1. TITLE PAGE

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)
Sponsor:	The Michael J. Fox Foundation for Parkinson's Research
Principal Investigator:	Tanya Simuni, MD
Protocol Number:	P2P-013
Date of Protocol:	29 Oct 2024
Final Version:	2.0

MASTER PROTOCOL AMENDMENT 1 SUMMARY OF CHANGES

Protocol Amendment 1 Revisions			
Topic	**Revision (changes are in red)**	**Rationale/Comments**	**Section(s) affected by change**
PDAQ Global Function Assessment	PDAQ-15 changed to **PDAQ-27** throughout.	Updated PDAQ-15 to PDAQ-27 to align with PPMI Amendment 4 SOA	4. Protocol Synopsis Table 1: Schedule of Assessments 6.3 Key Exploratory Endpoints 9. Master Protocol Schedule of Activities 15.8 Key Exploratory Endpoints
Amended Schedule of Activities description in protocol synopsis	Participants will be seen for the Master Protocol screening visit, and if qualified, will be randomized to a regimen ~~per randomization plan~~ **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 ~~treatment~~ **active drug** or placebo within a regimen per randomization plan. Following the Baseline visit, participants will follow the ~~Master Protocol~~ **RSSP** schedule of activities **for which they are enrolled**. ~~Additional visits and corresponding activities, if necessary, can be scheduled per RSSP.~~	Updated for clarity	4. Protocol Synopsis
Participant Flow through P2P Master Protocol	Revised to include additional scenarios such as screen failing and withdrawing from an RSSP, completing the RSSP intervention period, screen failing and withdrawing from the Master Protocol.	To outline additional scenarios in which participants may either return back to the P2P Master Protocol or return back to PPMI Observational Study.	Figure 2: Participant Flow through P2P Master Protocol

Background and Rationale	Utilizing NSD definition and staging in this interventional Master Protocol in what was previously defined as a prodromal **Parkinson's disease and/or prodromal Dementia with Lewy Bodies** ~~early PD~~ population will better define and ensure a more homogenous study population. Added the following statement: **We have developed operational definitions for NSD staged 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.**	To clarify previously defined population and include additional support for NSD staging	5.0 Background and Rationale
NSD Staging	PPMI will apply the NSD definition for all PPMI eligible participants. ~~It is not currently feasible to assess n-asyn SAA biomarkers required for NSD at the time of PPMI screening.~~ As such, PPMI participants are recruited based on ~~clinical phenotype followed by DAT imaging and NSD staging criteria are applied once~~ n-asyn SAA biomarker data **and NSD Staging Criteria is applied once DAT SPECT imaging is obtained**. ~~become available.~~ P2P is planned as a Master Protocol linked to PPMI. All P2P participants will be recruited from PPMI and will have NSD characterization and staging applied prior to P2P screening.	To align with PPMI Amendment 4 activities	5.1 PPMI Overview and Interface with the P2P Master Protocol
DAT SPECT Imaging	"DAT imaging", "DAT", "SPECT scan", "DaTscan" updated to **DAT SPECT** throughout where appropriate.	To use consistent language when referring to Dopamine Transporter Single-photon Emission Computed Tomography	4. Protocol Synopsis Table 1: SOA 5. Background and Rationale 6. Trial Objectives and Endpoints 7. Inclusion/Exclusion Criteria 9. Master Protocol Schedule of Activities 13. Imaging 15. Statistics

Shared Placebo Group	Specified use of concurrent and non-concurrent placebo groups, where applicable.	To better define the shared placebo group used in the statistical analysis.	4. Protocol Synopsis 5. Background and Rationale 15. Statistics
Treatment Duration	Treatment duration for placebo-controlled interventions will be minimum 24 months for each intervention. All participants may remain on the originally assigned treatment arm until the last randomized participant has the opportunity to complete 24 months of follow-up for that specific RSSP **or until 24 months since randomization have passed (if terminated early). The RSSP will be closed once all participants have completed the follow-up period.** Post-treatment follow-up duration for each intervention will be described in the RSSPs.	To clarify timing of end of each RSSP	4. Protocol Synopsis 5.9 Treatment Duration 9.6 Additional Treatment Visits 9.11 End of RSSP and Master Protocol
Site Investigator	Specified the role of Site Investigator versus Master Protocol Principal Investigator throughout. Removed generic term "investigator", where appropriate.	To differentiate roles of Site Investigator and Master Protocol Principal Investigator	4. Protocol Synopsis 6. Trial Objectives and Endpoints 7. Inclusion/Exclusion Criteria 8. Participant Selection and Enrollment 9. Master Protocol Schedule of Activities 10. Investigational Product 11. Clinical Assessments 12. Biologic Research Sampling 13. Imaging 14. Adverse Events and Serious Adverse Events 16. Ethics/Protection of Human Subjects 17. Data Handling and Record Keeping

Inclusion Criteria	Added the following inclusion criteria: **Female participants of childbearing potential and male participants must agree to use contraception as detailed in the RSSP.** **Age 60 years or older at Screening visit.**	To define that participants' eligibility may be impacted by contraception requirements and that those requirements may differ in each RSSP	4. Protocol Synopsis 7.1 Inclusion Criteria
Exclusion Criteria	Added the following exclusion criteria: **7. 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 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.** **8. Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section if this behavior occurred in the past 2 years, except for the "Non-Suicidal-Self Injurious Behavior" (item also included in the Suicidal Behavior section).** **9. Study participant has a current history of alcohol or drug use disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders: DSM-5-TR, within the previous 5 years before screening.** **10. Clinically significant abnormalities in laboratory test results at the screening visit, including hepatic and renal panels, complete blood**	To include current, common exclusion criteria for CNS trials in the Master Protocol rather than separately in each RSSP	4. Protocol Synopsis 7.2 Exclusion Criteria

	count, chemistry panel and urinalysis as determined by SI. **11. Presence of human immunodeficiency virus (HIV) infection based on either history or testing.** **12. Any of the following:** **a. Presence of hepatitis B surface antigen or positive HBV 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.**		
Baseline/Randomization Visit	Corrected the description of the of the procedures performed at the Baseline/Randomization Visit as follows: •Randomization to ~~an actively enrolling RSSP~~ **active study drug or placebo**	Correction to description of procedure	9.2 Baseline/ Randomization Visit
C-SSRS Since Last Visit	Corrected the description of the of the C-SSRS performed after the Baseline Visit as follows: •Administer C-SSRS ~~Change from Baseline Assessment~~ **Since Last Visit** Short Form	Correction to description of C-SSRS assessment	9. Master Protocol Schedule of Activities
Additional Treatment Visits/Every 3-month visits	All participants will continue on an ~~q3~~ **every 3** months visit schedule in the randomized RSSP until the last recruited participant completes the 24-month assessment **or until 24 months since randomization have passed (if terminated early)**. ~~Additional visits will follow the SOA (see table 1).~~ **Following Month 24, participants will continue study visits every 3 months until the last participant randomized in the RSSP has had the opportunity to complete 24 months of follow-up on intervention. Participants will repeat the Months 15 – 24 visit schedules until the End of RSSP Treatment (Table 4). Therefore, Month 27 will follow the same schedule of activities as Month 15; Month 30 will follow the same schedule of activities as Month 18; Month 33 will follow the same schedule of activities as Month 21; Month 36 will follow the same schedule of activities as Month 24 and so on.**	Clarified visit schedule after Month 24 visit	9.6 Additional Treatment Visits

	Table 4 added to clarify which visit schedule should be followed for visits after Month 24.		
End of RSSP Treatment Safety Call	**An End of RSSP Treatment** Safety ~~follow up~~ Call will be completed 30 days after end of treatment unless specified otherwise in the RSSP. A safety follow-up call is required when a skin biopsy, LP or DAT SPECT is performed. This follow-up phone call will assess adverse events occurring the day of and 2-3 days after the DAT SPECT, LP, or skin biopsy. ~~at month 24 visit.~~	To clarify that End of RSSP Treatment Safety Call is separate from the AE telephone assessment call that occurs after LP, DAT SPECT and skin biopsy	9.10 End of RSSP Treatment Safety Call 9.12 Early Termination Visit (ET)
Adverse Events of Special Interest	Added the following language to describe recording of AEs of Special Interest: **Adverse Events of Special Interest will be defined within the respective drug RSSPs**. ~~The individual RSSPs will define at TEAE per drug.~~	To clarify AESIs are specific to each RSSP	14.4 Recording Adverse Events
Medication Errors	Added language to describe recording and reporting of medication errors: **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.**	To align with EU requirements	14.4 Recording Adverse Events
Sample Size and Power Calculations	Significant revisions to the statistics section as power calculations were updated to reflect modeling based on the most recent data cut from PPMI. Table 5: Two-Year Decline in Primary Endpoints by PPMI Natural History Cohort added.	Updated to reflect most current PPMI data	4. Protocol Synopsis 15.3 Sample Size Considerations
References	Added following reference: **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.**	To provide additional support for NSD integrated staging system	18. List of References
Table 7: Staging Anchors for Application of the NSD-ISS	Included missing footnotes on Table 7.	Correction to table	Table 7: Staging Anchors for Application of the NSD-ISS
Minor Administrative Revisions	Other minor grammatical, spelling and administrative revisions throughout protocol.	For clarity	Throughout

Schedule of Assessments Revisions – Amendment 1	
Revision	**Rationale/Comments**
Removed "Additional Visits q3 month" column	Clarified in footnote #6 and Section 9.6 the visit schedule that should be followed after Month 24 visits.
"Safety Follow Up Calls" column revised to "End of RSSP Treatment Safety Call"	To clarify that the "End of RSSP Treatment Safety Call" occurs 30 days after completion/withdrawal from RSSP and this call is separate from the AE Telephone Assessment that is performed 2-3 days following DaTscan, Skin Biopsy or LP; See Footnote #11
Added "AE Telephone Assessment" at all visits with DAT SPECT, Skin Biopsy or Lumbar Puncture.	To clarify that AE Telephone Assessment occurs 2-3 business days after DaTscan, Skin Biopsy or Lumbar Puncture and to differentiate this AE Telephone Assessment from the End of RSSP Treatment Safety Call; See Footnote #10
Noted that IgE is collected at screening and as specified per each RSSP; HIV serology, HBV serology and Hep C antibody clinical safety labs are performed at screening only.	Clarified in Footnote #3
Removed "Neuropsych battery" as assessment	All assessments included in the neuropsych battery are listed individually in the SOA.
Included that MRI should be performed at all specified visits unless it is not feasible due to safety or medical reasons.	Described in Footnote #15
Included timing in which MDS-UPDRS Part III /Hoehn & Yahr OFF/ON and MDS-UPDRS Part IV should be performed.	Described in Footnote #16

PROTOCOL APPROVAL

Version 2.0 dated 29Oct2024

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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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. 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
AE	Adverse Event
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression Severity
CIRB	Central Institutional Review Board
CRF	Case Report Form
CSF	Cerebrospinal Fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DAT SPECT	Dopamine Transporter Single-photon Emission Computed Tomography
DLB	Dementia with Lewy Bodies
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
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMM	Independent Medical Monitor
IND	Investigational New Drug
IRB	Institutional Review Board (Local or Central)
IRT	Interactive Response Technology
ISS	Integrated Staging System
ITT	Intent-to-Treat Principle
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

Abbreviation or specialist term	Explanation
MJFF	Michael J. Fox Foundation for Parkinson's Research
MM	Medical Monitor
MoA	Mechanism of Action
MRI	Magnetic Resonance Imaging
MSA	Multiple System Atrophy
n-asyn	Neuronal α-synucleinopathies
Neuro-QoL	Quality of Life in Neurological Disorders
NSD	Neuronal Alpha-Synuclein Disease
PD	Parkinson's Disease
PDAQ-27	Penn Parkinson's Daily Activities Questionnaire-27
PET	Positron Emission Tomography
PGI-S	Participant Global Impression Severity
PI	Principal Investigator Master Protocol
PPMI	Parkinson Progression Marker Initiative
PRO	Participant Reported Outcomes
P2P	Path to Prevention
QoL	Quality of Life
QUIP	Questionnaire for Impulsive-Compulsive Disorders
RBD	Rapid Eye Movement Sleep Behavior Disorder
RSSP	Regimen Specific Sub Protocol
SAA	Seed Amplification Assay
SAE	Serious Adverse Event
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
TEAEs	Treatment Emergent Adverse Events
TEC	Therapy Evaluation Committee
TOM	Technical Operations Manual
UPSIT	University of Pennsylvania Smell Identification Test
WCG	WIRB Copernicus Group

4. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Michael J. Fox Foundation for Parkinson's Research
Title and Phase of Master Protocol: Path to Prevention **(**P2P) Platform Trial: A Phase 2A, Randomized, Double Blind, Placebo Controlled Study to Evaluate Investigational Interventions in Early-Stage Neuronal Alpha-Synuclein Disease (NSD)
Master Protocol Design: The Path to Prevention Platform Trial (P2P) is a perpetual multi-center, multi-regimen proof of concept phase 2A randomized clinical trial evaluating the safety and early efficacy of investigational products for the treatment of Early-Stage Neuronal Alpha-Synuclein Disease (NSD) populations. Early stage NSD includes participants with alpha-synuclein pathology, presence of dopamine dysfunction, motor, and non-motor clinical manifestations but lack of related functional impairment (see Table 3). These participants were previously defined as prodromal Parkinson's disease, and/or prodromal Dementia with Lewy Bodies. The trial is designed as a perpetual platform trial. This means that there is a single Master Protocol dictating the conduct of the trial. The Master Protocol describes the overall framework of the platform trial, including the target population, inclusion and exclusion criteria, intervention assignment and randomization schemes, RSSP endpoints, schedule of assessments, trial design, the mechanism for adding and removing interventions, and the statistical methodology and prespecified statistical methods for evaluating interventions. Each investigational product is tested in a trial regimen, which is described in its own Regimen Specific Sub Protocol (RSSP) amended to the Master Protocol.
Master Protocol Objectives: Assess the impact of putative NSD therapies in participants with Early Stage NSD on Dopamine Transporter Single-photon emission computed Tomography (DAT SPECT) imaging, clinical measures of symptom worsening**,** feasibility, safety, and tolerability. Additional analyses will examine many other exploratory clinical outcome measures and biomarkers.
Multiple Primary Endpoints: 1. DAT SPECT imaging as measured by the rate of progression in the mean striatum Specific Binding Ratio (SBR) from baseline through follow-up. 2. Clinical outcome as defined by the rate of progression in the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score from baseline through end of follow-up or the initiation of dopaminergic treatment. **Secondary Endpoints:** 1. Feasibility as defined by ability to recruit, retain participants, and complete Master Protocol activities as per schedule of activities. 2. Safety as measured by all treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs) for the active treatment arm versus placebo in each RSSP. 3. Tolerability as measured by ability to complete an RSSP on the assigned dose and treatment arm (active versus placebo)

Key Exploratory Endpoints (to be included in Final RSSP Study Reports):

1. The number of participants who progress from NSD stage 2B to NSD Stage 3 or higher.
2. Clinical outcome as defined by the rate of progression in MDS-UPDRS Total from baseline through follow-up or the initiation of dopaminergic treatment and rate of progression in Part I & II subscores from baseline through follow-up.
3. Change in cognition as defined by the number of participants developing new syndromes of mild cognitive impairment (MCI) or dementia.
4. Change in functional status as measured by Penn Parkinson's Daily Activities Questionnaire-15 (PDAQ-27) from baseline through follow-up.
5. Time to progression milestones as defined by Brumm et al[1]

Target population

Stage 2B NSD (see Table 3).

Main inclusion criteria:

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

1. Enrollment in PPMI observational study
2. Able to provide informed consent.
3. Diagnosis of NSD Stage 2B (see Table 3)
4. Female participants of childbearing potential and male participants must agree to use contraception as detailed in the RSSP.
5. Age 60 years or older at Screening visit.
6. Meet any additional inclusion criteria (if applicable) accessible at the time of screening for at least one active RSSP

Main exclusion criteria

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

1. Received any of the drugs associated with symptomatic parkinsonism within 6 months of Randomization Visit (see Appendix 2).
2. Received dopaminergic therapy (levodopa or dopamine agonist) for NSD motor syndrome or cholinesterase inhibitors for NSD cognitive syndrome within 90 days of the Randomization Visit.
3. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the site investigator (SI) might preclude Master Protocol participation.
4. Individuals taking any of the drugs that might interfere with the DaTscan read out unless they are willing and medically able to hold the medication for at least 5 half-lives before DAT SPECT imaging (see Appendix 1).
5. Women may not be pregnant, lactating or planning pregnancy during the Master Protocol.
6. Participation in other investigational drug studies less than 30 days prior to screening (unless specified otherwise in the RSSP)
7. History or current diagnosis of electrocardiogram (ECG) or cardiac abnormalities indicating significant risk of safety for participants such as:

- Myocardial infarction, unstable angina pectoris, transient ischemic attack, stent placement or coronary artery bypass graft, any of those within 6 months of screening.
- Cardiac failure [New York Heart Association (NYHA) functional class II-IV], stroke or clinically significant uncontrolled arterial hypertension.
- Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II- and third-degree AV block).
- Resting QTcF >450 ms (in males) or >460 ms (in females) and < 300 ms (regardless of sex) at screening or inability to determine the QTcF interval.
- Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome.

8. Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section if this behavior occurred in the past 2 years, except for the "Non-Suicidal-Self Injurious Behavior" (item also included in the Suicidal Behavior section).
9. Study participant has a current history of alcohol or drug use disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders: DSM-5-TR, within the previous 5 years before screening.
10. Clinically significant abnormalities in laboratory test results at the screening visit, including hepatic and renal panels, complete blood count, chemistry panel and urinalysis as determined by site investigator.
11. Presence of human immunodeficiency virus (HIV) infection based on either history or testing.
12. Any of the following:
    - Presence of hepatitis B surface antigen or positive HBV DNA at Screening
    - Positive hepatitis C antibody test result at Screening or within 3 months prior to starting study drug. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained. Where hepatitis C RNA testing is unavailable, a positive hepatitis C antibody test will lead to exclusion.

Investigational products: Multiple investigational products (i.e., interventions, or active agents, from different regimen partners) will be tested in this Platform Trial. Each investigational product will have an associated RSSP with the complete description of the tested product. Each active agent will have a matching placebo.

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

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

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

Sample Size:
Each regimen will randomize 125 participants with NSD Stage 2B to active treatment. For a specific regimen, "power" is defined as the probability of demonstrating success on at least one of the primary endpoints. The primary analysis population for each regimen includes shared concurrent and non-concurrent control participants. As a result, regimens that enter the platform trial later can be expected to see an increased power relative to that of the first regimen as a result. Assuming 95% of randomized participants within an RSSP fall into the < 7 MDS-UPDRS Part III baseline strata, the first regimen in the platform is estimated to have 74%, 84%, and 91% power to detect treatment effects when both of the endpoints achieve 30%, 35%, and 40% slowing of progression, respectively. Similarly, we have greater than 86% power to declare success if there is truly a 40% or greater reduction in slope/progression of MDS-UPDRS Part III as long as there is at least a simultaneous 30% or greater reduction in mean striatum SBR. We have around 83% or higher probability of declaring success if there is truly a 40% or greater reduction in slope/progression on the DAT SPECT imaging endpoint and at least a 30% reduction on slope/progression on the MDS-UPDRS Part III endpoint. Finally, the overall type I error probability (probability of meeting the criteria when there is no true reduction for either endpoint) is well controlled at 10.3%.

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

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

***MDS-UPDRS Part III Score*:** For each regimen, a Bayesian repeated measures model of MDS-UPDRS Part III score over time, adjusted for the baseline strata, will be used to compare the slope of active treatment versus the shared concurrent and non-concurrent placebo arm. The model allows for heterogeneity across individual baseline MDS-UPDRS Part III score values and individual slopes, heterogeneity across regimens due to minor differences in the inclusion/exclusion criteria or mode of administration. A greater positive slope indicates faster symptom accumulation and a greater progression rate. A hypothesis test for a smaller progression rate for active treatment versus placebo will be conducted using the Bayesian posterior distribution, with a predefined threshold 0.95 required to demonstrate superiority.
Schedule of activities Participants will be seen for the Master Protocol screening visit, and if eligible, will be randomized to a regimen with open enrollment. Participants will then be consented to the RSSP and assessed for any additional regimen specific eligibility requirements. If all additional regimen-specific eligibility requirements are met, participants will be randomized to active drug or placebo within a regimen per randomization plan. Following the Baseline visit, participants will follow the RSSP schedule of activities for which they are enrolled.

Table 1: Master Protocol RSSP Standard Schedule of Assessments

All P2P participants will be screened from PPMI and will have NSD characterization and staging applied prior to P2P screening.

Activity	**Master Protocol Screening[7] Group A**	**Master Protocol Screening[7] Group B**	**Baseline/ Randomization within RSSP**	Week 2	Mon 1	Mon 3	Mon 6	Mon 9	Mon 12	Mon 15	Mon 18	Mon 21	Mon 24 **/Early Termination[6]**	Initiation of Dopaminergic Tx[8]	End of RSSP Treatment	End of RSSP Treatment Safety Call[11]
	<6 months from last PPMI*	≥6 months from last PPMI*														
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Clinic	Clinic	Phone
Window days	-90 to -1	-90 to -1	0	3+	7+	14+	14+	14+	14+	14+	14+	14+	14+	14+	14+	3+
Informed Consent																
Documentation of informed consent	X	X														
Screening Activities																
Inclusion /exclusion criteria	X	X	X													
DAT eligibility	X	X														
General Activities																
Demographics[2]	*PPMI*	*PPMI*		*Data uploaded per PPMI EDC*												
Family History[2]	*PPMI*	*PPMI*														
Medical history [2]	*PPMI*	*PPMI*														
Socio-Economics[2]	*PPMI*	*PPMI*														
Physical Examination	X	X							X				X		X	
Height and Weight[9]	X	X	X		X	X	X		X		X		X	X	X	
Vital signs	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Orthostatic BP	X	X	X		X	X	X	X	X	X	X	X	X	X	X	

Activity	**Master Protocol Screening[7] Group A**	**Master Protocol Screening[7] Group B**	**Baseline/ Randomization within RSSP**	Week 2	Mon 1	Mon 3	Mon 6	Mon 9	Mon 12	Mon 15	Mon 18	Mon 21	Mon 24 **/Early Termination[6]**	Initiation of Dopaminergic Tx[8]	End of RSSP Treatment	End of RSSP Treatment Safety Call[11]
	<6 months from last PPMI*	≥6 months from last PPMI*														
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Clinic	Clinic	Phone
Window days	-90 to -1	-90 to -1	0	3+	7+	14+	14+	14+	14+	14+	14+	14+	14+	14+	14+	3+
Neuro/Motor Assessments																
Participant Motor Function Questionnaire		X				X	X	X	X	X	X	X	X	X	X	
Freezing and Falls		X							X				X		X	
Neurological Exam	X	X							X				X		X	
MDS-UPDRS Part Ia	X	X			X	X	X	X	X	X	X	X	X	X	X	
MDS-UPDRS Part III Hoehn & Yahr	X	X	X		X	X	X		X		X		X	X	X	
MDS- UPDRS Part III /Hoehn & Yahr OFF/ON[16]						Post Initiation of Dopaminergic Treatment										
MDS- UPDRS Part IV[16]						Post Initiation of Dopaminergic Treatment										
MDS-UPDRS Part Ib and Part II	X	X			X	X	X	X	X	X	X	X	X	X	X	
Modified Schwab & England ADL	X	X				X	X	X	X	X	X	X	X	X	X	
Features of Parkinsonism		X				X	X	X	X	X	X	X	X		X	
Other Clinical Features		X				X	X	X	X	X	X	X	X		X	
Clinical Diagnosis	X	X				X	X	X	X	X	X	X	X	X	X	
Primary Research Diagnosis	X	X				X	X		X		X		X	X	X	

Activity	**Master Protocol Screening[7] Group A**	**Master Protocol Screening[7] Group B**	**Baseline/ Randomization within RSSP**	Week 2	Mon 1	Mon 3	Mon 6	Mon 9	Mon 12	Mon 15	Mon 18	Mon 21	Mon 24 **/Early Termination[6]**	Initiation of Dopaminergic Tx[8]	End of RSSP Treatment	End of RSSP Treatment Safety Call[11]
	<6 months from last PPMI*	≥6 months from last PPMI*														
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Clinic	Clinic	Phone
Window days	-90 to -1	-90 to -1	0	3+	7+	14+	14+	14+	14+	14+	14+	14+	14+	14+	14+	3+
Non-Motor Assessments																
Olfactory Testing (UPSIT)		X							X				X		X	
RBD Screening Questionnaire.		X							X				X		X	
Epworth Sleepiness Scale		X							X				X		X	
SCOPA-AUT		X				X			X		X		X		X	
Neuro QoL		X							X				X		X	
Cognitive and Psychiatric Assessments																
Montreal Cognitive Assessment	X	X							X				X		X	
Clock Drawing		X							X				X		X	
Lexical Fluency		X							X				X		X	
Hopkins Verbal Learning Test-Revised		X							X				X		X	
Benton Judgment of Line Orientation		X							X				X		X	
Modified Semantic Fluency (Animals only)		X							X				X		X	
Letter Number Sequencing		X							X				X		X	

Activity	**Master Protocol Screening[7] Group A**	**Master Protocol Screening[7] Group B**	**Baseline/ Randomization within RSSP**	Week 2	Mon 1	Mon 3	Mon 6	Mon 9	Mon 12	Mon 15	Mon 18	Mon 21	Mon 24 **/Early Termination[6]**	Initiation of Dopaminergic Tx[8]	End of RSSP Treatment	End of RSSP Treatment Safety Call[11]
	<6 months from last PPMI*	≥6 months from last PPMI*														
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Clinic	Clinic	Phone
Window days	-90 to -1	-90 to -1	0	3+	7+	14+	14+	14+	14+	14+	14+	14+	14+	14+	14+	3+
Symbol Digit Modalities Test		X							X				X		X	
Trail Making Test (A and B)		X							X				X		X	
Modified Boston Naming Test		X							X				X		X	
Cognitive change	X	X				X	X	X	X	X	X	X	X		X	
Cognitive characterization	X	X				X	X	X	X	X	X	X	X		X	
State-Trait Anxiety Inventory for Adults		X					X		X		X		X		X	
Geriatric Depression Scale	X	X					X		X		X		X		X	
QUIP		X					X		X		X		X		X	
Global Function Assessment																
CGI-S		X	X			X			X		X		X		X	
PGI-S		X	X			X			X		X		X		X	
PDAQ-27		X	X			X	X		X		X		X		X	
Novel PRO		X	X			X			X		X		X		X	
Digital Assessment																
Digital Assessment			As needed per PPMI Digital Sub Study													
Safety Assessments																
Clinical safety labs[3]	X	X			X	X	X	X	X	X	X	X	X		X	

Activity	**Master Protocol Screening[7] Group A**	**Master Protocol Screening[7] Group B**	**Baseline/ Randomization within RSSP**	Week 2	Mon 1	Mon 3	Mon 6	Mon 9	Mon 12	Mon 15	Mon 18	Mon 21	Mon 24 **/Early Termination[6]**	Initiation of Dopaminergic Tx[8]	End of RSSP Treatment	End of RSSP Treatment Safety Call[11]
	<6 months from last PPMI*	≥6 months from last PPMI*														
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Clinic	Clinic	Phone
Window days	-90 to -1	-90 to -1	0	3+	7+	14+	14+	14+	14+	14+	14+	14+	14+	14+	14+	3+
ECG	X	X			X				X				X		X	
C-SSRS[13]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Biological Sample Collection																
Research samples[3] (blood & urine)		X	X				X		X				X		X	
Lumbar puncture		X[4]							X				X		X	
Skin biopsy		X[4]											X		X	
Imaging Activities																
Pregnancy Test (prior to DaTscan) if applicable	X	X							X				X		X	
DAT SPECT	X[5]	X[5]							X				X		X[14]	
MRI[15]		X							X				X		X	
Medications																
Concomitant meds review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LEDD Medication Initiation log				As needed												
Randomization to open RSSP																
Randomization	X	X	X													
Adverse Events (AE)																
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Telephone Assessment[10]	X	X							X				X		X	

Activity	**Master Protocol Screening[7] Group A**	**Master Protocol Screening[7] Group B**	**Baseline/ Randomization within RSSP**	Week 2	Mon 1	Mon 3	Mon 6	Mon 9	Mon 12	Mon 15	Mon 18	Mon 21	Mon 24 **/Early Termination[6]**	Initiation of Dopaminergic Tx[8]	End of RSSP Treatment	End of RSSP Treatment Safety Call[11]
	<6 months from last PPMI*	≥6 months from last PPMI*														
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Tele[1]	Clinic	Clinic	Clinic	Phone
Window days	-90 to -1	-90 to -1	0	3+	7+	14+	14+	14+	14+	14+	14+	14+	14+	14+	14+	3+
Current Medical Conditions Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Report of Pregnancy	X	X	X	As needed												
Other Assessments																
Study completion form															X	
Surgery for PD				As needed												
Visit Status[12]		X							X				X		X	

Footnote:

1. Tele (Video if possible) visits may be converted into in-person clinic visits as necessary at the discretion of the site investigator; vital signs and clinical safety labs will not be collected at Tele visits unless the visit is converted to an in-person clinic visit
2. Procedures, assessments, and samples collected as part of the main PPMI Clinical study (screening) may be used for this Master Protocol and will be uploaded into EDC by Data Management
3. Clinical Safety/Research Samples: See Section 12 and Appendix 3 for specific analytes. IgE should be collected at screening and as specified in each RSSP. HIV serology, HBV serology and Hep C antibody performed at screening only. Collect samples as outlined in the Laboratory Manuals; Collect Screening blood samples after other requisite tests for eligibility have been completed. For WOCBP, perform serum pregnancy test (HCG) at Screening; perform urine pregnancy test or (serum if required by the site) prior to injection of DaTscan and at all other indicated visits.
4. Skin biopsy and lumbar puncture tests will be repeated if last procedure/test performed ≧ 12 months of the P2P screening visit
5. Repeat DaTscan if last DaTscan was collected ≧ 3 months of the P2P screening visit.
6. The end of treatment is defined when last RSSP participant completes their month 24 visit for the assigned RSSP. All consented participants will remain active in the RSSP until the last subject completes the month 24 visit or until 24 months have passed since randomization (if terminated early). Following Month 24, participants will continue study visits every 3 months until the last participant randomized in the RSSP has had the opportunity to complete 24 months of follow-up on intervention. Participants will repeat the Months 15 – 24 visit schedules until the End of RSSP Treatment. Therefore, Month 27 will follow the same schedule of activities as Month 15; Month 30 will follow the same schedule of activities as Month 18; Month 33 will follow the same schedule of activities as Month 21; Month 36 will follow the same schedule of activities as Month 24 and so on (Table 4).

7. PPMI annual visit data may be used for P2P screening visits (group A or B)
8. This visit should be scheduled prior to initiation of Dopaminergic therapy (levodopa or dopamine agonists). If this visit occurs ≤ 90 days from the next in-clinic visit, replace this visit with the next in-clinic visit and follow the schedule of activities accordingly
9. Height is only collected at the screening visit. Weight will be collected at all in person office visits.
10. AE Telephone Assessment is performed 2-3 days after a skin biopsy, DAT SPECT, and lumbar puncture.
11. End of RSSP Treatment Safety call is performed 30 days after completion/ withdrawal from RSSP unless specified otherwise in the RSSP.
12. Visit status will be tracked in PPMI Clinical Study
13. Screening/Baseline C-SSRS use the long form. All other visits will complete the C-SSRS using the short form.
14. Repeat DaTscan if last DaTscan was collected ≧ 6 months prior to the End of RSSP Treatment visit.
15. An MRI is not required if completion of the MRI is not possible for a safety or medical reason.
16. The MDS-UPDRS Part III /Hoehn & Yahr OFF/ON and MDS-UPDRS Part IV will be performed only if the participant has initiated therapy on levodopa or dopamine agonists. These assessments will be performed at the visits in which MDS- UPDRS Part III /Hoehn & Yahr is required. 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 PD medication.

* See Section 5.1 for a description of the 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

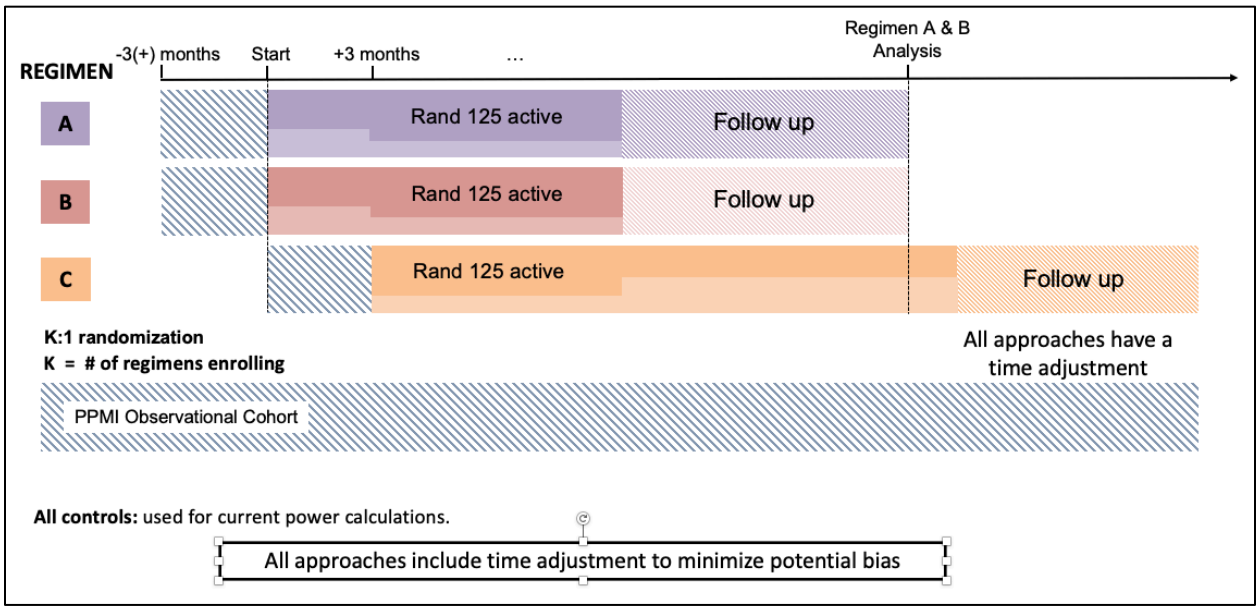
	Biologic anchors			Anchors of clinical signs or symptoms[1] (participants can meet any one of the 3 anchors to qualify for Stage 2B)	
Stage	**S**	**D** [a]	**G**	**Domain**	**Anchor(s)**
Stage 2B	+	+	±	(1) Cognitive	(1) Item 1.1 MDS-UPDRS = 1 AND MoCA ≥ 25; or
				(2) Motor	(2) Subthreshold parkinsonism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

[1] Participants can meet any one of the 3 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] D positivity defined as < 75% age/sex-expected lowest putamen SBR.
[b] Subthreshold parkinsonism defined as MDS-UPDRS-III ≥ 5 excluding postural and action tremor.
[c] Dopaminergic medication (levodopa formulations or dopamine agonists).
[d] Hyposmia defined as UPSIT percentile ≤ 15.

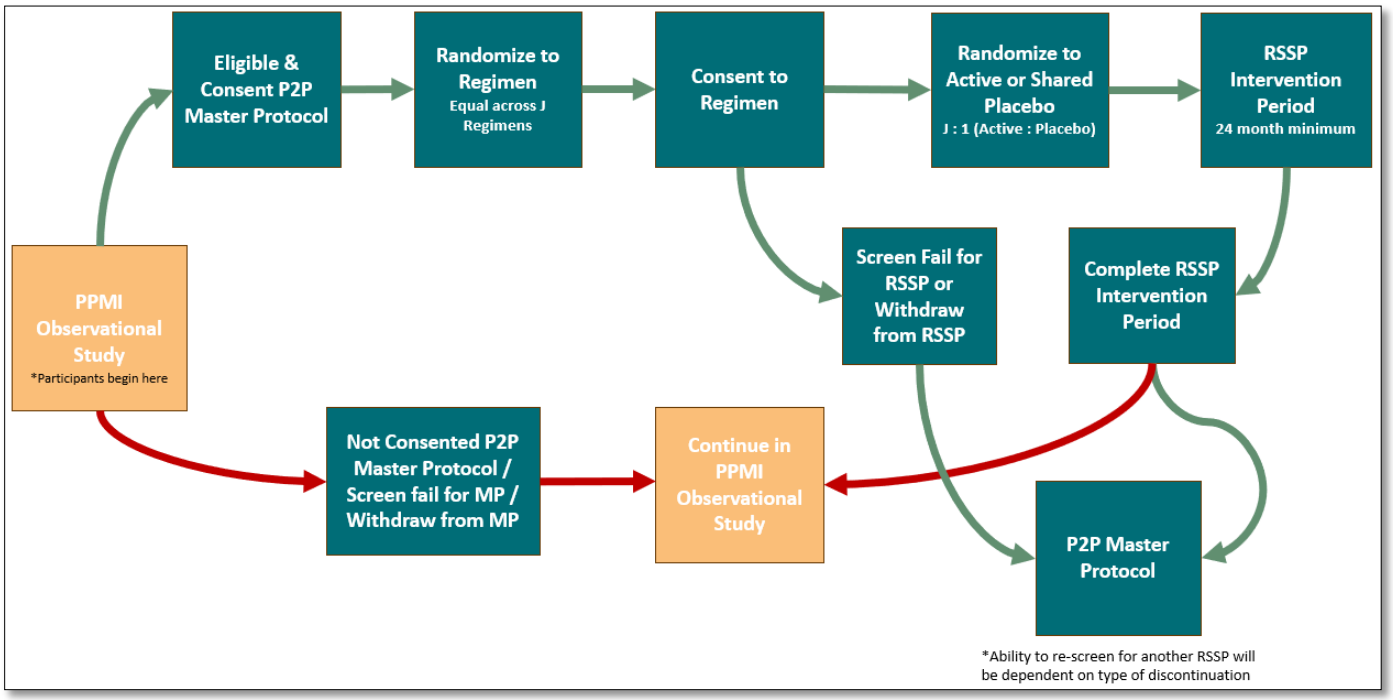
MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. MoCA=Montreal Cognitive Assessment. NSD=Neuronal Synuclein Disease. PD=Parkinson's disease. RBD=REM sleep behavior disorder. UPSIT= University of Pennsylvania Smell Identification Test

Figure 1: P2P Study Design Perpetual Platform Trial



Note: 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 Master Protocol



5. BACKGROUND AND RATIONALE

Neuronal Alpha- Synuclein Disease (NSD) is a new terminology based on the biologic definition of a-synucleinopathies encompassing both Parkinson 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] . Utilizing NSD definition and staging in this interventional Master Protocol in what was previously defined as a prodromal Parkinson's disease and/or prodromal Dementia with Lewy Bodies population will better define and ensure a more homogenous study population. PD and DLB are currently defined by their clinical features[3-5] with predominantly neuronal alpha-synuclein (n-asyn) pathology as the gold standard that establishes the definitive diagnosis. The prevalence of PD, based on the current diagnostic criteria, the second most common neurodegenerative disease, is 10 million worldwide and is expected to double by 2040[6]. DLB is the second most common degenerative dementia also caused by neuronal accumulation of aggregated n-asyn but associated with early cognitive manifestations[5]. 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[7]. 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[8]. 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[9], 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[10-14] 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[15] and therapeutic intervention prior to symptom onset to potentially prevent/halt progression[16], and identifying biologically-defined subsets[17] .

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 1). 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)[18] and Huntington's disease [19]. Similar to the AD field[18, 20], 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 the biologically targeted therapeutic interventions to slow progression of the disease. This progress was largely enabled by the Parkinson Progression Marker Initiative (PPMI)[21] . 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[2].

5.1 PPMI Overview and Interface with the P2P 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[21, 22]. 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[23-33]. Currently PPMI is recruiting a large cohort of participants with phenotypic prodromal features [hyposmia, REM behavior disorder (RBD), and other premotor features as well as relevant genetic variants (GBA, LRRK2, SNCA and rare variants)]. 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[34]. These data have enabled a biologic definition of PD, the shift to the more encompassing biologic term, NSD and the proposed NDS-ISS. PPMI will apply 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 DAT SPECT imaging is obtained. P2P is planned as a Master Protocol linked to PPMI. All P2P participants will be recruited from PPMI and will have NSD characterization and staging applied prior to P2P screening.

As of January 2024, PPMI has recruited ~ 3000 individuals including ~ 1400 in prodromal cohort and aims to recruit 2000 prodromal participants 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 protocol, PPMI already has the largest cohort of NSD Stage 2B participants[34]. Due to these efforts PPMI is uniquely positioned to be the pioneer in therapeutic development targeting the early NSD population via the P2P 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.

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; does a single investigational product 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 pre- specified end date: the platform remains open long-term and is

available to evaluate new investigational products as they become available[35]. 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 group, which The Master Protocol incorporates for trial efficiency.[35, 36]

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[35, 36].

5.3 Study Design

The P2P 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).

As a perpetual platform trial, it 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 assessments, 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 corresponding to an intervention. Each trial regimen is described in its own Regimen-Specific Sub Protocol (RSSP) 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, the specific target population (to be selected within the pre-defined subsets of the Master Protocol), additional enrollment criteria (if any), stopping rules, and other specific intervention-related information and assessments (safety or other assessmentsthat may be in addition to those outlined in the Master Protocol).

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 of the last PPMI annual visit. *Group A Screening is defined if screened into the Master Protocol <6 months from the last PPMI annual visit; _Group B is defined if screened into the Master Protocol ≥ 6 months from the last PPMI annual visit.* Those participants who meet the Master Protocol eligibility and are eligible

for at least one RSSP will be equally randomized to one of the *J* 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, but may be discontinued early due to safety concerns.

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 in a prespecified *J*: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 and non-concurrent placebo 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 mechanism of action, target engagement, previous pre-clinical 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 30 PPMI sites in the US.

5.9 Treatment Duration

Treatment duration for placebo-controlled interventions will be minimum 24 months for each intervention. All participants may remain on the originally assigned treatment arm until the last randomized participant has the opportunity to complete 24 months of follow-up for that specific RSSP or until 24 months since randomization have passed (if terminated early). The RSSP will be closed once all participants have completed the follow-up period. Post-treatment follow-up duration for each intervention will be described in the RSSPs. All participants will be encouraged to continue follow up in the PPMI clinical observational study as per PPMI Schedule of Activities (SOA).

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 Dopamine Transporter Single-photon emission computed Tomography (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 striatum Specific Binding Ratio (SBR) from baseline through follow-up.
2. Clinical outcome as defined by the rate of progression in the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score from baseline through follow-up or the initiation of dopaminergic treatment.

6.2 Secondary Endpoints

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

6.3 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].

6.4 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 SI clinical judgement.

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 (Brief Motor Screen)
i. Change from baseline in the global disability scale Participant Global Impression (PGI-S) and Clinical Global Impression (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 PPMI observational study
2. Able to provide informed consent.
3. Diagnosis of NSD Stage 2B (see Table 3)
4. Female participants of childbearing potential and male participants must agree to use contraception as detailed in the RSSP.
5. Age 60 years or older at Screening visit.

6. Meet any additional inclusion criteria 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. Received any of the drugs associated with symptomatic parkinsonism within 6 months of Randomization Visit (see Appendix 2).
2. Received dopaminergic therapy (levodopa or dopamine agonist) for NSD motor syndrome or cholinesterase inhibitors for NSD cognitive syndrome within 90 days prior to or at the time of randomization.
3. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the site investigator might preclude Master Protocol participation.
4. Individuals taking any of the drugs that might interfere with the DaTscan read out unless they are willing and medically able to hold the medication for at least 5 half-lives before DAT SPECT imaging (see Appendix 1).
5. Women may not be pregnant, lactating or planning pregnancy during the Master Protocol.
6. Participation in other investigational drug studies less than 30 days prior to screening (unless specified otherwise in the RSSP).
7. History or current diagnosis of electrocardiogram (ECG) or cardiac abnormalities indicating significant risk of safety for participants such as:
    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 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.
8. Score “yes” on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or “yes” on any item of the Suicidal Behavior section if this behavior occurred in the past 2 years, except for the “Non-Suicidal-Self Injurious Behavior” (item also included in the Suicidal Behavior section).
9. Study participant has a current history of alcohol or drug use disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders: DSM-5-TR, within the previous 5 years before screening.
10. Clinically significant abnormalities in laboratory test results at the screening visit, including hepatic and renal panels, complete blood count, chemistry panel and urinalysis as determined by SI.

11. Presence of human immunodeficiency virus (HIV) infection based on either history or testing.
12. Any of the following:
    a. Presence of hepatitis B surface antigen or positive HBV 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 initially conducted at selected PPMI qualified centers in the US and participants must be enrolled in the PPMI Clinical study. Potential eligibility for P2P Master Protocol will be determined based on the potential to meet Mater Protocol inclusion/ exclusion criteria and assessed centrally for consideration for further contact. Sites participating in this Master Protocol will be notified of potentially eligible PPMI participants enrolled at their site to be contacted for Master Protocol screening. Information about all research participants enrolled into the trial will be recorded in the Electronic Data Capture (EDC) system.

8.1.1 Ineligible Participants

All consented participants from the PPMI study will be screened for eligibility for P2P based on the Master Protocol inclusion/exclusion criteria. For participants who were deemed potentially eligible for the Master Protocol but did not qualify on 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. 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 actively enrolling regimens for which they are eligible. Here, regimen denotes both active treatment and placebo 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 Regimen-Specific Screening visit. If all additional regimen specific eligibility criteria are met, participants will be stratified by

their baseline MDS-UPDRS part III score (<7 vs. ≥ 7) and randomized in a *J*:1 manner via the IRT system to either the active treatment or placebo for the sub protocol. 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. 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.

The objective of the randomization scheme is to have approximately 1:1 randomization for each active treatment versus concurrently randomized controls.

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, randomized placebo control arm.

Research participants, SIs, and everyone involved in the conduct of the Master Protocol, will not be blinded to the regimen assignments but will be blinded to the randomized treatment assignments within an RSSP. The randomized treatment assigned for participants in that sub-protocol will be kept secure and will only be accessed according to the Unblinded Personnel List and Procedures and the Emergency Unblinding Plan.

8.2.3 Emergency Unblinding

In the event of a medical emergency that necessitates the unblinding of the Independent Medical Monitor (IMM) or a SI to assure safety for a participant, emergency unblinding of that single participant may be undertaken as outlined in the medical monitoring plan. 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. In that case the participant will be terminated from the RSSP but can remain in the Master Protocol following the procedures as outlined in Section 8.4.

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 either the Master Protocol or by continued participation in PPMI. These research participants will be encouraged to follow the study visits, off treatment, up to the Month 24 visit, following the Schedule of Activities. 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, at least 24-month visit should be encouraged. 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 CRF. 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). The participant will be encouraged to remain in the Master Protocol under the ITT principle, and can be later rescreened for another RSSP as outlined in Section 8.4.

For all research participants, the reason for RSSP termination must be recorded in the P2P CRF. These data will be included in the trial database and reported.

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 follow up in the PPMI observational study as per PPMI SOA. If a participant terminates from the Master Protocol prior to completing their full follow-up time in an RSSP, they have to be terminated in the RSSP. Relevant visits using PPMI observational study data can be used for the ITT analysis.

For all research participants, the reason for Master Protocol termination must be recorded in the P2P CRF. 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 Reassignment

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.

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 follow up in the PPMI observational 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 Schedule of Activities. 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 fails Master Protocol screening, participant will be encouraged to continue follow up in the PPMI observational study.

If a research participant who meets Master Protocol eligibility, is assigned to a regimen, and is randomized within that 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 participant will be considered enrolled in the Master Protocol for up to 6 months and during that time able to be randomized to any available RSSP for which they meet initial screening criteria. The research participant must provide written informed re-consent to the Master Protocol and must still meet the Master Protocol inclusion and exclusion eligibility criteria in order to be re-assigned into a different regimen. However, any participants who elect 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 also 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 6 months (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-screened 6 months after RSSP completion (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 rescreening until 24 months after their date of randomization into the original RSSP. They may be re-screened 6 months after their expected 24 month visit in the original RSSP (or longer if required by the RSSP-specific intervention).

8.5 Participant Withdrawal

8.5.1. Participant Withdrawal from an RSSP-Specific Protocol

If a participant withdraws consent from an RSSP for personal reasons (e.g., inconvenience of the intervention, mode of administration, required assessments) the participant cannot be re-assigned to a different RSSP. However, the SI or designee will encourage the research participant to remain in the Master Protocol and follow the Master Protocol under the ITT principle. These research participants will be encouraged to follow the study visits, off treatment, up to the Month 24 visit, following the Schedule of Activities as outlined in Section 8.3.1.

8.5.2. Participant Withdrawal from Master Protocol

If a participant chooses to withdraw from the Master Protocol as well as their assigned RSSP, the SI or designee will encourage the participant to maintain enrollment in the PPMI observational study.

9. MASTER PROTOCOL SCHEDULE OF ACTIVITIES

This section describes trial procedures that are common to all interventions tested in the P2P Platform Trial as detailed in the Master Protocol. 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 Master Protocol the P2P SOA (see Table 1) 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 has been separated into two groups depending on their last PPMI visit and is further defined in the schedule of assessment table. 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 IRB 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 screening procedures listed below will be performed and documented to assess whether a participant meets inclusion/exclusion criteria. Scope of activities at the screening visit will depend on the time of the visit in relation to the last PPMI annual visit.

Group A participants screened into the Master Protocol <6 months from the last PPMI visit
Group B participants screened into the Master Protocol ≥ 6 months from the last PPMI visit

Screening/General Activities:

- Obtain written informed consent
- Assess inclusion and exclusion criteria
- DAT SPECT eligibility
- *Demographics – collected previously from the PPMI study*
- *Obtain Medical and Family History - collected previously from the PPMI study*
- *Socioeconomics – collected previously from the PPMI study*
- Perform physical examination
- Measure vital signs, including height and weight
- Measure Orthostatic blood pressure

Neuro/Motor Assessment:

- Participant motor function questionnaire (group B only)*
- Freezing and Falls (group B only)*

- Neurological Exam
- MDS-UPDRS Part Ia
- MDS-UPDRS Part III Hoehn & Yahr
- MDS-UPDRS Ib & Part II
- Modified Schwab & England ADL
- Assess Features of Parkinsonism (group B only)*
- Other Clinical Features (group B only)*
- Clinical Diagnosis
- Primary Research Diagnosis

Non-Motor Assessments:

- Administer Olfactory Testing: University of Pennsylvania Smell Identification Test (UPSIT: group B only)*
- RBD Screening Questionnaire (group B only)*
- Epworth Sleepiness Scale (group B only)*
- SCOPA – AUT (group B only)*
- Neuro QoL (group B only)*

Cognitive & Psychiatric Assessments:

- Montreal Cognitive Assessment
- Clock Drawing (for group B only)*
- Lexical Fluency (group B only)*
- Hopkins Verbal Learning Test-Revised (group B only)*
- Benton Judgment of Line Orientation (group B only)*
- Modified Semantic Fluency (Animals only) (group B only)*
- Letter Number Sequencing (group B only)*
- Symbol Digit Modalities Test (group B only)*
- Trail Making Test (A and B) (group B only)*
- Modified Boston Naming Test (group B only)*
- Cognitive Change
- Cognitive Characterization
- State-Trait Anxiety Inventory for Adults (group B only)*
- Geriatric Depression Scale
- QUIP (group B only)*

Global Function Assessments (Group B only)*:

- CGI-S
- PGI-S
- PDAQ-27

- Novel PROs

Safety Assessments:

- Clinical safety labs
- Perform 12-lead electrocardiogram
- Administer the Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline questionnaire

Biological Sample Collection (Group B only)*:

- Research samples (blood and urine)
- Lumbar Puncture (LP)
- Skin biopsy

Imaging Activities:

- Collect blood sample for serum pregnancy test (for women of childbearing potential) prior to DAT SPECT Imaging (if applicable)
- Perform Dopamine Transporter SPECT Imaging
- MRI (group B only)*

Medications:

- Review and document concomitant medications

Randomization to RSSP:

- Randomization to open RSSP

Adverse Events (AE):

- Review and document adverse events related to Master Protocol procedures
- Current medical conditions review
- Report pregnancy

Other Assessments:

- Visit Status (group B only)*

9.2 Baseline/Randomization Visit

The Baseline/Randomization Visit will take place in-person after the Master Protocol Screening Visit. The following procedures will be performed and are listed in the order to be completed:

- Confirm Master Protocol inclusion/exclusion eligibility
- Measure Weight
- Measure Vital signs and Orthostatic Blood Pressure
- Administer Neurological and Motor Assessments including: MDS-UPDRS Part III and Hoehn & Yahr.
- Perform Global Function Assessments including: CGI-S, PGI-S, Novel PRO, PDAQ-27
- Administer the C-SSRS Baseline questionnaire
- Collect research samples (urine and blood)

- Review and document concomitant medications
- Assess any accessible inclusion/ exclusion criteria for eligibility into all available RSSPs. This is done via available data obtained or collected in the Master Protocol Screening visit.
- Randomization to active study drug or placebo
- Assess and document AEs related to Master Protocol procedures
- Assess current medical conditions
- Assess pregnancy status

9.3 Week 2 Telephone Visit

This visit will take place 14 ± 3 days after the Baseline Visit via telephone. The following procedures will be performed per the PPMI Assessment Manual and documented and are listed below:

- Digital Assessment per the PPMI Digital Sub Study (as needed)
- Administer C-SSRS Since Last Visit Short Form
- Concomitant medication review
- LEDD medication initiation log (as needed)
- Assess and document AEs
- Assess current medical conditions
- Assess pregnancy status (as needed)
- Surgery for PD (as needed)

9.4 Month 1 Visit

This visit will take place in person approximately 28 $\pm$ 7 days after the Baseline Visit. The following procedures will be performed:

- Measure Weight, Vital Signs & Orthostatic Blood Pressure
- Administer MDS-UPDRS Part I-III
- Digital Assessment per the PPMI Digital Sub Study (as needed)
- Collect blood samples for clinical safety labs
- Perform 12-lead electrocardiogram
- Administer C-SSRS Since Last Visit Short Form
- Concomitant medication review
- LEDD Medication Initiation Log (as needed)
- Assess and document AEs
- Current Medical Conditions Review
- Report of pregnancy (as needed)
- Surgery for PD (as needed)

9.5 Treatment Visits

Treatment visits will be conducted every 3 months (up to 24 months) ± 14 days after the Baseline Visit. Visits will be performed in person at the study clinic at months 3, 6, 12, 18, 24 and every 3 months after month 24 until the participant has completed the RSSP, or as necessary per the RSSP. Tele visits (audio/visual if possible) will be performed at visits 9, 15, and 21 unless in person visits are necessary at the discretion of the site investigator. Televisits will follow the same schedule of activities as outlined below with the exclusion of the assessments that cannot be completed remotely (see Schedule of Activities for details).

Month 3 Visit

- Measure Vital Signs & Orthostatic Blood Pressure, Weight
- Administer Neuro/Motor Assessments per the SOA (Table 1)
- Administer SCOPA-AUT
- Administer Cognitive and Psychiatric Assessments: Cognitive Change and Cognitive Characterization
- Perform Global Function Assessments: including CGI-S, PGI-S, PDAQ-27, Novel Participant Reported Outcomes
- Digital Assessment per the PPMI Digital Sub Study (as needed)
- Collect blood samples for clinical safety labs
- Administer C-SSRS Since Last Visit Short Form
- Concomitant medication review
- LEDD Medication Initiation Log (as needed)
- Assess and document AEs
- Current medical conditions review
- Report of Pregnancy (as needed)
- Surgery for PD (as needed)

Month 6 Visit

- Measure Vital Signs & Orthostatic Blood Pressure, Weight
- Administer Neuro/Motor Assessments per the SOA (Table 1)
- Administer Cognitive and Psychiatric Assessments: Cognitive Change, Cognitive Characterization, State Trait Anxiety Inventory for Adults, Geriatric Depression Scale, QUIP
- Perform Global Function Assessments: PDAQ-27
- Digital Assessment per the PPMI Digital Sub Study (as needed)
- Collect blood samples for clinical safety labs
- Administer C-SSRS Since Last Visit Short Form
- Collect research samples (blood and urine)
- Concomitant medication review

- LEDD medication initiation log (as needed)
- Assess and document AEs
- Current medical conditions review
- Report of Pregnancy (as needed)
- Surgery for PD (as needed)

Month 9 Visit

At month 9, a tele (audio/visual) visit will be performed, the following assessment will occur:

- Administer Neuro/Motor Assessments per the SOA (Table 1)
- Administer Cognitive and Psychiatric Assessments: Cognitive Change and Cognitive Characterization
- Digital Assessment per the PPMI Digital Sub Study (as needed)
- Administer C-SSRS Since Last Visit Short Form
- Concomitant medication review
- LEDD medication initiation log (as needed)
- Assess and document AEs
- Current medical conditions review
- Report of Pregnancy (as needed)
- Surgery for PD (as needed)

Please note, this visit can be converted to an in-person visit if needed, where the following would be collected in addition to the above:

- Measure Vital Signs & Orthostatic Blood Pressure, and Weight.
- Collect blood samples for clinical safety labs

Month 12 Visit

- Perform physical examination
- Measure Vital Signs & Orthostatic Blood Pressure, Weight
- Administer Neuro/and Motor Assessments per the SOA (Table 1)
- Administer Non-Motor Assessments: Olfactory testing UPSIT, RBD Screening Questionnaire, Epworth Sleepiness Scale, SCOPA– AUT, Neuro QoL
- Administer Cognitive & Psychiatric Assessments per the SOA (Table 1)
- Perform Global Function Assessments: including CGI-S, PGI-S, PDAQ-27, Novel Participant Reported Outcomes
- Digital Assessment per the PPMI Digital Sub Study (as needed)
- Collect blood samples for clinical safety labs
- Perform 12-lead electrocardiogram
- Administer C-SSRS Since Last Visit Short Form
- Collect research samples (blood and urine)

- LP
- Dopamine Transporter Injection & SPECT Imaging (with pregnancy test prior to DAT)
- MRI
- Concomitant medication review
- LEDD medication initiation log (as needed)
- Assess and document AEs
- Current medical conditions review
- Report of Pregnancy (as needed)
- Surgery for PD (as needed)
- Visit status

Month 15 Visit

At month 15, a tele (audio/visual) visit will be performed, the following assessments will occur:

- Administer Neuro/Motor Assessments per the SOA (Table 1)
- Administer Cognitive and Psychiatric Assessments: Cognitive Change and Cognitive Characterization
- Administer C-SSRS Since Last Visit Short Form
- Digital Assessment per the PPMI Digital Sub Study (as needed)
- Concomitant medication review
- LEDD medication initiation log (as needed)
- Assess and document AEs
- Current medical conditions review
- Report of Pregnancy (as needed)
- Surgery for PD (as needed)

Please note, this visit can be converted to an in-person visit if needed, where the following would be collected in addition to the above:

- Measure Vital Signs & Orthostatic Blood Pressure, and Weight.
- Collect blood samples for clinical safety labs

Month 18 Visit

- Measure Vital Signs & Orthostatic Blood Pressure, Weight
- Administer Neuro/Motor Assessments per the SOA (Table 1)
- Administer SCOPA– AUT
- Administer Cognitive and Psychiatric Assessments: Cognitive Change and Cognitive Characterization State-Trait Anxiety Inventory for Adults, QUIP, Geriatric Depression Scale
- Digital Assessment per the PPMI Digital Sub Study (as needed)
- Perform Global Function Assessments: including CGI-S, PGI-S, PDAQ-27, Novel

Participant Reported Outcomes

- Collect blood samples for clinical safety labs
- Administer C-SSRS Since Last Visit Short Form
- Concomitant medication review
- LEDD medication initiation log (as needed)
- Assess and document AEs
- Current medical conditions review
- Report of Pregnancy (as needed)
- Surgery for PD (as needed)

Month 21 Visit

At month 21, a tele (audio/visual) visit will be performed, the following assessments will occur:

- Administer Neuro/Motor Assessments per SOA (Table 1)
- Administer Cognitive and Psychiatric Assessments: Cognitive Change and Cognitive Characterization
- Digital Assessment per the PPMI Digital Sub Study (as needed)
- Administer C-SSRS Since Last Visit Short Form
- Concomitant medication review
- LEDD medication initiation log (as needed)
- Assess and document AEs
- Current medical conditions review
- Report of Pregnancy (as needed)
- Surgery for PD (as needed)

Please note, this visit can be converted to an in-person visit if needed, where the following would be collected in addition to the above:

- Measure Vital Signs & Orthostatic Blood Pressure, and Weight.
- Collect blood samples for clinical safety labs

Month 24 Visit

- Perform physical examination
- Measure Vital Signs & Orthostatic Blood Pressure, Weight
- Administer Neuro/and Motor Assessments per the SOA (Table 1)
- Administer Non-Motor Assessments: Olfactory testing UPSIT, RBD Screening Questionnaire, Epworth Sleepiness Scale, SCOPA– AUT, Neuro QoL
- Administer Cognitive & Psychiatric Assessments per the SOA (Table 1)
- Digital Assessment per the PPMI Digital Sub Study (as needed)
- Perform Global Function Assessments: including CGI-S, PGI-S, PDAQ-27, Novel Participant Reported Outcomes

- Collect blood samples for clinical safety labs
- Perform 12-lead electrocardiogram
- Administer C-SSRS Since Last Visit Short Form
- Collect research samples (blood and urine)
- LP
- Skin Biopsy
- Dopamine Transporter Injection & SPECT Imaging (pregnancy test prior to DaTscan)
- MRI
- Concomitant medication review
- LEDD medication initiation log (as needed)
- Assess and document AEs
- Current medical conditions review
- Report of Pregnancy (as needed)
- Study Completion Form (if that is End of RSSP visit)
- Surgery for PD (as needed)
- Visit status

9.6 Additional Treatment Visits

All participants will continue on an every 3 months visit schedule in the randomized RSSP until the last recruited participant completes the 24-month assessment or until 24 months since randomization have passed (if terminated early).

Following Month 24, participants will continue study visits every 3 months until the last participant randomized in the RSSP has had the opportunity to complete 24 months of follow-up on intervention. Participants will repeat the Months 15 – 24 visit schedules until the End of RSSP Treatment (Table 4). Therefore, Month 27 will follow the same schedule of activities as Month 15; Month 30 will follow the same schedule of activities as Month 18; Month 33 will follow the same schedule of activities as Month 21; Month 36 will follow the same schedule of activities as Month 24 and so on.

Table 4: Every 3-Month Visits After Month 24

Visit (After Month 24, Prior to End of RSSP Treatment)	**Follow This Visit Schedule of Activities**
Month 27	Month 15
Month 30	Month 18
Month 33	Month 21
Month 36	Month 24
Month 39	Month 15

Month 42	Month 18
Month 45	Month 21
Month 48	Month 24

9.7 Additional Safety Visits

Participants may have additional unscheduled visits if required for safety assessments. Additional details, including the timing of this visit can be found in the RSSP. At a minimum, these visits will involve an assessment and documentation of AEs and a review and documentation of concomitant medications.

9.8 Initiation of Dopaminergic Therapy Visit

In case the participants require initiation of dopaminergic therapy defined as Levodopa, dopamine agonists), an in-person visit should be scheduled prior to starting therapy. See schedule of activities in the SOA. If this visit occurs $\leq$ 90 days from the next in-clinic visit, replace this visit with the next in-clinic visit and follow the schedule of activities accordingly. The participants should be encouraged not to initiate dopaminergic therapy in between the in clinic P2P visits.

9.9 End of RSSP Treatment Visit

The schedule of activities for the End of RSSP Treatment Visit will follow the schedule listed in Section 9.5.

9.10 End of RSSP Treatment Safety Call

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

A safety follow-up call is required when a skin biopsy, LP, or DAT SPECT is performed. This follow-up phone call will assess adverse events occurring the day of and 2-3 days after the DAT SPECT, LP, or skin biopsy.

9.11 End of RSSP and Master Protocol

Participants will complete the RSSP after the last randomized participant has had the opportunity to complete 24 months on intervention or until 24 months since randomization have passed (if terminated early), and after all RSSP related activities have been completed. Participants who complete all activities for end of a specific RSSP may remain in the MP if they continue to meet all eligibility requirements described in Section 7 and wish to be screened for another RSSP as outlined in Section 8.4. Participants who complete their assigned RSSP and do not wish to be screened/ or 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.

9.12 Early Termination Visit (ET)

Participants who withdraw consent or early terminate from an RSSP will be asked to be seen for an in-person RSSP Early Termination Visit and complete Month 24 assessments.

The outcome measures that are required to be collected for each RSSP, and the timing of and activities for the RSSP Early Termination 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 observational study as per PPMI SOA regardless of enrollment status in the Master Protocol.

10. INVESTIGATIONAL PRODUCT

Investigational products will be provided and tested in RSSPs from different regimen partners. Each intervention may have multiple arms, such as different dosages, frequencies, or routes of administration.

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 pre-defined 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 concerns.
- 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(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. All regimens will be compliant with the Master Protocol, which outlines the majority of all clinical, biomarker, and safety assessments, making a shared placebo 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 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 pharmacist and designated pharmacy staff, SI, and clinical staff have 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 sub-protocol.

10.5 Concomitant Medications

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 sub-protocol. 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.

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.

Description of the MDS-UPDRS Part III as one of the primary outcome measures is provided in Section 11.1. Refer to the PPMI Operations 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 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 Site Investigator 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 schedule of activities. Only the OFF assessments will be used in the primary analyses. 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. All parts of the MDS-UPDRS will be conducted at study visits, as indicated on the schedule of activities. Ideally, the same SI should assess all participants in parts IA and III of the MDS-UPDRS at all study visits.

12. BIOLOGIC RESEARCH SAMPLING

Refer to the P2P Biologics Manual for the detailed description of the biologic samples collected and processing instructions.

12.1 Blood Samples

Whole blood (about 10 ml), serum (about 30 ml) and plasma (about 10 ml) will be collected as per Schedule of Activities to conduct proteomic, metabolomic, genetic and other research analyses. No more than 60 ml will be drawn at any visit, including both clinical safety labs and research blood samples.

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. Participants will not receive any individual results of research analysis or testing conducted on the biologic samples.

12.2 Urine

Urine (about 10 ml) will be collected to conduct analyte analyses.

12.3 Lumbar Puncture / Cerebral Spinal Fluid (CSF)

The LP is performed by the SI, or another qualified clinician appointed by the SI. An LP for the collection of 15-20 ml of CSF will be conducted for all PPMI participants per the PPMI visit schedule unless there is evidence of clinically significant coagulopathy or thrombocytopenia that would interfere with the safe conduct of the procedure. See PPMI procedure 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/working] days following an LP to assess for any adverse events. 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.

12.4 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 PPMI SOA (Table 1) unless specified otherwise in the RSSP. See PPMI procedure 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 Schedule of Activities. 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. Remaining samples may be used to evaluate other proteins, analytes, or potential biomarkers. Participants will not receive any individual results of analysis or testing conducted on the skin samples. Participants will be monitored the day of the procedure for adverse events. Participants will also be contacted by phone 2 to 3 business days following a skin biopsy to assess for any adverse events.

13. IMAGING

13.1 Dopamine Transporter (DAT) SPECT Imaging

Refer to the PPMI SPECT Technical Operations manual (TOM) 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 new participants will undergo DAT SPECT imaging at Master Protocol screening visit and at annual visits. P2P 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 TOM 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 adverse events on the day that a DAT SPECT is obtained. Participants will also be contacted by phone 2 to 3 [business/working] days following the injection/scan to assess adverse events.

DaTscan is being used "off-label" in the PPMI Clinical study. The imaging result obtained from the scan is not intended to provide information about a clinical diagnosis and will not be shared with participants.

13.2 Magnetic Resonance Imaging (MRI)

Participants will undergo an MRI brain scan at the RSSP screening visit and will also undergo follow up MRI scans as indicated in the visit schedule. P2P 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 RSSP screening visit (or follow-up) MRI scan, but these participants may still participate in the Master Protocol.

Refer to the PPMI MRI Technical Operations manual for a detailed description of the MRI imaging procedures.

13.3 Digital Assessment

The PPMI Observational Study has associated sub-studies containing various digital assessments. If a participant is enrolled in one of the PPMI digital sub-studies, they will continue enrollment in that sub-study while enrolled in the Master Protocol. The data collected can be assessed in the Master Protocol to support associated exploratory endpoints. If a Master Protocol participant is not currently enrolled in a PPMI digital sub-study, the site coordinator will encourage the participants to enroll in such digital sub-studies, if available. In addition, other digital health technologies may be incorporated in the individual RSSPs (refer to RSSP for details).

14. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The AE definition and reporting procedures for this Master Protocol comply with all applicable US Food and Drug Administration (FDA) regulations and International Conference on Harmonization 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 treatment-emergent adverse event (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 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 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 consent and randomization to RSSP. AEs, whether or not, they are related to the 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 adverse event.
- 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 AE/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 and confirmation that the event should be considered related to the investigational product for the purposes of expedited regulatory reporting.

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 that, 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 RSSP. Adverse Events 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.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. 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 a 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 adverse event and serious adverse events 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 AEs will be collected from the signing of consent form until the end of RSSP or 30 days following the last dose of RSSP drug (whichever comes first). SIs and coordinators will be instructed to assess for adverse events 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 AE should be followed until resolution or stabilization. AEs reported following a premature withdrawal or conclusion of participation visit should be followed for 30 days from last drug administration unless specified otherwise in the RSSP.

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 one business day of the first awareness of the event. The SI must 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 IND, Inc.

Relevant regulatory authorities must be notified by the appropriate IND holders of certain events. It is the SI's responsibility to notify the IRB or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. SIs will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

14.6 Medical Monitor (MM)

At least one MM will be appointed for this Master Protocol. 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 also serve as a liaison between the IMM and sites to collect any additional information required or requested by the IMM to complete their reviews in a timely manner. Finally, the MM will conduct protocol safety training and address any safety related questions from the CRO, study monitors, and other project team members.

14.7 Independent Medical Monitor (IMM)

At least one IMM will be appointed for this Master Protocol. The IMM 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. For any such reported SAEs or AEs, the IMM will be notified 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. If additional information is required to complete the evaluation of an SAE, the IMM may contact the MM to request more information from the site.

The unblinded statistician will provide aggregate reports of all AEs to the IMM for review on a quarterly basis (or as specified in each RSSP). These aggregate reports will summarize all AEs by severity (serious/not serious), attribution (anticipated or unanticipated), and relationship to the regimen-specific treatment. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA: version 26.1). The IMM will review these quarterly reports for any trends of interest or safety signals. Should any concerns arise due to observed trends, the IMM may send a written recommendation to the unblinded statistician via email requesting that the report be forwarded to the Data and Safety Monitoring Board (DSMB) for future review, as appropriate.

14.8 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 IMM'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 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

15.1 Primary Endpoints and Analyses

Primary scientific question: Does the treatment slow the rate of progression in DAT SPECT mean striatum 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 striatum SBR across time and (b) MDS-UPDRS Part III score across time. Both endpoints are measured until the final participant randomized has the opportunity to complete their 24 month follow up visit in the assigned RSSP. This results in greater than 24 months 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 concurrent and non-concurrent placebo. Analyses of treatment superiority will be performed assuming one-sided type I error of 5%. Each primary endpoint will be tested with equal priority with respect to active treatment superiority versus shared concurrent and non-concurrent placebo.

1) **DAT SPECT Mean Striatum SBR.** A Bayesian repeated measures model of mean striatum SBR, adjusted for baseline MDS-UPDRS part III score strata, will be used to compare the slope of active treatment versus the shared concurrent and non-concurrent placebo arm. The model allows for heterogeneity across individual baseline mean striatum SBR values and individual slopes, heterogeneity across regimens due to minor differences in the inclusion/exclusion criteria or mode of administration.

   It is hypothesized that an effective treatment will decrease the progression rate and slow the decline in mean striatum 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 groups will be conducted using the Bayesian posterior distribution.

   H_0: The active treatment group's average mean striatum SBR slope is equal to or less than that of the shared placebo arm.

   H_a: The active treatment group's average mean striatum SBR slope is greater than that of the shared placebo arm

   If the Bayesian posterior probability of active treatment superiority (H_a) is greater than or equal to a prespecified threshold of 0.95, the null hypothesis will be rejected, and the active treatment will be deemed superior to placebo with respect to the mean striatum SBR endpoint. This decision threshold 0.95 has been calibrated to control analysis one-sided type I error at approximately 5% per regimen via simulation.

2) **MDS-UPDRS Part III score.** A Bayesian repeated measures model of MDS-UPDRS Part III score over time, adjusted for the baseline score strata, will be used to compare the slope of active treatment with the shared concurrent and non-concurrent placebo arm. The model allows for heterogeneity across individual baseline MDS-UPDRS Part III score values and individual slopes, heterogeneity across regimens due to minor differences in the inclusion/exclusion criteria or mode of administration.

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 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 placebo arm.

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

If the Bayesian posterior probability of active treatment superiority (H_a) is greater than or equal to a prespecified threshold of 0.95, the null hypothesis will be rejected, and the active treatment will be deemed superior to placebo with respect to the MDS-UPDRS Part III score endpoint. This decision threshold of 0.95 has been calibrated to control analysis one-sided type I error at approximately 5% per regimen with simulation.

15.2 Randomization

The platform trial incorporates two stages of randomization.

1) Equal randomization to all currently *J* actively enrolling regimens for which a participant is eligible, where regimen denotes both active treatment and placebo groups.
2) After confirming any additional regimen specific eligibility criteria are met, stratification by baseline MDS-UPDRS part III score (<7 vs. ≥7), and then *J*:1 randomization within assigned regimen to either active treatment or placebo.

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 and at least 125 shared concurrent and non-concurrent control participants. To assess the required sample size, analyses were conducted using the observational cohort of participants in PPMI who meet NSD Stage 2B criteria and all eligibility criteria for the Master Protocol (based on a download of the PPMI data from 07/2024). These PPMI participants were recruited in two different cohorts: sporadic PD & prodromal. The participant's enrollment cohort significantly affects progression. Summaries of the two-year decline in the PPMI natural history data by subgroup (PD vs. prodromal) are included in Table 5 below. Assuming that 95% of the randomized participants for the P2P study are expected to come from the < 7 MDS-UPDRS Part III baseline strata, these data were used to inform assumptions for simulating virtual participant outcomes for longitudinal DAT SPECT mean striatum SBR and longitudinal MDS-UPDRS Part III.

Table 5: Two-Year Decline in Primary Endpoints by PPMI Natural History Cohort

Endpoint	PD Cohort (N = 76)	Prodromal Cohort (N = 94)
Mean Striatum SBR	-0.26 (0.17)	-0.12 (0.20)
MDS-UPDRS Part III	6.9 (8.0)	2.9 (3.9)

For a specific regimen, "power" is defined as the probability of demonstrating success on at least one of the primary endpoints. The primary analysis population for each regimen includes shared concurrent and non-concurrent control participants. As a result, regimens that enter the platform trial later can be expected to see an increased power relative to that of the first regimen as a result. Assuming 95% of randomized participants within an RSSP fall into the < 7 MDS-UPDRS Part III baseline strata, Table 6 demonstrates the benefits of the stated criteria by showing the probability of success for the first regimen under various assumed true values for the change on each endpoint. The first regimen in the platform is estimated to have 74%, 84%, and 91% power to detect treatment effects when both of the endpoints achieve 30%, 35%, and 40% slowing of progression, respectively. Similarly, we have greater than 86% power to declare success if there is truly a 40% or greater reduction in slope/progression of MDS-UPDRS Part III as long as there is at least a simultaneous 30% or greater reduction in mean striatum SBR. Finally, we have around 83% or higher probability of declaring success if there is truly a 40% or greater reduction in slope/progression on the DAT SPECT imaging endpoint and at least a 30% reduction on slope/progression on the MDS-UPDRS Part III endpoint. 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 10.3%. 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 Statistical Analysis Plan.

Table 6: Overall RSSP Power (Win on Either Endpoint)

UPDRS Slowing	DAT Slowing	Power
0%	0%	10.3%
0%	30%	49%
0%	40%	67%
0%	50%	82%
30%	0%	56%
30%	30%	74%
30%	40%	83%
30%	50%	91%
40%	0%	77%
40%	30%	86%

40%	40%	91%
40%	50%	94%
50%	0%	92%
50%	30%	95%
50%	40%	97%
50%	50%	98%

15.4 Missing Data

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 24 months) 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 sub protocol. 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 sub protocol.

To further assess the potential dependence of the results of the primary analysis to 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:

- 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-Based Imputation: Under this model, RSSP treatment participants with missing data are assumed to follow the same trajectory as placebo participants. Data from placebo participants only will be used to impute all missing data (from both RSSP treatment and placebo 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

ITT: The primary analysis for each analysis regimen is based on the intent to treat principle and includes all participants randomized to the active treatment arm of the analysis regimen and all

participants in a shared concurrent and non-concurrent control group, regardless of the adherence to the RSSP or duration of follow-up. The analysis shared control group includes all participants randomized to any control arm within any regimen who met the initial eligibility requirements for the specific RSSP of interest at randomization. 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.

Per-Protocol: 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 per protocol population. The PP population includes the subset of all ITT 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 PPMI data will be utilized for participants that drop out of the RSSP but remain in PPMI).

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 essentially important for the RSSP objectives. As such, no interim efficacy or futility analyses will be conducted.

15.7 Secondary Endpoints

15.7.1 Feasibility

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

15.7.2 Safety

Analyses to examine safety of each active treatment versus placebo 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 either chi-square tests of logistic regression models. 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. SAEs will be analyzed in the same manner as described above. Additional analyses will assess treatment-related SAEs and unanticipated SAEs in a comparable manner.

15.7.3 Tolerability

The assessment of tolerability will examine the percentage of participants on each treatment 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.

15.8 Key Exploratory Endpoints

15.8.1 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. Participants will be staged at all RSSP visits. 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.

15.8.2 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 15.1. The only difference will be that the outcome is modified accordingly.

15.8.3 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 15.8.1.

15.8.4 Change from 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 15.1.

15.8.5 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 15.8.1.

16. ETHICS/PROTECTION OF HUMAN SUBJECTS

16.1 Ethical Conduct of the Master Protocol

The Master Protocol and each accompanying RSSP will be conducted in accordance with GCP defined by the International Conference on Harmonization (ICH) and the ethical principles of the Declaration of Helsinki.

Each RSSP will be conducted in compliance with both the Master Protocol and corresponding RSSP. The Master Protocol, RSSP, and any amendments to either document as well as the participant informed consents for each will receive central IRB approval prior to initiation of the Master Protocol and/or RSSP.

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)

This Master Protocol will be conducted in compliance with current GCP and Title 21 Part 56 of the United States of America Code of Federal Regulations (CFR) relating to IRBs. The WIRB Copernicus Group (WCG) has been selected by the Michael J. Fox Foundation for Parkinson's Research to serve as the central IRB (cIRB) for the Master Protocol. Sites participating in this Master Protocol must have an executed Central IRB Authorization Agreement (Reliance Agreement) to rely on the MJFF to participate.

16.3 Participant Information & Informed Consent

This Master Protocol will be conducted in compliance with Title 21 Part 50 of the United States of America CFR, Federal Regulations 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 MP, 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 in that sub-protocol.

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 Screen Failures and Reassignment.

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 Site Investigator'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 is a Master Protocol for a platform study that determines participation in the RSSP, and all eligible participants are enrolled in PPMI observational 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 Observational trial.

Participants may develop AEs or abnormalities in vital signs, ECG, physical examination, or laboratory determinations during their participation in the Master Protocol. If these occur, the SI may discontinue a participant from the RSSP-specific intervention if, in his/her clinical judgment, continued participation would result in undue risk or further worsening of the condition. Such participants will be encouraged to continue in the Master Protocol off intervention.

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 MP will be documented in a protocol amendment, issued by the Sponsor. MP amendments will be submitted for approval to the central IRB prior to implementation. Written informed re-consent for continued participation in the Master Protocol may be required by participants already enrolled in the MP.

As additional RSSPs are added to the Platform Trial, they will be submitted for approval to the central IRB prior to implementation. Each sub protocol will be added as an appendix to the Master Protocol prior to any participant being assigned to that intervention. Addition of sub protocols will not require re-consent. Sub protocols that are stopped for futility or ended early due to success (if applicable) 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 MP detailed in this document and agree that any changes to the protocol must be approved by the cIRB. Each SI will be responsible for enrolling into the MP only those participants who have met all MP 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 US FDA, the Office for Human Research Protections, the sponsor, all pertinent national and local health and regulatory authorities, Master Protocol monitoring personnel, and the central IRB.

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 site investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of MJFF or its representatives. This will be documented in a Clinical Study Agreement between MJFF and the SI.

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

- Provide information and support to the site investigator(s) and MP 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 site investigator'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 protocol deviations 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 IRB.
- Review SI regulatory files to ensure the Trial Master File is current.

The monitor will be available between visits if the site investigator(s) or other staff needs 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. It is the responsibility of the SI to consider the participant's privacy and confidentiality when completing study visits and related protocol activities.

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 Site Management Core (SMC), 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 Florence electronic trial master file. Identifiable participant information may be stored within this system, which has been validated and deemed compatible with 21 CFR Part 11 requirements. Only site staff requiring access to related Master Protocol documentation will have permission to view identifiable information.

17.4 Data and Sample Sharing and Storage for Future Use

Additional data collected for this Master Protocol will be maintained and stored indefinitely on secure, password protected system(s). 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.

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 PPMI Executive Steering Committee will set the policy for publication of results from the P2P Trial and all RSSPs. No data or results generated from the P2P Platform Trial or its RSSPs may be published without written agreement from the PPMI Executive Steering Committee.

The responsibilities of the PPMI Executive Steering Committee are outlined in the P2P Platform Trial Governance Plan. Please, refer to the PPMI publication policy and the P2P Publication Addendum for further details.

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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) (Exception: low dose for RSL treatment-contact SMC for medical monitor approval) • Ropinirole (REQUIP, REQUIP XL) (Exception: low dose for RSL treatment-contact SMC for medical monitor approval) • 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)
Allowed PD medications	

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) • 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) • 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:	• 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 Aspartate aminotransferase (AST) Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Creatinine Direct Bilirubin Gamma-glutamyl transferase (GGT) Glucose Immunoglobulin E (IgE) Indirect Bilirubin LDH Magnesium Potassium Sodium Phosphate Total bilirubin Total protein Uric Acid TSH Serum pregnancy test
Urine	Blood Glucose Ketones Leukocytes Nitrite PH Protein Specific Gravity Pregnancy test

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 site investigator to assess clinical significance and pathological changes.

Table 7: 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 3 domains.
[2] Presence of qualifying functional impairment in any single domain qualifies for stage 3-6 but individuals can have combination in all 3 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.