PROTOCOL

Title:

Early Longitudinal Imaging in Parkinson's Progression Markers Initiative Using [18F] AV-133 and DaTscanTM (PPMI Early

Imaging 2.0)

Institute for Neurodegenerative Disorders **Sponsor:**

Principal Investigator: Kenneth Marek, MD

> **Protocol Number:** 004

Date of Protocol: June 19, 2020

Final Version: 2.0

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Michael J Fox Foundation

PROTOCOL APPROVAL

Amendment 1, Version 2.0 dated 19 June 2020

PPMI Early Imaging 2.0

Eun March B68E9E01CA243D	6/25/2020			
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1 PURPOSE OF STUDY

The Parkinson Progression Marker Initiative 2.0 (PPMI 2.0) 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 2.0 is to identify markers of disease progression for use in clinical trials of therapies to reduce progression of PD disability.

PPMI 2.0 is a broad program, expanding the goals of the original PPMI study. This protocol is a companion to the PPMI 2.0 Clinical protocol. It is a longitudinal, multi-center study to assess progression of clinical features and imaging and biomic biomarkers in Parkinson disease patients for at least 18 months.

1.1 Primary objective

Primary objective is to estimate the mean rates of change and the variability around the mean of imaging outcomes in early PD patients, and where appropriate the comparison of these rates between PD patient subsets at study intervals ranging from 6 months to 18 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.

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 [18F] 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 PD patients, and where appropriate the comparison of these rates between PD patient subsets at study intervals ranging from 6 months to 18 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 [18F] AV-133 and DaTscan.

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- 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 [18F] 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. 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, 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 PD patients in comparison to healthy controls and/or in sub-sets of 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.

3.2 Rationale for study

In PPMI all PD participants underwent dopamine transporter (DAT) imaging with ¹²³I Ioflupane or vesicular monoamine transporter (VMAT-2) imaging with ¹⁸F-AV133 (Australia only) and were only eligible if they demonstrated a DAT or VMAT-2 deficit consistent with PD in addition to clinical features of the disease. DAT or VMAT2 imaging was repeated after 12, 24, and 48 months for 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.

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 1.

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Figure 1 Change in DAT SBR in PD participants

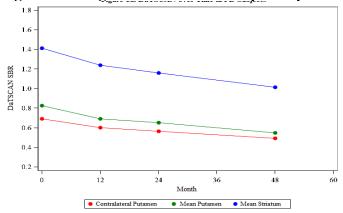


Table 1 Percent change from baseline in DaTscan in PD participants

Variable	% Change at Year 1	% Change at Year 2	% Change at Year 4
Contralateral Putamen			
N Completed	369	345	235
Mean (SD)	-7.24 (32.5)	-13.74 (30.5)	-23.96 (27.8)
(Min, Max)	(-77.4, 204.8)	(-92.5, 207.1)	(-79.6, 143.8)
Mean Putamen			
N Completed	369	345	235
Mean (SD)	-13.49 (21.8)	-19.07 (21.4)	-30.61 (21.3)
(Min, Max)	(-83.1, 141.2)	(-86.7, 167.7)	(-83.3, 123.2)
Mean Caudate			
N Completed	369	345	235
Mean (SD)	-9.65 (16.1)	-15.74 (16.8)	-25.63 (18.3)
(Min, Max)	(-59.8, 164.9)	(-87.7, 136.7)	(-82.9, 96.0)
Mean Striatum			
N Completed	369	345	235
Mean (SD)	-11.17 (15.1)	-17.04 (16.6)	-27.43 (17.3)
(Min, Max)	(-59.6, 124.8)	(-87.5, 146.2)	(-83.0, 104.3)

Report Generated on Data Submitted as of: 23Oct2017.

In addition, a small subset of PPMI participants (N=17) were imaged with AV133 targeting VMAT2 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 (Table 2).

Table 2 DaTscan and AV133 changes in PD participants in PPMI

	DaTscan Mean (SD) Change From Baseline – Mean striatum	AV133 Mean (SD) Change From Baseline – Mean striatum
Time	N=372	N=17
1 Year	-11% (15.1)	-11.7% (12.1)
2 Year	-17% (16.1)	-20.9% (10.8)

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Current PPMI DaTscan and AV133 data have provided sample size estimates to power developing clinical trials. These data are limited in that the initial assessment is at 12 months for both tracers and the [18F] AV-133 data were further limited by a small sample size due to tracer availability.

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.
- Elucidate the longitudinal change in AV-133 with an adequate sample of 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 current study is a longitudinal, multi-center study to assess progression of DaTscan and [18F] AV-133 imaging in PD patients. Participants will be followed for at least 18 months. Approximately 50 PD participants will be recruited from up to 5 sites. All participants will be comprehensively assessed at baseline and every six months thereafter. Participants will undergo imaging assessments with DaTscan and [18F] AV-133, clinical (motor, neuropsychiatric and cognitive) assessments, as well as biospecimen collection for biomic analysis. 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 PD participants will be recruited from up to 5 sites.

6 PARTICIPANT ELIGIBILITY

Note: Active PD participants previously enrolled in this study do not require re-assessment of eligibility criteria listed below for enrollment. Active participants do need to be able to provide informed consent for participation.

6.1 Inclusion Criteria

- a) Enrolled in PPMI 2.0 Clinical protocol.
- 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 ¹⁸F-AV-133 injection.
 - Includes a negative urine pregnancy test prior to injection of ¹⁸F-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 ¹⁸F-AV-133.
 - o Non-childbearing potential is defined as a female that must be either postmenopausal (no menses for at least 12 months prior to Screening) or

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- 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 ¹⁸F- AV-133 PET imaging: tetrabenazine (TBZ) or methylphenidate, reserpine, or amphetamine derivative, within 1 month prior to the Baseline ¹⁸F-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

Participants who were previously enrolled under the PPMI Early Imaging 1.0 protocol, will be re-consented to resume participation from the last completed visit and continue their 18 months follow up. Newly enrolled PPMI Early Imaging PD participants will be enrolled in the PPMI 2.0 Clinical protocol and will provide informed consent to participate in the additional activities under this Early Imaging 2.0 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 study.

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, including screening 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 an annual study visit that the participant continues to understand the

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procedures and requirements of the study).

7.2 Permission to be Contacted for Follow Up of Persons with Neurologic Disease

The Follow Up of Persons with Neurologic Disease (FOUND) study (Caroline Tanner MD, Principal Investigator, University of California-San Francisco (UCSF)) provides a parallel, centralized system to prospectively collect vital status and disease progression information from persons with parkinsonism, related disorders and healthy controls who are participating in clinical research studies. Participation in FOUND complements in-person assessment, enables continuity of follow up of individuals who complete or withdraw from a study, and may also aid in PPMI study retention. Participation in FOUND will enable centralized contact both during and after completion of PPMI 2.0, using convenient methods for systematic data collection (e.g., regular mail, telephone, internet contacts).

During the initial consent process, and as needed at a subsequent follow up visit, participants will be asked if their contact information may be shared with the FOUND study team at UCSF. The participant's decision will be documented in the informed consent and the PPMI database. If a participant agrees, UCSF will be notified and will proceed with contacting the individual to invite participation into FOUND. UCSF will share with the referring sites their participants' status in FOUND at regular intervals. Participants who have incomplete enrollment in FOUND will be asked by the site to discuss this with the participant to identify if there are any issues impeding enrollment and address any such issues. The data collected from the FOUND study will be uploaded into the PPMI 2.0 data repository at the Laboratory of Neuro Imaging (LONI), The Institute for Neuroimaging and Informatics in Los Angeles, California, at regular intervals.

7.3 Permission to be Contacted from Pathology Core

Post-mortem analysis of brain tissue is pivotal to Parkinson's disease research, allowing researchers to examine changes noted in the post-mortem brain tissue and correlate it with changes in neuropsychological, imaging, and biomic data collected throughout the PPMI 2.0 Clinical study. However, there is limited availability to this type of tissue, leading to organized efforts to facilitate brain donation planning through the PPMI Pathology Core.

The PPMI Pathology Core is a collaboration between Indiana University and Stanford University. Indiana University is responsible for coordinating all logistics up-to death, including obtaining consent, identifying a removal specialist, coordinating with clinical sites, and interfacing with the decedent's family. Indiana University also ensures the removal specialist follows outlined removal and shipping guidelines to transfer the whole brain to the Stanford team, while a small tissue sample is shipped to Indiana University for DNA extraction. Stanford University is responsible for post-mortem activities including receiving specimens, specimen dissection and preparation for embedding and processing, performing neuropathological evaluation of tissue, coordinating clinicopathological case conferences (CPCs), and long-term storage of brain tissue samples.

For clinical sites based in the United States, site coordinators will discuss the PPMI Pathology Core with participants and provide them with an information packet at initial consent to PPMI 2.0, or subsequent study visits as applicable. Participants will be asked to

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provide permission to allow their contact information to be transferred to the Pathology Core team. Participants may also contact the team at Indiana University directly to learn more about enrollment. The Pathology Core team will contact participants to discuss tissue donation further and answer questions. If participants are agreeable to continue with donation planning, they will first be asked to sign a consent form that reflects their intent to donate brain tissue and other relevant tissue upon death. This consent is approved by the Indiana University IRB. After consent, the participant will provide additional information to help with their local planning and coordination.

The Indiana and Stanford teams will also provide support to international PPMI sites that are interested in contributing to PPMI brain tissue donation activities. Stanford University will work with neuropathologists at local sites to ensure the harmonization of brain tissue collection and processing across all PPMI sites. Indiana University will help establish workflows from consent to donation and ensure regulatory considerations are met for participant inclusion in the PPMI Pathology Core.

The data collected across the Pathology Core will be collated by the team at Indiana University and transferred to the PPMI 2.0 data repository at the Laboratory for Neuro Imaging (LONI), The Institute for Neuroimaging and Informatics in Los Angeles, California, at regular intervals. It is possible that collected tissues may be distributed to approved researchers for future analysis.

8 PARITCIPANT ID ASSIGNMENT

8.1 Participant ID Number

A Participant ID number will be assigned to all participants. Active participants transitioning from Early Imaging 1.0 will keep their previously assigned PPMI ID number, while newly enrolled participants will be assigned a new 6-digit ID number, generated automatically by the electronic database capture (EDC) system as part of their participation in PPMI 2.0 Clinical protocol. The PPMI Participant ID number will be used to identify a participant on all study related documentation (e.g., clinical database, biological specimens).

8.2 Globally Unique Identifier (GUID) Number

Information required to generate a 9-digit GUID number will be collected at the Screening Visit, unless a site is otherwise restricted from providing the data. This ID system can track individual participants across multiple studies without storing any personally identifiable information. The protected system uses an algorithm of nine data element inputs (last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth, and mother's maiden name), and produces an electronic "fingerprint" output. The system stores only the "fingerprint" and clears the individual's inputted data elements from memory. The participant is then assigned a 9-digit Unique ID Number that is associated with their electronic "fingerprint."

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9 STUDY PROCEDURES

Screening, Baseline and Annual 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.

The Baseline visit should be completed within 60 days of the Screening visit. Follow up 6 month and annual visits should be completed with <u>+</u>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
- Neurological Examination
- MDS-UPDRS Parts Ia, III, IV, UPDRS Repeat Part III, Hoehn & Yahr
- Modified Schwab & England ADL
- Features of Parkinsonism
- Other Clinical Features
- Primary Diagnosis
- Cognitive Categorization

9.1 Active Early Imaging 1.0 Participants Transitioning to Early Imaging 2.0

Refer to the PPMI Early Imaging 2.0 Schedule of Activities for Transitioning Participants (see Appendix 1) to determine the activities to be conducted at each visit for participants who were previously enrolled. Participants will continue with their PPMI Early Imaging 1.0 study schedule into the next planned study visit under PPMI Early Imaging 2.0. Note that additional "Transition Activities" must be completed as outlined in the Schedule of Activities for all participants transitioning into Early Imaging 2.0 at their first in-person visit.

Active participants enrolled under the Early Imaging PPMI 1.0 protocol will not require a Screening or Baseline visit. Early Imaging PPMI 1.0 participants who agree to continue participation and transition into Early Imaging PPMI 2.0 will complete the next planned study visit based on the last completed visit in Early Imaging PPMI 1.0. The process of obtaining informed consent, including an explanation of study activities, will be conducted prior to completing any Early Imaging PPMI 2.0 study activities. Active PPMI 1.0 participants transitioned into PPMI 2.0 will continued to be followed through their 18-month visit. Active PPMI Early Imaging 1.0 participants choosing not to continue into PPMI Early Imaging 2.0 will be tagged by the site as "Complete".

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9.2 Screening Visit

Refer to the PPMI Early Imaging 2.0 Schedule of Activities for New Participants (Appendix 2) to determine the activities to be conducted at the Screening visit.

For new PPMI Early Imaging 2.0 participants, after consenting to PPMI 2.0 Clinical protocol, participants interested in completing additional scans under this study will be asked to complete an additional consent for PPMI Early Imaging 2.0 and complete additional assessments as part of the PPMI Early Imaging 2.0 study.

Once consent is obtained, all newly consented participants will undergo a screening evaluation prior to the Baseline visit. The Screening visit will take about 8 hours to complete in combination with the PPMI 2.0 Clinical protocol activities and could occur over more than one day.

9.3 Baseline Visit (Day 0):

Refer to the PPMI Early Imaging 2.0 Schedule of Activities for New Participants for the activities to be conducted at the Baseline visit.

For new PPMI Early Imaging 2.0 participants, once all Baseline activities have been completed and the Investigator determines that all eligibility criteria have been met, the participant may be enrolled into the study. The activities at the Baseline visit will be completed within 60 days of the Screening visit and will be completed in combination with the PPMI 2.0 Clinical protocol activities. The combined visit is anticipated to take about 8 hours and could occur over more than one day.

9.4 Follow up visits

Refer to the PPMI Early Imaging 2.0 Schedule of Activities (see Appendices) for the activities to be conducted at follow up visits (transitioning or new participant).

All participants will be evaluated in clinic every 6 months for 18 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. For new PPMI Early Imaging 2.0 participants, follow up visits will be completed in combination with their PPMI 2.0 Clinical protocol activities. Study visits may occur over more than one day.

9.5 Premature Withdrawal Visit

If a participant withdraws from the study during a scheduled visit, proceed with the visit as outlined. Ensure the Visit Status data form indicates the type of visit is a "Premature Withdrawal visit".

If a participant withdraws from the study outside of a scheduled visit and agrees to be seen for one more visit, the next scheduled visit should be completed. Study procedures will be the same as outlined in the schedule of activities for that respective visit, *except for the activities as outlined below*. Alternatively, if the participant is unwilling or unable to return for a final in person visit, the premature withdrawal visit could be completed by video link or telemedicine. In addition to completing the activities outlined in the schedule of

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activities, the site will complete the Conclusion of Participation assessment and indicate the reason for study withdrawal. *Ensure the Visit Status data form indicates the type of visit is a "Premature Withdrawal visit"*.

Premature Withdrawal Visit – Activity Exceptions:

- Blood and urine research sample collection only if not done in the last 3 months
- DaTscan Imaging only if not done in the last 3 months
- VMAT-2 PET Imaging only if not done in the last 3 months

9.6 Unscheduled Visits (Visit U01, U02, etc.), if required

An unscheduled visit may be performed only if required (i.e., deemed necessary to follow up on adverse events, or deemed clinically relevant by the site Investigator to ensure the safety of the participant). The following activities may be completed:

- Vital signs
- *Neurological examination
- *Blood sample for clinical laboratory assessments
- Review of current medical conditions
- Review of concomitant medications
- Review of adverse events
- *Conducted only if clinically indicated

Any Unscheduled Visits for newly enrolled participants will be completed under the PPMI 2.0 Clinical protocol.

10 CLINICAL ASSESSMENTS

Refer to the PPMI 2.0 Assessment Manual for a detailed description of the clinical assessments and instructions for administration.

All clinical assessments for newly enrolled participants will be completed under the PPMI 2.0 Clinical protocol. For participants transitioning from 1.0 Early Imaging protocol, clinical assessments will be completed according to the PPMI 2.0 Early Imaging Schedule of Activities.

11 SAFETY ASSESSMENTS

All applicable safety assessments, including the routine Screening clinical lab tests, will be completed for newly enrolled participants under the PPMI 2.0 Clinical protocol. For participants transitioning from 1.0 Early Imaging protocol, a neurological exam will also be conducted at month 12 and at a premature withdrawal visit, should one occur.

12 BIOLOGIC RESEARCH SAMPLING

Refer to the PPMI 2.0 Biologics Manual for the detailed description of the biologic samples collected and processing instructions.

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All biologic research samples will be collected for newly enrolled participants under the PPMI 2.0 Clinical protocol. For participants transitioning from 1.0 Early Imaging protocol, the following will be collected:

12.1 Blood Samples

Whole blood (about 10 ml), serum (about 30 ml) and plasma (about 10 ml) will be collected to conduct proteomic, metabolomic, genetic and other research analyses. No more than 50 ml will be drawn.

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.

13 Imaging

13.1 Dopamine Transporter SPECT Imaging

Refer to the PPMI 2.0 SPECT Imaging manual for a detailed description of the SPECT imaging procedures.

Participants will undergo dopamine transporter imaging to measure dopamine transporter binding using single photon emission computed tomography (SPECT) as indicated in their visit schedule. Newly enrolled participants will only complete SPECT scans under this protocol that are in addition to the PPMI 2.0 Clinical protocol schedule of activities.

The SPECT imaging procedure will be performed at the individual sites using DaTscanTM as the dopamine transporter. DaTscan imaging eligibility will be determined using prespecified 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 DaTscanTM. The result must be confirmed as negative prior to proceeding with the injection. Before the DaTscanTM injection, participants will be pre-treated with stable iodine (10 drops of a saturated solution of potassium iodide) to reduce the uptake of DaTscanTM 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).

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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 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.

13.2 VMAT-2 PET Imaging

Refer to the PPMI 2.0 PET Imaging manual for a detailed description of the PET imaging procedures.

Participants will undergo [¹⁸F] AV-133 PET imaging targeting the vesicular monoamine transporter. All participants will undergo an initial [¹⁸F] AV-133 PET imaging scan at baseline and repeat imaging as indicated in the visit schedule. [¹⁸F] AV-133 will be provided to the imaging sites from local production sites under an IND sponsored 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 [18F] AV-133 PET scan is obtained. Participants will also be contacted by phone 2 to 3 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 [18F] AV-133 injection is described below and detailed in the PPMI PET Imaging manual.

13.2.1 [18F] AV-133 Imaging Procedures

Women of childbearing potential must have a serum pregnancy test prior to injection of [¹⁸F] AV-133. The result must be confirmed as negative prior to proceeding with the injection. During the [¹⁸F] AV-133 PET imaging visit, subjects will receive a single I.V. administration of 222 MBq (6 mCi) +/- 10% of [¹⁸F] 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.

13.3 Magnetic Resonance Imaging (MRI)

The MRI for newly enrolled participants will be completed under the PPMI 2.0 Clinical protocol.

14 CONCOMITANT MEDICATIONS

14.1 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 DaTscanTM injection: alpha methyldopa,

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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 Screening visit and for the duration of participation are recorded on the study medication logs.

14.2 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.

15 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 the study drug and dosage after it is unmasked.

16 RISKS TO PARTICIPANTS

16.1 Imaging

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

- Radiation exposure from DaTscanTM, [¹⁸F] AV-133
- Potential pharmacological effects of DaTscanTM, ¹⁸F-AV-133
- Having an intravenous injection.

16.2 DaTscanTM Imaging

Risks of DaTscanTM: DaTscanTM is administered at radiotracer doses and is not expected to have any pharmacological or toxicological effects. DaTscanTM binds to the dopamine and serotonin transporter. At pharmacologic doses DaTscanTM might be expected to have stimulant-like effects and affect cardiovascular responses. However, in the proposed study the estimated mass dose of DaTscanTM 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.

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16.3 [¹⁸F] AV-133

Risks of [¹⁸F] AV-133: The most up-to-date and complete information regarding the use of [¹⁸F] AV-133 can be found in the investigator's brochure. [¹⁸F] AV-133 is an experimental imaging agent that will be used at relatively low (tracer) doses. However, because [¹⁸F] AV-133 is in the early stages of clinical investigation, subjects receiving [¹⁸F] 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 [¹⁸F] 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 [¹⁸F] AV-133. [¹⁸F] AV-133 for injection must not be administered to females who are pregnant or lactating.

16.4 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 DaTscanTM injection will be asked to have a urine pregnancy test.

17 REFERRALS IN THE CASE OF CLINICALLY RELEVANT FINDINGS

If a research assessment reveals a clinically significant abnormality, the participant will 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.

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 the option to receive funds using either a pre-paid card, direct deposit to a personal account, or a paper check.

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. Any information that has already been

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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 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 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 ¹⁸F-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 ¹⁸F-AV-133 injection.
- c. Any serious adverse event occurring within 24 hours following the DaTscanTM 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 DaTscanTM or not.
- d. Any serious adverse event occurring more than 24 hours following the DaTscanTM injection that is assessed as being related to the DaTscanTM injection will be documented on the Adverse Event Log and reported to GE Healthcare using the PPMI GE Healthcare SAE Report Form.

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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.

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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.

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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 2.0 Steering Committee has the responsibility to monitor all procedures for safety, GCP, and applicable 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), and is in compliance 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, 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

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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 Data Management and Analytics Core at Blackfynn, LLC (Philadelphia, PA), the Participant and Biorepository Core at Indiana University (Indianapolis, IN), the Site Management Core at the Institute for Neurodegenerative Disorders (New Haven, CT), and the Statistical Core at the University of Iowa (Iowa City, IA) for conducting analyses as pertains to the study including, but not limited to, enrollment, compliance, study outcomes. 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 ¹⁸F-AV-133 and DaTscan. The analyses will examine the change during 18 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 18 months.
- Examination of whether short-term change in ¹⁸F-AV-133 and DaTscan is predictive of change in long-term endpoints. This analysis will examine whether short-term change in the ¹⁸F-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 18 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.
- Examination of 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.

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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 PD subjects for this study was based on existing data from the PPMI study demonstrating an approximately 11-12% reduction from baseline in DAT and AV133 during a 12-month interval. Based on the assumption that the 6-month change in DAT and AV133 will be approximately 5.5-6% from baseline, the sample size will be adequate to examine the longitudinal change in DAT and AV133 at each imaging timepoint.

Other analyses comparing imaging and clinical and biologic outcomes are exploratory.

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29 Appendix 1 – Schedule of Activities for Transitioning Participants

PPMI Early Imaging 2.0 Schedule of Activities (Transition Participants)

	Visit Number	V02	V04	V05	Unscheduled Visit	^a Transition Activities
Assessment	**Timepoint	6 mths	12 (Y1)	18 mths		
Consent Activi	ties					
Documentation	of Informed Consent					I
Continuing Con	nsent	X	X			
Consent to shar	e contact information		As Ne	eeded		X
Informed Cons	ent Tracking Log		As Ne	eeded		X
General Activit	ties					
Demographics						X
Family History						X
Vital Signs		X	X	X	X	
Visit Status		X	X	X	X	
Conclusion of	Study Participation			As Needed		
Neurological/M	Iotor Assessments					
Participant Mot	tor Function Questionnaire		P			
Freezing and F	alls		X			
Neurological E	xamination		I		I	
MDS-UPDRS	Part Ia, Part III and Hoehn & Yahr	I	I	I		
MDS-UPDRS	Part Ib and Part II	P	P	P		
Modified Schw	ab & England ADL	I	I	I		
MDS-UPDRS	Part IV	I	I	I		
MDS-UPDRS	ON/OFF Determination & Dosing	X	X	X		
MDS-UPDRS	Repeat Part III/Hoehn & Yahr	I	I	I		
Features of Pari	kinsonism	I	I	I		
Other Clinical l	Features	I	I	I		
Primary Clinica	al Diagnosis	I	I	I		
Non-Motor As	sessments					
REM Sleep Bel	havior Disorder Screening Questionnaire		P			
Epworth Sleepi	ness Scale		P			
SCOPA-AUT			P			
Neuro QoL			P			
Cognitive Assessments						
Montreal Cogn	itive Assessment		X			
Clock Drawing			X			
Lexical Fluency	у		X			
Hopkins Verba	l Learning Test-Revised		X			

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	Visit Number	V02	V04	V05	Unscheduled Visit	^a Transition Activities
Assessment	**Timepoint	6 mths	12 (Y1)	18 mths		
Benton Judgme	ent of Line Orientation		X			
Semantic Fluer	ncy (Animals only)		X			
Letter Number	Sequencing		X			
Symbol Digit I	Modalities Test		X			
Trail Making T	Cest (A and B)		X			
Modified Bosto	on Naming Test		X			
Cognitive Char	nge	P	P	P		
Cognitive Cate	gorization		I			
Neuropsycholo	ogical Assessments					
State-Trait An	xiety Inventory for Adults		P			
Geriatric Depre	ession Scale		P			
QUIP			P			
Clinical and B	iological Samples					
Research samp	les (blood + urine)	X	X	X	X	
Imaging Activ	ities					
Pregnancy Tes (prior to DaTso	t can and AV-133 injection), if applicable	Х	X	Х		
DaTscan Imag	ing	X	X	X		
VMAT-2 Imag	ping ^b	X	X	X		
Safety and Ger	neral Health					
[#] Adverse Even	ts	X	X	X	X	
Adverse Event	Telephone Assessment	X	X	X		
Current Medic	al Conditions Review	X	X	X	X	
Concomitant N	fedication Review	X	X	X	X	
LEDD Concon	nitant Medication Log	X	X	X	X	
Surgery for PD	Log	As Needed				
Report of Preg	nancy	As Needed				

^{**}Window of <u>+4</u>5 days either side of Target Visit Date

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 $I = Investigator\ completed\ assessment$

P = Participant completed assessment

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

a = Transition Activities completed for all 1.0 participants transitioning into 2.0 at first 2.0 visit only

b = Urine pregnancy test prior to injection on day of imaging for women of childbearing potential.

[#]Adverse events collected only day of and 2-3 days post DaTscan injection or AV-133 injection per protocol.

30 Appendix 2 – Schedule of Activities for New Participants

PPMI Early Imaging 2.0 Schedule of Activities (New Participants)

	Visit Number	Screening	Baseline (BL)	V02	V04	V05	
Assessment	**Timepoint	-60 days	0	6 mths	12 (Y1)	18 mths	
Consent Activitie	es						
Documentation of	of Informed Consent	I					
Continuing Cons	ent		X	X	X		
Informed Conser	nt Tracking Log	X		As N	eeded		
Additional AV-1	33 Activities						
Review Early Im Criteria	aging Inclusion/Exclusion		X				
ECG			X				
DaTscan Imagin	g ^b			X		X	
Pregnancy Test (prior to AV-133	injection), if applicable		X	X	X	X	
VMAT-2 Imagin	gʻ		X	X	X	X	
Early Imaging So	creen Fail	As Needed					
Conclusion of Ea Participation	arly Imaging Study		As Needed X			X	
Safety and General Health							
[#] Adverse Events		X	X	X	X		
Adverse Event T	elephone Assessment	X	X	X	X		
Report of Pregna	ncy		As Needed				

^{**}Window of ±45 days either side of Target Visit Date

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 $I = Investigator\ completed\ assessment$

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 screening for women of childbearing potential; Urine pregnancy test prior to injection on day of imaging for women of childbearing potential.

[#]Adverse events collected only day of and 2-3 days post DaTscan injection or AV-133 injection per protocol.