PROTOCOL

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

Sponsor: The Michael J. Fox Foundation for Parkinson's Research

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PPMI AV-133 Prodromal 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.

This protocol is a sub-study under the PPMI Program. It is a longitudinal, multi-center study to assess progression of [^{18}F] AV-133 imaging in individuals enrolled with Prodromal Parkinson's disease 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 [^{18}F] AV-133 imaging outcomes in individuals with Prodromal Parkinson's disease, and where appropriate the comparison of these rates between patient subsets at study intervals ranging from 12 months to 24 months. Prodromal subsets may be defined by baseline assessments, genetic mutation, progression milestones and/or rate of clinical, imaging, or biomarker change.

1.2 Secondary Objectives

Secondary Objectives include:

- To establish the predictive value of prodromal [^{18}F] AV-133 imaging for of motor and nonmotor PD symptoms, and imaging and blood and CSF biomarkers and sensor outcomes.
- To compare the longitudinal change of [^{18}F] AV-133 imaging outcomes and UPDRS and other clinical outcomes, imaging 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 [^{18}F] AV-133 PET SUVr in Prodromal PD patients, and where appropriate the comparison of these rates between patient subsets at study intervals ranging from 12 months to 24 months.

2.2 Secondary Outcomes

- [^{18}F] AV-133 imaging prediction of longitudinal clinical non-motor features, imaging and blood and CSF biomarkers and sensor outcomes.
- Develop [^{18}F] AV-133 SUVr cutoffs for prediction of clinical diagnosis of PD. Compare [^{18}F] AV-133 with DaTscan SBR cutoffs.
- 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.
- Descriptive safety data following injection of [^{18}F] AV-133.

3. BACKGROUND AND RATIONALE

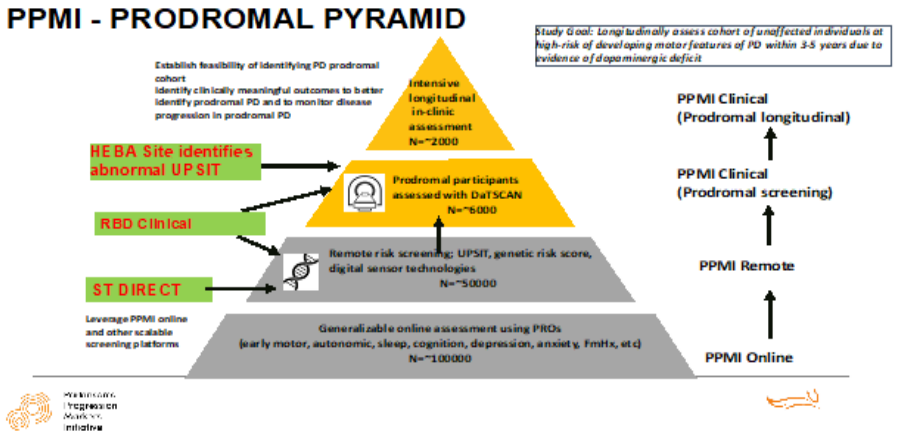
3.1 Background for Longitudinal Imaging

The defining clinical 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 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 therapeutics studies to slow PD progression (ClinicalTrials.gov Identifier: NCT01141023). PPMI, begun in 2010 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

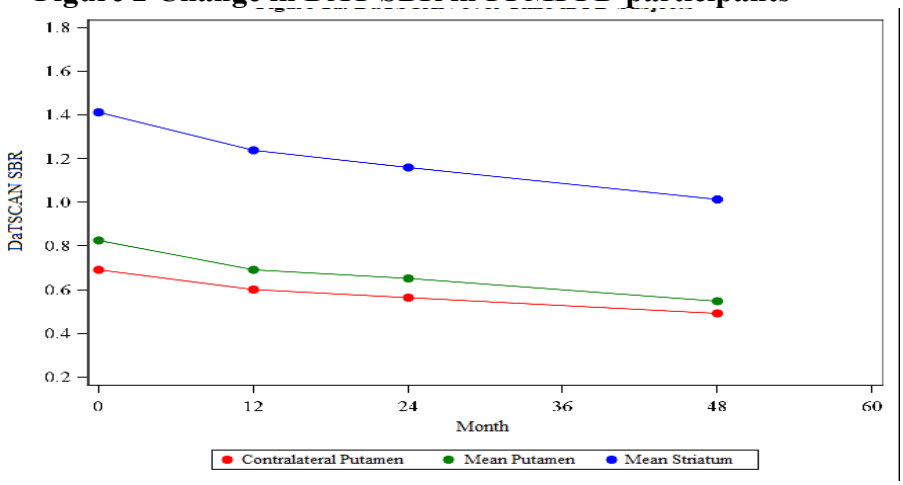
A key focus of PPMI is to identify biomarkers during the period when PD neurodegeneration is already present, but symptoms of PD have not yet occurred. This prodromal cohort would enable us to investigate PD biomarker signatures prior to onset of typical symptoms of PD. PPMI has developed an extensive stage risk paradigm (Fig 1) in which individuals may be evaluated remotely first with questionnaires and then olfactory function testing. Based on this remote testing eligible individuals would be further evaluated with dopamine transporter (DAT) imaging to determine PPMI eligibility and then to monitor longitudinal change in DAT specific binding ration (SBR).

Figure 1



Data from PPMI shows a robust change in DAT striatal SBR of about 28% during a four-year follow-up (Figure 2)

Figure 2 Change in DAT SBR in PPMI PD participants



In a prior study designed to compare DAT and [^{18}F] AV-133 PET imaging PPMI PD participants (N=30) were imaged with both DAT and AV133 targeting VMAT2. These data suggest that [^{18}F] AV-133 may provide an improved striatal signal to noise and reduced variance in the longitudinal imaging outcome (Table 1).

Table 1

Direct Within-Subject Evaluation of AV-133 PET and Ioflupane SPECT in 30 PD Participants Suggests AV-133 May be a More Robust Biomarker of Longitudinal Changes in Dopaminergic Function

Mean Striatum	Norm Percent Change SBR		Signal:Noise	
	AV-133	DAT	AV-133	DAT
Year 1	-13.77	-7.71	0.52	0.35
Year 2	-19.72	-13.40	1.09	0.79

The more robust [^{18}F] AV-133 PET imaging characteristics provide more power to detect change in the imaging outcome and would enable a clinical therapeutic trial to detect a reduction in the change in [^{18}F] AV-133 PET with fewer research participants and/or a shorter interval of evaluation (Table 2).

Table 2

Pct Slowing Striatal SBR Change Signal	Subjects/arm 1 Year Study		Subjects/arm 2 Year Study	
	AV-133	DAT	AV-133	DAT
30%	651	1398	146	273
40%	366	786	82	154
50%	234	502	52	100

Sample size per arm
Assumes two arms, double-blind, placebo-controlled trial with 80% power to detect a 50, 40, or 30% slowing of the percent loss of SBR at 1 and 2 years follow-up, p<0.05, two-tailed.

AV-133 requires about half the number of subjects as DaTscan for similar power to detect a significant slowing in longitudinal signal loss.

A key goal of PPMI is to establish the optimal tools to examine the biomarker signature of PD biology prior to the onset of typical PD symptoms. These AV133 data in PD provide the rationale to examine whether AV133 imaging will provide an effective biomarker of early dopamine dysfunction in a biomarker/clinical marker derived PD cohort.

The study will

- Determine the longitudinal change in AV-133 binding in a prodromal PD cohort during a two-year interval. These data may be used to determine the sample size required to power a clinical trial to reduce disease progress prior to the onset of PD symptoms.
- Investigate AV133 in a prodromal PD cohort to explore the reduction in binding that is predictive of development of typical symptoms of PD. Compare the reduction in AV133 and DaTscan binding in these subjects.
- To compare the longitudinal change in AV133 to clinical, imaging and biofluid markers in this prodromal PD cohort.

4. STUDY DESIGN

The study is a longitudinal, multi-center study to assess progression of [^{18}F] AV-133 imaging in Prodromal PD participants. Participants will be followed for up to 24 months. Approximately 100 Prodromal participants will be recruited from up to 10 sites. Participants will be comprehensively assessed at baseline and follow up according to the Schedule of Activities. Participants will undergo imaging assessments with [^{18}F] AV-133 and clinical (motor, neuropsychiatric, cognitive and imaging and biomarker) assessments (conducted under the PPMI Clinical protocol). 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 100 Prodromal PD participants will be recruited from up to 10 sites in North America, UK, Europe, and Israel.

6. PARTICIPANT ELIGIBILITY

6.1 Inclusion Criteria:

a) A Prodromal PD participant confirmed eligible to proceed to PPMI Clinical Baseline visit.
b) Able to provide informed consent.
c) Male or Female (females must meet additional criteria specified below as applicable)
   - Females must be of non-childbearing potential or using a highly effective method of birth control 14 days prior to until at least 24 hours after 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 PET scan) 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.
   - Females of childbearing potential must not be pregnant, breastfeeding or lactating.
     - Includes a negative urine pregnancy test prior to injection of ^{18}F-AV-133 on day of PET scan.

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) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.

7. OBTAINING INFORMED CONSENT

Potential participants will be screened for the PPMI Clinical protocol and, if deemed eligible, will then be asked to provide informed consent to participate in the additional activities under this 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, if possible.

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 form.

8. PARTICIPANT ID ASSIGNMENT

All participants will use their assigned PPMI study ID. The PPMI Participant ID number will be used to identify a participant on all study related documentation (e.g., clinical database, imaging data).

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. Annual visits should be completed within $\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 Early Longitudinal Imaging in the Parkinson's Progression Markers Initiative Using [^{18}F] AV-133 Schedule of Activities for the activities to be conducted at the Baseline visit.

After consenting and being screened for PPMI Clinical protocol, eligible participants interested in completing additional scans under this study will be asked to complete the Early Longitudinal Imaging in the Parkinson's Progression Markers Initiative Using [^{18}F] AV-133 consent.

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- 12 and 24 Month

Refer to the Early Longitudinal Imaging in the Parkinson's Progression Markers Initiative Using [18F] AV-133 Schedule of Activities (see Appendix) for the activities to be conducted at the follow up visits.

All 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). 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

All applicable clinical assessments will be completed under the PPMI Clinical protocol. Information collected from those assessments will be combined with the imaging data and any additional information collected for this protocol.

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. 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.

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 are described below and detailed in the PPMI PET Imaging manual.

12.1 [^{18}F] AV-133 Imaging Procedures

Women of childbearing potential must have a urine 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

Concomitant medications, including over the counter (OTC), dietary supplements (e.g., herbal remedies) or prescriptions, are permitted except as restricted by the PPMI Clinical protocol. All concomitant medications reported (per instruction in PPMI Clinical Assessments Manual) at the time of the VMAT-2 PET Imaging visit are recorded on the study medication log in the PPMI database.

14. PARTICIPATION IN CLINICAL TRIALS

It is preferred that participants do not participate in clinical trials of investigational study drugs during participation in this 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 radiation exposure

The radiation exposure from [^{18}F] AV-133 is within FDA guidelines, and the cumulative radiation exposure within PPMI will be monitored prior to injection with [^{18}F] AV-133 to ensure that it is within radiation exposure guidelines.

15.2 Risks Specific to [^{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.

15.3 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 [^{18}F] AV-133 injection will be asked to have a urine pregnancy test.

16. 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.

17. COSTS FOR PARTICIPATION

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

18. PAYMENT FOR PARTICIPATION

Participants will receive a stipend of $200.00 for completing each study visit.

19. 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 Site 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.

20. ADVERSE EVENTS

20.1 Adverse Event Reporting Requirements

Site investigators and coordinators will be instructed to assess for adverse events at the study visit when 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 AV-133 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.

20.2 Serious Adverse Event Reporting Requirements

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

a. Any serious and unexpected adverse event occurring within 48 hours following ^{18}F-AV-133 injection, regardless of relatedness to AV-133, will be documented on the Adverse Event Log within the EDC and reported by the site to the Site Management Core (SMC) using the PPMI AV-133 SAE Report Form.

b. The SMC will notify the appropriate responsible person(s) to report any serious and unexpected adverse events to the respective Health Authority as soon as possible, but no later than within 15 calendar days of first being notified of the event, as well as additional regulatory and Sponsor entities per respective reporting requirements.

c. 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.

20.3 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.

20.4 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.

20.5 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.

21. 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).

22. 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 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.

23. DATA SHARING AND STORAGE FOR FUTURE USE

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.

24. ANALYSIS PLAN

Information summarizing planned analyses is described as follows.

- Determine the Longitudinal change of ^{18}F-AV-133. The analyses will examine the change during 24 months in ^{18}F-AV-133 binding. 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 12 and 24 months.
- Compare baseline [^{18}F] AV-133 SUVr with DaTscan SBR to explore [^{18}F] AV-133 SUVr cutoffs for risk of developing progression to motor PD in participants developing motor PD.
- Compare baseline [^{18}F] AV-133 SUVr with Synuclein Seed Amplification assay in CSF to determine the temporal pattern of these biomarkers.
- Comparison of longitudinal change in progression endpoints. The analyses will examine the change during 24 months in clinical, DAT imaging, biofluid outcomes to better assess these prodromal biomarker signatures. 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.
- Examination of Prodromal Subsets. Each of the above analyses will be repeated comparing subsets of prodromal subjects (RBD vs hyposmia) understanding that the sample size for this study is modest.

24.1 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.

The planned sample size of 100 Prodromal PD participants for this study was based on existing data from the PPMI study demonstrating an approximately 13.7%. and 19.7% reduction from baseline AV133 during a 12 and 24month interval in early PD. Based on the assumption that

- The change in AV133 in Prodromal PD will be similar to that in early PD
- Then the 12-month change AV133 will be approximately 14% from baseline easily detected with a sample size of 100 participants

It is anticipated that this samples size will also enable other analyses assessing the AV133 binding cutoff to predict progression to PD and the comparison of imaging and clinical and biologic outcomes.

25. REFERENCES

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26. Appendix 1- Early Longitudinal Imaging in the Parkinson's Progression Markers Initiative Using [^{18}F] AV-133 (PPMI AV-133 Prodromal Imaging) Schedule of Activities

	Visit Number	Baseline (BL)	V01	V02
Assessment	**[**]Timepoint**	**0**	**12 mths (Y1)**	**24 mths (Y2)**
Consent Activities				
AV-133 Prodromal Imaging Documentation of Informed Consent		I		
AV-133 Prodromal Imaging Informed Consent Tracking Log		X	As Needed	
Additional AV-133 Activities				
AV-133 Prodromal Imaging Inclusion/Exclusion Criteria		X		
AV-133 Prodromal Imaging Urine Pregnancy Test (prior to AV-133 injection), if applicable		X	X	X
AV-133 Prodromal Imaging VMAT-2 Imaging[c]		X	X	X
AV-133 Prodromal Imaging Screen Fail		As Needed		
AV-133 Prodromal Imaging Conclusion of Study Participation			As Needed	
Safety and General Health				
[#] AV-133 Prodromal Imaging Adverse Event In-Clinic Assessment		X	X	X
AV-133 Prodromal Imaging Adverse Event Telephone Assessment		X	X	X
AV-133 Prodromal Imaging 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 = Urine pregnancy test prior to injection on day of scans for women of childbearing potential.

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