Name of Sponsor/Company: Michael J. Fox Foundation

Title and Phase of Study: A Phase 2A, Proof of Concept, Randomized, Double Blind, Placebo Controlled Study to evaluate investigational interventions in prodromal a-synucleinopathies.

Study Design:
The PPMI Path To Prevention Platform Trial (P2P) is a perpetual multi-center, multi-regimen clinical trialevaluating the safety and early efficacy of investigational products for the treatment of prodromal α- synucleinopathies (αSN). The trial is designed as a perpetual platform trial. This means that there is a single Master Protocoldictating 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 removinginterventions, and the statistical methodology and recommended 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 impact of interventions on DAT imaging, efficacy**,** safet , tolerability and exploratory biomarkers in participants with prodromal aSN.

Multiple Primary endpoints:

- Impact of interventions on DAT imaging as measured by the change in the mean striatum Specific Binding Ratio (SBR) in the active treatment arm versus placebo from baseline to 24 months.
- The time to observe a clinically meaningful change (i.e. progression) in either motor or cognitive domain (composite)
    - Clinically meaningful change will be defined as any of the following:
        - Change in MDS-UPDRS Part III > 5 points
        - Change in cognition as measured by proportion of participants developing new diagnosis of MCI or dementia as per established diagnostic criteria

Secondary Endpoints:

- Feasibility as defined by ability to recruit, retain participants and complete study activities as per schedule of activities
- Safety will be assessed as measured by all adverse events (AEs), serious adverse events (SAEs), treatment emergent AEs (TEAEs) from the time of interventions administration through a follow-up visit.
- Tolerability will be measured by ability to complete the study on the assigned dose in active treatment arm 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 from BL in MDS-UPDRS total score
    - Change from BL in MDS-UPDRS Part I, II and III subscore
    - Change in Cognitive battery (TBD)
    - Change in digital outcome measures of activity, sleep and cognition
    - Change in SCOPA-Aut
    - Change in QOL

- Change in functional status as measured by PDA-15
- Change in 9 -item Tanner PD symptom screening questionnaire
- Time to new symptoms on MDS- UPDRS Part Ib and II
- Change in the global disability scale (PGIC-7)
- 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
- Biomarkers of disease progression
- An array of imaging (MRI) and biofluids/ tissue biomarkers 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 AB and Tau imaging depending on the profile of intervention)
  - Inflammatory biomarkers
  - Neurodegeneration (NFL) Genotyping

Target population

Prodromal aSN with a high risk of developing clinically defined degenerative aSN

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 <10% for age and sex
   c. Participants with relevant genetic variants will be allowed provided that they have either RBD or hyposmia
   d. Other prodromal features associated with increased risk of developing clinically defined aSN
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. Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine within 6 months of Screening Visit.
3. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude study participation.
4. Prior exposure to investigational agents included in the study
5. Meet defined assigned ISSP exclusion criteria

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 to the protocol.
Duration of treatment per arm: All participants will remain on the originally assigned treatment arm until the last participant completes 24 months intervention.
Randomization: The platform trial incorporates two stages of randomization: 1) Equal randomization to regimens enrolling participants, 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
Sample size: The platform trial incorporates an adaptive sample size for each regimen, ranging between 50 and 250 participants on active treatment, with a concurrently shared placebo arm of equal sample size. Pre-specified interim analyses will be conducted to evaluate sample size according to pre-specified rules, which will be based on Bayesian predictive probabilities of success for each of the respective endpoints. Sample size calculations demonstrate that 222 and 125 participants per arm (active and shared placebo) are required for 80% power of detecting a 30% or 40% reduction in slope/progression with a one-sided Type I error of 0.05, respectively, not accounting for multiple interim analyses and multiple primary endpoints. Comprehensive virtual trial simulations will be used prospectively to evaluate power and Type I error of the adaptive platform trial design.
Primary Analysis: Both primary endpoints will be tested with equal priority with respect to active treatment superiority versus placebo. ***DAT endpoint*:** A Bayesian repeated measures model of DAT 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 DAT 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 hypothesis test for a difference in slopes between active treatment and placebo will be conducted using the Bayesian posterior distribution, with a pre-defined threshold (e.g. 0.98) required to demonstrate superiority. ***Time to MDS-UPDRS3/Cognitive progression*:** A Bayesian piecewise exponential model will be used to compare the hazard ratio of time to progression for active treatment versus the shared placebo arm. The model allows for heterogeneity across individuals with respect to baseline values of MDS-UPDRS Part III, 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 hypothesis test of the hazard ratio comparing active treatment and placebo will be conducted using the Bayesian posterior distribution, with a pre-defined 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 visits, 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. The Table of Schedule of Activities will be added to the Synopsis

Activity	Master protocol screening	Regiment specific screening	Baseline	Week 2 Safety	Mon 1 Safety	Mon 3	Mon 6	Mon 9	Mon 12	Mon 15	Mon 18	Mon 21	Mon 24	Additional visits q 3mon	Early termination	Study completion
	clinic	Clinic	Clinic	Phone	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
Window	-60-1		0	14+												
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	
Orthostatic BP	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	
Freezing and Falls			X						X				X	X	X	
Neurological Exam	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	
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	
Modified Schwab & England ADL			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	
Other Clinical Features			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	
Non motor assessments																
Olfactory Testing (UPSIT)	X		X						X				X		X	
REM Sleep Behavior Disorder Screening Questionnaire.	X		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 Assessments																
Montreal Cognitive Assessment*			X						X				X		X	
Neuropsych battery			X						X				X		X	
Cognitive change			X			X	X	X	X	X	X	X	X		X	
Cognitive characterization			X			X	X	X	X	X	X	X	X		X	
Global function assessment																
CGI	X		X			X			X		X		X		X	
PGI/ other	X		X			X			X		X		X		X	
Novel PRO			X			X			X		X		X		X	
Digital assessment																
In office			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	
ECG	X				X				X				X		X	
Biological samples																
Research samples (blood & urine)			X				X		X				X		X	
Lumbar puncture			X						X				X		X	
Skin biopsy			X										X		X	
Imaging activities																

Pregnancy Test (prior to DaTscan) if applicable																
DAT	X								X				X		X?	
MRI		X							X				X		X?	
Medications																
Concomitant meds review	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	
Adverse events (AE)																
AE Assessment	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