1. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Michael J. Fox Foundation
Title and Phase of Study: P2P Therapeutics Platform Trial: A Phase 2A, Randomized, Double Blind, Placebo Controlled Study to Evaluate Investigational Drugs in Prodromal Parkinson's Disease (PD).
Study Design: The Path To Prevention Platform Trial (P2P) is a perpetual multi-center, multi-regimen clinical trial evaluating the safety and early efficacy of investigational products for the treatment of prodromal PD and related disorders (α-synucleinopathies, αSN). 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, study 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 will have its own Intervention Specific Sub Protocol (ISSP) to the Master Protocol.
Study Objectives: Proof of concept Phase 2A randomized double blind study to assess the impact of interventions on DAT SPECT imaging, efficacy**,** safety, tolerability and exploratory biomarkers in participants with prodromal aSN.
Multiple Primary endpoints: 1. Impact of interventions on DAT imaging as measured by a difference in the rate of progression in the mean striatum Specific Binding Ratio (SBR) in the active treatment arm versus placebo from baseline through follow-up. 2. Impact of interventions on the clinical outcome as defined by a difference in the rate of progression in MDS-UPDRS total score (sum of parts I, II, and III) in the active treatment arm versus placebo from baseline through follow-up.

Secondary Endpoints:

1. Feasibility as defined by ability to recruit, retain participants and complete study activities as per schedule of activities
2. Safety will be assessed as measured by all treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs) for the active treatment arm versus placebo
3. Tolerability will be measured by ability to complete the study on the assigned dose and treatment arm (active versus placebo)

Exploratory Endpoints:

A range of clinical and biomarkers variables as per PPMI protocol including but not limited to

- The number of participants developing clinically defined aSN including diagnosis of Parkinson's disease, Dementia with Lewy bodies or MSA as per established diagnostic criteria.
- Other exploratory clinical outcome measures will include:
  - Change in MDS-UPDRS Part I, II and III subscore
  - Change in Cognitive battery (TBD)
  - Change in cognition as defined by the number of participants developing new diagnosis of mild cognitive impairment (MCI) or dementia
  - Change in neuropsychiatric domain including measures of depression and anxiety
  - Change in digital outcome measures of activity, sleep and cognition
  - Change in SCOPA-Aut and other autonomic measures
  - Change in QOL
  - Change in functional status as measured by PDA-15
  - Change in11-item PD symptom screening questionnaire (Brief Motor Screen)
  - Time to new symptoms on MDS- UPDRS Part Ib and II
  - Change in the global disability scale (PGI and CGI)
  - Change in the novel Participant Reported Outcomes (PRO)

Pharmacokinetic measures:

- Serum and CSF concentration of drug as defined in each sub protocol
- Correlation between drug exposure and safety/ efficacy outcome measures

Pharmacodynamic measures:

- Biomarkers of target engagement based on intervention profile as defined in each sub protocol
- An array of imaging (MRI), biofluids, and tissue biomarkers of disease progression and state will be included based on the PPMI panel inclusive but no limited to
    - MRI imaging (structural and advanced imaging sequences as per PPMI protocol)
    - Biomarkers of aSN pathology (plasma, CSF, skin, potentially other tissue)
    - AD biomarkers (plasma, CSF, potentially Amyloid and Tau PET imaging depending on the profile of intervention)
    - Inflammatory biomarkers
    - Neurodegeneration (NFL)
    - Genotyping

Target population

Prodromal PD and related disorders (αSN). αSN are conditions defined by accumulation of aggregated αSN, include PD and Dementia with Lewy bodies (DLB). Given our enrollment criteria we are unlikely to enroll participants with Multiple System Atrophy (MSA). PD is the most common aSN. We are using the term 'prodromal PD participants' as an operational definition of the target prodromal α-synucleinopathies, αSN population.

Main inclusion criteria:

Participants eligible for inclusion in this study only if they meet all the following criteria:

1. Prodromal aSN as defined by presence of any of the following:
    a. Idiopathic RBD (probable or definite) as per established diagnostic criteria
    b. Hyposmia defined as <15% for age and sex
    c. Other prodromal features that qualify for enrollment in PPMI prodromal cohort.
2. Presence of DAT deficit at baseline as defined by lowest putamen SBR<65 percentile for age and sex
3. Enrollment in PPMI observational study for minimum of 6 months
4. Male or female age 60 years or older at Screening visit.

5. Individuals taking any of the drugs that might interfere with the DAT scan read out must be willing and medically able to hold the medication for at least 5 half-lives before DaTscan imaging.
6. Able to provide informed consent.
7. Women may not be pregnant, lactating or planning pregnancy during the study.
8. Meet defined assigned sub-protocol inclusion criteria

Main exclusion criteria

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

1. Clinical diagnosis of PD, other parkinsonism, or dementia.
2. Participants with relevant genetic variants will be allowed provided that they have either RBD or hyposmia
3. Received any of the following drugs: dopamine receptor blockers, metoclopramide and reserpine within 6 months of Screening Visit.
4. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude study participation.
5. Prior exposure to investigational agents included in the study
6. Meet exclusion criteria defined in the assigned ISSP

Investigational products: Investigational products will be tested at different times (in parallel and sequentially) as described in this Master Protocol. This Master Protocol describes the common framework of the study. Each investigational product will have its own ISSP added to the protocol.

Duration of treatment per arm: All participants will remain on the originally assigned treatment arm (regimen) until the last participant randomized to that ISSP has the opportunity to complete 24 months of follow-up on intervention.

Randomization: The platform trial incorporates two stages of randomization.

1. Equal randomization to all regimens, where regimen denotes both active treatment and placebo groups
2. *K*:1 randomization within a regimen to either active treatment or placebo, where *K* is the number of enrolling regimens in the platform trial at any time.

Sample size: Overall platform trial sample size is based on the number of regimens, with each regimen comparing active treatment versus a shared placebo group. For the purposes of sample size planning, we examined regimen sample sizes range from 80 to 250 participants concurrently randomized in an equal 1:1 manner to active treatment versus shared placebo.

Interim analyses are conducted to select a sample size for each regimen according to a prespecified algorithm using Bayesian predictive probabilities. Sample size calculations demonstrate that 225, 125, and 80 participants per regimen on active treatment, compared to an equal number of participants concurrently randomized to shared placebo, are required for 80% power to detect a 30%, 40%, or 50% reduction in slope/progression on DAT imaging endpoint. In the same setting with the MDS-UPDRS endpoint, we can detect a 35% and 45% risk reduction with 225 and 125 active participants per regimen on active treatment, compared to an equal number of participants concurrently randomized to shared placebo. In both settings, we test with a one-sided Type I error of 0.05, not accounting for multiple interim analyses and multiple primary endpoints. Comprehensive virtual trial simulations are being conducted to prospectively evaluate power and Type I error of the adaptive platform trial design, including multiple interim analyses and endpoints.
Primary Analyses: Both primary endpoints will be tested with equal priority with respect to active treatment superiority versus placebo. ***Mean Striatum SBR*:** A Bayesian repeated measures model of mean striatum SBR over time 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, and the ability to leverage the natural history arm (i.e. non-randomized participants). 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 (e.g. 0.98) required to demonstrate superiority. ***MDS-UPDRS total score*:** A Bayesian repeated measures model of MDS-UPDRS total score over time 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 total score values and individual slopes, heterogeneity across regimens due to minor differences in the inclusion/exclusion criteria or mode of administration, and the ability to leverage the natural history arm (i.e. non-randomized participants). A greater positive slope indicates fast 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 (e.g. 0.98) required to demonstrate superiority.
Schedule of activities Participants will be seen for sequential Master protocol and ISSP screening visits, and if qualified, will be randomized per randomization plan. Following the Baseline visit, participants will be seen at Month 1, Month 3 and then every 3 months for the duration of the study. The scope of assessments will align with the PPMI SOA for the annual visits. Additional visits and assessments will be completed as per individual ISSP. Please, refer to the Table 3 of Schedule of Activities.

Table 3: Study Schedule of Assessments

Activity	Master protocol screening	ISSP screening	Baseline	Week 2 Safety	Mon 1 Safety	Mon 3	Mon 6	Mon 9	Mon 12[1]	Mon 15	Mon 18	Mon 21	Mon 24[1]	Additional visits q 3mon	End of Treatment Visit	Early termination	Study completion
	clinic	Clinic	Clinic	Phone	Clinic	Clinic	Clinic	Tele[2]	Clinic	Tele[2]	Clinic	Tele[2]	Clinic	Clinic/ Tele[2]	Clinic	Clinic	Clinic
Window	-60-1	-46 -1	0	3±	3±	7±	7±	7±	7±	7±	7±	7±	7±	7±	7+	7+	7+
Informed consent	X																
Documentation of informed consent	X																
Screening activities	X	X															
Inclusion /exclusion criteria	X	X															
DAT eligibility	X																
General activities																	
Demographics	X																
Family History	X																
Medical history	X																
Socio-Economics	X																
Physical Examination	X																
Height and Weight BL + Annually)	X																
Vital signs	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	
Neuro/ motor assessments																	
Participant Motor Function Questionnaire			X			X	X	X	X	X	X	X	X	X	X	X	
Freezing and Falls			X						X				X	X	X	X	
Neurological Exam	X		X						X				X	X	X	X	
MDS-UPDRS Part Ia, Part III and Hoehn & Yahr			X			X	X	X	X	X	X	X	X	X	X	X	
MDS- UPDRS Part III OFF/ON					Post initiation of DT												
MDS- UPDRS PART IV					Post initiation of DT												

MDS-UPDRS Part Ib and Part II			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	
Features of Parkinsonism	X		X			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	X	
Primary Clinical Diagnosis	X		X			X	X	X	X	X	X	X	X	X	X	X	
Non motor assessments																	
Olfactory Testing (UPSIT)	X		X						X				X		X	X	
REM Sleep Behavior Disorder Screening Questionnaire.	X		X						X				X		X	X	
Epworth Sleepiness Scale			X						X				X		X	X	
SCOPA-AUT			X			X			X		X		X		X	X	
Neuro QoL			X						X				X		X	X	
Cognitive and Psychiatric Assessments																	
Montreal Cognitive Assessment	X		X						X				X		X	X	
Neuropsych battery			X						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	X	
State-Trait Anxiety Inventory for Adults			X				X		X		X		X				
Geriatric Depression Scale	X		X				X		X		X		X				
QUIP			X				X		X		X		X				
Global function assessment[1]																	
CGI	X		X			X			X		X		X		X	X	
PGI/ other	X		X			X			X		X		X		X	X	
Novel PRO			X			X			X		X		X		X	X	

Digital assessment																	
In office			X			X	X		X		X		X		X	X	
At home																	
Safety assessments																	
Clinical safety labs	X	X	X		X	X	X	X	X	X	X	X	X		X	X	
ECG	X				X				X				X		X	X	
C-SSRS	X					X	X	X	X	X	X	X	X		X		
Biological samples																	
Research samples (blood & urine)			X				X		X				X		X	X	
Lumbar puncture			X						X				X		X	X	
Skin biopsy			X										X		X	X	
Imaging activities																	
Pregnancy Test (prior to DaTscan) if applicable																	
DAT	X								X				X		X	X?	
MRI		X							X				X		X	X?	
Medications																	
Concomitant meds review	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
LEDD Medication Initiation log		As needed															
Study drug																	
Randomization		X	X														
Dispensing			X		As per ISSP protocol												
Compliance			X	X	X	X	X	X	X	X	X	X	X		X	X	
Adverse events (AE)																	
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Current Medical Conditions Review			X														
Report of Pregnancy			As needed														
Participation in Other Studies				As needed													
Study completion form																X	X

*Additional blood work as specified ISSP

1. Procedures, assessments and/or samples collected as part of the main PPMI Clinical study (Visit 12 & 24 months) may be used for this study
2. Tele visits may be converted into in person clinic visit as necessary at the discretion of the investigator