Name of Sponsor/Company: Michael J. Fox Foundation
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 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-15) 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. 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 investigator might preclude Master Protocol participation.
4. Individuals taking any of the drugs that might interfere with the DAT scan read out unless they are willing and medically able to hold the medication for at least 5 half-lives before DaTscan imaging (see Appendix 2).
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)

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.

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 the purposes of initial power calculations, we assumed three regimens enrolling. This corresponds to a minimum of 500 total participants, with 125 participants on active treatment in each of the three regimens and at least 125 controls shared across the 3 regimens. Under the criteria where success is defined by meeting either of the primary endpoints, we have greater than 85% power to declare success if there is truly a 40% or greater reduction and greater than 62% power to declare success if there is truly a 30% or greater reduction in slope/progression of MDS-UPDRS Part III. Similarly, we have 75% power to declare success if there is truly a 30% or greater reduction in slope/progression on the DAT imaging endpoint if the MDS-UPDRS Part III also achieves a 30% or greater reduction and 85% or higher probability of declaring success if there is truly a 40% or greater reduction in slope/progression on the DAT imaging endpoint regardless of the true change on the MDS-UPDRS endpoint.
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*:** 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 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*:** 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 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 qualified, will be randomized to a regimen per randomization plan. Participants will then be assessed for any additional regimen specific eligibility requirements. If all additional eligibility requirements are met, participants will be randomized to treatment or placebo within a regimen per randomization plan. Following the Baseline visit, participants will follow the Master Protocol schedule of activities. Additional visits and corresponding activities, if necessary, can be scheduled per RSSP.

Activity	**Master Protocol Screening[7] Group A**	**Master Protocol Screening[7]**	**Baseline/ Randomization within RSSP**	Week 2	Mon 1	Mon 3	Mon 6	Mon 9	Mon 12	Mon 15	Mon 18	Mon 21	Mon 24 **/Early Termination[6]**	Additional visits q 3 Mon	Initiation of Dopaminergic Tx[8]	End of RSSP treatment	Follow-Up Safety calls
	<6 months from last PPMI*	≥ 6 months from last PPMI		Phone	Clinic	Clinic	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Clinic/ Tele[1]	Clinic	Clinic	Phone
	Clinic	Clinic	Clinic														
Window days	-90 to -1	-90 to -1	0	3±	7±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	3±
Informed Consent																	
Documentation of informed consent	X	X															
Screening Activities																	
Inclusion /exclusion criteria	X	X	X														
DAT eligibility	X	X															
General Activities																	
Demographics[2]	*PPMI*	*PPMI*		*Data uploaded per PPMI EDC*													
Family History[2]	*PPMI*	*PPMI*															
Medical history [2]	*PPMI*	*PPMI*															
Socio-Economics[2]	*PPMI*	*PPMI*															
Physical Examination	X	X							X				X			X	
Height and Weight[9]	X	X	X		X	X	X		X		X		X		X	X	
Vital signs	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Orthostatic BP	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Neuro/Motor Assessments																	
Participant Motor Function Questionnaire		X				X	X	X	X	X	X	X	X	X	X	X	

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	Clinic	Clinic	Clinic														
Window days	-90 to -1	-90 to -1	0	3±	7±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	3±
Freezing and Falls		X							X				X	X		X	
Neurological Exam	X	X							X				X	X[12]		X	
MDS-UPDRS Part Ia	X	X			X	X	X	X	X	X	X	X	X	X	X	X	
MDS-UPDRS Part III Hoehn & Yahr	X	X	X		X	X	X		X		X		X	X[12]	X	X	
MDS- UPDRS Part III /Hoehn & Yahr OFF/ON						Post Initiation of Dopaminergic Treatment											
MDS- UPDRS PART IV						Post Initiation of Dopaminergic Treatment											
MDS-UPDRS Part Ib and Part II	X	X			X	X	X	X	X	X	X	X	X	X	X	X	
Modified Schwab & England ADL	X	X				X	X	X	X	X	X	X	X	X	X	X	
Features of Parkinsonism		X				X	X	X	X	X	X	X	X	X		X	
Other Clinical Features		X				X	X	X	X	X	X	X	X	X		X	
Clinical Diagnosis	X	X				X	X	X	X	X	X	X	X	X	X	X	
Primary Research Diagnosis	X	X				X	X		X		X		X		X	X	
Non Motor Assessments																	
Olfactory Testing (UPSIT)		X							X				X			X	

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	Clinic	Clinic	Clinic														
Window days	-90 to -1	-90 to -1	0	3±	7±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	3±
RBD Screening Questionnaire.		X							X				X			X	
Epworth Sleepiness Scale		X							X				X			X	
SCOPA-AUT		X				X			X		X		X			X	
Neuro QoL		X							X				X			X	
Cognitive and Psychiatric Assessments																	
Montreal Cognitive Assessment	X	X							X				X			X	
Clock Drawing		X							X				X			X	
Lexical Fluency		X							X				X			X	
Hopkins Verbal Learning Test-Revised		X							X				X			X	
Benton Judgment of Line Orientation		X							X				X			X	
Modified Semantic Fluency (Animals only)		X							X				X			X	
Letter Number Sequencing		X							X				X			X	
Symbol Digit Modalities Test		X							X				X			X	

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Window days	-90 to -1	-90 to -1	0	3±	7±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	3±
Trail Making Test (A and B)		X							X				X			X	
Modified Boston Naming Test		X							X				X			X	
Neuropsych battery		X							X				X			X	
Cognitive change	X	X				X	X	X	X	X	X	X	X			X	
Cognitive characterization	X	X				X	X	X	X	X	X	X	X			X	
State-Trait Anxiety Inventory for Adults		X					X		X		X		X			X	
Geriatric Depression Scale	X	X					X		X		X		X			X	
QUIP		X					X		X		X		X			X	
Global Function Assessment																	
CGI-S		X	X			X			X		X		X			X	
PGI-S		X	X			X			X		X		X			X	
PDAQ-15		X	X			X	X		X		X		X			X	
Novel PRO		X	X			X			X		X		X			X	
Digital Assessment																	
Digital Assessment			As needed per PPMI Digital Sub Study														
Safety Assessments																	

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	Clinic	Clinic	Clinic														
Window days	-90 to -1	-90 to -1	0	3±	7±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	3±
Clinical safety labs[3]	X	X			X	X	X	X	X	X	X	X	X			X	
ECG	X	X			X				X				X			X	
C-SSRS[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Biological Sample Collection																	
Research samples[3] (blood & urine)		X	X				X		X				X			X	
Lumbar puncture		X[4]							X				X			X	X[10]
Skin biopsy		X[4]											X			X	X[10]
Imaging Activities																	
Pregnancy Test (prior to DaTscan) if applicable	X	X							X				X			X	
DAT	X[5]	X[5]							X				X			X[15]	X[10]
MRI		X							X				X			X	
Medications																	
Concomitant meds review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
LEDD Medication Initiation log				As needed													
Randomization to open RSSP																	
Randomization	X	X	X														

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	Clinic	Clinic	Clinic														
Window days	-90 to -1	-90 to -1	0	3±	7±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	3±
Adverse Events (AE)																	
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X[11]
Current Medical Conditions Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Report of Pregnancy	X	X	X		As needed												
Other Assessments																	
Study completion form																X	
Surgery for PD					As needed												
Visit Status[13]		X							X				X			X	

Footnote:

1. Tele (Video if possible) visits may be converted into in person clinic visit as necessary at the discretion of the site Principal Investigator; vital signs and clinical safety labs will not be collected at Tele visits unless the visit is converted to an in-person clinic visit
2. Procedures, assessments, samples collected as part of the main PPMI Clinical study (screening) may be used for this Master Protocol and will be uploaded into EDC by Data Management
3. Clinical Safety/Research Samples: See Sections 12 and Appendix 3 for specific analytes. Collect samples as outlined in the Laboratory Manual; Collect Screening blood samples after other requisite tests for eligibility have been completed. For WOCBP, perform serum pregnancy test (HCG) at Screening; perform urine pregnancy test or (serum if required by the site) prior to injection of DaTscan and at all other indicated visits.
4. Skin biopsy and lumbar puncture tests will be repeated if last procedure/test performed ≧ 12 months of the P2P screening visit
5. Repeat DaTscan if last DaTscan was collected ≧ 3 months of the P2P screening visit.
6. The end of treatment is defined when the last RSSP participant completes their month 24 visit for the assigned RSSP. All consented participants will remain active in the RSSP until the last subject completes the month 24 visit.

7. PPMI annual visit data may be used for P2P screening visits (group A or B)
8. This visit should be scheduled prior to initiation of Dopaminergic therapy (levodopa or dopamine agonists). If this visit occurs ≤ 90 days from the next in clinic visit, replace this visit with the next in clinic visit and follow the schedule of activities accordingly
9. Height is only collected at the screening visit. Weight will be collected at all in person office visits.
10. Follow-up Safety call is performed 2-3 days after a skin biopsy, DaTscan, and lumbar puncture.
11. Follow-up Safety call is performed 30 days after completion/ withdrawal from RSSP unless specified otherwise in the RSSP.
12. MDS-UPDRS part III Hoehn & Yahr and neurologic exams are only performed at in office visits.
13. Visit status will be tracked in PPMI Clinical Study
14. Screening/Baseline C-SSRS use the long form. All other visits will complete the C-SSRS using the short form.
15. Repeat DaTscan if last DaTscan was collected ≧ 6 months prior to the End of Treatment visit

* See Section 5.1 for a description of the PPMI Clinical study