4. PROTOCOL SYNOPSIS

Name of Sponsor/Company: 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 Platform Trial (P2P) 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, and/or prodromal Dementia with Lewy Bodies. 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, RSSP endpoints, schedule of assessments, 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) amended to 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 striatum 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. **Secondary Endpoints:** 1. Feasibility as defined by ability to recruit, retain participants, and complete Master Protocol activities as per schedule of activities. 2. Safety as measured by all treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs) for the active treatment arm versus placebo in each RSSP. 3. Tolerability as measured by ability to complete an RSSP on the assigned dose and treatment arm (active versus placebo)

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-15 (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 PPMI observational study
2. Able to provide informed consent.
3. Diagnosis of NSD Stage 2B (see Table 3)
4. Female participants of childbearing potential and male participants must agree to use contraception as detailed in the RSSP.
5. Age 60 years or older at Screening visit.
6. Meet any additional inclusion criteria (if applicable) accessible at the time of screening 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. Received any of the drugs associated with symptomatic parkinsonism within 6 months of Randomization Visit (see Appendix 2).
2. Received dopaminergic therapy (levodopa or dopamine agonist) for NSD motor syndrome or cholinesterase inhibitors for NSD cognitive syndrome within 90 days of the Randomization Visit.
3. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the site investigator (SI) might preclude Master Protocol participation.
4. 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 5 half-lives before DAT SPECT imaging (see Appendix 1).
5. Women may not be pregnant, lactating or planning pregnancy during the Master Protocol.
6. Participation in other investigational drug studies less than 30 days prior to screening (unless specified otherwise in the RSSP)
7. History or current diagnosis of electrocardiogram (ECG) or cardiac abnormalities indicating significant risk of safety for participants such as:

- Myocardial infarction, unstable angina pectoris, transient ischemic attack, stent placement or coronary artery bypass graft, any of those within 6 months of screening.
- Cardiac failure [New York Heart Association (NYHA) functional class II-IV], stroke or clinically significant uncontrolled arterial hypertension.
- Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II- and third-degree AV block).
- 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.
- Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome.

8. Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the 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).
9. 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.
10. 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 site investigator.
11. Presence of human immunodeficiency virus (HIV) infection based on either history or testing.
12. Any of the following:
    - Presence of hepatitis B surface antigen or positive HBV DNA at Screening
    - 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.

Duration of treatment per arm: All participants will remain on the originally assigned regimen-specific arm for a minimum of 24 months and will remain on the originally assigned regimen-specific arm until the last participant randomized to that RSSP has completed 24 months of follow-up on intervention or until 24 months since randomization have passed (if terminated early). The RSSP will be closed once all participants have completed the follow-up period.

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

1. Equal randomization to all eligible regimens based on information easily accessible at the time of screening, where each regimen contains both active treatment and placebo groups.
2. After confirming any additional regimen specific eligibility requirements, participants will be stratified by MDS-UPDRS Part III score at baseline (<7 vs. ≥ 7). Within the corresponding strata, each participant will be randomized in a *J*:1 manner to either active treatment or placebo, where *J* (<*K*) is the number of enrolling regimens for which the participant was eligible at the time of randomization.

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 concurrent and non-concurrent control participants. 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. Assuming 95% of randomized participants within an RSSP fall into the < 7 MDS-UPDRS Part III baseline strata, the first regimen in the platform is estimated to have 74%, 84%, and 91% power to detect treatment effects when both of the endpoints achieve 30%, 35%, and 40% slowing of progression, respectively. Similarly, we have greater than 86% 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 striatum SBR. We have around 83% 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 10.3%.

Primary Analyses:
Both primary endpoints will be tested with equal priority with respect to active treatment superiority versus placebo. Specifically, we maintain a one-sided type I error control of 0.05 for each primary endpoint, not accounting for multiple primary endpoints. Each individual RSSP will meet its pre-specified criteria as a success if either of the endpoints achieves statistical significance.

***Mean Striatum SBR*:** For each regimen, a Bayesian repeated measures model of mean striatum SBR over time, adjusted for baseline MDS-UPDRS Part III strata, will be used to compare the slope/progression of active treatment versus the shared concurrent and non-concurrent placebo arm. The model allows for heterogeneity across individual baseline mean striatum SBR values and individual slopes, heterogeneity across regimens due to minor differences in the inclusion/exclusion criteria or mode of administration. 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 will be conducted using the Bayesian posterior distribution, with a predefined threshold 0.95 required to demonstrate superiority.

***MDS-UPDRS Part III Score*:** For each regimen, a Bayesian repeated measures model of MDS-UPDRS Part III score over time, adjusted for the baseline strata, will be used to compare the slope of active treatment versus the shared concurrent and non-concurrent placebo arm. The model allows for heterogeneity across individual baseline MDS-UPDRS Part III score values and individual slopes, heterogeneity across regimens due to minor differences in the inclusion/exclusion criteria or mode of administration. 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 will be conducted using the Bayesian posterior distribution, with a predefined threshold 0.95 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 within a regimen per randomization plan. Following the Baseline visit, participants will follow the RSSP schedule of activities for which they are enrolled.