PROTOCOL

Title: Early Longitudinal Imaging in Parkinson's Progression Markers Initiative Using [^{18}F] AV-133 and DaTscan™ (PPMI Early Imaging)

Sponsor: Institute for Neurodegenerative Disorders

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PPMI Early Imaging

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1. PURPOSE OF STUDY

The Parkinson Progression Marker Initiative (PPMI) is a longitudinal, observational, multi-center natural history study to assess progression of clinical features, digital outcomes, and imaging, biologic and genetic markers of Parkinson's disease (PD) progression in study participants with manifest PD, Prodromal PD, and Healthy Controls. The overall goal of PPMI is to identify markers of disease progression for use in clinical trials of therapies to reduce progression of PD disability.

PPMI is a broad program, expanding the goals of the original PPMI study. This protocol is a sub-study to the PPMI Clinical Protocol. It is a longitudinal, multi-center study to assess progression of clinical features and imaging and biomic biomarkers in individuals with Prodromal and manifest Parkinson's disease patients for up to 24 months.

1.1 Primary Objectives

Primary objective is to estimate the mean rates of change and the variability around the mean of imaging outcomes in individuals with Prodromal and manifest Parkinson's disease , and where appropriate the comparison of these rates between PD patient subsets at study intervals ranging from 6 months to 24 months. Specific examples of outcomes include dopamine transporter striatal uptake and vesicular monoamine transporter type-2 uptake. PD and Prodromal subsets may be defined by baseline assessments, genetic mutation, progression milestones and/or rate of clinical, imaging, or biomic change.

1.2 Secondary Objectives

Secondary Objectives include:

- To establish the predictive value of early imaging, clinical non-motor features, baseline imaging and biomic outcomes for future course of disease.
- To compare the longitudinal change of imaging outcomes and UPDRS and other clinical and blood and CSF biomarkers and sensor outcomes.
- To acquire safety data following injection of [^{18}F] AV-133.

2. STUDY OUTCOMES

2.1 Primary Outcomes

The mean rates of change and the variability around the mean of imaging outcomes in early and Prodromal PD patients, and where appropriate the comparison of these rates between PD patient subsets at study intervals ranging from 6 months to 24 months. Specific examples of outcomes include dopamine transporter striatal uptake and vesicular monoamine transporter type-2 uptake**.** PD patient subsets may be defined by baseline assessments, genetic mutation, progression milestones and/or rate of clinical, imaging, or biomic change.

2.2 Secondary Outcomes

- Baseline prediction value of early imaging for longitudinal clinical non-motor features, baseline imaging and biomic outcomes for future course of disease.
- Correlation between the longitudinal change of [^{18}F] AV-133 and DaTscan.
- Correlation between the longitudinal change of imaging outcomes and MDS-UPDRS, other clinical and blood biomarkers and sensor outcomes.

- Establish [^{18}F] AV-133 SUVr cutoffs for risk of developing progression to motor PD.
- Compare [^{18}F] AV-133 SUVr cutoffs with DaTscan SBR cutoffs for Prodromal PD participants.
- Descriptive safety data following injection of [^{18}F] AV-133.

3. BACKGROUND AND RATIONALE

3.1 Background for Longitudinal Imaging

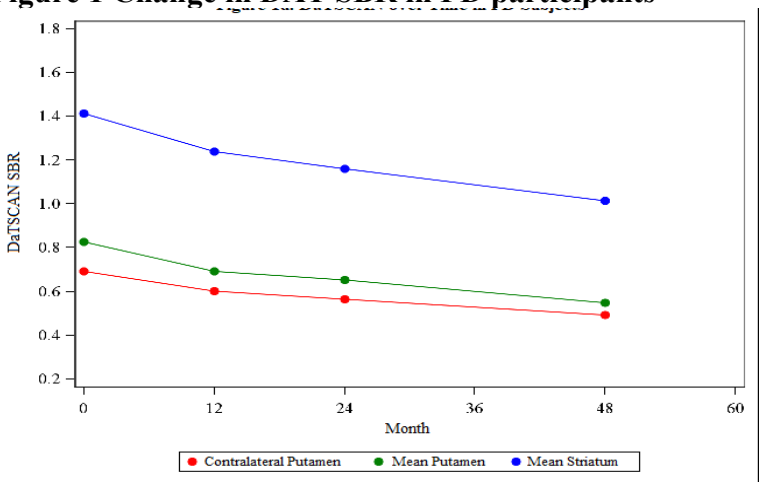
The defining motor features of Parkinson disease (PD) are characterized by their insidious onset and inexorable but variable progression. Reliable and well-validated biomarkers to monitor PD progression would dramatically improve patient care and accelerate research into both PD etiology and therapeutics (1). The Parkinson's Progression Marker Initiative (PPMI) is an observational, international, multi-center study designed to identify PD progression biomarkers both to improve understanding of disease etiology and course and to provide the necessary tools to enhance the likelihood of success of PD disease modifying therapeutic trials (ClinicalTrials.gov Identifier: NCT01141023). PPMI, begun in 2010 and expanded in 2019, continues to acquire longitudinal clinical, imaging and biologic data to identify PD progression markers that individually or in combination will rapidly reflect interval change in Prodromal and manifest PD patients in comparison to healthy controls and/or in sub-sets of Prodromal and manifest PD patients defined by baseline assessments, genetic mutations, progression milestones and/or rate of clinical, imaging or biospecimen change. PPMI has established a robust infrastructure of study cores and study sites that continue to work together and continue to expand the PPMI scope to include additional cohorts (Prodromal and Genetic) and additional assessments via companion protocols (FOUND, Digital Sensors). PPMI clinical and imaging data has been utilized by several pharmaceutical and biotech companies and academic groups to design and power developing and ongoing clinical trials for PD (2,3).

3.2 Rationale for study

In PPMI all Prodromal and manifest PD participants evaluated with dopamine transporter (DAT) imaging with ^{123}I Ioflupane or vesicular monoamine transporter (VMAT-2) imaging with ^{18}F-AV133 (Australia only) to determine eligibility. DAT (VMAT2 in Australia) imaging is repeated after 12, 24, and 48 months for Prodromal and manifest PD participants. In PPMI UPDRS and DAT imaging were identified as the two data anchors that could be used to assess longitudinal change in PD symptoms and degeneration (4,5).

Longitudinal DAT data acquired during a four-year interval have now demonstrated a robust change in DaTscan in PD participants as indicated below in Figure 1 and Table 1a and Table 1b.

Figure 1 Change in DAT SBR in PD participants



Data from a small subset of PPMI participants (N=17) were imaged with AV133 targeting VMAT2 and PD participant already enrolled in the early imaging protocol, in addition to or instead of (in Australia) DaTscan. While this data set is very small and must be viewed with caution, these data suggest that the change in VMAT is similar in magnitude to DaTscan, but with less variance in the rate of change resulting in a reduced sample size required to detect a therapeutic benefit in a clinical trial (Table 1a and Table 1b).

Table 1a AV133 and Table 1b DaTscan changes in PD participants in PPMI

Region	Norm PCT CHNG SBR	SD	S:N
Y1 lo put	-11.97	22.28	0.54
Y2 lo put	-17.98	18.56	0.97
Y1 hi put	-14.18	21.73	0.65
Y2 hi put	-20.12	18.09	1.11
Y1 mn stria	-13.77	26.6	0.52
Y2 mn stria	-19.72	18.02	1.09

AV-133 PET

Sample size/arm

Two arms, 80% or 90% power

p<. 0.05, two-tailed

n=30

Effect Size % Slowing SBR Change	Region	Norm PCT CHNG SBR	SD	S:N	80% power	90% power
30% Reduction in Rate of Change SBR	Y1 lo put	-8.4	22.28	0.38	604	809
	Y2 lo put	-12.6	18.56	0.68	186	249
	Y1 hi put	-9.9	21.73	0.46	410	548
	Y2 hi put	-14.1	18.09	0.78	141	189
	Y1 mn stria	-9.6	26.6	0.36	651	871
	Y2 mn stria	-13.8	18.02	0.77	146	195
40% Reduction in Rate of Change SBR	Y1 lo put	-7.2	22.28	0.32	340	455
	Y2 lo put	-10.8	18.56	0.58	105	140
	Y1 hi put	-8.5	21.73	0.39	230	308
	Y2 hi put	-12.1	18.09	0.67	79	106
	Y1 mn stria	-8.3	26.6	0.31	366	490
	Y2 mn stria	-11.8	18.02	0.66	82	110
50% Reduction in Rate of Change SBR	Y1 lo put	-6.0	22.28	0.27	218	291
	Y2 lo put	-9.0	18.56	0.48	67	90
	Y1 hi put	-7.1	21.73	0.33	147	197
	Y2 hi put	-10.1	18.09	0.56	51	68
	Y1 mn stria	-6.9	26.6	0.26	234	314
	Y2 mn stria	-9.9	18.02	0.55	52	70

Region	Norm PCT CHNG SBR	SD	S:N	Effect Size % Slowing SBR Change	Region	Norm PCT CHNG SBR	SD	S:N	80% power	90% power
Y1 lo put	-11	27.1	0.41	30% Reduction in Rate of Change SBR	Y1 lo put	-7.7	27.1	0.28	1037	1388
Y2 lo put	-25.5	37.9	0.67		Y2 lo put	-17.8	37.9	0.47	385	515
Y1 hi put	-12.6	32.3	0.39		Y1 hi put	-8.8	32.3	0.27	1155	1546
Y2 hi put	-18.9	25.6	0.74		Y2 hi put	-13.3	25.6	0.52	322	432
Y1 mn stria	-7.71	21.8	0.35		Y1 mn stria	-5.4	21.8	0.25	1398	1871
Y2 mn stria	-13.4	16.9	0.79		Y2 mn stria	-9.3	16.9	0.55	273	365
				40% Reduction in Rate of Change SBR	Y1 lo put	-6.6	27.1	0.24	587	786
Ioflupane SPECT					Y2 lo put	-15.3	37.9	0.40	216	290
					Y1 hi put	-7.6	32.3	0.23	648	867
					Y2 hi put	-11.4	25.6	0.44	181	242
Sample size/arm					Y1 mn stria	-4.6	21.8	0.21	786	1052
Two arms, 80% or 90% power					Y2 mn stria	-8.0	16.9	0.47	154	207
p<. 0.05, two-tailed				50% Reduction in Rate of Change SBR	Y1 lo put	-5.5	27.1	0.20	381	510
					Y2 lo put	-12.8	37.9	0.34	139	186
n=30					Y1 hi put	-6.3	32.3	0.20	412	552
					Y2 hi put	-9.5	25.6	0.37	115	184
					Y1 mn stria	-3.9	21.8	0.18	502	672
					Y2 mn stria	-6.7	16.9	0.40	100	134

Current PPMI DaTscan and AV133 data have provided preliminary sample size estimates to power developing clinical trials.

This PPMI Early Imaging study will:

- Directly examine whether early (6-month) imaging with DaTscan and [18F] AV-133 will provide an early signal of disease progression in recently diagnosed untreated PD patients.
- Investigate AV133 in Prodromal PD to explore the reduction in binding that is predictive of development of manifest PD. Compare the reduction in AV133 and DaTscan binding in Prodromal PD.
- Elucidate the longitudinal change in AV-133 with an adequate sample of Prodromal and early PD participants to accurately determine the sample size required to power a clinical trial for disease progression.
- To explore analyses of the longitudinal changes in imaging outcomes using an exponential fit to assess sample size required to power a clinical trial for disease progression.

4. STUDY DESIGN

The study is a longitudinal, multi-center study to assess progression of DaTscan and [^{18}F] AV-133 imaging in PD and Prodromal patients. Participants will be followed for up to 24 months. Approximately 50 early PD participants and 100 Prodromal participants will be recruited from up to 15 sites. Participants will be comprehensively assessed at baseline and follow up according to the Schedule of Activities for the respective cohort. Participants will undergo imaging assessments with DaTscan and [^{18}F] AV-133 and clinical (motor, neuropsychiatric and cognitive) assessments. Data will be collected by each site under uniformly established protocols and data will be stored and analyzed at designated core facilities.

5. STUDY POPULATION

Approximately 50 early PD and 100 Prodromal participants will be recruited from up to 15 sites internationally.

6. PARTICIPANT ELIGIBILITY

6.1 Inclusion Criteria:

a) A PD participant consented to PPMI Clinical, or, a Prodromal participant confirmed eligible to proceed to PPMI Clinical Baseline visit.
b) Able to provide informed consent.
c) Women may not be pregnant, lactating or planning pregnancy during the study.
   - Includes a negative serum pregnancy test prior to Baseline ^{18}F-AV-133 injection.
   - Includes a negative urine pregnancy test prior to injection of ^{18}F-AV-133 on day of Baseline PET scan.
   - Women participating in the study must be of *non-childbearing potential* or be using a *highly effective method of birth control* 14 days prior to until at least 24 hours after the last injection of ^{18}F-AV-133.
     - Non-childbearing potential is defined as a female that must be either postmenopausal (no menses for at least 12 months prior to Baseline) or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy).
     - Highly effective method of birth control is defined as practicing at least one of the following: A birth control method that results in a less than 1% per year failure rate when used consistently and correctly, such as oral contraceptives for at least 3 months prior to injection, an intrauterine device (IUD) for at least 2 months prior to injection, or barrier methods, e.g., diaphragm or combination condom and spermicide. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) is not acceptable.

6.2 Exclusion Criteria:

a) Received any of the following medications that might interfere with ^{18}F- AV-133 PET imaging: tetrabenazine (TBZ) or methylphenidate, reserpine, or amphetamine derivative, within 1 month prior to the Baseline ^{18}F-AV-133 injection.
b) Have current clinically significant cardiovascular disease or abnormalities on screening ECG (including but not limited to QTc > 450 msec).
c) Are currently taking medications that are known to cause QT- prolongation
d) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.

7. OBTAINING INFORMED CONSENT

PPMI Early Imaging participants will be screened for the PPMI Clinical protocol and will then provide informed consent to participate in the additional activities under this Early Imaging protocol.

7.1 Obtaining Informed Consent

The procedures and requirements of the study, together with any potential hazards/risks, and the freedom to withdraw from participation in the study at any time, will be explained to each potential participant as part of the consent process. The consent process will take place in a space that allows for privacy and confidentiality and should allow for enough time for the individual to consider participation and ask any questions. Consent will be obtained by the study Investigator or delegated study staff, as applicable. Each participant will sign such an informed consent to document agreement to participate in the study, as well as to document HIPAA authorization and compliance with GDPR regulation, as applicable. The signed informed consent will be uploaded to a secure portal for remote monitoring. Consent may be obtained electronically, once this process is established for the site.

It is the responsibility of the Investigator (or as delegated to the person obtaining consent) to make sure that the participant understands what she/he is agreeing to and that written informed consent is obtained before the participant is involved in any protocol-defined procedures. Each participant will be provided a copy of the consent forms. In addition to obtaining initial consent to participate, Investigators must ensure ongoing consent as part of this longitudinal study (for example, documentation at subsequent study visits that the participant continues to understand the procedures and requirements of the study).

8. PARTICIPANT ID ASSIGNMENT

8.1 Participant ID Number

All participants will already have a PPMI Participant ID assigned under the PPMI Clinical Protocol. This same number will be used to identify participants on all Early Imaging study related documentation.

9. STUDY PROCEDURES

Study visits may occur over the period of more than one day due to the complexity of the visits and resources required at the site. The date each assessment was completed will be captured within the EDC system and will therefore reflect whether a visit required a duration of more than one day to complete.

Baseline visit will be considered day 0. Once all Baseline activities have been completed and the Investigator determines that all eligibility criteria have been met, the participant may be considered enrolled into the study. Follow up 6 month (early PD cohort) and annual visits (Prodromal and early PD cohorts) should be completed with $\pm$45 days of the target visit date. Out of window visits will not be considered a protocol deviation but will be monitored throughout the study for each site.

Assessments that require completion by the Site Investigator (or trained designee) include the following (it is the goal of the study that the clinical assessments be conducted by the same individual throughout the study):

- Informed Consent
- Review Inclusion/Exclusion criteria
- All other clinical assessments as designated in the PPMI Clinical protocol

9.1 Baseline Visit (Day 0):

Refer to the PPMI Early Imaging Schedule of Activities for the activities to be conducted at the Baseline visit.

After consenting and being screened for PPMI Clinical protocol, participants interested in completing additional scans under this study will be asked to complete the PPMI Early Imaging consent. Prodromal participants interested in participating must additionally be deemed eligible to proceed to the Clinical Baseline visit in order to be considered for participation in this Early Imaging study.

Once all Baseline activities have been completed and the Investigator determines that all eligibility criteria have been met, the participant may be considered enrolled into the study. The activities at the Baseline visit will be completed in combination with the PPMI Clinical protocol activities. The combined visit is anticipated to take about 8 hours and could occur over more than one day.

9.2 Follow up Visits

Refer to the PPMI Early Imaging Schedule of Activities (see Appendices) for the activities to be conducted at follow up visits (Early PD or Prodromal).

All early PD participants will be evaluated in clinic at 6, 12, and 24 months. All Prodromal participants will be evaluated at 12 and 24 months. Annual visits are anticipated to take about 6-8 hours (could occur over more than one day), while the 6-month in clinic visits will take about 2-4 hours. Follow up visits will be completed in combination with participant's PPMI Clinical protocol activities. Study visits may occur over more than one day.

9.3 Withdrawal from the Study

If a participant withdraws from the study, determine if participant is willing to complete one last VMAT-2 PET scan (if not done in the last 3 months). If the participant does not want to be seen for any more assessments, complete the Conclusion of Participation assessment under the last completed visit.

10. CLINICAL ASSESSMENTS

Refer to the PPMI Assessment Manual for a detailed description of the clinical assessments and instructions for administration.

11. SAFETY ASSESSMENTS

All applicable safety assessments, including the routine Screening clinical lab tests, will be completed for enrolled participants under the PPMI Clinical protocol.

12. IMAGING

12.1 Dopamine Transporter SPECT Imaging

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

Early PD participants will undergo one additional dopamine transporter imaging scan to measure dopamine transporter binding using single photon emission computed tomography (SPECT) under this protocol at the 6-month visit. All participants will otherwise complete SPECT scans according to the PPMI Clinical Protocol Schedule of Activities.

The SPECT imaging procedure will be performed at the individual sites using DaTscan™ as the dopamine transporter. DaTscan imaging eligibility will be determined using pre-specified imaging cut-offs. DaTscan 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 dopamine transporter. Within a 4-hour (+/- 30 minute) window following the injection, participants will undergo DaTscan 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 dopamine transporter SPECT scan is obtained. Participants will also be contacted by phone 2 to 3 business days following the injection/scan to assess adverse events. These events will be reported by the site investigator, as required, to the site's Institutional Review/Ethics Board and to his/her Radiation Safety Committee.

12.2 VMAT-2 PET Imaging

Refer to the PPMI PET Imaging manual for a detailed description of the PET imaging procedures.

Participants will undergo [^{18}F] AV-133 PET imaging targeting the vesicular monoamine transporter. All participants will undergo an initial [^{18}F] AV-133 PET imaging scan at baseline and repeat imaging as indicated in the visit schedule. [^{18}F] AV-133 will be provided to the imaging sites from local production sites with necessary local regulatory approvals. The production of [^{18}F] AV-133 PET will be overseen by Invicro, LLC.

Since AV-133 PET imaging is investigational, it cannot provide definite information about a clinical diagnosis. Participants will be monitored by study personnel for adverse events on the day that a [^{18}F] AV-133 PET scan is obtained. Participants will also be contacted by phone 2 to 3 business days following the injection/scan to assess adverse events. These events will be reported by the site investigator as required to the site's Institutional Review/Ethics Boards and to his/her Radiation Safety Committee.

The procedures that would take place for [^{18}F] AV-133 injection is described below and detailed in the PPMI PET Imaging manual.

12.2.1 [^{18}F] AV-133 Imaging Procedures

Women of childbearing potential must have a serum pregnancy test prior to injection of [^{18}F] AV-133. The result must be confirmed as negative prior to proceeding with the injection. During the [^{18}F] AV-133 PET imaging visit, subjects will receive a single I.V. administration of 222 MBq (6 mCi) +/- 10% of [^{18}F] AV-133, approximately 80 minutes prior to first PET imaging scan. The data and quality assurance procedures to be employed in this study are described in the PPMI PET Imaging manual.

13. CONCOMITANT MEDICATIONS

13.1 Use of Concomitant Medications

Concomitant medications, including over-the-counter (OTC), dietary supplements (e.g., herbal remedies) or prescriptions, are permitted during the study period, except for the following medications that might interfere with dopamine transporter SPECT imaging which are restricted for 5 half-lives prior to a DaTscan™ injection: alpha methyldopa, methylphenidate, modafinil, amphetamine derivatives and other CNS stimulants. Medications known to be associated with drug induced parkinsonism will not be allowed for 6 months prior to screening and for the duration of the study, dopamine receptor blockers (neuroleptics), metoclopramide and reserpine. All concomitant medications reported at the time of the Baseline visit and for the duration of participation are recorded on the study medication logs.

13.2 Initiation of PD Medications

It is anticipated that PD participants will not require PD medications for at least 6 months after Baseline. However, PD medications may be initiated at any time after enrollment at the discretion of the participant or treating physician. The medication used is at the discretion of the treating physician. The Investigator will document any new medications or changes in medication at each study visit on the study medication logs.

14. PARTICIPATION IN CLINICAL TRIALS

It is preferred that participants do not participate in clinical trials of investigational study drugs during participation in this Early Imaging study. The investigator will document the study drug dosage, if applicable, and, if unknown, will report on the identity of any study drug and the dosage after it is unmasked.

15. RISKS TO PARTICIPANTS

15.1 Imaging

Specific potential risks for dopamine transporter SPECT imaging and VMAT-2 PET imaging are as follows:

- Radiation exposure from DaTscan™, [^{18}F] AV-133
- Potential pharmacological effects of DaTscan™, ^{18}F-AV-133
- Having an intravenous injection.

15.2 DaTscan™ Imaging

Risks of DaTscan™: DaTscan™ is administered at radiotracer doses and is not expected to have any pharmacological or toxicological effects. DaTscan™ binds to the dopamine

and serotonin transporter. At pharmacologic doses DaTscan™ might be expected to have stimulant-like effects and affect cardiovascular responses. However, in the proposed study the estimated mass dose of DaTscan™ is very low (<30/pmol kg). More than 500,000 doses of the radiotracer have been administered to human participants.

Iodine: Prior to each injection participants will be pretreated with Lugol's solution, 10 drops of a saturated solution of potassium iodide) to reduce thyroid uptake of the radioactive agent. Participants may experience a metallic or bitter taste in their mouths from the iodine. Participants with allergies to iodine might get itching, a rash, bloating, severe blood pressure changes (shock), and death if given iodine. Participants who are allergic to iodine may be imaged without Lugol's or if available may be administered potassium perchlorate rather than Lugol's.

15.3 [^{18}F] AV-133

Risks of [^{18}F] AV-133: The most up-to-date and complete information regarding the use of [^{18}F] AV-133 can be found in the investigator's brochure. [^{18}F] AV-133 is an experimental imaging agent that will be used at relatively low (tracer) doses. However, because [^{18}F] AV-133 is in the early stages of clinical investigation, subjects receiving [^{18}F] AV-133 for injection will be followed closely by means of adverse event reporting and vital signs. The potential for drug-drug interactions is not presently known. There is no data on the effects of [^{18}F] AV-133 in human prenatal development. For this reason, fertile females must avoid becoming pregnant and must use adequate contraceptive methods 14 days prior to until at least 24 hours after injection of [^{18}F] AV-133. [^{18}F] AV-133 for injection must not be administered to females who are pregnant or lactating.

15.4 Unknown Risks

In addition to the known risks listed above, the imaging procedures in this study may cause unknown risks to the participant, or a developing embryo or fetus or possible risks to the future offspring of male participants. Female subjects or a female partner of a male subject who report a pregnancy within 30 days of DaTscan™ injection will be asked to have a urine pregnancy test.

16. REFERRALS IN THE CASE OF CLINICALLY RELEVANT FINDINGS

If a research assessment reveals a clinically significant abnormality, the participant will be informed of this result and instructed to follow up with his or her primary care physician. Should there be a safety concern warranting a referral for medical or psychiatric follow-up, the Investigator should provide the participant with the appropriate referral as necessary. The sites will follow their standard procedures for urgent and non-urgent medical situations identified during study visits.

17. RETURN OF RESEARCH FINDINGS

In addition to the standard of care/clinically relevant results described above, information collected may result in obtaining research findings that could impact a participant's clinical care choices or decisions due to the extensive clinical and biomarker characterization that participants undergo in PPMI to achieve the goals of this study (for example, genetic results from non-CLIA certified testing, change in research diagnosis). The Investigator will use his/her judgment in determining whether to discuss these findings with the participant.

18. POTENTIAL BENEFITS TO PARTICIPANTS

There are no direct anticipated benefits to study participants in this study. However, new information may be generated by the study that will support development of better treatments for Parkinson's disease.

19. COSTS FOR PARTICIPATION

All research travel, assessments and tests will be provided with no cost to the study participant.

20. PAYMENT AND REIMBURSEMENT FOR PARTICIPATION

Participants will be paid for completed study visits based on the visit type. Participants who require travel to the clinical site, or incur other costs associated with a study visit, will be reimbursed according to the study reimbursement guidelines. Participants will have options to receive funds which will be explained during the consent process.

21. PARTICPANT WITHDRAWALS

Study participants will be informed during the consent process that they have the right to withdraw from the study at any time without prejudice and may be withdrawn at the Investigator's or Sponsor's discretion at any time. Participants who withdraw may remain in the main PPMI Clinical study. Any information that has already been collected prior to the study participant's withdrawal will not be removed.

22. ADVERSE EVENTS

22.1 Adverse Event Reporting Requirements

Site investigators and coordinators will be instructed to assess for adverse events at the study visit when dopamine transporter SPECT imaging or AV-133 PET imaging is conducted, as well as by telephone 2 to 3 business days following such activity. Adverse experiences, whether observed by the investigator, or elicited from or volunteered by the participant, should be recorded on the Adverse Event Log. Events occurring outside of the study procedure adverse event reporting period defined above do not require documentation for study purposes (i.e., will not be listed on the Adverse Event Log).

Any adverse event ongoing at the 2 to 3 business day reporting telephone visit, should be followed until resolution or stabilization. Adverse events reported following a premature withdrawal or conclusion of participation visit should be followed not more than 30 days from last study procedure (i.e., SPECT imaging, PET imaging).

Adverse events will be reported by the site as required by the site's Institutional Review/Ethics Board and to the Radiation Safety Committee, as applicable.

22.2 Serious Adverse Event Reporting Requirements

Serious adverse events pertaining to DaTscan SPECT imaging or AV-133 PET imaging will be reported as follows:

a. Any serious adverse event occurring within 24 hours following ^{18}F-AV-133 injection will be documented on the Adverse Event Log and reported by the site to Invicro using the PPMI AV-133 SAE Report Form.

b. Notwithstanding the estimated data availability timeframe, Invicro will report to sponsors of companion studies involving therapeutic agents per the respective protocol within 24 hours of notification from the site of an occurrence of any SAE occurring within 48 hours post ^{18}F-AV-133 injection.

c. Any serious adverse event occurring within 24 hours following the DaTscan™ injection will be documented on the Adverse Event Log and reported to GE Healthcare using the PPMI GE Healthcare SAE Report Form, whether assessed as related to administration of DaTscan™ or not.

d. Any serious adverse event occurring more than 24 hours following the DaTscan™ injection that is assessed as being related to the DaTscan™ injection will be documented on the Adverse Event Log and reported to GE Healthcare using the PPMI GE Healthcare SAE Report Form.

e. The Investigator will comply with his/her local Institutional Review Board (IRB)/Ethics Board, and Radiation Safety Committee (as applicable), regarding the reporting of adverse experiences.

22.3 Adverse Event Definitions

Adverse Events (AE)
An AE is any undesirable experience occurring to a participant during study participation, whether or not considered related to the study procedure.

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 investigator, 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 participant 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

Unexpected Adverse Event

For FDA reporting purposes, an unexpected AE is an AE not previously reported or an AE that occurs with specificity, severity or frequency that is not consistent with the current investigator's brochure.

22.4 Assessing Relationship of Adverse Events

The assessment of the relationship of an AE to the imaging 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) and the study procedure should be considered:

- Unrelated - No possible relationship
  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 - Not reasonably related, although a causal relationship cannot be ruled out. 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.

- Possible - Causal relationship is uncertain
  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.

- Probable - High degree of certainty for causal relationship
  The temporal relationship between study procedure and the adverse event onset/course is reasonable and other causes have been eliminated or are unlikely.

- Definite - Causal relationship is certain
  The temporal relationship between study procedure and the adverse event onset/course is reasonable and other causes have been eliminated.

22.5 Assessing Intensity/Severity of Adverse Events

In addition to assessing the relationship of the adverse event to the study procedure, an assessment is required of the intensity (severity) of the event. The following classifications should be used:

- *Mild:*
  A mild AE is an AE, usually transient in nature and generally not interfering with normal activities.
- *Moderate:*
  A moderate AE is an AE that is sufficiently discomforting to interfere with normal activities.
- *Severe:*
  A severe AE is an AE that incapacitates the participant and prevents normal activities. Note that a severe event is not necessarily a serious event. Nor must a serious event necessarily be severe.

23. SIGNIFICANT STUDY EVENTS

There are important events that might occur during a participant's follow up in the study, such as initiation of PD medication, new clinical diagnosis, an SAE, pregnancy, or death. This information will be captured within the study database and may result in additional follow up with the site. These events are fully described in the PPMI Operations Manual.

24. STUDY MONITORING AND SITE MANAGEMENT

The PPMI Steering Committee has the responsibility to monitor all procedures for safety, GCP, and regulatory compliance. The study sites will be managed and overseen in an ongoing manner to verify:

(a) The rights and well-being of human participants are protected.
(b) The reported study data are accurate, complete, and attributable.
(c) The conduct of the study follows the currently approved protocol/amendment(s) , with GCP, and with the applicable regulatory requirement(s).

25. 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 study. It is the responsibility of the site Investigator to consider the participant's privacy and confidentiality when completing study visits and related protocol activities.

The Site Investigator 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 study participants under the Health Insurance Portability and Accountability Act (HIPAA), while European sites have additional obligations under the EU General Data Protection Regulation (GDPR). Participants will be identified by participant ID numbers on data forms and other study materials submitted to the Site Management Core (SMC), the central laboratory (if applicable), and central biorepository.

The Site Investigator will permit the study monitor or designated SMC representative to review signed informed consent(s) and that portion of the participant's medical record that is

directly related to the study (or provide certified copies of source documentation upon request). This shall include all study 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 study, and autopsy reports for deaths occurring during the study (when available). In addition, electronic document storage will be maintained with 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 study staff requiring access to related study documentation will have permission to view identifiable information.

26. DATA AND SAMPLE SHARING AND STORAGE FOR FUTURE USE

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

Data collected for this study may be transferred and shared across participating PPMI Cores including the Clinical Trials Statistical and Data Management Core (CTSDMC) at the University of Iowa, Indiana University PPMI Cores (Indianapolis, IN), the Site Management Core and Data Systems and Technology Operations at the Institute for Neurodegenerative Disorders (New Haven, CT)for conducting analyses as pertains to the study including, but not limited to, enrollment, compliance, study outcomes and, in combination from the data received from PPMI Online and PPMI Remote studies, to enable modifications to the predictive Prodromal eligibility criteria. All PPMI data will be incorporated into the PPMI database to create a fully harmonized PPMI database.

All data obtained during the conduct of this study will be sent to the Laboratory of Neuro Imaging (LONI) in Los Angeles, California to be stored indefinitely for research purposes. Research data will be made available to researchers to conduct analyses related to PD and other disorders. Researchers will be required to comply with the PPMI data agreement to receive data. All personally identifiable information will be removed before it is shared outside the study.

27. ANALYSIS PLAN

Information summarizing planned analyses is described as follows.

- Longitudinal change in ^{18}F-AV-133 and DaTscan. The analyses will examine the change during 24 months in each imaging outcome. The change will be modeled using both linear modeling and exponential fit. Continuous variables will be examined using a t-test. The change in each imaging outcome will be compared at 6, 12 and 24 months.
- Examination of whether short-term change in ^{18}F-AV-133 and DaTscan is predictive of change in long-term endpoints. This analysis will examine whether short-term change in the ^{18}F-AV-133 and DaTscan is predictive of changes in long-term endpoints such as MDS-UPDRS score and other clinical and biologic endpoints. If successful, the final model will identify short-term progression imaging endpoints that are predictive of the change in one or more of the long-term endpoints. This would suggest

that these short-term progression endpoints are valid biomarkers for future studies of interventions in PD patient populations.

- Comparison of longitudinal change in progression endpoints. The analyses will examine the change during 24 months in clinical, biologic and compare with imaging outcomes. The change will be modeled using both linear modeling and exponential fit. For continuous progression endpoints, the change over time will be modeled using a mixed model approach. For dichotomous progression endpoints, a logistic regression model will be fit.
- Compare baseline [^{18}F] AV-133 SUVr with DATscan SBR for Prodromal PD participants and explore [^{18}F] AV-133 SUVr cutoffs for risk of developing progression to motor PD in participants developing motor PD.
- Examination of Prodromal and early PD Subsets. Each of the first three sets of analyses will be repeated comparing subsets of PD subjects understanding that the sample size for this study is modest. If successful, the final model from these subset comparisons will determine whether the short-term progression endpoints are more predictive of long-term change in the MDS-UPDRS score for some subsets of PD subjects and less predictive for other subsets of PD subjects.

27.1 Determination of Sample Size

As summarized above, much of the proposed analysis plan for the study is focused on a set of exploratory analyses with the goal of identifying longitudinal change in imaging outcomes and whether short-term imaging change can be used as biomarkers for future studies in PD patient population.

The planned sample size of 50 early PD and 100 Prodromal participants for this study was based on existing data from the PPMI study demonstrating an approximately 8-13%. 5% and 13-19% reduction from baseline in DAT and AV133 during a 12 and 24month interval in early PD. Based on the assumption that

- The change in DAT and AV133 in Prodromal PD will be similar to that in early PD
- The 6-month change in DAT and AV133 in early PD will be approximately 4-7% from baseline, then the sample size will be adequate to examine the longitudinal change in DAT and AV133 at each imaging timepoint.

Other analyses assessing the AV13 binding cutoff to predict progression to PD and the comparison of imaging and clinical and biologic outcomes are exploratory.

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29 Appendix 1- Schedule of Activities for Early PD Participants

PPMI Early Imaging Schedule of Activities
(Early PD Participants)

	Visit Number	Baseline (BL)	V02	V04	V06
Assessment	**[**]Timepoint**	**0**	**6 mths**	**12 mths (YR1)**	**24 mths (YR2)**
Consent Activities					
Documentation of Informed Consent		I			
Continuing Consent			X	X	X
Informed Consent Tracking Log		X	As Needed		
Additional AV-133 Activities					
Review Early Imaging Inclusion/Exclusion Criteria		X			
ECG		X			
Dopamine Imaging[b]			X		
Pregnancy Test (prior to AV-133 injection), if applicable		X	X	X	X
VMAT-2 Imaging[c]		X	X	X	X
Early Imaging Screen Fail		As Needed			
Conclusion of Early Imaging Study Participation			As Needed		
Safety and General Health					
[#]Adverse Events		X	X	X	X
Adverse Event Telephone Assessment		X	X	X	X
Report of Pregnancy		As Needed			

**Window of ±45 days either side of Target Visit Date
I = Investigator (or trained designee) completed assessment
X = Investigator or Coordinator completed assessment (or as otherwise delegated)
b = Urine pregnancy test prior to injection on day of imaging for women of childbearing potential.
c = Serum pregnancy test at BL for women of childbearing potential; Urine pregnancy test prior to injection on day of follow up scans for women of childbearing potential.
#Adverse events collected only day of and 2-3 business days post DaTscan injection or AV-133 injection per protocol.

30 Appendix 2- Schedule of Activities for Prodromal Participants

PPMI Early Imaging Schedule of Activities
(Prodromal Participants)

	Visit Number	Baseline (BL)	V04	V06
Assessment	**[**]Timepoint**	**0**	**12 mths (Y1)**	**24 mths (Y2)**
Consent Activities				
Documentation of Informed Consent		I		
Continuing Consent			X	X
Informed Consent Tracking Log		X	As Needed	
Additional AV-133 Activities				
Early Imaging Inclusion/Exclusion Criteria		X		
ECG		X		
Pregnancy Test (prior to AV-133 injection), if applicable		X	X	X
VMAT-2 Imaging[c]		X	X	X
Early Imaging Screen Fail		As Needed		
Conclusion of Study Participation			As Needed	
Safety and General Health				
[#]Adverse Events		X	X	X
Adverse Event Telephone Assessment		X	X	X
Report of Pregnancy		As Needed		

**Window of ±45 days either side of Target Visit Date

I = Investigator (or trained designee) completed assessment

X = Investigator or Coordinator completed assessment (or as otherwise delegated)

c = Serum pregnancy test at BL scan for women of childbearing potential; Urine pregnancy test prior to injection on day of follow up scans for women of childbearing potential.

#Adverse events collected day of and 2-3 business days post AV-133 injection per protocol.