribonucleic Acid (DNA) at Screening
    b. Positive hepatitis C antibody test result at Screening or within 3 months prior to starting study drug. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained. Where hepatitis C RNA testing is unavailable, a positive hepatitis C antibody test will lead to exclusion

Investigational Products: Multiple investigational products (i.e., interventions, or active agents, from different regimen partners) will be tested in this platform trial. Each investigational product will have an associated RSSP with the complete description of the tested product. Each active agent will have a matching placebo control.

Duration of Treatment per Arm: All participants will remain on the assigned regimen specific arm for a minimum of 96 weeks and up to 144 weeks or until 96 weeks since randomization of the last participant have passed, whichever comes first. An RSSP will be closed once all participants have completed the follow-up period.

Randomization: With K representing the number of actively enrolling RSSPs at a given time, the platform trial incorporates two stages of randomization.

1. Equal randomization to all J ($\leq$ K) eligible enrolling regimens for which the participant was eligible at the time of randomization based on information easily accessible at the time of screening, where each regimen contains both active treatment and placebo control groups.
2. After confirming any additional regimen specific eligibility requirements, participants will be randomized in a K:1 manner to either active treatment or placebo control.

Sample Size:

Each regimen will randomize 125 participants with NSD Stage 2B to active treatment. For a specific regimen, "power" is defined as the probability of demonstrating success on at least one of the primary endpoints. The primary analysis population for each regimen includes shared RSSP controls, concurrent controls (placebo control participants randomized to any RSSP within the Master Protocol during the time period randomization was active for the regimen of interest), non-concurrent controls (placebo control participants randomized to any RSSP within the Master Protocol prior to the time randomization was active for the regimen of interest), and concurrent non-randomized controls (participants who were deemed to be potentially eligible and were either contacted and declined to participate OR were at sites not recruiting for P2P-013). As a result, regimens that enter the platform trial later can be expected to see an increased power relative to that of the first regimen as a result. On average, the three regimens in the platform are estimated to have 62%-63% and 77%-80% power to detect treatment effects when both of the endpoints achieve 30% and 40% slowing of progression, respectively – depending on the number of concurrent non-randomized controls available at the time of analysis. Similarly, we have greater than 69%-71% power to declare success if there is truly a 40% or greater reduction in slope/progression of MDS-UPDRS Part III as long as there is at least a simultaneous 30% or greater reduction in mean

putamen SBR. We have around 71%-74% or higher probability of declaring success if there is truly a 40% or greater reduction in slope/progression on the DAT SPECT imaging endpoint and at least a 30% reduction on slope/progression on the MDS-UPDRS Part III endpoint. Finally, the overall type I error probability (probability of meeting the criteria when there is no true reduction for either endpoint) is well controlled at 18%.

Primary Analyses:

Both primary endpoints will be tested with equal priority with respect to active treatment superiority versus placebo control. Specifically, we maintain a one-sided type I error control of 0.10 for each primary endpoint, which corresponds to an overall target type I error rate at or below 0.20. Each individual RSSP will meet its prespecified criteria as a success if either of the endpoints achieves statistical significance.

For each regimen, both primary endpoints will be analyzed using a Bayesian repeated measures model of the outcome over time to compare the slope/progression of active treatment versus the shared RSSP placebo controls, concurrent placebo controls, non-concurrent placebo controls, and concurrent non-randomized participants. This model allows for heterogeneity across individual outcomes values and individual slopes, heterogeneity across regimens due to minor differences in the inclusion/exclusion criteria or mode of administration.

***Mean Putamen SBR*:** A greater negative slope indicates a reduction in the biomarker and a greater progression rate. A hypothesis test for a smaller progression rate for active treatment versus placebo control will be conducted using the Bayesian posterior distribution, with a predefined threshold 0.90 required to demonstrate superiority.

***MDS-UPDRS Part III Score*:** A greater positive slope indicates faster symptom accumulation and a greater progression rate. A hypothesis test for a smaller progression rate for active treatment versus placebo control will be conducted using the Bayesian posterior distribution, with a predefined threshold 0.90 required to demonstrate superiority.

Schedule of Activities

Participants will be seen for the Master Protocol screening visit, and if eligible, will be randomized to a regimen with open enrollment. Participants will then be consented to the RSSP and assessed for any additional regimen specific eligibility requirements. If all additional regimen specific eligibility requirements are met, participants will be randomized to active drug or placebo control within a regimen per randomization plan. Beginning at the Baseline Visit, participants will follow the RSSP SOA activities for which they are enrolled.