# PROTOCOL

**Title:** Longitudinal TSPO PET imaging with [$^{18}$F]DPA-714 in PPMI **(PPMI DPA-714 PET Imaging)**

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

**Principal Investigator:** David Standaert

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# PROTOCOL APPROVAL

## Version 1.1 dated 27 Sep 2023

Longitudinal TSPO PET imaging with [$^{18}$F]DPA-714 in PPMI
**(PPMI DPA-714 PET Imaging)**

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## 1. PURPOSE OF STUDY

The overall goal of this protocol is to investigate [$^{18}$F]DPA-714 binding in prodromal and early manifest Parkinson's Disease (PD) and to determine the baseline and change from baseline in [$^{18}$F]DPA-714 binding in PD participants during a 24-month interval.

### 1.1 Primary Objectives

- To compare [$^{18}$F]DPA-714 binding in prodromal and manifest PD and healthy volunteers.
- To determine the longitudinal change in [$^{18}$F]DPA-714 during a 24-month interval for prodromal and early initially untreated PD participants.

### 1.2 Secondary Objectives

- To evaluate the correlation between baseline [$^{18}$F]DPA-714 and PPMI clinical and biomarker outcomes.
- To evaluate the correlation between the longitudinal change of [$^{18}$F]DPA-714 and PPMI clinical and biomarker outcomes
- To acquire safety data following injection of [$^{18}$F]DPA-714

## 2. STUDY OUTCOMES

The primary study outcome will be the regional brain binding of [$^{18}$F]DPA-714 PET imaging assessment of brain synaptic density at baseline and annually for 24 months.

[$^{18}$F]DPA-714, a $^{18}$Fluorine-labelled tracer, is proposed for this study due to its demonstrated high affinity for Translocator protein (TSPO), also known as peripheral benzodiazepine receptor, low background signal, and experience at UAB-The University of Alabama at Birmingham with [$^{18}$F]DPA-714 imaging and analysis. Only individuals identified as high binders at the known TSPO gene polymorphism (rs6971) will be included in this study. Images will be compared with age-matched and historical healthy volunteer controls. [$^{18}$F]DPA-714 brain binding will be compared with PPMI clinical outcomes including motor and cognitive assessments, DaTscan and MRI imaging, and blood and cerebrospinal fluid (CSF).

## 3. BACKGROUND AND RATIONALE

Identifying reliable and well-validated biomarkers for Parkinson's Disease (PD) progression are crucial to advance research to develop therapeutics that may slow or prevent PD symptoms and pathology. The Parkinson's Progression Marker Initiative (PPMI) is an observational, international, multi-center study designed to establish biomarker defined cohorts and to identify PD progression biomarkers to improve understanding of disease etiology and enhance the likelihood of success of PD disease modifying therapeutic trials (ClinicalTrials.gov Identifier:NCT01141023). PPMI is a collaborative study of researchers with expertise in biomarker development, PD clinical study design and implementation, bioinformatics, statistics, and data management. The study is a public-private partnership of academic researchers, sponsored and largely funded by The Michael J Fox Foundation (MJFF) and supported by approximately thirty-five pharmaceutical and biotech industry partners.

Neuroinflammation has long been recognized in PD, and emerging evidence suggests that it may be a driving force for progression (Schonhoff et al., 2020). At postmortem neuropathological examination, the evidence for inflammatory activation in PD is clear, with histological evidence of activation of microglia, infiltration of T cells into the brain, and deposition of immunoglobulins.

There is evidence for inflammation in PD detectable outside the brain, with increased cytokines and chemokines in blood and CSF (Zimmermann & Brockmann, 2022). There are also changes in circulating immune cells including the appearance of T lymphocytes sensitized to alpha-synuclein (Garretti et al., 2022; Sulzer et al., 2017), and an increase in neutrophil to lymphocyte ratio (Munoz-Delgado et al., 2021), an index of inflammation also observed in other disorders. None of the blood or CSF markers identified to date, however, has the characteristics of a desirable biomarker as the magnitude of change in these measures is often small and requires large sample sizes for detection. In addition, correlation of blood and CSF biomarkers to disease activity remains uncertain.

A direct approach to assessing brain inflammation in PD is PET imaging . Most studies have used ligands targeted to TSPO, an 18kDa translocator protein associated with inner mitochondrial membranes (Zhang & Gao, 2022). TSPO is abundant in cells from macrophage lineages, including both intrinsic brain microglia as well as circulating monocytes that may enter tissue in response to inflammation (Nutma et al., 2021; Nutma et al., 2022). Lower levels of TSPO are also found in vascular endothelial cells.

Early studies of brain inflammation has primarily used [$^{11}$C]PK11195, a PET ligand for TSPO (Gerhard, 2016). Those studies demonstrated increased signal in the midbrain and cortex of patients with PD. Recently, a "second generation" TSPO ligand was developed with more desirable imaging properties including a higher signal to noise ratio. The UAB team has established protocols for the use of [$^{18}$F]DPA714]DPA-714, obtaining the first IND for use of this tracer in North America, synthesizing the tracer at the UAB Cyclotron facility, and successfully imaging more than 70 participants (Yacoubian et al., 2023).

An important consideration in imaging with TSPO is that affinity of ligands is modified by genetic variation at a specific polymorphic locus (rs6971) (Owen et al., 2012). Genotyping for this locus divides patients into low, medium, and high affinity binders. At UAB, we found that about 10% of our PD patients were low affinity binders while the remainder were evenly divided between medium and high affinity binders. In our studies with [$^{18}$F]DPA714]DPA-714, we imaged only medium and high affinity binders (Yacoubian et al., 2023).

In a study recently reported in the journal *Movement Disorders* (Yacoubian et al., 2023), we enrolled 58 patients with early, untreated ("de novo") PD and 62 matched controls. The selection criteria were nearly identical to the entry criteria for PPMI. 37 controls and 30 PD participants were imaged using [$^{18}$F]DPA714]DPA-714. After adjusting for TSPO genotype and sex, we found that PD participants had higher [$^{18}$F]DPA714]DPA-714 binding potentials in the putamen, thalamus, SN, temporal cortex, parietal cortex, and occipital cortex compared to controls. Interestingly, changes in these regions were

correlated with a subset of both neurocognitive variables and measurements of plasma and CSF cytokines. No adverse events related to imaging were observed. Our study is the largest to examine TSPO in PD, and the first to examine a de novo cohort and demonstrate the presence of increased TPSO signal in early clinical PD.

As a biomarker, brain imaging with TSPO has several important advantages. The imaging is direct, non-invasive, and can be followed over time in individual patients. It is also proximate to presumed disease processes, as microglial activation and monocyte entry are believed to be an essential part of the PD inflammatory process. Preclinical studies have demonstrated that interrupting the immune response at the level of microglia and monocytes can present neurodegeneration in PD model systems (Harms et al., 2018; Schonhoff et al., 2020; Williams et al., 2021; Williams et al., 2018). Lastly, TSPO imaging has the potential to serve both as a means of selecting patients for studies of anti-inflammatory agents, and as a measure of on-target efficacy of anti-inflammatory treatments.

## 4. STUDY DESIGN

This is a longitudinal observational study evaluating the imaging characteristics of the [$^{18}$F]DPA-714 in PPMI participants with prodromal and early manifest PD, and healthy volunteers. The manifest PD cohort will include individuals who are untreated for PD. Up to 50 Prodromal and early manifest PD participants and 10 healthy participants will be enrolled at PPMI sites in North America and Europe. All screening and longitudinal clinical activities will be completed at the clinical sites. Data will be reviewed on an ongoing basis by the Investigator and the study team. Initial enrollment will focus on prodromal PD participants. Based on our experience, most of the difference between PD and control groups is driven by images obtained from participants who are homozygous (C/C) at rs6971. All potential participants will undergo genetic evaluation at screening. We anticipate that approximately 45% of the PD and control populations will have this genotype. At present, there are no known clinical or biological differences among participants based on the rs6971 genotype. Genotyping for rs6971 is done on a research basis, but CLIA-approved testing for rs6971 is not currently available, and we do not intend to disclose the results other than to indicate whether the subject is eligible to proceed with imaging.

The general design is shown in the following study schematic for PD*

| | **Screening** | **Baseline (BL)** | **12 month** | **24 month** |
|---|---|---|---|---|
| | Visit can be completed within any PPMI visit after PPMI screening visit | within 60 days of Informed Consent, genetic testing, and eligibility review | 12 mo (±60 days) | 24 mo (±60 days) |
| **Performed at Clinical Sites** | Informed consent discussion, eligibility review, and genetic testing | [$^{18}$F] DPA-714 PET | [$^{18}$F] DPA-714 PET | [$^{18}$F] DPA-714 PET |

## 5. STUDY POPULATION

Participants will be recruited until a total of up to 50 Prodromal and manifest (PD) participants, and 10 healthy participants have completed an evaluable baseline [$^{18}$F]DPA-714. Note that the baseline [$^{18}$F]DPA-714 may occur at any PPMI study visit.

## 6. RECRUITMENT METHODS

PPMI participants who are potentially eligible will be provided information regarding this sub-study and invited to participate. The clinical site staff will be responsible for recruiting participants into this sub-study.

## 7. PARTICIPANT ELIGIBILITY

Participants must meet the following criteria to enroll.

### 7.1 Inclusion Criteria

a) A prodromal PD and Healthy participant enrolled in PPMI Clinical protocol
b) A PD participant enrolled in PPMI Clinical protocol who has not started symptomatic treatment at time of enrollment or in the first 2 years of participation.
c) Able to provide informed consent
d) Must have screening genetic testing documenting high binder at the at the known TSPO gene polymorphism (rs6971)
e) 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]DPA-714
     - 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]DPA-714 on day of PET scan.

### 7.2 Exclusion Criteria

a) Exposure to a total effective dose equivalent of 50 mSv for the whole body, which is the annual limit established by the US Code of Federal Regulations , during the past year.
b) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the Site Investigator might preclude participation.

## 8. 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 either in person or remotely using witnessed paper signature or electronic signature by the Site 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, if appropriate. The signed informed consent may be uploaded to a secure portal for remote monitoring, if possible.

It is the responsibility of the Site 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.

## 9. 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).

## 10. STUDY PROCEDURES

Assessments for this study will be performed as described below and in the PPMI TSPO PET Imaging Schedule of Activities.
Participants enrolled in PPMI Clinical, that meet eligibility criteria and are interested in completing an additional scan under this study will be asked to complete consent and additional assessments as part of this study.

At the screening visit for this study, consent will be obtained, an initial eligibility will be confirmed by the Site Investigator and, the participant will be scheduled for genetic testing. The screening visit for this study can be completed within any PPMI study visit after the participant has enrolled in PPMI. Once genetic testing results are received eligibility will be checked again with the participant and may be enrolled into the study and will receive [$^{18}$F]DPA-714 PET Imaging at Baseline (BL) visit, 12-month visit, and 24-month visit. Any activities required for this protocol will be completed in combination with the PPMI Clinical protocol visit activities. The combined visit is anticipated to take about 8 hours and could occur over more than one day.

## 11. GENETIC TESTING

All potential participants will undergo genetic evaluation at screening. We anticipate that approximately 45% of the PD and control populations will have this genotype.

Blood samples will be collected at the clinical sites and will be shipped to an approved genetic lab for analysis and reporting. For US sites, samples will be shipped to UAB

research lab for DNA extraction, analysis (research based assay), and reporting to clinical sites.

The results of genetic testing for rs6971 have no known clinical significance other than for the imaging method, and results of this test will not be reported to participants other than to indicate their eligibility to proceed with imaging.

## 12. 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.

## 13. SAFETY ASSESSMENTS

All applicable safety assessments will be completed under the PPMI Clinical protocol, according to the visit at which the [$^{18}$F]DPA-714 Imaging is conducted.

## 14. TSPO PET IMAGING WITH [$^{18}$F]DPA-714

[$^{18}$F]DPA-714 GMP production will be managed locally by the UAB, and Invicro New Haven and UK sites. Each participating site will produce and distribute, provide quality control, and conduct the analysis. All imaging data will undergo quality control analysis. Quantitative outcomes will be acquired for all images. Participants will be monitored by study personnel for adverse events on the day that a [$^{18}$F]DPA-714 PET scan is obtained. Participants will also be contacted by phone 2 to 3 [business/working] 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 Board, Ethics , and Radiation Safety Committees, as applicable.

The procedures that will take place at Baseline (BL) visit, 12-month visit, and 24-month visit for PET imaging are described below.

- Women of childbearing potential must have a urine pregnancy test prior to injection of [$^{18}$F]DPA-714. The result must be confirmed as negative prior to proceeding with the injection.
- Participants will receive a dose of no more than 6 mCi {222 MBq} of [$^{18}$F]DPA-714.
- They will then undergo up to 60 minutes of dynamic PET image acquisition, starting at 60 minutes post-injection.
- Safety and tolerability will be assessed throughout the imaging visit, including appropriate vital signs pre and post injection. Adverse events will be recorded in the Adverse Event Log.

Each participating site will be responsible for Imaging site training, data quality and data analysis. The data acquisition and analysis plan will be detailed in the Technical Operations Manual.

## 15. CONCOMITANT MEDICATIONS

Concomitant medications, including over the counter (OTC), 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 TSPO PET Imaging visit are recorded on the study medication log in the PPMI database.

## 16. RISK TO PARTICIPANTS

16.1 Imaging radiation exposure

The radiation exposure from [$^{18}$F]DPA-714 is within FDA guidelines, and the cumulative radiation exposure within PPMI will be monitored prior to injection with [$^{18}$F]DPA-714 to ensure that it is within radiation exposure guidelines.

16.2 Risks Specific to [$^{18}$F]DPA-714 PET Imaging

[$^{18}$F]DPA-714 is an experimental imaging agent that will be used at relatively low (tracer) doses. However, because [$^{18}$F]DPA-714 is in the early stages of clinical investigation, participants receiving [$^{18}$F]DPA-714 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 have been no serious events attributed to use of this tracer. There are also no data on the effects of [$^{18}$F]DPA-714 in human prenatal development. For that reason, fertile females must avoid becoming pregnant and must use adequate contraceptive methods 14 days prior to injection of [$^{18}$F]DPA-714 until at least 24 hours after injection of [$^{18}$F]DPA-714. [$^{18}$F]DPA-714 must not be administered to females who are pregnant or lactating.

16.3 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. Women of childbearing age should not take part in the study unless they are on a reliable form of contraception, and even if this is the case, a urine pregnancy test prior to the PET scans will be performed. Female participants or a female partner of a male subject who report a pregnancy within 30 days of [$^{18}$F]DPA-714 injection will be asked to have a urine pregnancy test.

## 17. POTENTIAL BENEFITS TO PARTICIPANTS

There are no anticipated medical 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.

## 18. COST FOR PARTICIPATION

All research travel and imaging will be provided at no cost to the study participant.

## 19. PAYMENT FOR PARTICIPATION

Participants will be paid at least $200 for completing each scan visit. Participants will be informed if additional payments will be made.

## 20. PARTICIPANT 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. Any information that has already been collected prior to the study participant's withdrawal will not be removed.

## 21. ADVERSE EVENTS

21.1 Adverse Event Reporting Requirements

Site Investigators and coordinators will be instructed to assess for adverse events at the study visit when [$^{18}$F]DPA-714 PET imaging is conducted, as well as by telephone 2 to 3 [business/working] days following such activity. Adverse experiences, whether observed by the Site 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/working] 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 [$^{18}$F]DPA-714 PET imaging.

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

21.2 Serious Adverse Event Reporting Requirements

Serious adverse events pertaining to [$^{18}$F]DPA-714 PET imaging will be reported as follows:

a. Any serious adverse event occurring within 24 hours following the [$^{18}$F]DPA-714 injection will be documented on the Adverse Event Log and reported using the PPMI TSPO PET Imaging SAE Report Form, whether assessed as related to administration of [$^{18}$F]DPA-714 or not.

b. Any serious adverse event occurring more than 24 hours following the [$^{18}$F]DPA-714 injection that is assessed as being related to the [$^{18}$F]DPA-714 injection will be documented on the Adverse Event Log and reported using the PPMI TSPO PET Imaging SAE Report Form.

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

21.3 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 Site 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

21.4 Assessing Relationship of Adverse Events

The assessment of the relationship of an AE to the [$^{18}$F]DPA-714 PET imaging procedure and/or PET tracer 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 or drug 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 or drug 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 or drug.
- Possible - Causal relationship is uncertain

The temporal relationship between study procedure or drug 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 or drug does not appear probable.

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

21.5 Assessing Intensity/Severity of Adverse Events

In addition to assessing the relationship of the adverse event to the study procedure or drug, 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.

## 22. 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).

## 23. 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). Participants will be identified by participant ID numbers on data forms and other study materials.

The Site Investigator will permit the study monitor or designated Site Management Core (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, if possible and consistent with site policies and procedures). 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, as consistent with the site's internal policies. 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.

## 24. DATA SHARING AND STORAGE FOR FUTURE USE

Data collected for this study will be maintained and stored indefinitely at respective study Cores on secure, password protected systems. All study information (data) 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.

The PPMI statistics core will manage the study statistical analysis. The demographic and baseline characteristics will be summarized using descriptive statistics for continuous variables and using frequency count and percentage for discrete variables.

All PPMI data will be incorporated into the PPMI database to create a fully harmonized PPMI database.

## 25. ANALYSIS PLAN

This is an exploratory study and therefore no formal sample size estimates are provided. The baseline regional [$^{18}$F]DPA-714 binding and change in binding at 12 and 24 months will be compared between prodromal, and manifest PD. Each cohort will also be compared with healthy participants. The regional change in binding from baseline to each follow-up visit will be measured and compared. The study and sample size estimates are exploratory. Additional analysis will compare [$^{18}$F]DPA-714 binding and clinical and biomarker outcomes.

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# 27. APPENDIX 1- PPMI DPA-714 PET Imaging Schedule of Activities

| PPMI DPA-714 PET Imaging<br>Schedule of Activities | | | | |
|---|---|---|---|---|
| **Visit Number** | **Screening** | **BL** | **V01** | **V02** |
| **Assessment** | **DPA-714 PET Imaging Screening Visit[a]** | **DPA-714 PET Imaging Baseline Visit[a]** | DPA-714 PET Imaging 12 Month Visit (±60 days) | DPA714 PET Imaging 24 Month Visit[c] (±60 days) |
| ***Consent Activities (≤*** | | | | |
| DPA-714 PET Imaging Documentation of Informed Consent[a] | X | | | |
| DPA-714 PET Imaging Informed Consent Tracking Log | X | | | |
| ***Screening Activities*** | | | | |
| Review DPA-714 PET Inclusion/Exclusion Criteria[a] | I | | | |
| DPA-714 Genetic Testing for TSPO gene[a] | X | | | |
| ***PET Imaging Activities*** | | | | |
| Review DPA-714 PET Imaging Inclusion/Exclusion Criteria | | I | | |
| DPA-714 PET Imaging Urine Pregnancy Test (prior to [$^{18}$F]DPA-714} injection)[b], if applicable | | X | X | X |
| DPA-714 PET Imaging[c] | | X | X | X |
| ***Safety and General Health*** | | | | |
| [#] DPA-714 PET Imaging Adverse Events- In-Clinic Assessment | | X | X | X |
| DPA-714 PET Imaging Adverse Event Telephone Assessment | | X | X | X |
| DPA-714 PET Imaging Report of Pregnancy | | As needed | As needed | As Needed |
| ***General Activities*** | | | | |
| DPA-714 PET Imaging Screen Fail | As needed | | | |
| DPA-714 PET Imaging Conclusion of Study Participation[d] | | | | X |

| |
|---|
| I = Investigator completed assessment |
| X = Investigator or Coordinator completed assessment (or as otherwise delegated) |
| a = Informed Consent, genetic testing, and eligibility review to be completed prior to Baseline Visit for DPA-714 PET imaging. Blood samples will be collected at the clinical sites. For US sites samples will be shipped to UAB research lab for DNA extraction, analysis, and reporting to clinical sites. |
| b =; Urine pregnancy test prior to injection on day of scans for women of childbearing potential. |
| c = Vital signs to be recorded 5-60 minutes Pre and 15-30 minutes Post [$^{18}$F]DPA-714 injection. If PPMI SPECT scan is completed first, then the DPA-714 PET scan can be completed anytime. If the DPA-714 PET scan is completed first, then the PPMI SPECT scan should be completed at least 24 hours after the DPA-714 PET scan. |
| d= To be completed at 24 month visit once all requirements for the study have been met, unless the participant withdraws prior to 24-month visit |
| #Adverse events collected only day of and 2-3 [business/working] days post [$^{18}$F]DPA-714 injection per protocol. |