1. TITLE PAGE

Master Protocol Title:	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)
Short Title:	Path to Prevention (P2P)
Sponsor:	The Michael J. Fox Foundation for Parkinson's Research Grand Central Station P.O. Box 4777 New York, NY 10163-4777 United States of America
Principal Investigator:	Tanya Simuni, MD
Protocol Number:	P2P-013
Date of Protocol:	20 Jul 2026
Final Version:	4.0

PROTOCOL APPROVAL

Version 4.0 dated 20 Jul 2026

Study Title: 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)

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Signer Name: Tanya Simuni
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7/21/2026

Tanya Simuni, MD — Date
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7/21/2026

Sohini Chowdhury — Date
The Michael J. Fox Foundation for Parkinson's Research (Sponsor)

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled, "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)" and agree to conduct the study as outlined, adhering to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP), and with applicable regulatory requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Site Name

_____

Printed Name of Site Investigator

_____

Signature of Site Investigator

_____

Date

2. TABLE OF CONTENTS

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this Master Protocol.

Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
AD	Alzheimer's Disease
ADL	Activities of Daily Living
AE	Adverse Event
AV	Atrioventricular
BRC	Biospecimen Review Committee
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression of Severity
CIRB	Central Institutional Review Board
CRF	Case Report Form
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
CT Scan	Computed Tomography Scan
C-SSRS	Columbia-Suicide Severity Rating Scale
DAT SPECT	Dopamine Transporter Single-photon Emission Computed Tomography
DaTscan	^{123}I-ioflupane injection; radioactive imaging agent
DLB	Dementia with Lewy Bodies
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMM	Independent Medical Monitor

Abbreviation or specialist term	Explanation
IND	Investigational New Drug
IRB	Institutional Review Board (Local or Central)
IRT	Interactive Response Technology
ISS	Integrated Staging System
ITT	Intent-to-Treat Principle
LEDD	Levodopa Equivalent Daily Dose
LP	Lumbar Puncture
MCI	Mild Cognitive Impairment
MDS-UPDRS	Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MJFF	The Michael J. Fox Foundation for Parkinson’s Research
MM	Medical Monitor
MoA	Mechanism of Action
MRI	Magnetic Resonance Imaging
MSA	Multiple System Atrophy
MSMP	Medical Safety Management Plan
n-asyn	Neuronal α-synucleinopathies
Neuro QoL	Quality of Life in Neurological Disorders
NSD	Neuronal Alpha-Synuclein Disease
NYHA	New York Heart Association
PD	Parkinson’s Disease
PDAQ-27	Penn Parkinson’s Daily Activities Questionnaire-27
PET	Positron Emission Tomography
PGI-S	Participant Global Impression of Severity
PI	Principal Investigator Master Protocol
PP	Per Protocol
PPMI	Parkinson's Precision Medicine Initiative
PRO	Participant Reported Outcomes
P-SYN	Phosphorylated Alpha-Synuclein
P2P	Path to Prevention
QoL	Quality of Life
QUIP	Questionnaire for Impulsive-Compulsive Disorders
RBD	Rapid Eye Movement Sleep Behavior Disorder
REM	Rapid Eye Movement
RNA	Ribonucleic Acid
RSSP	Regimen Specific Sub Protocol
SAA	Seed Amplification Assay

Abbreviation or specialist term	Explanation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBR	Specific Binding Ratio
SCOPA-AUT	Scales for Outcome in Parkinson's Disease – Autonomic
SI	Site Investigator
SMC	Site Management Core
SOA	Schedule of Activities
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAEs	Treatment Emergent Adverse Events
TEC	Therapy Evaluation Committee
UK	United Kingdom
US	United States
UPSIT	University of Pennsylvania Smell Identification Test
WCG	WIRB Copernicus Group

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's Precision Medicine 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.

Table 1: Master Protocol Standard Schedule of Activities

All P2P-013 participants will be screened from PPMI. If NSD status and staging were not established prior to P2P-013 screening, it must be done as part of the Master Protocol screening.

Activity	MP Screening	Baseline	W2	W4	W12	W24	W36	W48	W60	W72	W84	W96[2]/ ET	W108	W120	W132	W144	Initiation of Dopaminergic Tx[3]	End of RSSP Treatment	End of RSSP Treatment Safety Call[4]
	Clinic	Clinic	Phone	Clinic	Clinic	Clinic	Tele[1]	PPMI Annual Visit	Tele[1]	Clinic	Tele[1]	PPMI Annual Visit	Tele[1]	Clinic	Tele[1]	PPMI Annual Visit	Clinic	Clinic	Phone
Window (days)	-90 to -1	0	3±	7±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	3±
Informed Consent																			
Documentation of Informed Consent	X																		
Research Proxy Designation	X			As needed															
Informed Consent Tracking Log	X	As needed																	
Screening Activities																			
Inclusion /Exclusion Criteria	X	X																	
Screen Fail	As needed																		
General Activities																			
Demographics	X[a]																		
Family History	X[a]																		
Medical History	X[a]																		
Socioeconomics	X[a]																		
Features of REM Behavior Disorder	X[a]																		
Physical Examination	X					X		X				X				X		X	

Activity	MP Screening	Baseline	W2	W4	W12	W24	W36	W48	W60	W72	W84	W96[2]/ ET	W108	W120	W132	W144	Initiation of Dopaminergic Tx[3]	End of RSSP Treatment	End of RSSP Treatment Safety Call[4]
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Window (days)	-90 to -1	0	3±	7±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	3±
Height and Weight[5]	X	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	
Orthostatic BP	X	X		X	X	X		X		X		X		X		X	X	X	
Neuro/Motor Assessments																			
Participant Motor Function Questionnaire	X[b]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Freezing and Falls	X[b]							X				X				X		X	
Neurological Examination	X					X		X				X				X		X	
Initiation of Dopaminergic Therapy			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MDS-UPDRS Part Ia	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MDS-UPDRS Part Ib and Part II	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MDS-UPDRS Part III Treatment Determination/ Motor Exam/Hoehn & Yahr	X	X		X	X	X		X		X		X		X		X	X	X	
MDS-UPDRS Repeat Part III/ Hoehn and Yahr[6]				X	X	X		X		X		X		X		X	X	X	
MDS- UPDRS Part IV[6]				X	X	X		X		X		X		X		X	X	X	
Modified Schwab and England ADL	X				X	X		X		X		X		X		X	X	X	
Features of Parkinsonism	X[b]				X	X		X		X		X		X		X		X	
Other Clinical Features	X[b]				X	X		X		X		X		X		X		X	

Activity	MP Screening	Baseline	W2	W4	W12	W24	W36	W48	W60	W72	W84	W96[2]/ ET	W108	W120	W132	W144	Initiation of Dopaminergic Tx[3]	End of RSSP Treatment	End of RSSP Treatment Safety Call[4]
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Clinical Diagnosis	X				X	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	X	
Non-Motor Assessments																			
Olfactory Testing (UPSIT)	X[c]							X				X				X		X	
RBD Screening Questionnaire	X[b]							X				X				X		X	
Epworth Sleepiness Scale	X[b]							X				X				X		X	
SCOPA-AUT	X[b]				X			X		X		X		X		X		X	
Neuro QoL	X[b]							X				X				X		X	
Cognitive and Psychiatric Assessments																			
Montreal Cognitive Assessment	X							X				X				X		X	
Clock Drawing	X[b]							X				X				X		X	
Lexical Fluency	X[b]							X				X				X		X	
Hopkins Verbal Learning Test-Revised	X[b]							X				X				X		X	
Benton Judgment of Line Orientation	X[b]							X				X				X		X	
Modified Semantic Fluency (Animals only)	X[b]							X				X				X		X	
Letter Number Sequencing	X[b]							X				X				X		X	
Symbol Digit Modalities Test	X[b]							X				X				X		X	

Activity	MP Screening	Baseline	W2	W4	W12	W24	W36	W48	W60	W72	W84	W96[2]/ ET	W108	W120	W132	W144	Initiation of Dopaminergic Tx[3]	End of RSSP Treatment	End of RSSP Treatment Safety Call[4]
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Window (days)	-90 to -1	0	3±	7±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	3±
Trail Making Test (A and B)	X[b]							X				X				X		X	
Modified Boston Naming Test	X[b]							X				X				X		X	
Cognitive Change	X				X	X	X	X	X	X	X	X	X	X	X	X		X	
Cognitive Categorization	X				X	X		X		X		X		X		X		X	
State-Trait Anxiety Inventory for Adults	X[b]					X		X		X		X		X		X		X	
Geriatric Depression Scale	X					X		X		X		X		X		X		X	
QUIP	X[b]					X		X		X		X		X		X		X	
Global Function Assessments																			
CGI-S	X[b]	X				X		X		X		X		X		X	X	X	
PGI-S	X[b]	X				X		X		X		X		X		X	X	X	
PDAQ-27	X[b]	X				X		X		X		X		X		X	X	X	
Novel PRO	X	X				X		X		X		X		X		X	X	X	
Digital Assessment																			
Digital Assessment		As needed																	
Safety Assessments																			
Clinical Safety Labs[7]	X			X	X	X		X		X		X		X		X		X	
ECG	X			X				X				X				X		X	
C-SSRS[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Biological Sample Collection																			

Activity	MP Screening	Baseline	W2	W4	W12	W24	W36	W48	W60	W72	W84	W96[2]/ ET	W108	W120	W132	W144	Initiation of Dopaminergic Tx[3]	End of RSSP Treatment	End of RSSP Treatment Safety Call[4]
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Research Samples (blood and urine)	X[c]	X[13]				X		X				X				X		X	
Lumbar Puncture	X[c]							X				X				X		X[14]	
Skin Biopsy	X[c]							X				X				X		X[14]	
Imaging Activities																			
Pregnancy Test[7]	X							X				X				X		X	
DAT SPECT	X[b]							X				X				X		X[12]	
MRI[9]	X[b]							X				X				X		X[14]	
CT Scan[10]	X																		
Medications																			
Concomitant Medications Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LEDD Concomitant Medication Log			As needed																
Randomization																			
Randomization	X	X																	
Adverse Events (AEs)																			
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Telephone Assessment[11]	X							X				X				X		X	
Current Medical Conditions Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Report of Pregnancy	As needed																		
Other Assessments																			

Activity	MP Screening	Baseline	W2	W4	W12	W24	W36	W48	W60	W72	W84	W96[2]/ ET	W108	W120	W132	W144	Initiation of Dopaminergic Tx[3]	End of RSSP Treatment	End of RSSP Treatment Safety Call[4]
	Clinic	Clinic	Phone	Clinic	Clinic	Clinic	Tele[1]	PPMI Annual Visit	Tele[1]	Clinic	Tele[1]	PPMI Annual Visit	Tele[1]	Clinic	Tele[1]	PPMI Annual Visit	Clinic	Clinic	Phone
Window (days)	-90 to -1	0	3±	7±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	14±	3±
Study Completion Form			As needed																
Procedures for PD Log			As needed																
Participation in Other Studies	As needed																		
Visit Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: If any screening assessment indicated above was not completed as part of PPMI Clinical (e.g., the participant was identified from myPPMI or other remote platform), it must be completed as part of the P2P-013 Master Protocol screening visit.

a. Data will be pulled in from PPMI Clinical, if available, and must be verified during the screening visit by the clinical site.

b. Data from these assessments will be pulled in from participant's last annual PPMI Clinical visit if the assessment was performed < 6 months prior to the Master Protocol screening visit. In case of re-screening for the Master Protocol, the participant does not need to repeat these assessments if performed < 6 months prior to the Master Protocol re-screening visit.

c. Data from these assessments will be pulled in from participant's last annual PPMI Clinical visit if the assessment was successfully performed < 12 months prior to the Master Protocol screening visit. In case of re-screening for the Master Protocol, the participant does not need to repeat these assessments if performed < 12 months prior to the Master Protocol re-screening visit.

1. Tele (video if possible) visits may be converted into in-person clinic visits as necessary at the discretion of the site investigator. If converted into in-person visits, vital signs (including orthostatic blood pressure) and clinical safety laboratory samples should be collected.
2. The end of treatment is defined when the last participant randomized to an RSSP completes their Week 96 visit for the assigned RSSP or until 96 weeks have passed since randomization (if terminated early). All consented participants will remain active in the RSSP for a maximum of 144 weeks or until the last participant has had the opportunity to complete the Week 96 visit (whichever occurs first).
3. This visit should be scheduled prior to the initiation of dopaminergic therapy. If this visit occurs < 90 days from the next annual (Week 48, Week 96, or Week 144) in-clinic visit, replace this visit with the next annual in-clinic visit and follow the SOA accordingly.
4. End of RSSP Treatment Safety Call is performed 30 days (±3 days) after completion/ withdrawal from RSSP unless specified otherwise in the RSSP.
5. Height is only collected at the screening visit. Weight will be collected at all indicated visits.
6. The MDS-UPDRS Repeat Part III /Hoehn and Yahr and MDS-UPDRS Part IV will be performed only if the participant has initiated dopaminergic therapy (levodopa or dopamine agonists). When OFF testing is required, it is preferred that the OFF exam be performed first. OFF testing should occur at least 6 hours post last dose of dopaminergic medication.

7. Clinical Safety Labs: See Appendix 3 for specific analytes. HIV serology, HBV serology, Hep C antibody, and Urine Drug Screen performed at Screening only. Collect samples as outlined in the laboratory manual; Collect Screening blood samples after other requisite tests for eligibility have been completed. For women of childbearing potential, 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.
8. At the screening visit, use the C-SSRS baseline/screening version of the form. At all other visits, use the C-SSRS Since Last Visit version of the form. If any concern is noted, the patient will be promptly referred to a specialist for further evaluation and, if deemed warranted, therapy.
9. An MRI is not required if completion of the MRI is not possible for a safety or medical reason.
10. CT Scan is optional and can be performed if required by the site for pre-LP imaging.
11. AE Telephone Assessment is performed 2-3 business days after a skin biopsy, DAT SPECT, and lumbar puncture.
12. Repeat DATSPECT if last DATSPECT was collected ≥ 6 months prior to the End of RSSP Treatment visit.
13. Collect research samples if not completed at Screening.
14. To be completed only if done ≥12 months before this time point.

Abbreviations: ET = Early Termination; MP = Master Protocol; Tx = Therapy; W = Week

See Section 5.1 for a description of the Parkinson's Precision Medicine Initiative (PPMI) Clinical study

Table 2: NSD Staging Criteria

Disease Continuum	Stage	Stage Definition	aSyn Biomarker (S)	Dopamine Dysfunction Biomarker (D)	Clinical Signs and Symptoms Attributable to PD, DLB and other NSD syndromes	Functional Impairment Attributable to PD, DLB and other NSD syndromes
Genetic risk	R^L	(G) Genetic risk variants – Low age adjusted risk (constantly redefined)	-	-	No clinical signs or symptoms	No functional impairment
Genetic risk	R^H	(G) Genetic risk variants – High age adjusted risk (constantly redefined)	-	-	No clinical signs or symptoms	No functional impairment
NSD	0	(G) Fully penetrant *SNCA* variant	-	-	No clinical signs or symptoms	No functional impairment
NSD	1A	Characteristic pathological changes but no evidence of clinical signs/ symptoms	+	-	No clinical signs or symptoms	No functional impairment
NSD	1B	Characteristic pathologic changes plus dopaminergic dysfunction but no evidence of clinical signs/ symptoms	+	+	No clinical signs or symptoms	No functional impairment
NSD	2A	Characteristic pathological changes and subtle detectable clinical signs and symptoms but no functional impairment	+	-	Subtle clinical signs or symptoms. Can be motor (including digital) or relevant non-motor: hyposmia, RBD, cognitive abnormalities, constipation, dysautonomia, depression, anxiety	No functional impairment
NSD	2B	Characteristic pathologic changes plus dopaminergic dysfunction and subtle detectable clinical signs and symptoms but no functional impairment	+	+	*Same as Stage 2A*	No functional impairment
NSD	3	Characteristic pathologic changes plus dopaminergic dysfunction and clinical signs and symptoms causing slight functional impairment	+	+	*Relevant* motor and non-motor signs and symptoms increasing in severity, but stage is defined by the degree of functional impairment	Slight: Functional impairment not severe enough to cause uncompensated impairment in complex tasks of daily life and usual activities, such as: finances, transportation, food, household, conversation
NSD	4	Characteristic pathologic changes plus dopaminergic dysfunction and clinical signs and symptoms causing mild functional impairment	+	+	*See entry for Stage 3*	Mild: Functional impairment severe enough to cause some uncompensated impairment in complex tasks of daily life and usual activities, but basic tasks of daily life related to personal care are intact, such as: bathing, dressing, walking, using the toilet, eating

NSD	5	Characteristic pathologic changes plus dopaminergic dysfunction and clinical signs and symptoms causing moderate functional impairment	+	+	*See entry for Stage 3*	Moderate: Functional impairment severe enough to require assistance with basic tasks of daily life
NSD	6	Characteristic pathologic changes plus dopaminergic dysfunction and clinical signs and symptoms causing severe functional impairment	+	+	*See entry for Stage 3*	Severe: Functional impairment severe enough to require dependence on others for basic tasks of daily life

Table 3: Stage 2B Anchors

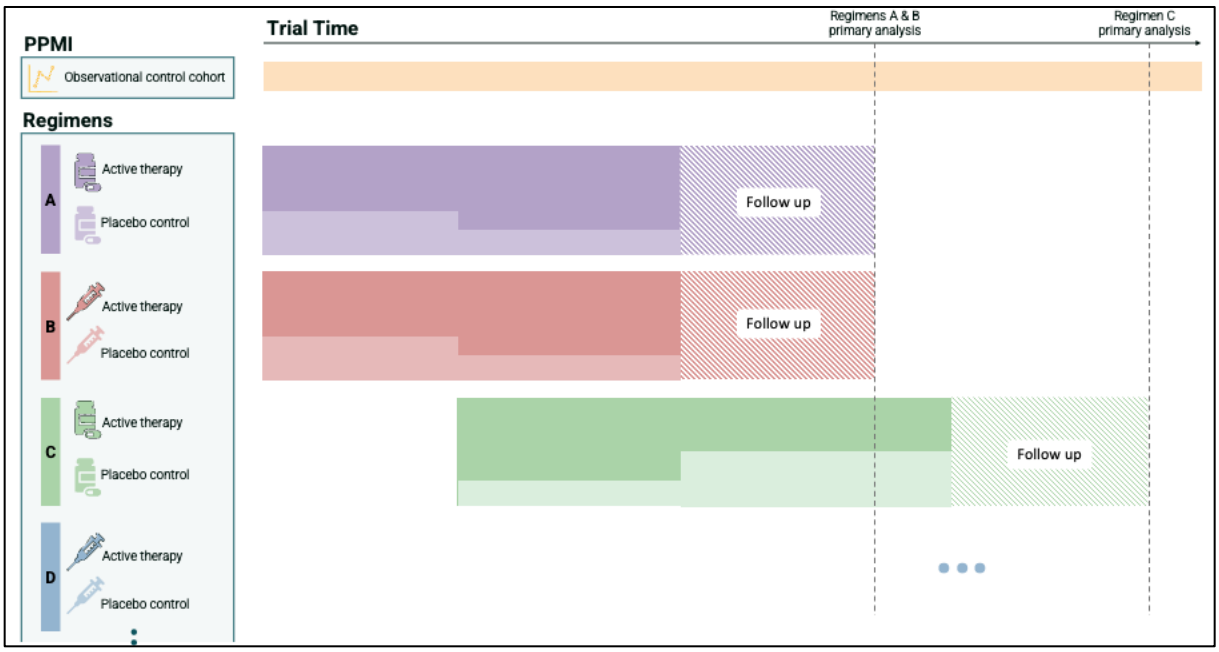
	Biologic anchors			**Anchors of clinical signs or symptoms[1] (participants can meet any one of the three anchors to qualify for Stage 2B)**	
Stage	**S [a]**	**D [b]**	**G**	**Domain**	**Anchor(s)**
Stage 2B	+	+	±	(1) Cognitive	(1) Item 1.1 MDS-UPDRS = 1 AND MoCA ≥ 25; or
				(2) Motor	(2) Subthreshold parkinsonism [c] AND MDS-UPDRS-II ≤ 2 AND not on PD meds [d]; or
				(3) Other non-motor	(3a) Has RBD [f]; or (3b) is hyposmic [e]

[1] Participants can meet any one of the three anchors to qualify for Stage 2B BUT SHOULD NOT EXCEED CRITERIA for other anchors. Specifically, if the participants meet criteria (2) Motor, their scores for Criteria (1) Cognitive should not exceed Item 1.1= 1 and MOCA <=24 AND (3) Other non-motor MDS-UPDRS-I total score (excluding items 1.1) should be <= 12

[a] S positivity as defined by positive results of aSyn seed amplification assay.
[b] D positivity defined as < 75% age/sex-expected lowest putamen SBR.
[c] Subthreshold parkinsonism defined as MDS-UPDRS-III ≥ 5 excluding postural and action tremor.
[d] Dopaminergic medication (levodopa formulations or dopamine agonists).
[e] Hyposmia defined as UPSIT percentile ≤ 15.
[f] Rapid Eye Movement sleep behavior disorder (RBD) defined by report of polysomnography (PSG) confirmed RBD.

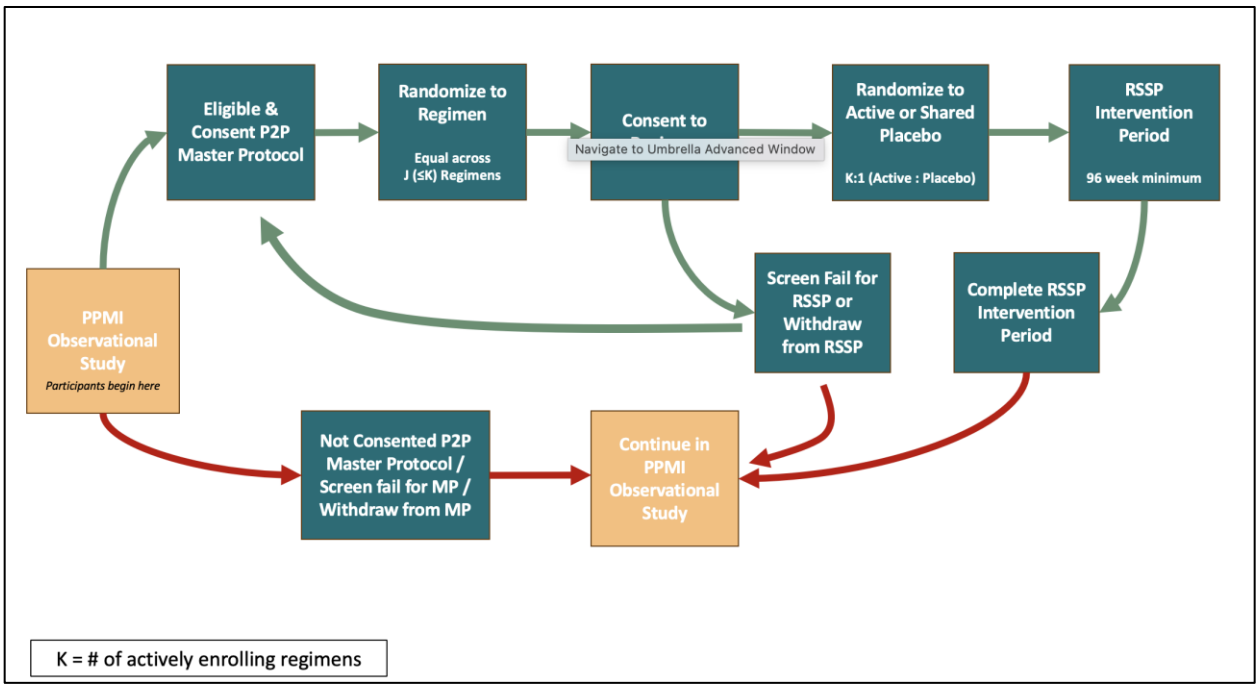
Abbreviations: MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. MoCA=Montreal Cognitive Assessment. NSD=Neuronal Synuclein Disease. PD=Parkinson's disease. RBD=REM sleep behavior disorder. UPSIT= University of Pennsylvania Smell Identification Test

Figure 1: P2P-013 Study Design Perpetual Platform Trial



Note: Participants are randomized using a two-stage process. First, participants are randomized in an equal manner to one of the K regimens that are actively enrolling and for which they qualify. Second, participants are randomized within a regimen to active treatment or placebo in a K:1 ratio. Note that K can change (which changes the randomization ratio) over the course of the RSSP. There is no limit to the number of regimens able to be added to the Master Protocol study design.

Figure 2: Participant Flow through P2P-013 Master Protocol



Note: Green arrow denotes participants flow within P2P-013 Master Protocol and RSSP; red arrows denote completing P2P-013 and continuing follow-up in PPMI.

5. BACKGROUND AND RATIONALE

Neuronal Alpha- Synuclein Disease (NSD) is a new terminology based on the biologic definition of a-synucleinopathies encompassing both Parkinson's disease (PD) and Dementia with Lewy Bodies (DLB). Enrollment in this Master Protocol is based on the biological definition of NSD and the NSD integrated staging system (NSD-ISS)[2, 3] (see Appendix 5). Utilizing NSD definition and staging in this interventional Master Protocol in what was previously defined as prodromal PD and/or prodromal DLB population will better define and ensure a more homogenous study population. PD and DLB are currently defined by their clinical features[4-6] with predominantly neuronal alpha-synucleinopathy (n-asyn) as the gold standard that establishes the definitive diagnosis. Based on the current diagnostic criteria, the prevalence of PD makes it the second most common neurodegenerative disease at 10 million worldwide, and is expected to double by 2040[7]. DLB is the second most common degenerative dementia also caused by neuronal accumulation of aggregated n-asyn but associated with early cognitive manifestations[6]. While there is a wide armamentarium of therapeutics to manage motor manifestations of PD, the disease continues to progress relentlessly leading to significant disability in advanced stages. As such, development of effective options to slow / halt disease progression remains an area of urgent need[8]. A large number of PD disease modification trials have been conducted but none of them have been successful so far. There are many potential reasons for lack of success of such studies including until recently, lack of biomarkers of early n-asyn diagnosis and progression[9]. However, the field has made tremendous progress in the last 10 years. Until recently, n-asyn could only be reliably measured post-mortem. In 2016, an assay[10], now known as seed amplification assay (SAA), was developed

that could detect n-asyn in the cerebrospinal fluid (CSF) *in vivo* with high accuracy. Its rapid, rigorous optimization and validation[11-15] has been a landmark advancement for the field.

Availability of SAA biomarker to measure *in vivo* misfolded, pathological n-asyn, the pathologic hallmark of PD and DLB, enabled the field to transition to a biological definition under the new term NSD, defined by *in vivo* detection of n-asyn (S). We further proposed that individuals with n-asyn are at high risk for developing dopaminergic neuronal dysfunction (D), a second key biologic anchor for NSD. Defining NSD by its biology is crucial to further understanding disease pathophysiology, enabling biology specific therapeutic development[16] and therapeutic intervention prior to symptom onset to potentially prevent/halt progression[17], and identifying biologically-defined subsets[18] .

We have further developed an integrated biologic and clinical staging system for NSD that begins at the start of disease and continues through the development of increasing severity of functional impairment (Table 2). The key rationale for a staging system is to accelerate therapeutic development in all disease stages, critically including those defined by biomarkers prior to the onset of symptoms as well as those in later stages, anchored by clinical features. Our approach builds on similar efforts in other neurodegenerative diseases, including Alzheimer's disease (AD)[19] and Huntington's disease[20]. Similar to the AD field[19,21], a major near-term focus is to provide a research framework to accelerate therapeutic development. As such, we are launching the first interventional therapeutic Master Protocol in early NSD population to test the ability of biologically targeted therapeutic interventions to slow progression of the disease. This progress was largely enabled by the Parkinson's Precision Medicine Initiative (PPMI)[22]. The NSD definition can easily be linked to currently traditionally defined syndromes of early PD, DLB and/or prodromal populations unified by common pathology and staged based on data driven criteria rather than poorly defined term of "early disease" or term of "prodromal" that has no regulatory definition. We have developed operational definitions for NSD staging associated with functional impairment and demonstrated consistent baseline staging data across PPMI and two recently completed interventional studies supporting face validity of the proposed staging anchors[3].

5.1 PPMI Overview and Interface with the P2P-013 Master Protocol

The Michael J. Fox Foundation for Parkinson's Research (MJFF) launched PPMI in 2010 as a longitudinal, observational, multi-center natural history study to assess progression of clinical features, digital outcomes, and imaging, biologic and genetic markers of progression in study participants with manifest PD, prodromal PD, and healthy controls[22, 23]. The overall goal of PPMI is to identify markers of disease progression to accelerate therapeutic development. PPMI made substantial progress in defining and developing a robust data and biosample repository that has enabled the design of numerous PD clinical trials planned or currently in progress[24-34]. PPMI is an umbrella term for a multiprong observational study that recruits participants into PPMI Online and PPMI Clinical protocols. In addition, PPMI Remote serves as a platform for widespread population identification and screening, and myPPMI is a virtual platform for interactive communication with the participants. Currently PPMI is recruiting a large cohort of participants with phenotypic prodromal features [hyposmia, Rapid Eye Movement sleep behavior disorder (RBD), and other premotor features as well as relevant genetic variants (GBA, LRRK2, SNCA and rare variants)] via all the above recruitment platforms. Many of these prodromal participants are enriched for abnormal DAT SPECT imaging as a marker of presynaptic dopamine deficiency. Further, PPMI

data and CSF samples have recently validated CSF n-asyn SAA as a biomarker for neuronal a-synuclein in manifest and prodromal PD[35]. These data have enabled a biologic definition of PD, the shift to the more encompassing biologic term, NSD and the proposed NDS-ISS. PPMI is applying the NSD definition for all PPMI eligible participants. As such, PPMI participants are recruited based on n-asyn SAA biomarker data and NSD Staging Criteria is applied once Dopamine Transporter Single-photon emission computed Tomography (DAT SPECT) imaging is obtained. P2P-013 is planned as a Master Protocol linked to PPMI. All P2P-013 participants will be enrolled in PPMI and will have NSD characterization and staging applied prior to or during P2P-013 screening.

As of January 2026, PPMI Clinical has recruited over 4400 individuals including ~2500 in prodromal cohort (with ~500 NSD Stage 2B at baseline) utilizing novel widespread community and in clinic recruitment strategies via PPMI Online, PPMI Remote and PPMI Clinical protocols. While not all of these participants will qualify for the NSD definition and/or P2P-013 protocol, PPMI already has the largest cohort of NSD Stage 2B participants[35]. Due to these efforts PPMI is uniquely positioned to be the pioneer in therapeutic development targeting the early NSD population via the P2P-013 Platform Trial. Enrollment of NSD participants into interventional studies offers a unique opportunity to test potential disease modifying interventions at earlier stages of neurodegenerative process. If successful, this approach will create a scientific and regulatory path for future disease prevention studies.

Up until 2025, the PPMI inclusion criteria for prodromal participants required an age of 60 years and above. Such age cut off was justified by age dependent prevalence of PD, with the majority of individuals developing PD in their early 60s. As such, currently available data on prevalence of NSD, NSD stage progression and risk of progression are available in the cohort with the recruitment age $\geq$60 years. PPMI has expanded the age spectrum of prodromal participants to >40 years in 2025, but the currently available dataset is not sufficient to assess prevalence and risk of NSD in the younger population which warrants the higher age cut off for P2P-013 of $\geq$60 years.

5.2 Platform Trials: An Efficient Strategy to Accelerate Drug Development and Scientific Discovery

Traditionally, clinical trials are designed to test a single investigational therapy or regimen; does a single investigational product or regimen work? These trials include a prespecified number of treatment arms (generally limited to two or three arms) and have a finite duration based on the time required to answer the trial question. Moreover, each trial requires an expensive, ad hoc trial infrastructure that is dismantled at the end of the trial. In contrast, platform trials are designed to investigate multiple investigational products in parallel and sequentially with the capability to adapt over time. Platform trials do not have a prespecified end date: the platform remains open long-term and is available to evaluate new investigational products as they become available. The trial infrastructure is built at the beginning and is shared across different treatments, leading to both operational and statistical efficiencies. Each investigational product is compared to a shared combined concurrent and non-concurrent placebo control group, which the Master Protocol incorporates for trial efficiency.[36, 37]

Platform trials are an ideal infrastructure to advance the scientific understanding of the disease and novel endpoints with a coordinated strategy. With the testing of multiple investigational products using a common protocol and uniform data and sample acquisition processes, the platform is

designed to answer multiple scientific questions and to serve as a source of data that can be used to enhance the design of other research projects. Further, accumulated learnings about endpoint behavior can be leveraged to adapt the Master Protocol so that future investigational products will be studied using more efficient biomarkers, outcome measures, and analyses[36, 37].

5.3 Study Design

The P2P-013 Trial is a perpetual multi-center, multi-regimen clinical trial evaluating the safety and early efficacy of investigational products for the treatment of participants with stage 2B NSD. Participants will be recruited based on presence of n-asyn pathology as determined by n-asyn SAA or other validated biomarkers (as such become available) and dopaminergic dysfunction as determined by DAT SPECT imaging and clinical features as defined by inclusion criteria (see Table 3). If alternative methods of assessing these biomarkers become available, such modifications to the study design would generate a protocol amendment for consideration.

As a perpetual platform trial, P2P-013 can continue to assess relevant NSD interventions with the Master Protocol as its guiding trial framework. 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, regimen assignment and randomization schemes, Master Protocol endpoints, schedule of acvtivities, trial design, the mechanism for adding and removing interventions, and the statistical methodology and recommended statistical methods for evaluating interventions.

Interventions (i.e., investigational products) are tested in trial regimens, in which a regimen denotes both the active intervention and placebo control corresponding to an intervention. Each trial regimen is described in its own Regimen Specific Sub Protocol (RSSP) appended to the Master Protocol. The RSSP will describe the nature of the intervention and its mechanism of action (MoA) including the mode and frequency of administration, dosage, additional enrollment criteria (if any), stopping rules (if any), and other specific intervention-related information and assessments (safety or other assessmentsthat may be in addition to those outlined in the Master Protocol). At the time of writing the initial version of the Master Protocol, three RSSPs are foreseen, but this number may increase over time.

5.4 Allocation to Regimen

PPMI participants that provide consent to the Master Protocol will be screened for both Master Protocol and all active RSSP level inclusion and exclusion criteria that are accessible at the time of screening. The schedule of screening activities will depend on the date an assessment may have been completed either at the last annual PPMI Clinical visit (if applicable) or at the last P2P-013 Master Protocol screening visit (in the case of re-screening). With K representing the number of actively enrolling RSSPs at a given time, those participants who meet the Master Protocol eligibility and are eligible for at least one RSSP based on information easily accessible at the time of screening will be equally randomized to one of the J ($\leq$ K) actively enrolling regimens for which they are eligible. During the trial, enrollment to a therapeutic product will be discontinued once the target number of randomized participants in that regimen has been reached.

5.5 Allocation to Intervention

After randomization to a specific RSSP, participants will be consented to the assigned RSSP and screened for any additional regimen specific inclusion and exclusion criteria. Participants meeting all additional regimen specific criteria will be randomized to the RSSP specific active treatment or placebo control in a prespecified K:1 ratio (see Figure 1). Participants who do not meet one or more regimen specific eligibility criteria will be given the option to be randomized to an alternate regimen (assuming at least one additional regimen is actively enrolling). Eligible participants who elect not to participate in their assigned regimen will not be allowed to be randomized to an alternative regimen.

5.6 Number of Planned Participants and Treatment Arms

The sample size for each regimen is approximately 125 participants on active treatment and at least 125 corresponding shared concurrent placebo control participants. In this trial, multiple investigational therapeutic products for NSD Stage 2B will be tested simultaneously or sequentially. These investigational products will be provided by different partners, including pharmaceutical companies or academic groups.

5.7 Selection of Investigational Products

Selection of interventions will be done by the Therapeutic Evaluation Committee (TEC) based on evidence supporting the intended MoA, target engagement, previous preclinical data and Phase I or other clinical data (including safety data available for each intervention), and compatibility with the Master Protocol study design (see Section 5.3). During the trial, a therapeutic product may be discontinued early due to safety concerns.

5.8 Planned Number of Sites

Research participants will be enrolled from approximately 50 PPMI sites in North America, the European Union and United Kingdom (UK).

5.9 Treatment Duration

Treatment duration for placebo-controlled interventions will be minimum of 96 weeks for each RSSP. All participants will remain on the originally assigned treatment arm up to 144 weeks or until 96 weeks since randomization of the last participant have passed, whichever comes first. The RSSP will be closed once all participants have completed the follow-up period. Post-treatment follow-up duration for each intervention will be described in the RSSPs. Upon completion, all participants will be encouraged to continue participation in the PPMI study and may be randomized to other P2P-013 platform regimens 6 months after completion of the initial RSSP, assuming continued eligibility for the Master Protocol.

6. TRIAL OBJECTIVES AND ENDPOINTS

In this trial, multiple investigational products for NSD Stage 2B will be tested simultaneously or sequentially. The Master Protocol objective is to assess the impact of putative NSD therapies in participants with Early-Stage NSD on DAT SPECT imaging, a clinical measure of symptom

worsening, feasibility, safety, and tolerability. Additional analyses may examine many other exploratory clinical outcome measures and biomarkers.

6.1 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 follow-up or the initiation of dopaminergic treatment.

6.2 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 control in each RSSP.

6.3 Secondary Endpoints

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

6.4 Key Exploratory Endpoints

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 the MDS-UPDRS Total score 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].

6.5 Other Exploratory Endpoints

A range of additional exploratory clinical, pharmacokinetic, and biomarker variables as per PPMI protocol will also be assessed, including but not limited to:

1. Clinical Measures
    a. The number of participants developing clinically defined syndromes including PD, DLB, or Multiple System Atrophy (MSA) as per established diagnostic criteria as determined by the site investigator (SI) clinical judgment
    b. Change in the clinical diagnosis as determined by the SI or treating physician
    c. Change from baseline in the PPMI neuropsychological cognitive battery
    d. Change in neuropsychiatric domain including measures of depression and anxiety

e. Change from baseline in digital outcome measures of function, activity, sleep, and cognitive
f. Change from baseline in Scales for Outcome in Parkinson's Disease-Autonomic (SCOPA-AUT) and other autonomic measures
g. Change from baseline in Quality of Life (Neuro-QoL)
h. Change from baseline in 11-item PD symptom screening questionnaire (Participant Motor Function Questionnaire)
i. Change from baseline in the global disability scale Participant Global Impression of Severity (PGI-S) and Clinical Global Impression of Severity (CGI-S)
j. Change from baseline in the novel Participant Reported Outcomes (PRO)

2. Pharmacokinetic Measures
   a. Pharmacokinetic parameters of the intervention as defined in each RSSP
   b. Correlation between drug exposure and safety/efficacy outcome measures as defined in each RSSP
3. Pharmacodynamic Measures
   a. Biomarkers of target engagement based on intervention profile as defined in each RSSP.
   b. An array of imaging including molecular imaging and Magnetic Resonance Imaging (MRI), biofluids, and tissue biomarkers of disease progression and state may be included based on the PPMI panel inclusive but not limited to:
      - MRI imaging (structural and advanced imaging sequences as per PPMI protocol)
      - Biomarkers of n-asyn pathology (plasma, CSF, skin, potentially other tissue)
      - Plasma, CSF Amyloid, tau, ptau, and Amyloid/Tau Positron emission tomography (PET) imaging depending on the profile of the intervention)
      - Inflammatory biomarkers
      - Neurodegeneration (Neurofilament light chain)
      - Genotyping

7. INCLUSION/EXCLUSION CRITERIA

7.1 Inclusion Criteria

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

1. Enrollment in the PPMI study
2. Age 60 years or older at the 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

7.2 Exclusion Criteria

Participants fulfilling any of the following criteria are not eligible for inclusion in this Master Protocol, or able to participate in an RSSP:

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 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

8. PARTICIPANT SELECTION AND ENROLLMENT

8.1 Identifying Participants

This Master Protocol will be conducted at selected PPMI qualified centers and participants must be enrolled in the PPMI study. Potential eligibility for P2P-013 Master Protocol will be determined based on the potential to meet Mater Protocol inclusion/exclusion criteria and participants will be identified by the PPMI study centrally for consideration to be contacted for enrollment into P2P-013. Sites participating in this Master Protocol will be notified by the PPMI study team of potentially eligible PPMI participants referred to their site by the central PPMI Screening Core to be contacted for Master Protocol screening. Information about all research participants that sign consent for the P2P-013 Master Protocol will be recorded in the Electronic Data Capture (EDC) system.

8.1.1 Ineligible Participants

Consented participants from the PPMI study will be screened for eligibility for P2P-013 based on the Master Protocol inclusion/exclusion criteria. For participants who were deemed potentially eligible for the Master Protocol but did not qualify upon further screening, the reason for ineligibility for the Master Protocol will be tracked. Similarly, participant ineligibility for any individual RSSP will also be documented.

8.2 Randomization

8.2.1 Randomization Procedures

Randomization will be conducted using an interactive response technology (IRT) system embedded within the EDC. With K representing the number of actively enrolling RSSPs at a given

time, the randomization for the Master Protocol consists of a two-stage tiered randomization as described below (see Figure 1).

1. In the first stage, participants will initially be assessed according to the Master Protocol inclusion and exclusion criteria. All eligible participants will then be assessed for any additional RSSP specific inclusion and exclusion criteria above that for the Master Protocol that are accessible at the time of screening. Assuming a research participant qualifies for one or more of the ongoing RSSPs, the participant will be randomized equally among all J ($\leq$ K) actively enrolling regimens for which they are eligible. Here, regimen denotes both active treatment and placebo control groups.
2. In the second stage, once assigned to a regimen the participant will then provide informed consent for that specific regimen at their scheduled RSSP screening visit. If all additional regimen specific eligibility criteria are met, participants will be randomized in a K:1 manner via the EDC system to either the active treatment or placebo control. If the participant screen fails for the assigned regimen (prior to randomization within the regimen), they can be re-randomized to one of the other actively enrolling regimens and complete the required screening procedures for that RSSP. Eligible participants who choose not to consent to their assigned regimen will not be given the opportunity to be re-randomized into an alternative regimen.

As each RSSP is added (or closed), the randomization will be adjusted accordingly to maintain the overall approach and aim for 1:1 randomization of active treatment versus concurrently shared placebo controls within each RSSP. This approach will maximize the efficiency of the shared placebo controls. The potential to include different regimens and routes of administration within the pooled placebo control group is important to maintain blinding within an individual RSSP and reduce bias. Within each blinded RSSP, the placebo control will match the relevant RSSP treatment arm and will be compliant with the Master Protocol as well as the relevant RSSP, all of which supports using all shared placebo controls for analyses.

8.2.2 Blinding

In this trial, investigational products may have a different mode (e.g., oral, subcutaneous, intravenous) or frequency of administration and may be introduced at different time points. Each regimen will have its own concurrent RSSP randomized placebo control arm.

Research participants, SIs, and everyone involved in the conduct of the Master Protocol, will not be blinded to the RSSP assignments but will be blinded to the randomized treatment assignments within an RSSP. The randomized treatment assigned for participants in that RSSP will be kept secure and will only be accessed according to the Unblinded Personnel List. Further details are outlined in the Medical Safety Management Plan (MSMP).

8.2.3 Emergency Unblinding

In the event of a medical emergency that necessitates the unblinding of a SI to assure safety for a participant, emergency unblinding of that single participant may be undertaken as outlined in the MSMP and EDC Manual. Every effort should be made by the SI to notify the medical monitor prior to emergency unblinding taking place. The Master Protocol PI, RSSP PI and Data Management Core will be notified of unblinding, without disclosing the treatment assignment, as soon as possible. Emergency unblinding for a research participant will only be undertaken when

it is essential to treat the participant safely. It must only be used in an emergency when the identity of the treatment arm must be known to the SI to provide appropriate medical treatment or otherwise ensure the safety of research participants or others exposed to investigational products. In most cases, investigational product discontinuation and knowledge of the possible treatment assignments will be sufficient to treat a study participant who presents with an emergency condition. However, if unblinding is necessary, the blind may be broken only for that participant.

If the blind is broken for a participant, that participant will be discontinued from the investigational product and encouraged to remain in the RSSP (See Section 8.3.1 Discontinuation of Investigational Product). Otherwise, participant must be terminated from the RSSP (See Section 8.3.2).

8.3 Discontinuation of Treatment and Terminations

8.3.1 Discontinuation of Investigational Product

A SI or designee may discontinue the investigational product for a research participant within an RSSP if a medical condition or other situation occurs such that continued intervention would not be in the best interest of the participant. Similarly, a research participant may choose to discontinue the investigational product within an RSSP at any time for any reason. However, the SI or designee will encourage the research participant to follow the SOA under the intent-to-treat principle (ITT) under the RSSP. These research participants will be encouraged to follow the study visits, off treatment, up to the Week 96 visit. At a minimum, collection of the primary endpoints, AEs, Concomitant Medications, and other outcome measures should be encouraged. If a complete visit schedule is not feasible, the participant should remain in the RSSP on a reduced in-person visit schedule. The reduced in-person schedule would require completion of at least the Week 48 and the Week 96 visits, unless otherwise specified by the RSSP. Lost to follow-up should be prevented whenever possible.

Upon discontinuation of investigational product, the research participant should return any unused product (if applicable).

For all research participants, the reason for permanent discontinuation of investigational product must be recorded in the P2P-013 EDC. These data will be included in the trial database and reported.

8.3.2 Termination of Participation in the RSSP

A research participant may withdraw consent from an individual RSSP at any time, with no justification required for the decision. Upon termination, the research participant should return any unused investigational product (if applicable). All participants will be encouraged to continue participation in the PPMI study. Relevant visits using PPMI Clinical Study data may be used for sensitivity analyses. For all research participants, the reason for RSSP termination must be recorded in the P2P-013 EDC. These data will be included in the trial database and reported.

If a participant withdraws consent from an RSSP for personal reasons or intervention-related reasons (e.g., inconvenience of the intervention, mode of administration, required assessments), the ability for the participant to be re-randomized and re-screened for another RSSP will be determined by the Master Protocol PI on a case-by-case basis. If the Master Protocol PI allows the participant to re-randomize and re-screen for another RSSP, the participant cannot be re-screened

until 120 weeks after their original date of randomization in the RSSP from which they withdrew consent.

8.3.3 Termination of Participation in the Master Protocol

A research participant may withdraw consent for study participation in the Master Protocol at any time. No justification is required for the decision.

All participants will be encouraged to continue participation in the PPMI study. If a participant terminates from the Master Protocol prior to completing their full follow-up time in an RSSP, they must be terminated in the RSSP. Relevant visits using PPMI Clinical Study data may be used for sensitivity analysis.

For all research participants, the reason for Master Protocol termination must be recorded in the P2P-013 EDC. These data will be included in the trial database and reported.

8.3.4 Termination of the Master Protocol or of the Intervention by the Investigational New Drug (IND) Holder/ Sponsor - MJFF

The IND-holder/Sponsor reserves the right to terminate the overall Master Protocol or any individual regimen at any time. If there are intervention specific criteria for terminating a regimen, they will be detailed in the RSSP.

8.4 Screen Failures and Re-assignment

Any participant who signs the Master Protocol consent form will be considered enrolled in the platform trial. If a participant fails the Master Protocol screening, at a minimum the following information should be captured in the EDC system:

- Demographics (including any prior screening identifiers)
- Reason for screen failure
- Any eligibility criteria that were assessed prior to when the research participant failed to meet an inclusion criterion or met an exclusion criterion
- Any study-related adverse events (AEs) requiring reporting after signing consent as outlined in Section 14.1

If a research participant fails to meet a Master Protocol eligibility criterion, then that participant will be considered to have screen failed and encouraged to continue participation in the PPMI study. Research participants may be re-screened for Master Protocol eligibility immediately after resolution of the disqualifying condition. If a participant is re-screened for Master Protocol eligibility, they must complete a full Master Protocol screening visit as outlined in the SOA (Table 1). In order to proceed with the Master Protocol, the research participant must qualify for all Master Protocol eligibility requirements and any additional eligibility requirements for at least one active RSSP.

If a research participant who meets Master Protocol eligibility is assigned to and consents to a regimen, but their participation in that regimen is discontinued due to screen failure, that participant may have the opportunity to be re-randomized to a different RSSP. The research participant must still meet the Master Protocol eligibility criteria in order to be re-assigned into a different regimen. Master Protocol screening determination remains valid for up to 90 days after

the Master Protocol screening visit and, during that time, the participant is able to be randomized to any available RSSP for which they meet initial screening criteria.

If a research participant is not able to re-randomize to another RSSP within the 90-day Master Protocol screening window, the participant will be required to re-screen for the Master Protocol before randomizing to another RSSP. If there have been no Master Protocol amendments and no changes to the ICF, the participant will not need to re-consent if re-screening for the Master Protocol occurs within 1 year of the original consent date. If 1 year or more has passed since the original consent date, the participant must re-consent to the Master Protocol prior to re-screening.

Any participant who elects not to consent to their assigned RSSP will not be given the opportunity to be re-randomized. Re-screening for the Master Protocol and potential re-assignment into a different regimen, if available, may occur due to the following situations:

- An RSSP is stopped early due to concerns about the safety of the intervention.
    - The research participant may be re-screened after 24 weeks from the date of study closure (or longer if required by the RSSP specific intervention).
- A research participant completes all activities in the assigned RSSP.
    - The research participant may be re-consented and re-screened to the Master Protocol 24 weeks after they complete their assigned RSSP (or longer if required by the RSSP specific intervention).
- A research participant is withdrawn due to an adverse event or is discontinued by the SI.
    - The research participant cannot be considered for re-screening until 120 weeks after their date of randomization into the original RSSP (or longer if required by the RSSP specific intervention).

9. MASTER PROTOCOL SCHEDULE OF ACTIVITIES

The P2P-013 SOA (Table 1) describes trial procedures that are common to all interventions tested in the P2P-013 Platform Trial. Each RSSP will follow these procedures and may add additional procedures as described in the corresponding RSSP.

No new data or previously collected data will be used until participants sign the Master Protocol Informed Consent Form (ICF).

Once a participant is enrolled in the P2P-013 Master Protocol, the P2P-013 SOA will be followed instead of the PPMI SOA.

9.1 Master Protocol Screening Visit

Screening evaluations will occur within 90 days prior to the Baseline Visit. Screening activities to be completed will depend on the amount of time that has passed since an assessment was previously performed as part of their last annual PPMI Clinical visit, if applicable, or their last Master Protocol screening visit (if re-screening) and is further defined in the P2P-013 SOA (Table 1). Participants identified via PPMI Online or other PPMI remote platforms, will undergo all screening activities. Before any of the screening evaluations are performed for the specific purpose of this Master Protocol, the participant must provide informed consent for this Master Protocol in compliance with Good Clinical Practice (GCP) and applicable regulatory requirements.

Collection of AE data will begin after the informed consent is signed and will continue until the participant completes their assigned RSSP, 30 days after treatment discontinuation (whichever comes first), or per the defined terms in the RSSP.

The following visits will be performed once the participant has successfully consented, has been screened and has been randomized to one of the active RSSPs.

9.2 Baseline Visit

The Baseline Visit will take place in-person after the Master Protocol screening visit and after the RSSP screening visit. For an overview of the baseline assessments, see Table 1.

9.3 Week 2 Telephone Safety Visit

This visit will take place 14 ± 3 days after the Baseline Visit via telephone. The primary objective of this visit is to collect short-term safety data after initiation of the study drug. For an overview of the assessments, see Table 1.

9.4 Week 4 Safety Visit

This visit will take place in-person approximately 28 ± 7 days after the Baseline Visit. The primary objective of this visit is to collect safety data after initiation of the study drug. For an overview of the assessments, see Table 1.

9.5 Treatment Visits

Treatment visits will be conducted every 12 weeks ± 14 days after the Baseline Visit up to 144 weeks or until 96 weeks since randomization of the last participant into the RSSP have passed, whichever comes first. Visits will be performed in person at the study clinic at Weeks 12, 24, 48, 72, 96, 120 and 144 until the participant has completed the RSSP regimen, or as necessary per the RSSP regimen. Tele visits (audio/visual if possible) will be performed at Weeks 36, 60, 84, 108 and 132 unless in-person visits are necessary at the discretion of the site investigator (SI) or per the RSSP. Tele visits will follow the same SOA as in-person visits, except for the assessments that cannot be completed remotely. Tele visits can be converted to in-person visits, and will then include some additional assessments, as clarified in Table 1.

9.6 Additional Safety Visits

Participants may have additional unscheduled visits if required for RSSP specific safety assessments. At a minimum, these visits will involve an assessment and documentation of AEs and a review and documentation of concomitant medications.

9.7 Initiation of Dopaminergic Therapy Visit

In case the participants require initiation of dopaminergic therapy for PD, an in-person visit should be scheduled prior to starting therapy. See Initiation of Dopaminergic Therapy visit in the SOA. If this visit occurs < 90 days from the next in-clinic visit, replace this visit with the next in-clinic visit and follow the SOA accordingly. The participants should be encouraged not to initiate dopaminergic therapy in between P2P-013 clinic visits.

9.8 End of RSSP Treatment Visit

If the participant completes RSSP treatment as per SOA between the annual visits, End of Treatment Visit needs to be performed. The SOA for the End of RSSP Treatment Visit will follow the schedule of Week 96 visit listed in Section 9.5, but LP and MRI do not need to be repeated at that visit unless it coincides with the annual visit.

9.9 End of RSSP Treatment Safety Call

An End of RSSP Treatment Safety Call will be completed 30 days (± 3 days) after end of treatment unless specified otherwise in the RSSP.

9.10 End of RSSP and Master Protocol

Participants will complete the RSSP after they complete up to 144 weeks in the assigned regimen specific arm or once 96 weeks since randomization of the last participant have passed (including if terminated early), whichever occurs first, and after all RSSP related activities have been completed. Participants who wish to be considered for another RSSP must re-consent and re-screen for the Master Protocol first to confirm they continue to meet all eligibility requirements. Participants who complete their assigned RSSP and do not qualify for another RSSP will complete their enrollment in the Master Protocol and continue follow-up through the PPMI study. In those cases, end of RSSP visit will serve as the end of Master Protocol visit. The RSSP will be closed once all participants have completed the follow-up period.

The end of an RSSP regimen is defined as the last Master Protocol or RSSP visit (an in-person visit, outpatient visit, phone call, or other planned method of contact) of the last participant in relation to that RSSP.

9.11 Early Termination (ET) Visit

Participants who withdraw consent or early terminate from an RSSP will be asked to be seen for an in-person RSSP Early Termination (ET) Visit and complete Week 96 assessments.

The outcome measures that are required to be collected for each RSSP, and the timing of activities for the RSSP ET Visit and End of RSSP Treatment Safety Call, will be detailed in each respective RSSP.

All participants will continue to be enrolled in the PPMI study regardless of enrollment status in the Master Protocol.

10. INVESTIGATIONAL PRODUCT

Investigational products will be provided and tested in RSSPs from different regimen partners.

The RSSP will describe the nature of the intervention and its MoA including the mode and frequency of administration, dosage, the specific target population (to be selected within the predefined subsets of the Master Protocol), additional enrollment criteria (if any), and other specific intervention-related information and assessments (safety or other assessments) that may be in addition to those outlined in the Master Protocol. At a minimum, each RSSP will include:

- A description of RSSP specific trial treatment(s), the dosage and dosage regimen of the investigational product(s) and any known safety or risk/benefit concerns, including supportive data
- A description of the dosage form, packaging, and labeling of the investigational product(s)
- A description of RSSP specific "stopping rules" or "discontinuation criteria" for individual participants, parts of RSSP, and entire RSSP
- Accountability procedures for RSSP specific investigational product(s), including the placebo control(s) and comparator(s), if any
- Maintenance of RSSP specific procedures for breaking codes
- The identification of RSSP specific data to be recorded on the associated RSSP CRFs

Each active agent will have a matching placebo control. All regimens will be compliant with the Master Protocol, which outlines the majority of all clinical, biomarker, and safety assessments, making a shared placebo control group both desirable and feasible.

Packaging and labeling will follow Good Manufacturing Practices (GMP) regulations and distributed via a central pharmacy to each site.

10.1 Investigational Product Manufacturer

Details identifying the investigational product manufacturer will be included in the corresponding RSSP.

10.2 Labeling and Packaging

Investigational product for each regimen will be provided by the regimen partner, as the drug manufacturer, and will be described in the corresponding RSSP. Packaging and labeling will follow GMP regulations.

Samples of labels will be kept with the Trial Master Files.

The participants will be instructed to return all remaining investigational product including empty package material, if applicable, to the study site. Drug accountability will be performed as described in the pharmacy manual.

Details for packaging, labeling, and re-supply will be described in the corresponding RSSP.

10.3 Acquisition and Storage

Investigational product for all interventions will be received at the study site by designated study staff, handled and stored safely and properly at the site pharmacy or other designated location, and kept in a secure location to which only the trial unblinded pharmacist (if applicable) and designated pharmacy staff have access, unless otherwise specified within the RSSP. SI and clinical staff have blinded access. Upon receipt, the investigational product will be stored according to the instructions specified on the labels. Storage conditions will be adequately monitored and temperature in the area in which the investigational product is stored will be controlled, monitored, and recorded, at a minimum daily.

In accordance with local regulatory requirements, the SI, designated site staff, or head of the medical institution (where applicable) at each site must document the amount of investigational product dispensed and/or administered to RSSP participants, the amount received from the Central Pharmacy, and the amount destroyed upon completion of the RSSP. The SI is responsible for ensuring product accountability records are maintained throughout the course of the study. The research pharmacist or designated study staff will be responsible for maintaining an accurate record of the shipment and dispensing of investigational product in a drug accountability log.

Additional investigational product specific details will be provided in the RSSP.

10.4 Destruction of Investigational Product

Details on how the investigational product will be destroyed, who is responsible for the destruction, and how long documentation will be retained at sites, will be provided in the RSSP.

10.5 Concomitant Medications

See Appendix 2. Additional details on medications that may not be taken during the trial will be included in the RSSP.

10.6 Treatment Compliance

Compliance for each treatment will be defined in the specific RSSP. In cases of non-compliance, the participant will be reminded of the importance of taking the investigational product per protocol.

10.7 Dose Adjustment Criteria

Dose adjustment criteria will be outlined in the RSSPs.

10.8 Auxiliary Medications

The following authorized and commercially available medications will be used:

- For the skin biopsy: lidocaine; for more details, see Section 12.6.
- For the lumbar puncture: according to local procedures.
- For the DAT SPECT imaging: potassium iodide or potassium perchlorate, and DaTscan solution. for more details, see Section 13.1.

MRIs will be performed according to local procedures, which could include use of authorized and commercially available sedation.

These medications will be used in accordance with the terms of their marketing authorization, except for DaTscan that is authorized for diagnostic use only; see also Section 13.1.

11. CLINICAL ASSESSMENTS

Assessments will be performed at designated time-points throughout each RSSP for clinical evaluation. In addition to the assessments evaluated below, participants will provide information

on their demographics, past medical history, as well as concomitant medication usage. Demographics will include race and ethnicity, to allow determination of possible differences in pharmacogenomic responses to treatment across races and ethnicities.

Description of the MDS-UPDRS Part III as one of the primary outcome measures is provided in Section 11.1. Refer to the PPMI Assessment and eCRF Completion Manual for a detailed description of all clinical assessments and instructions for administration.

Details of any additional specific clinical assessments required for an intervention will be reported in the corresponding RSSP.

11.1 MDS-UPDRS

The primary endpoint will involve a comparison of the MDS-UPDRS Part III score over time. The MDS-UPDRS has four parts:

- Part I (Non-motor experiences of daily living), compromising:
    - Part IA concerning behaviors that are assessed by the SI with all pertinent information from patients and caregivers
    - Part IB that is completed by the patient with or without the aid of the caregiver, but independently of the SI
- Part II (Motor experiences of daily living), designed to be a self-administered questionnaire like Part 1B, but similarly can be reviewed by the SI to ensure completeness and clarity
- Part III (Motor examination) has instructions for the rater to give or demonstrate to the patient; it is completed by the clinician rater
- Part IV (Motor complications) to be completed by the clinician rater

Once participants initiate dopaminergic medications, participants will have an assessment of the motor exam (Part III) in both the practically defined dopaminergic medications OFF (6 hours post dose per PPMI protocol) and ON (based on the participant / SI defined best ON and/or approximately 1-hour post dose) states for designated visits per the SOA. Participants will self-administer Parts IB and II but will review responses for accuracy and clarity with the SI or coordinator. Parts IA, III, and IV must be conducted by the SI or appropriately trained designee. All parts of the MDS-UPDRS will be conducted at study visits, as indicated on the SOA. Ideally, the same site staff should assess all participants in parts IA and III of the MDS-UPDRS at all study visits. Results of MDS-UPDRS Part III will not be shared with participants until the primary data for that RSSP are presented to the sponsor and regimen partner.

11.2 Digital Assessment

Digital assessments or other digital health technologies may be implemented and will be detailed in the individual RSSPs.

12. CLINICAL SAFETY LABORATORY ASSEMENTS AND BIOLOGIC RESEARCH SAMPLING

12.1 Clinical Safety Laboratory Assessments

Whole blood and urine will be collected as per SOA for the safety laboratory samples. Refer to the P2P-013 Safety Laboratory Manual for the detailed description of the biologic samples collected and the processing instructions.

12.2 Biologic Research Sampling

Whole blood, CSF, urine and skin biopsies will be collected as per SOA to conduct proteomic, metabolic, genetic and other research analyses. Refer to the PPMI Biologics Manual for the detailed description of the research biologic samples collected and the processing instructions.

12.3 Blood Samples

Whole blood may be used to obtain plasma, buffy coat, DNA, RNA, and serum.

It is strongly advised that the research blood samples are collected in a fasted state (i.e., minimum of 8 hours since last meal/food intake) to ensure the quality of samples for future analyses. If fasting is not possible, then participants should be advised to eat a low lipid diet. All research samples will be sent to a central biorepository to be stored indefinitely for research purposes. Samples will be made available to researchers to conduct analyses related to PD and other disorders per the established approval process. Participants will not receive any individual results of research analysis or testing conducted on the biologic samples until the statistical analysis on those samples is complete.

12.4 Urine

Urine will be collected to conduct analyte analyses.

12.5 Lumbar Puncture / Cerebrospinal Fluid (CSF)

The LP is performed by the SI, or another qualified clinician appointed by the SI, according to local procedures and may be conducted under fluoroscopy. An LP for the collection of 15-20 mL of CSF will be conducted for all P2P-013 participants per the P2P-013 visit schedule unless there is evidence of clinically significant coagulopathy or thrombocytopenia that would interfere with the safe conduct of the procedure. See PPMI Biologics Manual for details. Additional LPs may be conducted if required for the specific RSSP.

If an LP procedure is performed, participants will also be contacted by phone 2 to 3 business days following an LP to assess for any AEs. The CSF samples will be sent to a central biorepository to be stored indefinitely for research purposes. The CSF samples will be made available to researchers to conduct analyses related to PD and other disorders per the established approval process.

12.6 Skin Biopsy

The skin biopsy is performed by the SI, or another qualified clinician appointed by the SI. Skin biopsy will be performed as part of the P2P-013 SOA (Table 1) unless specified otherwise in the

RSSP. See PPMI Biologics Manual for details. Additional skin biopsies may be conducted if required for the specific RSSP.

If skin punch biopsy is performed, it will be done under local anesthesia (lidocaine) in the posterior neck according to the SOA. Up to two punches will be completed and the skin samples will be processed as described in the PPMI Biologics Manual and shipped to the central biorepository for storage and analysis. Samples will be analyzed to assess a skin marker of NSD severity, called phosphorylated alpha-synuclein (P-SYN). Remaining samples may be used to evaluate other proteins, analytes, or potential biomarkers. Participants will be monitored the day of the procedure for AEs. Participants will also be contacted by phone 2 to 3 business days following a skin biopsy to assess for any AEs.

13. IMAGING

13.1 Dopamine Transporter (DAT) SPECT Imaging

Refer to the PPMI SPECT Imaging Procedure Manual for a detailed description of the SPECT imaging procedures.

Participants will undergo dopamine transporter imaging to measure dopamine transporter binding using single-photon emission computed tomography (SPECT). All participants will undergo DAT SPECT imaging as per Master Protocol SOA. P2P-013 can utilize a previously acquired scan completed as part of the PPMI study provided that it was performed within the allowed time window. Please refer to the Imaging Procedure Manual for further details.

The DAT SPECT imaging procedure will be performed at the individual sites using DaTscan to target the dopamine transporter and all imaging data will be submitted for analysis to the Imaging core. DAT SPECT imaging eligibility will be determined using prespecified imaging cut-offs. DAT SPECT eligibility result will be made available to the participant's clinical site.

Women of childbearing potential must have a urine (or serum if required by the site) pregnancy test prior to injection of DaTscan. The result must be confirmed as negative prior to proceeding with the injection. Before the DaTscan injection, participants will be pre-treated with stable iodine (10 drops of a saturated solution of potassium iodide) to reduce the uptake of DaTscan by the thyroid. If the participant is allergic to iodine, then potassium perchlorate (400 mg) can be substituted for potassium iodide. Participants will be injected with up to 5 mCi of DaTscan. Within a 4-hour (+/- 30 minute) window following the injection, participants will undergo DAT SPECT imaging for approximately 30 minutes (or up to an hour if the participant moved during scanning).

Participants will be monitored by study personnel for AEs on the day that a DAT SPECT is obtained. Participants will also be contacted by phone 2 to 3 business days following the injection/scan to assess AEs.

DaTscan is being used "off-label" in P2P-013. The imaging result obtained from the scan is not intended to provide information about a clinical diagnosis and will not be shared with participants until the primary data for that RSSP are presented to the sponsor and regimen partner.

13.2 Magnetic Resonance Imaging (MRI)

Participants will undergo an MRI brain scan at the screening visit and will also undergo follow-up MRI scans as indicated in the visit schedule. P2P-013 can utilize a previously acquired scan completed as part of the PPMI study provided that it was performed within a 6-month window.

At the discretion of the SI and Imaging staff, participants who have presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin or body or any other known contra-indication to MRI may be advised not to complete a screening visit or follow-up MRI scan, but these participants may still participate in the Master Protocol.

Refer to the PPMI MRI Imaging Procedure Manual for a detailed description of the MRI imaging procedures.

14. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The AE definition and reporting procedures for this Master Protocol comply with all applicable international and local regulations and International Conference on Harmonization (ICH) guidelines.

14.1 Adverse Events (AEs)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no RSSP treatment has been administered. A TEAE is an AE that occurs following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

The SI will carefully monitor each participant throughout the enrollment period of each RSSP for AEs. Participants will be monitored for AEs from the time they provide consent to the Master Protocol through the end of the enrollment period of the RSSP or 30 days after end of treatment (whichever comes first). However, only AEs related to study procedures will be collected and reported during the period between Master Protocol consent and randomization to treatment or placebo within an RSSP. AEs, whether or not they are related to the MP or RSSP of interest, must be recorded on forms provided by the sponsor.

Examples of AEs include new conditions, worsening or pre-existing conditions, clinically significant abnormal physical examination signs (e.g., skin rash, peripheral edema, etc.), or clinically significant abnormal test results (e.g., lab values or vital signs). Stable chronic conditions (e.g., diabetes, arthritis) that are present prior to the start of the specific RSSP and do not worsen during the RSSP are NOT considered AEs. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity would be considered worsened and therefore would be recorded as AEs.

AEs are generally detected in two ways:

Clinical → symptoms reported by the participant or signs detected on examination

Ancillary Tests → abnormalities of vital signs, laboratory tests, and other diagnostic procedures

14.2 Serious Adverse Event (SAE)

An SAE is an AE that is fatal or life-threatening, or results in hospitalization, prolongation of hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. A life-threatening AE is an AE that, in the view of the SI, places the participant at immediate risk of death from the reaction, as it occurred. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Inpatient admission in the absence of a precipitating, treatment emergent, clinical adverse event is not subject to immediate reporting. For example:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE.
- Social admission (e.g., participant has no place to sleep).
- Protocol specific admission during a clinical study (e.g., for a procedure required by another study protocol).
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery).

Inpatient admission does not include the following:

- Emergency Room/Accident and Emergency/Casualty Department visits
- Outpatient/same-day/ambulatory procedures
- Observation/short-stay units
- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Custodial care facilities

14.3 Assessing Relationship to RSSP Drug & Study Procedures

An SI with appropriate expertise must make the determination of relationship to the investigational product for each AE. The SI should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product or study procedures (including imaging, LP, or skin biopsy). The assessment of the relationship of an AE to the RSSP drug or study procedures is a clinical decision based on all available information at the time the event is being documented. The following definitions of the relationship between the AE (including SAEs) drug and/or the study procedure should be considered:

- **Unrelated -** No possible relationship
    - Concomitant illness, accident, or event with no reasonable association with treatment

- The temporal relationship between study procedure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study procedure is implausible.

- **Unlikely to be Related -** Not reasonably related, although a causal relationship cannot be ruled out.
  - The reaction has little or no temporal sequence from administration of treatment, and/or a more likely alternative etiology exists.
  - While the temporal relationship between study procedure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study procedure.

- **Possibly Related -** Causal relationship is uncertain.
  - The reaction follows a temporal sequence from administration of the treatment and follows a known response pattern to treatment; the reaction could have been produced by the treatment or could have been produced by the RSSP participant's clinical state, or by other modes of therapy administered to the participant (Suspected treatment-related AE)
  - The temporal relationship between study procedure and the adverse event onset/course is reasonable or unknown, and while other potential causes may not exist, a causal relationship to the study procedure does not appear probable.

- **Probably Related –** High degree of certainty for causal relationship
  - The reaction follows a temporal sequence from administration of treatment; is confirmed by discontinuation of treatment or by re-challenge; and cannot be reasonably explained by the known characteristics of the RSSP participant's clinical state (Suspected treatment-related AE)
  - The temporal relationship between study procedure and the adverse event onset/course is reasonable and other causes have been eliminated or are unlikely.

- **Definitely Related -** Causal relationship is certain.
  - The reaction follows a reasonable temporal sequence from administration of treatment; that follows a known or expected response pattern to treatment; and that is confirmed by improvement on stopping or reducing the dosage of the treatment, and reappearance of the reaction on repeated exposure (Suspected treatment-related AE)
  - The temporal relationship between study procedure and the adverse event onset/course is reasonable and other causes have been eliminated.

If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the SAE and the investigational product is determined to be "possibly", "probably", or "definitely" related to RSSP treatment the event will be escalated to the IMM for

review that the event should be considered related to the investigational product for the purposes of expedited regulatory reporting in compliance with local regulatory requirements.

An unanticipated AE is any AE for which the specificity or severity is not consistent with the current Investigators Brochure, current Package Insert or described in the sub protocol.

An unexpected, suspected treatment-related AE is any unexpected AE for which, in the opinion of the SI or Sponsor, there is a reasonable probability that the treatment caused the event.

14.4 Recording Adverse Events

AEs spontaneously reported by the participant and/or in response to an open question from the site personnel or revealed by observation will be recorded during the RSSP at the investigational site. The AE term should be reported in standard medical terminology when possible. For each AE, the SI will evaluate and report the type of event, onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the participant to discontinue the investigational product. AEs of Special Interest will be defined within the respective drug RSSPs.

The relationship of the AE to the investigational product should be specified by the SI based on temporal relationship and his/her clinical judgment, using the definitions specified in Section 14.3.

Severity will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) grading. Refer to Appendix 4.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 14.2. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on sponsor's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the participant was discontinued from the RSSP and/or Master Protocol.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

Medications errors and study drug use outside of what is described in the protocol, including misuse and abuse of the investigational product, must be reported and recorded as defined in each RSSP.

14.5 Reporting Adverse Events

This section summarizes the procedures for eliciting reports of and for recording and reporting AEs and SAEs in the Master Protocol. Additional AE/SAE reporting and stopping rules may be included in an RSSP.

14.5.1 Adverse Event Reporting Requirements

Information about (S)AEs will be collected from the signing of consent form until the End of RSSP Treatment Safety Call. SAEs will be collected until final study visit or 30 days following the last dose of RSSP investigational product (whichever comes first). SIs and coordinators will be instructed to assess for AEs at all study visits (in person and virtual), following initiation of investigational intervention, unless defined differently in each RSSP. Adverse experiences, whether observed by the SI, or elicited from or volunteered by the participant, should be recorded in the EDC.

Any SAE should be followed until resolution or stabilization.

AEs will be reported by the site as required by the site's Institutional Review/Ethics Board.

14.5.2 Serious Adverse Event Reporting Requirements

All SAEs (related and unrelated) will be recorded in a similar manner to AEs, unless further defined in the RSSP. All SAEs must be reported by the SI within 24 hours of the first awareness of the event. The SI must enter the SAE in the EDC and there will be a notification alert sent to all relevant team members.

As a backup the SI can complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and notify the safety department.

A Medical Monitor (MM) will work closely with the site to obtain additional follow-up information, if required or available. As additional information is obtained, one or more follow-up SAE forms should be completed. SAE notifications will be provided to the sponsor MJFF and INDD, Inc.

Both the P2P-013 sponsor and the pharma partner have shared legal responsibility to notify the relevant reviewing bodies about the safety of a study treatment under clinical investigation. The P2P-013 sponsor and pharma partner will comply with country specific regulatory requirements relating to safety reporting. If required per local regulations, it is the SI's responsibility to notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. SIs of the relevant RSSP will also be notified of all suspected unexpected serious adverse reactions (SUSARs) that occur during the RSSP.

14.6 Medical Monitor (MM) and Independent Medical Monitor (IMM)

Detailed description of study safety monitoring will be outlined in the MSMP and specific RSSP.

Medical Monitor
At least one MM will be appointed for this Master Protocol. The MM is the assigned physician or designee responsible for coordinating all activities related to the medical monitoring of the specified study. The role of the MM is to ensure the:

- Safety and welfare of participants are carefully monitored
- Clinical trial is conducted, recorded, and reported in accordance with the protocol and GCP
- Data resulting from the trial are valid and reliable

The MM will interact with all sites to ensure that sites collect as much information as possible for all reported AEs and SAEs. The MM will review all reported SAEs, AEs deemed to be severe, and AEs deemed to be treatment-related by the site in near real-time in order to evaluate them to identify the need for expedited reporting and notify IMM. The MM will conduct protocol safety training and address any safety related questions from the contract research organization (CRO), study monitors, and other project team members.

Independent Medical Monitor

A designated independent medical monitor (IMM) will be appointed for the study. The IMM offers external, unbiased review of safety data. The IMM will be responsible for determining causality, relatedness for SAEs, review of cumulative safety data, including assessment of AEs, SAEs, and SUSARS (unblinded). The IMM would support the Data Monitoring Committee if needed. The IMM will not have any contact with the regular study team.

The IMM will be notified for any reportable SAEs to prompt a review of the event for seriousness, causality, expectedness, and additional factors which may affect reporting responsibilities. The IMM will review the SAE within 24 hours of receipt notification.

14.7 Data and Safety Monitoring Board (DSMB)

An independent DSMB, consisting of independent experts who will review and evaluate safety data, will be assembled for the trial. A DSMB Charter will detail the processes of this group. The DSMB will receive blinded and unblinded summary reports, as specified in the DSMB Charter, consisting of the following topics:

- Performance Monitoring: A report of participant recruitment, comparison with targeted recruitment, retention, protocol adherence, and quality of data collection procedures.
- Treatment Monitoring: The DSMB will be provided data on treatment integrity and adherence.
- Safety Monitoring: The DSMB will examine data related to safety of all Master Protocol participants, including all AEs related to each RSSP study treatment. This includes a summary of the MM's quarterly reviews since the prior DSMB meeting.

Reports will be provided for each RSSP at planned periodic meetings throughout the RSSP as specified in the DSMB Charter. The DSMB will receive separate reports per trial intervention specific RSSPs to review independently. These reports will contain data comparing the intervention to all concurrent placebo controls and the regimen specific placebo controls for that RSSP. The DSMB will also review data on the conduct of the Master Protocol. Meetings will be held in-person or via teleconference, depending on the preference of the DSMB Chair.

As necessary, the DSMB can review the frequencies of clinical and laboratory abnormalities. Recommendations for modification or termination of the RSSP based on safety data will be made by the DSMB to the sponsor. The DSMB will review safety data throughout the trial and may recommend stopping enrollment into a treatment arm if safety concerns arise that lead them to determine that there is a significant difference in the rate of a particular AE that would indicate a risk that is greater than the possible benefit of the investigational product. A notable increase in the frequency of any AE should be examined by the DSMB, although it may not lead to a recommendation.

Complete information can be found in the DSMB Charter.

15. STATISTICS

The P2P Statistics Core will develop a Statistical Analysis Plan (SAP), in collaboration with the Master Protocol Principal Investigator, Steering Committee, and partners with Berry Consultants. The SAP and accompanying appendix will include a detailed description of the statistical analyses that will be employed for this study. A brief discussion of the analyses of the primary and secondary endpoints is provided below. All analyses will be conducted using either R or SAS version 9.4 by the study biostatistician(s).

Each RSSP in the P2P-013 trial will include a concurrent placebo control that is appropriate to the IMP(s) associated with that RSSP based on formulation, route of administration and dosing regimen with the intention of pooling all placebo data across regimens to produce a single placebo control dataset for analyses. Importantly, there are four types of controls for each RSSP primary analysis:

- **RSSP Concurrent Placebo Controls:** Placebo controls used within a particular RSSP
- **Concurrent Placebo Controls:** Placebo controls enrolled within a separate RSSP during the time period that a given RSSP was open to enrollment
- **Non-concurrent Placebo Controls:** Placebo controls enrolled within separate RSSPs during the time period prior to the initiation of enrollment within a given RSSP
- **Concurrent Non-Randomized Controls:** Participants who were thought to be potentially eligible for P2P-013 during the conduct of the RSSP but were not enrolled (see SAP for further details).

15.1 Primary Endpoints and Analyses

Primary Scientific Question: Does the treatment slow the rate of progression in DAT SPECT mean putamen SBR or MDS-UPDRS Part III score for those with NSD Stage 2B?

Primary Endpoints. To explore this question from the perspective of a biomarker and a clinical measure of symptom worsening, there are two primary endpoints: (a) DAT SPECT mean putamen SBR across time and (b) MDS-UPDRS Part III score across time. Both endpoints are measured for a minimum of 96 weeks for each participant, and up to 144 weeks or until 96 weeks since randomization of the final participant have passed in the assigned RSSP, whichever comes first. This results in greater than 96 weeks of follow-up on participants randomized earlier in enrollment.

Primary Analyses. The Bayesian primary analysis models estimate a difference in the rate of change of each primary endpoint from baseline through last visit, comparing active treatment versus a shared group consisting of RSSP concurrent placebo controls, concurrent placebo controls, non-concurrent placebo controls, and concurrent non-randomized controls. Each primary endpoint will be tested with equal priority with respect to active treatment superiority versus shared concurrent and non-concurrent placebo controls.

For both primary endpoints, a Bayesian repeated measures model of mean outcome will be used to compare the slope of active treatment versus a shared group consisting of RSSP concurrent placebo controls, concurrent placebo controls, non-concurrent placebo controls, and concurrent non-randomized controls. The model allows for heterogeneity across individual baseline values

and individual slopes, as well as heterogeneity across regimens due to minor differences in the inclusion/exclusion criteria or mode of administration.

For each endpoint, if the Bayesian posterior probability of active treatment superiority (H_a) is greater than or equal to a prespecified threshold of 0.90, the null hypothesis will be rejected, and the active treatment will be deemed superior to placebo control (i.e., less progression) with respect to mean endpoint. This decision threshold of 0.90 has been calibrated via simulation to control the regimen-specific one-sided type I error at approximately 10% per regimen.

1) **DAT SPECT Mean Putamen SBR.**

It is hypothesized that an effective treatment will decrease the progression rate and slow the decline in mean putamen SBR. A greater negative slope indicates a greater reduction in the biomarker and a greater progression rate. The following hypothesis test for a difference in slopes between active treatment and placebo control groups will be conducted using the Bayesian posterior distribution.

H_0: The active treatment group's average mean putamen SBR progression is equal to or less than that of the shared control arm.

H_a: The active treatment group's average mean putamen SBR progression is less than that of the shared control arm

2) **MDS-UPDRS Part III score.**

It is hypothesized that an effective treatment will decrease the progression rate and slow the increase in symptoms as measured by MDS-UPDRS Part III score. A greater positive slope indicates faster symptom accumulation and a greater progression rate. The following hypothesis test for a difference in slopes between active treatment and placebo control groups will be conducted using the Bayesian posterior distribution.

H_0: The active treatment group's average MDS-UPDRS Part III slope is equal to or greater than that in the shared control arm.

H_a: The active treatment group's average MDS-UPDRS Part III slope is less than that of the shared control arm

15.2 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 J ($\leq$ K) eligible regimens 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 RSSP active treatment or placebo control.

15.3 Sample Size Considerations

Overall platform trial sample size is based on the number of regimens. The sample size for each regimen will include 125 participants on active treatment, at least 125 shared concurrent and non-concurrent placebo control participants, and concurrent non-randomized participants providing

data from the PPMI study. To allow for uncertainty regarding the number of concurrent non-randomized participants available for any given RSSP analysis, we considered a range from none to 100 concurrent non-randomized controls when assessing power. To further assess the required sample size, analyses were conducted using the observational prodromal cohort of participants in PPMI Clinical who meet NSD Stage 2B criteria and all eligibility criteria for the Master Protocol (based on a download of the PPMI data from September 2025). Summaries of the two-year decline in this PPMI Clinical natural history data are included in Table 4 below. These data were used to inform assumptions for simulating virtual participant outcomes for longitudinal DAT SPECT mean putamen SBR and longitudinal MDS-UPDRS Part III.

Table 4: Two-Year Decline in Primary Endpoints by PPMI Clinical Natural History Cohort

Endpoint	Prodromal Cohort (N = 275)
Mean Putamen SBR	-0.06 (0.21)
MDS-UPDRS Part III	2.6 (5.3)

For a 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 placebo controls, non-concurrent placebo controls, and concurrent non-randomized 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. Table 5 demonstrates the average probability of success for the first three regimens under various assumed true values for the change on each endpoint. The regimens in the platform are estimated to have between 62%-63% and 77%-80% power to detect treatment effects when both of the endpoints achieve 30% and 40% slowing of progression, respectively. 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. Finally, 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. The table also demonstrates that 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%. For more details about the operating characteristics for each regimen and the assumptions used to calculate power, refer to the Design Report Appendix in the P2P-013 SAP.

Table 5: Overall RSSP Power (Win on Either Endpoint)

UPDRS Slowing	DAT Slowing	Power
0%	0%	18%
0%	30%	47%-49%
0%	40%	57%-59%%
0%	50%	71%-73%%

UPDRS Slowing	DAT Slowing	Power
30%	0%	41%-45%
30%	30%	62%-63%
30%	40%	71%-74%
30%	50%	79%-81%
40%	0%	53%-56%
40%	30%	69%-71%
40%	40%	77%-80%
40%	50%	84%-87%
50%	0%	65%-69%
50%	30%	78%-81%
50%	40%	83%-87%
50%	50%	89%

15.4 Missing Data and Sensitivity Analyses

The primary analysis will include all randomized participants analyzed in the treatment group to which they were initially assigned. Thus, a participant who has partial visit data (less than 96 weeks) may still be included in the primary analyses and it will be critically important to minimize the occurrence of missing data. Obviously, the optimal strategy for dealing with missing data is to make every effort to obtain complete data during the conduct of each RSSP. Our team will work diligently and use a variety of methods to minimize the percentage of missing data in each RSSP. Nevertheless, there is likely to be a small percentage of missing data. We will employ strategies to mitigate and then assess the impact of missing data within each RSSP.

To further assess the potential dependence of the results of the primary analysis on these missing values, a series of sensitivity analyses may be conducted as specified within each sub protocol. For participants that do not provide complete data, we will analyze using the following strategies:

- Shared Placebo Controls: Comparison of RSSP treatment group to shared group consisting only of RSSP placebo controls, concurrent placebo controls, and non-concurrent placebo controls (i.e., concurrent non-randomized controls excluded).
- Supplemented ITT Analysis: Any PPMI Clinical Data collected at annual visits during the 96-week window that map into missing data for P2P-013 participants will be added to the primary model.
- Last Observation Carried Forward: Missing values will be imputed using the participant's last observed data value.
- Multiple Imputation: Two different imputation methods (described below) will be used.

- Multiple Imputation w/ Treatment-Based Imputation: Under this model, missing data are assumed to follow the same pattern as the respective treatment, age, gender, and baseline value complete data. Missing data will be imputed using a regression approach. If needed, Monte Carlo Markov Chain methodology will be used to impute missing values to obtain a monotone missing data pattern.
- Pattern-Mixture Model with Placebo Control-Based Imputation: Under this model, RSSP treatment participants with missing data are assumed to follow the same trajectory as placebo control participants. Data from placebo control participants only will be used to impute all missing data (from both RSSP treatment and placebo control participants) using the full conditional specification regression method.

The results of these analyses will provide valuable information regarding the sensitivity of the findings to the missing data and will be critical in assessing the full value of the RSSP results.

15.5 Analysis Populations

Intent-to-Treat All Controls Population: The primary analyses for each analysis regimen will be based on the ITT principle and includes all participants randomized to the active treatment arm of the analysis regimen and all shared controls (RSSP placebo, concurrent placebo, non-concurrent placebo, and concurrent non-randomized), regardless of the adherence to the assigned RSSP or duration of follow-up. The analysis shared placebo control groups include all participants randomized to any placebo control arm within any RSSP from the start of the Master Protocol to the end of randomization for the specific RSSP of interest. All data gathered before the regimen's primary analysis date will be included in the regimen's primary analysis unless otherwise agreed upon and noted in the RSSP.

Intent-to-Treat All Placebo Controls Population: Sensitivity primary analyses for each analysis regimen will include all participants randomized to the active treatment arm of the analysis regimen and all shared placebo controls (non-concurrent, concurrent, and RSSP concurrent), regardless of the adherence to the assigned RSSP or duration of follow-up.

Intent-to-Treat Concurrent Controls Population: All secondary analyses will utilize an ITT population that consists of all participants randomized to the active treatment arm and all concurrent shared placebo control participants randomized to any RSSP within the MP during the time period randomization was active for the RSSP of interest. This population will also be used to conduct sensitivity analyses for the primary analyses.

Intent-to-Treat RSSP Controls Population: Further sensitivity analyses will be conducted using an ITT population that consists only of participants randomized to the active treatment and placebo control within the RSSP of interest.

Per-Protocol (PP) Population: To assess the sensitivity of the results, and to obtain knowledge regarding potential effects when the protocol was strictly adhered to, we will also replicate the primary objective using a PP population. The PP population includes the subset of all ITT RSSP participants who satisfy the following conditions:

- Have satisfactory compliance to assigned treatment, as specified in the RSSP
- Have no major protocol deviations due to "protocol compliance" (defined as any alteration/modification that has the potential to negatively impact participant safety,

integrity of the RSSP, ability to draw conclusions from RSSP data, or affect the participant's willingness to participate in the RSSP)

Only data collected as part of the RSSP will be included in the per-protocol analysis (i.e., no concurrent or non-concurrent placebo controls).

15.6 Interim Analyses

Considering the objectives and nature of this Master Protocol, collecting safety, tolerability, and feasibility data for the full duration of each RSSP as well as the wide spectrum of exploratory endpoints are important for the RSSP objectives. As such, no interim efficacy or futility analyses will be conducted.

15.7 Safety Endpoint

Analyses to examine safety of each active treatment versus RSSP placebo controls will involve comparisons of the percentage of participants within each RSSP reporting at least one treatment emergent AE during the RSSP. This will be assessed via chi-square tests. Analyses will be repeated to compare the frequency of AEs within each MedDRA system organ class (SOC). If there are significant differences between groups within any specific SOC, then additional tests will compare differences across groups for specific MedDRA preferred terms in order to further explore the cause of the observed difference. Additional analyses will assess treatment emergent SAEs, treatment-related SAEs, and unanticipated SAEs in a comparable manner.

15.8 Secondary Endpoints

15.8.1 Feasibility

No formal analyses are specified for this secondary objective. However, key feasibility metrics such as enrollment timelines, retention, and visit compliance will be tracked throughout each RSSP.

15.8.2 Tolerability

The assessment of tolerability will examine the percentage of participants on treatment vs RSSP placebo control group (within each RSSP) who complete the full RSSP on their initially actively assigned treatment regimen. Participants who withdraw from treatment early will be counted as having not tolerated treatment, whether the withdrawal was due to an AE or not. The percentage meeting the tolerability definition within each group will be assessed via chi-square tests or logistic regression models.

15.9 Key Exploratory Endpoints

15.9.1 Progression to NSD Stage 3 or Higher

A key exploratory endpoint will assess whether there are group differences that exist in the rate at which participants progress from NSD Stage 2B to NSD Stage 3 or higher. The outcome of interest will be the time (visit) at which a participant first meets NSD Stage 3 or higher criteria. Participants who remain stage 2B throughout the RSSP will be censored at the last observed visit. Kaplan-Meier curves and a log-rank test, stratified by baseline MDS-UPDRS Part III score strata, will be used to compare the groups.

15.9.2 Change from Baseline in MDS-UPDRS Total and Part I & II Subscores

All three of these analyses will proceed in the same manner as the primary analysis specified for the MDS-UPDRS Part III score, as specified in Section 15.9.1. The only difference will be that the outcome is modified accordingly.

15.9.3 Change in Cognition

The change in cognition key exploratory endpoint will be defined by whether a participant develops new syndromes of MCI or dementia. Participants who never develop a new syndrome will be censored at their last observed visit. Time-to-event analyses will be implemented in the same manner specified in Section 15.9.1.

15.9.4 Change in Functional Status

The change in functional status key exploratory endpoint will be assessed by examining changes across treatment groups in the PDAQ-27 using a model similar to that specified in Section 15.9.1.

15.9.5 Time to Progression Milestones

The time to progression milestones key exploratory endpoint will be assessed by measuring the time that a participant first meets a progression milestone as defined in by Brumm et al[36]. Participants who never meet a milestone will be censored at their last observed visit Time-to-event analyses will be implemented in the same manner as specified in Section 15.9.1.

16. ETHICS/PROTECTION OF HUMAN SUBJECTS

16.1 Ethical Conduct of the Master Protocol

The overall study and each regimen will be conducted in accordance with the Master Protocol and the relevant accompanying RSSP, and in accordance with GCP defined by the ICH, the ethical principles of the Declaration of Helsinki, the European Clinical Trial Regulation 536/2014 (as applicable, depending on the countries involved), and any other international and local regulations.

The Master Protocol, RSSP, and any amendments to either document as well as the participant informed consents will not be implemented before applicable full regulatory approval is received.

Personnel involved in conducting this Master Protocol will be qualified to perform their respective task(s) as confirmed by the site and collection of required documentation.

This Master Protocol will not use the services of personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

16.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

This overall study and each regimen will be conducted in compliance with Title 21 Part 56 of the United States of America Code of Federal Regulations (CFR) relating to IRBs, regulatory requirements provided via the European Clinical Trial Regulation 536/2014, and requirements from local ECs, as regionally applicable.

Before study initiation, the SI must have full approval from the relevant reviewing bodies for the protocol, consent form, and participant recruitment materials/process (e.g., advertisements), and,

where applicable according to local regulations, for any other written information to be provided to participants.

The reviewing bodies should be provided with reports, updates, and other information (e.g., Safety Updates, Amendments, Administrative Letters) according to regulatory requirements or institution procedures.

16.3 Participant Information & Informed Consent

The overall study and each regimen will be conducted in compliance with Title 21 Part 50 of the United States of America CFR, regulatory requirement provided via the European Clinical Trial Regulation 536/2014, as regionally applicable, and ICH Guidance Documents pertaining to informed consent.

At the first visit, prior to initiation of any Master Protocol-related procedures, participants will be informed about the nature and purpose of the Master Protocol, participation/termination conditions, and risks and benefits. Participants will be given adequate time to ask questions and become familiar with the Master Protocol prior to providing consent to participate. Participants will give their documented informed consent to participate in the Master Protocol and will be provided with a copy of the fully executed Master Protocol consent form for their records. Participants meeting Master Protocol eligibility criteria will be randomly assigned to an actively enrolling RSSP.

Participants will then be informed about the intervention specific to their assigned RSSP and any participation/termination conditions or risks and benefits specific to that regimen as per RSSP protocol. Participants meeting additional eligibility criteria required by their assigned RSSP, if any, will be randomized in a *K*:1 ratio to receive either active treatment or matching placebo control in that RSSP.

In some situations, an individual may be re-assigned to multiple different regimens, if eligible. The procedures detailing the re-assignment process can be found in Section 8.4.

16.4 Participant Withdrawal Criteria

Master Protocol participants will be informed during the consent process that they have the right to withdraw from the Master Protocol at any time without prejudice and may be withdrawn at the SI's or Sponsor's discretion at any time. Any information that has already been collected prior to the participant's withdrawal will not be removed.

Considering that P2P-013 is a Master Protocol for a platform study that determines participation in the RSSP, and all eligible participants are enrolled in PPMI study, withdrawal criteria and rules for termination may apply to different scenarios as outlined in Section 8.

If premature withdrawal occurs for any reason, the SI must make every effort to determine the primary reason for a participant's premature withdrawal from the study and document this information in the study source. The SI will encourage the participant to remain enrolled in the PPMI study.

For participants who are lost to follow-up (i.e., those participants whose status is unclear because they fail to appear for RSSP visits without stating an intention to withdraw), the SI should show

due diligence by documenting attempts to contact the participant, e.g., dates of telephone calls, registered letters, or other attempts to communicate.

16.5 Changes in Conduct of the Master Protocol

16.5.1 Protocol Amendments

Any change to the Master Protocol will be documented in a protocol amendment, issued by the sponsor. Master Protocol amendments will be submitted for approval to the relevant reviewing bodies prior to implementation in accordance with local regulations. Written informed re-consent for continued participation in the Master Protocol may be required by participants already enrolled in the Master Protocol.

As additional RSSPs are added to the platform trial, they will be submitted for approval to the relevant reviewing bodies prior to implementation. Each RSSP will be added to the Master Protocol prior to any participant being assigned to that intervention. Addition of RSSPs will not require re-consent to the Master Protocol. RSSPs that are stopped early will not result in an amendment to the Master Protocol.

16.5.2 Premature Termination of a Master Protocol Site

The sponsor reserves the right to terminate the participation of individual Master Protocol sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter participants at an acceptable rate.

16.5.3 Protocol Adherence

Each SI must adhere to the Master Protocol detailed in this document and agree that any changes to the protocol must be approved by the relevant reviewing bodies. Each SI will be responsible for enrolling into the Master Protocol only those participants who have met all Master Protocol eligibility criteria, and for enrolling into a subprotocol only those participants who have met the additional eligibility criteria (if any) of the corresponding RSSP.

17. DATA HANDLING AND RECORD KEEPING

17.1 Inspection of Records

Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of this Master Protocol. Data generated by this Master Protocol must be available for inspection by representatives of the USA FDA, the Office for Human Research Protections, the sponsor, all pertinent national and local health and regulatory authorities, Master Protocol monitoring personnel, and the cIRB/relevant IEC.

17.2 Master Protocol Monitoring

Before an investigational site can enter a participant into the Master Protocol, a monitor from the sponsor (MJFF), its representative or designee will confirm site qualification was performed for the existing PPMI site or if requalification is necessary, the following will be performed:

- Determine the adequacy of the facilities

- Discuss with the SI(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of MJFF or its representatives.

During the Master Protocol, a monitor from the sponsor or representative will have regular contact with the investigational site, including for example the following:

- Provide information and support to the SI(s) and Master Protocol Principal Investigator (PI)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participants medical records at the hospital or SI's practice, and other records relevant to the Master Protocol and/or assigned RSSP. This will require direct access to all original records for each participant (e.g., clinic charts)
- Record and report any PDs not previously sent to MJFF or its representatives
- Confirm AEs and SAEs have been properly documented in the CRFs and confirm any SAEs have been forwarded to MJFF or its representatives and those SAEs that met criteria for reporting have been submitted to the applicable reviewing bodies
- Review SI regulatory files to ensure the Trial Master File is current

The monitor will be available between visits if the SI(s) or other staff need information or advice.

17.3 Privacy and Confidentiality

Privacy of participants will be protected in that each person will have the option to voluntarily choose whether to participate in this Master Protocol per the ICF, which defines data privacy in detail. The sponsor complies with all relevant and applicable laws and regulations, including the European General Data Protection Regulation [2016/679] and the UK General Data Protection Regulation and Data Protection Act 2018, that protect personal information to ensure participant confidentiality and privacy. It is the responsibility of the SI to consider the participant's privacy and confidentiality when completing study visits and related protocol activities. In case of a data breach, this will be reported and handled in accordance with international and local regulations.

The SI must assure that the confidentiality of participants, including their personal identity and personal medical information, will be maintained at all times. U.S. sites have additional confidentiality obligations to participants under the Health Insurance Portability and Accountability Act (HIPAA). Participants will be identified by a unique participant ID and other Master Protocol study materials submitted to the central laboratory, and central biorepository.

The SI will permit the designated team member to review signed informed consent(s) and that portion of the participant's medical record that is directly related to the Master Protocol (or provide certified copies of source documentation upon request). This shall include all Master Protocol relevant documentation including participant medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the participant is in the Master Protocol, and autopsy reports for deaths occurring during an RSSP

within the Master Protocol (when available). In addition, electronic document storage will be maintained within the electronic trial master file. Identifiable participant information may be stored within this system, which meets 21 CFR Part 11 requirements. Only site staff requiring access to related Master Protocol documentation will have permission to view identifiable information.

As part of the PPMI, each participant will have been assigned a unique participant identifier. Any participant records or datasets that are transferred to the sponsor will contain this identifier only; participant names or any information that would make the participant identifiable will not be transferred. The key to the unique participant identifiers will be stored at a secure location at the site.

The participant will be informed that his/her personal study-related data will be used by the sponsor in accordance with applicable data protection laws and regulations. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities, as applicable according to international and local regulations.

17.4 Data and Sample Sharing and Storage for Future Use

Additional data collected for this Master Protocol will be maintained and stored on secure, password protected system(s), as per the PPMI data policy. All Master Protocol information (data and samples) will be accessed only by those who require access as pertains to the individual's role on the Master Protocol. All organizations responsible for data storage and review will observe the highest precautions to ensure data integrity and security.

Data and sample sharing policies will be specified in the P2P Data Sharing Policy and legal agreements governing the trial, as applicable. Samples will be stored indefinitely and may be used for further analyses that are part of the PPMI trial, this Master Protocol or the relevant RSSP.

17.5 Retention of Records

The SI must maintain all documentation relating to the Master Protocol for minimally a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the RSSP drugs for investigation, or longer if required per RSSP. If it becomes necessary for the sponsor or the Regulatory Authority to review any documentation relating to the Master Protocol or an accompanying RSSP, the SI must permit access to such records.

17.6 Publication Policy

The P2P Steering Committee will set the policy for publication of results from the P2P-013 Trial and all RSSPs. Refer to P2P Publication and Data Sharing policies for further details.

18. LIST OF REFERENCES

1. Brumm MC, Siderowf A, Simuni T, et al. Parkinson's Progression Markers Initiative: A Milestone-Based Strategy to Monitor Parkinson's Disease Progression. J Parkinsons Dis 2023;13:899-916.
2. Simuni T, Chahine LM, Poston K, et al. A biological definition of neuronal alpha-synuclein disease: towards an integrated staging system for research. Lancet neurology 2024;23:178-190.
3. Dam T, Pagano G, Brumm MC, et al. Neuronal alpha-Synuclein Disease integrated staging system performance in PPMI, PASADENA, and SPARK baseline cohorts. NPJ Parkinsons Dis 2024;10:178.
4. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591-1601.
5. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113-1124.
6. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017;89:88-100.
7. Dorsey ER, Sherer T, Okun MS, Bloem BR. The Emerging Evidence of the Parkinson Pandemic. J Parkinsons Dis 2018;8:S3-S8.
8. Obeso JA, Stamelou M, Goetz CG, et al. Past, present, and future of Parkinson's disease: A special essay on the 200th Anniversary of the Shaking Palsy. Mov Disord 2017;32:1264-1310.
9. Espay AJ, Lang AE. Parkinson Diseases in the 2020s and Beyond: Replacing Clinico-Pathologic Convergence With Systems Biology Divergence. J Parkinsons Dis 2018;8:S59-S64.
10. Fairfoul G, McGuire LI, Pal S, et al. Alpha-synuclein RT-QuIC in the CSF of patients with alpha-synucleinopathies. Ann Clin Transl Neurol 2016;3:812-818.
11. Siderowf A, Concha-Marambio L, Lafontant D-E, et al. Assessment of heterogeneity and disease onset in the Parkinson’s Progression Markers Initiative (PPMI) cohort using the α-synuclein seed amplification assay: a cross-sectional study. Lancet Neurol 2023;22:407-417.
12. Bellomo G, De Luca CMG, Paoletti FP, Gaetani L, Moda F, Parnetti L. α-Synuclein Seed Amplification Assays for Diagnosing Synucleinopathies: The Way Forward. Neurology 2022;99:195-205.
13. Brockmann K, Quadalti C, Lerche S, et al. Association between CSF alpha-synuclein seeding activity and genetic status in Parkinson's disease and dementia with Lewy bodies. Acta Neuropathol Commun 2021;9:175.
14. Rossi M, Candelise N, Baiardi S, et al. Ultrasensitive RT-QuIC assay with high sensitivity and specificity for Lewy body-associated synucleinopathies. Acta Neuropathol 2020;140:49-62.

15. Grossauer A, Hemicker G, Krismer F, et al. α-Synuclein Seed Amplification Assays in the Diagnosis of Synucleinopathies Using Cerebrospinal Fluid-A Systematic Review and Meta-Analysis. Mov Disord Clin Pract 2023;10:737-747.
16. Sardi SP, Cedarbaum JM, Brundin P. Targeted Therapies for Parkinson's Disease: From Genetics to the Clinic. Mov Disord 2018;33:684-696.
17. Berg D, Crotty GF, Keavney JL, Schwarzschild MA, Simuni T, Tanner C. Path to Parkinson Disease Prevention: Conclusion and Outlook. Neurology 2022;99:76-83.
18. Mestre TA, Fereshtehnejad SM, Berg D, et al. Parkinson's Disease Subtypes: Critical Appraisal and Recommendations. J Parkinsons Dis 2021;11:395-404.
19. Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535-562.
20. Tabrizi SJ, Schobel S, Gantman EC, et al. A biological classification of Huntington's disease: the Integrated Staging System. Lancet Neurol 2022;21:632-644.
21. NIA-AA Revised Clinical Criteria for Alzheimer's Disease [online]. Available at: https://aaic.alz.org/downloads2023/NIA-AA-Revised-Clinical-Criteria-AAIC-2023.pdf. Accessed August 9.
22. Marek K, Chowdhury S, Siderowf A, et al. The Parkinson's progression markers initiative (PPMI) - establishing a PD biomarker cohort. Ann Clin Transl Neurol 2018;5:1460-1477.
23. Parkinson Progression Marker I. The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol 2011;95:629-635.
24. Caspell-Garcia C, Simuni T, Tosun-Turgut D, et al. Multiple modality biomarker prediction of cognitive impairment in prospectively followed de novo Parkinson disease. PLoS One 2017;12:e0175674.
25. Chahine LM, Brumm MC, Caspell-Garcia C, et al. Dopamine transporter imaging predicts clinically-defined alpha-synucleinopathy in REM sleep behavior disorder. Ann Clin Transl Neurol 2021;8:201-212.
26. Mollenhauer B, Caspell-Garcia CJ, Coffey CS, et al. Longitudinal analyses of cerebrospinal fluid alpha-Synuclein in prodromal and early Parkinson's disease. Mov Disord 2019;34:1354-1364.
27. Simuni T, Caspell-Garcia C, Coffey CS, et al. Baseline prevalence and longitudinal evolution of non-motor symptoms in early Parkinson's disease: the PPMI cohort. Journal of neurology, neurosurgery, and psychiatry 2018;89:78-88.
28. Weintraub D, Simuni T, Caspell-Garcia C, et al. Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. Mov Disord 2015;30:919-927.
29. Chahine LM, Iranzo A, Fernandez-Arcos A, et al. Basic clinical features do not predict dopamine transporter binding in idiopathic REM behavior disorder. NPJ Parkinsons Dis 2019;5:2.
30. Chahine LM, Urbe L, Caspell-Garcia C, et al. Cognition among individuals along a spectrum of increased risk for Parkinson's disease. PLoS One 2018;13:e0201964.

31. Chahine LM, Xie SX, Simuni T, et al. Longitudinal changes in cognition in early Parkinson's disease patients with REM sleep behavior disorder. Parkinsonism Relat Disord 2016;27:102-106.
32. Irwin DJ, Fedler J, Coffey CS, et al. Evolution of Alzheimer's Disease Cerebrospinal Fluid Biomarkers in Early Parkinson's Disease. Annals of neurology 2020;88:574-587.
33. Kang JH, Irwin DJ, Chen-Plotkin AS, et al. Association of cerebrospinal fluid beta-amyloid 1-42, T-tau, P-tau181, and alpha-synuclein levels with clinical features of drug-naive patients with early Parkinson disease. JAMA Neurol 2013;70:1277-1287.
34. Kang JH, Mollenhauer B, Coffey CS, et al. CSF biomarkers associated with disease heterogeneity in early Parkinson's disease: the Parkinson's Progression Markers Initiative study. Acta Neuropathol 2016;131:935-949.
35. Siderowf A, Concha-Marambio L, Lafontant DE, et al. Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using alpha-synuclein seed amplification: a cross-sectional study. Lancet neurology 2023;22:407-417.
36. Saville BR, Berry SM. Efficiencies of platform clinical trials: A vision of the future. Clin Trials 2016;13:358-366.
37. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med 2017;377:62-70.

Appendix 1: Medications to Hold Prior to DaTscan

The following medications can interfere with the read out of DaTscan. These medications should be held for at least five half-lives before DAT SPECT imaging if the participant is willing and medically able to do it.

Drug Class	**Hold Time**
Methylphenidates	
Methylphenidate (CONCERTA) *(long acting/ slow release)*	18 Hrs
Methylphenidate (DAYTRANA) *(transdermal patch)*	20 Hrs
Methylphenidate (METHYLIN)	14 Hrs
Methylphenidate hydrochloride (RITALIN)	48 Hrs
Amphetamine Derivatives	
Amphetamine-dextroamphetamine (ADDERALL)	48 Hrs
Lisdexamfetamine (VYVANSE)	48 Hrs
Pseudoephedrine (SUDAFED)	24 Hrs
Armodafinil (NUVIGIL)	72 Hrs
Modafinil (PROVIGIL)	72 Hrs
Phentermine (LOMAIRA, ADIPEX-P)	5 Days
Bupropion (WELLBUTRIN)	24 Hrs

Appendix 2: Medications: Exclusionary and Precautions

Exclusionary Drugs (at Screening/Baseline)	
Class	**Specific examples**
Levodopa replacement therapy	• Carbidopa/ levodopa (SINEMET) • Carbidopa/ levodopa CR (SINEMET CR, RYTARY) • Carbidopa/ levodopa/ entacopone (STALEVO) • Carbidopa/ levodopa dual-release (MADOPAR DR) Levodopa inhaler (INBRIJA) • Carbidopa/ levodopa enteral infusion (DUOPA, DUODOPA, LECIGON) • Subcutaneous foslevodopa/ foscarbidopa (VYALEV) • Mucuna Pruriens (*herbal supplement*)
Dopamine Agonists	• Apomorphine (KYNMOBI, APOKYN, APO-GO PEN BROMOCRIPTINE) • Cabergoline (CABASER, DOSTINEX) • Pergolide (PERMAX) • Piribedil (PRONORAN, TRIVASTAL RETARD, TRASTAL, TRIVASTAN, CLARIUM) • Pramipexole (MIRAPEX, MIRAPEX ER) • Ropinirole (REQUIP, REQUIP XL) • Rotigotine (NEUPRO)
Dopamine depleting agents	• Reserpine • Tetrabenazine (TBZ, XENAZINE) • Deutetrabenazine (DBZ, AUSTEDO) • Valbenazine (VBZ, INGREZZA)
Cholinesterase inhibitors	• Donepezil (ARICEPT, ARICEPT OTC, ADLARITY) • Donepezil/ memantine (NAMZERIC) • Galantamine (RAZADYNE, RAXZADYNE ER, REMINYL) • Rivastigmine (EXELON, EXELON PATCH) • Tacrine (COGNEX)
MAO-B Inhibitors:	• Isocarboxazid (MARPLAN) • Phenelzine (NARDIL) • Rasagiline (AZILECT) • Safinimide (XADAGO) • Selegiline (ELDEPRYL, ZELAPAR) • Tranylcypromine (PARNATE)

Miscellaneous treatments for PD	• Amantadine (GOCOVRI, SYMMETREL, OSMOLEX ER)
	• Anti-Cholinergics (including but not limited to):
	  • Trihexyphenidyl (ARTANE)
	  • Benztropine Mesylate (COGENTIN)
	• A2A antagonists
	  • Istradefylline (NOURIANZ)

Medications to be discussed with the medical monitor	
Neuroleptics/Anti-Psychotics:	• Acetophenazine (TINDAL) • Aripiprazole (ABILIFY, ABILIFY MAINTENA, ARISTADA) • Brexpiprazole (REXULTI) • Butaperazine (REPOISE, TYRYLEN) • Cariprazine >3 mg (VRAYLAR) • Chlorpromazine (THORAZINE, LARGACTIL) • Chlorprothixene (TRUXAL) • Clozapine (CLOZARIL, FAZACLO ODT, VERSACLOZ) • Fluphenazine (MODECATE, MODECATE CONCENTRATE, MODITEN, PROLIXIN (discontinued brand), RHOFLUPHENAZINE) • Haloperidol (HALDOL, HALDOL DECANOATE, HALOPERIDOL LA, PERIDOL) • Loxapine (ADASUVE) • Lursidone (LUTUDA) • Mesoridazine (SERENTIL) • Metoclopramide (REGLAN) • Molindone (MOBAN) • Olanzapine (ZYPREXA, ZYPREXA RELPREVV, ZYPREXA ZYDIS) • Perphenazine (TRILAFON (single drug), ETRAFON, TRIAVIL, TRIPTAFEN) • Pimozide (ORAP) • Piperacetazine (QUIDE) • Prochlorperazine (STEMETIL, BUCCASTEM) • Promazine (PHENERGAN, PHENADOZ) • Quetiapine (SEROQUEL, SEROQUEL XR) • Risperidone (RISPERDAL, RISPERDAL CONSTA, RISPERADAL M-TAB) • Thioridazine (MELLARIL, MELLARIAL-S) • Thiothixene (NAVANE) • Trifluoperazine (STELAZINE) • Triflupromazine (STELAZINE) • Ziprasidone (GEODON)
List of medications that have to be held (if medically safe[a]) prior to performing LP (time will depend on the specific anticoagulant)	
Anticoagulants (examples) :	• Dabigatran (PRADAXA, PRADAX, PRAZAXA) • HEPARIN • Warfarin (COUMADIN, JANTOVEN) • Lepirudan (REFLUDAN) • Bivalirudin (ANGIOMAX) • Desirudin (LPRIVASK)

[a] *Discuss with primary care provider*

Appendix 3: Clinical Laboratory Assessments

Hematology:	Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count Mean corpuscular volume (MCV) Lymphocytes % Monocytes % Eosinophils % Basophils % White blood cell (WBC) count (total and differential) Absolute neutrophil count (ANC)
Coagulation:	International normalized ratio (INR) Prothrombin time (PT) Activated Partial Thromboplastin Time (APTT-FSL)
Biochemistry:	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Amylase Aspartate aminotransferase (AST) Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Creatinine Direct Bilirubin Gamma-glutamyl transferase (GGT) Glucose Indirect Bilirubin LDH Lipase Magnesium Potassium Sodium Phosphate Total bilirubin Total protein Uric Acid TSH
Urine	Blood Glucose Ketones Leukocytes Nitrite pH Protein Specific Gravity Pregnancy Test Drug Screen

Virology	HIV serology: HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody HBV serology: HBsAg, total hepatitis B core antibody (HBcAb)*, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA *If a patient has a negative HBsAg test and a positive total HBcAb test at Screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. Hep C antibody

Note: Reference ranges will be supplied by a central laboratory and used by the SI to assess clinical significance and pathological changes.

Appendix 4: The Common Terminology Criteria for Adverse Events (CTCAE) grading

Based on version 5.0 of the CTCAE, the following definitions apply.

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

Activities of Daily Living (ADL) *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Appendix 5: Staging anchors for application of the NSD-ISS

	Biologic anchors			Anchors of clinical signs or symptoms (stages 2A and 2B) and functional impairment (stages 3-6)	
Stage	**S**	**D** [a]	**G**	**Domain**	**Anchor(s)**
Stage 0	-	-	*SNCA* [b]	—	—
Stage 1A	+	-	±	(1) Cognitive	(1) MDS-UPDRS item 1.1 = 0; and
				(2) Motor	(2a) Does not have subthreshold parkinsonism [c]; and (2b) is not on PD meds; and
Stage 1B	+	+	±	(3) Other non-motor	(3a) Does not have RBD; and (3b) is not hyposmic [d]
Stage 2A	+	-	±	(1) Cognitive	(1) Item 1.1 = 1 AND MoCA ≥ 25; or
				(2) Motor	(2a) Has subthreshold parkinsonism [c]; or (2b) is on PD meds; or
Stage 2B	+	+	±	(3) Other non-motor	(3a) Has RBD; or (3b) is hyposmic [d]
Stage 3	+	+	±	(1) Cognitive	(1a) Item 1.1 = 1 AND MoCA ≤ 24; or (1b) Item 1.1 = 2 AND MoCA ≥ 25; or
				(2) Motor	(2) MDS-UPDRS-II = 3-13 AND either subthreshold parkinsonism [c] or PD meds
Stage 4	+	+	±	(1) Cognitive	(1a) Item 1.1 = 2 and MoCA ≤ 24; or (1b) item 1.1 = 3 AND MoCA ≥ 25; or
				(2) Motor	(2) MDS-UPDRS-II = 14-26; or
				(3) Other non-motor	(3) MDS-UPDRS-I (excluding item 1.1) = 13-24 [e]
Stage 5	+	+	±	(1) Cognitive	(1a) Item 1.1 = 3 AND MoCA ≤ 24; or (1b) item 1.1 = 4 AND MoCA ≥ 25; or
				(2) Motor	(2) MDS-UPDRS-II = 27-39; or
				(3) Other non-motor	(3) MDS-UPDRS-I (excluding item 1.1) = 25-36
Stage 6	+	+	±	(1) Cognitive	(1) Item 1.1 = 4 AND MoCA ≤ 24; or
				(2) Motor	(2) MDS-UPDRS-II ≥ 40; or
				(3) Other non-motor	(3) MDS-UPDRS-I (excluding item 1.1) ≥ 37

[1] Presence of qualifying signs/ symptoms in any single domain qualifies for stage 2 but individuals can have combination in all three domains.
[2] Presence of qualifying functional impairment in any single domain qualifies for stage 3-6 but individuals can have combination in all three domains.
[a] D positivity defined as < 75% age/sex-expected lowest putamen SBR.
[b] Only fully penetrant pathogenic *SNCA* variants qualify for Stage 0.
[c] Subthreshold parkinsonism defined as MDS-UPDRS-III ≥ 5 excluding postural and action tremor.
[d] Medication for treating the symptoms of PD as per MDS-UPDRS item 3a
[e] Hyposmia defined as UPSIT percentile ≤ 15 (age and sex adjusted).
[f] MDS-UPDRS-I (excluding item 1.1) ≥ 13 is sufficient for stage 4 provided that stage 2 criteria are met.

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