PROTOCOL

Title:	**Evaluation of [18F]FD4 PET targeting alpha synuclein in Parkinson Disease**
Sponsor:	The Michael J Fox Foundation for Parkinson's Research
Principal Investigator:	Neha Prakash, MBBS
Protocol Number:	XI-004
PPMI Protocol ID:	PPMI 032
Date of Protocol:	16 Sep 2025
Final Version:	1.0

PROTOCOL SIGNATURE PAGE

Version 1.0 dated 16Sep2025

^{18}F-FD4 α-synuclein tracer

Signed by:
Neha Prakash
Signer Name: Neha Prakash
Signing Reason: I approve this document
Signing Time: 9/19/2025 | 10:45:41 AM EDT
69830A9B5657440FB03691410E994828

9/19/2025

Neha Prakash, MBBS — Date
Principal Investigator

Signed by:
Ken Marek
Signer Name: Ken Marek
Signing Reason: I have reviewed this document
Signing Time: 9/19/2025 | 10:13:32 AM PDT
B68E9EE01CA243DB883A885DB8BFCFFF

9/19/2025

Ken Marek, MD — Date
Principal Scientist, Institute for Neurodegenerative Disorders

Signed by:
Sohini Chowdhury
Signer Name: Sohini Chowdhury
Signing Reason: I approve this document
Signing Time: 9/19/2025 | 7:48:52 AM PDT
C152A26F061C42B488544D2CCD297564

9/19/2025

Sohini Chowdhury, Deputy CEO — Date
The Michael J Fox Foundation for Parkinson's Research

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1. PURPOSE OF STUDY

The purpose of this proof-of-concept clinical study is to assess [^{18}F]FD4 binding in Parkinson's disease (PD), Prodromal, and in healthy volunteers. The tracer is designed to detect alpha-synuclein (α-syn) pathology in vivo, a hallmark of PD. This study also aims to compare the binding of two enantiomers of [^{18}F]FD4 to establish the one with most favorable imaging characteristics for its future development as a molecular imaging biomarker of α-syn pathology. The study participants will be enrolled from the ongoing Parkinson Progression Marker Initiative (PPMI), a longitudinal study designed to identify biomarkers of disease. PPMI participants (symptomatic PD and prodromal synucleinopathies) now characterized as Neuronal synuclein disease (NSD) will be enrolled (Marek et al., 2018; Simuni et al., 2018) (ClinicalTrials.gov Identifier: NCT01141023).

This study will take advantage of XingImaging's new ultra-high-performance brain positron emission tomography (PET) scanner, the United Imaging NeuroEXPLORER scanner (NX). The NX provides a fundamental change in PET imaging technology for the brain with unparalleled PET sensitivity (Sensitivity= 46 kcps/kBq and Absolute Sensitivity = 11.8%) and resolution (1.4 mm FWHM) (Carson et al., 2023; Li et al., 2024; Omidvari et al., 2025). The technology may be particularly valuable in evaluating candidate α-synuclein PET tracers in Parkinson's diseases as it enables signal detection in small regions like the substantia nigra and Locus coeruleus.

1.1 Primary Objectives

Primary objective is to compare the brain uptake and signal characteristics of [^{18}F] FD4-R (XI-0002) and [^{18}F] FD4-S (XI-0004) enantiomers in PD, Prodromal and Healthy Control (HC) participants using the NeuroEXPLORER (NX) positron emission tomography (PET).

1.2 Secondary Objectives

Secondary Objectives include:

- To assess the safety and tolerability of both [^{18}F]FD4 enantiomers in human participants.
- To evaluate the regional distribution of tracer uptake in brain regions typically affected by alpha-synuclein pathology in PD using NX.
- To inform the design and logistics of a potential future multicenter validation study of the optimal enantiomer.
- To compare the performance of selected [^{18}F]FD4 enantiomer obtained using the NX versus standard PET camera.

2. STUDY OUTCOMES

2.1 Primary Outcomes

- To compare Standard Uptake Value Ratio (SUVR) in brain regions in [^{18}F] FD4-R (XI-0002) and [^{18}F] FD4-S (XI-0004) enantiomers in both PD and HC participants.

2.2 Secondary Outcomes

- To assess the number and severity of adverse events for both [^{18}F]FD4 enantiomers in human participants.
- To evaluate the regional distribution of tracer uptake in form of SUVR in brain regions typically affected by alpha-synuclein pathology in PD.

- To compare [^{18}F]FD4 binding with clinical assessments including motor and cognitive rating scale.
- To compare the quantitative visualization of selected [^{18}F]FD4 enantiomer in all brain regions using NX versus the standard PET camera.

3. BACKGROUND AND RATIONALE

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by development of motor and nonmotor symptoms. PD is defined the loss of dopaminergic neurons and accumulation of misfolded alpha-synuclein (α-syn) aggregates, which is considered the pathological hallmark for PD and other synucleinopathies such as dementia with Lewy body (DLB), and Multiple system atrophy (MSA) (Braak et al., 2003; McCann et al., 2014). Currently, PD diagnosis is made primarily based on the clinical features and utilization of diagnostic tools which demonstrate dopaminergic degeneration. Diagnostic tools that help detect α-syn can enrich the clinical and research landscape. Such tools can help with the diagnosis and monitoring the progression of the pathology. α-syn tools could also help enrich the inclusion of appropriate participants in interventional drug trials. The current landscape of α-syn diagnostic tool is limited to biological samples such as cerebrospinal fluid or skin (Gibbons et al., 2024; Kannarkat et al., 2025; Parnetti et al., 2025). Radiotracers targeting synuclein would allow for more accurate quantification of regional a-syn pathology and to track brain α-syn longitudinally (Xiang et al., 2025).

Preliminary exploratory studies in PD and MSA with [^{18}F]FD4 PET, developed by SynuSight Biotech (SynuSight BioTech, n.d.) suggest that this tracer demonstrates pre-clinical characteristics promising to show binding in PD patients. The tracer shows high affinity (Kd value of 2.59 nM) and selectivity for synuclein. Initial human studies comparing PD and healthy participants with [^{18}F]FD4 show good brain uptake and suggest that substantia nigra binding is increased in PD compared to healthy participants.

The current study is designed to further investigate whether FD4 shows increased binding in well characterized PPMI PD and prodromal participants compared to healthy volunteers and to further assess whether there are differences between [^{18}F]FD4-R (XI-0002) and [^{18}F]FD4-S (XI-0004) enantiomers in these cohorts.

4. STUDY DESIGN

This is a single-center, proof-of-concept clinical imaging study designed to evaluate and compare the invivo characteristics of two enantiomers of a novel PET radiotracer, [^{18}F]FD4 (FD4-R (XI-0002) and FD4-S (XI-0004)), in participants with Parkinson's disease (PD)/PD prodromal and healthy control (HC) participants.

Each participant will undergo PET imaging with one or both [^{18}F]FD4 enantiomers. The study will begin with imaging of up to 4 PD/prodromal and 4 HC participants, ideally scanned with both enantiomers. However, if a participant chooses to receive only one tracer, additional subjects may be enrolled to ensure up to 4 PD and 4 HC participants are scanned using each enantiomer.

After imaging of the initial 8 participants per enantiomer has been completed, review of the data

will be conducted to assess FD4 binding and regional distribution. Based on this analysis, the enantiomer with the most favorable profile will be selected for continued imaging. Up to 8 additional (6 PD/Prodromal and 2 HC) newly enrolled participants will then be scanned with the selected enantiomer on both the standard PET scanner and the NX PET scanner to further characterize tracer binding performance. Venous metabolite analysis will be done with each scan for radiometabolite correction. Blood sampling, Electrocardiogram (ECG), and urinalysis will be conducted before and after each tracer injection for safety monitoring.
The study will be conducted at the Institute for Neurodegenerative Disorders and XingImaging, LLC clinic and imaging site based in New Haven, CT. The primary aim is to compare the brain uptake and signal characteristics of [^{18}F] FD4-R (XI-0002) and [^{18}F]FD4-S (XI-0004) enantiomers in PD, prodromal, and HC participants using the NeuroEXPLORER (NX) positron emission tomography (PET). The study will include participants already enrolled in the PPMI 002 Clinical study and utilize clinical and biomarker assessments obtained during the PPMI Clinical study visit to reduce the participant burden and enable longitudinal PPMI study data to be used in the study analysis.

Participants will be assessed according to the Schedule of Activities (SOA). Participants will undergo imaging assessments with [^{18}F]FD4 and clinical assessments (conducted under the PPMI Clinical protocol). Data will be collected under uniformly established protocols. Data will be stored and analyzed at designated core facilities.

5. STUDY POPULATION

Up to 24 participants from the PD, Prodromal and Healthy Control cohorts will be enrolled from the PPMI 002 Clinical study at one site.

6. RECRUITMENT METHODS

PPMI clinical participants who are potentially eligible will be provided information regarding this study and invited to participate.

7. PARTICIPANT ELIGIBILITY

7.1 Inclusion Criteria:

General inclusion criteria include the following:

a) Ability to comply with the study procedures.
b) Written informed consent from the participant.
c) Male or Female 40 years of age and older (Females must meet additional criteria specified below, as applicable)
    a. 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]FD4.
        i. 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).

ii. 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.

b. Females of childbearing potential must not be pregnant, breastfeeding or lactating, or planning pregnancy during the duration of the study.

Healthy Controls inclusion control:

a) Enrolled in the PPMI study as a healthy subject.

Parkinson's Disease and Prodromal inclusion criteria:

a) Enrolled in the PPMI study as a PD or prodromal participant.

7.2 Exclusion Criteria:

a) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
b) Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine, within 6 months of Baseline Visit.
c) Any structural abnormality or finding on previously obtained or screening brain MRI suggestive of clinically significant neurological disorders other than the diseases of interest (in the opinion of the investigator).
d) Any other reason that in the opinion of the investigator, including abnormal labs, that could interfere with the safety with radiotracer injection, would render the participant unsuitable for the study enrollment.

8. OBTAINING INFORMED CONSENT

As part of the consenting process, each potential participant will be explained 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. 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. 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.

9. PARTICIPANT ID ASSIGNMENT

All PPMI 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

The study visit may occur over a period of more than one day due to the tracer injection requirements, if more than one tracer is given. The date each assessment was completed will be captured within the EDC system. Assessments are to be completed by the Investigator or trained designee as indicated on the schedule of activities.

10.1 Baseline Visit

Refer to the Schedule of Activities (see Appendix) for the activities to be conducted at the Baseline visit.

Eligible participants consented for the PPMI Clinical protocol interested in completing additional scans under this study will be asked to complete the FD4 PET imaging consent and complete any additional assessments as part of the study.

Once all Baseline activities for this protocol have been completed and the Investigator determines that all eligibility criteria have been met, the participant may be considered enrolled in the FD4 PET study. The study activities are anticipated to take about 3-5 hours. Participants who receive 2 tracer versions will be asked to return for Day 2 of the study visit for the second scan. The FD4 PET imaging visit activities could be combined with the PPMI Clinical visit or completed within +/- 45 days of it.

10.2 Withdrawal from the Study

If a participant withdraws from the study, the study team will complete the Conclusion of Participation case report form (CRF) under the last completed visit, with withdrawal reason.

11. CLINICAL ASSESSMENTS

All applicable clinical assessments for PPMI participants will be completed under the PPMI 002 Clinical protocol.

12. SAFETY ASSESSMENTS

Routine clinical lab tests are completed for enrolled PPMI participants under the PPMI 002 Clinical protocol. Additional blood sampling, ECG, and urinalysis will be completed before and after each tracer injection for safety monitoring. At minimum, the safety labs and tests will include a complete blood count, comprehensive metabolic panel, urinalysis, and ECG. Blood will also be collected before and during the imaging for metabolite analysis for radio metabolite correction.

13. FD4 PET IMAGING

The radiotracer, [^{18}F]FD4, will be produced and distributed by XingImaging. Each participant will receive a single intravenous (IV) dose of one of the enantiomers of [^{18}F]FD4 (FD4-R (XI-0002) and/or FD4-S (XI-0004)), administered prior to PET imaging. Participants who agree to being scanned with both enantiomers will receive radiotracer dose followed by PET imaging twice, preferably on consecutive days. The second enantiomer will be injected at least 24 hours after the first injection to account for five half-lives and allow for adequate wash out period in between tracer injection. The order of enantiomer will be selected randomly. If participant opts to be imaged with only one enantiomer, they will receive an injection and PET imaging once.

All participants will undergo [^{18}F]FD4 PET imaging using the NX camera. Some participants may be asked to be imaged as well on the standard PET biograph. This would not require any additional tracer injection.

Since [^{18}F]FD4 imaging is still investigational, it cannot provide definite information about a clinical diagnosis. Participants will be monitored for adverse events by the study personnel on the day that a [^{18}F]FD4 PET scan is obtained. A safety follow-up will also be conducted where the participants will be contacted by phone (or in person) 1 to 3 business days following the injection/scan to assess for adverse events. Identified adverse events will be reported by the site investigator to the site's Institutional Review/Ethics Boards and to his/her Radiation Safety Committee to meet the reporting requirements. In addition, all adverse events will be reported in the applicable clinical databases and reported to FDA, as required.

The procedures that would take place for [^{18}F]FD4 injection are described below and detailed in the Image Acquisition Plan (IAP).

13.1 [^{18}F] FD4 Imaging Procedures

- All women of childbearing potential must have a urine pregnancy test prior to injection of [^{18}F]FD4. The result must be confirmed as negative prior to proceeding with the injection. Pregnant and lactating individuals are excluded from the study.
- Participants will receive a single I.V. administration of up to ≤8mCi of [^{18}F]FD4.
- Participants will undergo PET image acquisition using the NX camera after the injection for up to 3 hours, in accordance with the Image Acquisition Protocol (IAP). Participants may be asked to be imaged as well on the standard PET biograph. This will take place within the 3-hour imaging period. Participants will have breaks every 60 to 90 minutes or as needed during the scan.
- Safety labs (about 10ml), ECG, and urine sample will be drawn before and after each injection. Venous samples for radiometabolite correction (about 40 ml) will be drawn during the imaging at time points detailed in the IAP. A total blood volume of approximately 60 ml will be obtained from the participant for each tracer injection.
- Vital signs will be monitored pre and post injection. Vital signs (supine heart rate and supine blood pressure) will be assessed approximately 30 minutes prior to [^{18}F]FD4 administration. The vitals will be repeated within 30 minutes (± 5 minutes) post [^{18}F]FD4 injection and within 30 minutes (+/- 5 minutes) after completion of imaging. Any clinically significant changes in vital signs will be reviewed by the site investigator before the participant is discharged.

- Safety and tolerability will be assessed throughout the imaging visit. Adverse events will be recorded in the adverse events log in the EDC database.
- XingImaging will be responsible for imaging site training, data quality, and data analysis. The data and quality assurance procedures to be employed in this study are described in the IAP.

14. 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 for PPMI participants. All concomitant medications reported at the time of the FD4 PET Imaging visit are recorded on the study medication log in the PPMI clinical database.

15. PARTICIPATION IN CLINICAL TRIALS

It is preferred that participants do not participate in investigational clinical trials of 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.

16. RISKS TO PARTICIPANTS

16.1 Imaging radiation exposure

The radiation exposure from [^{18}F]FD4 is within FDA guidelines, and the cumulative radiation exposure for PPMI participants will be monitored prior to injection with [^{18}F]FD4 to ensure that it is within radiation exposure guidelines. This will be reviewed by the study site's radiation safety officer.

16.2 Risks Specific to [^{18}F]FD4

Risks of [^{18}F]FD4: [^{18}F]FD4 is an experimental imaging agent that will be used at low mass dose with minimal potential pharmacological risks. To date limited clinical studies have been performed which have shown a favorable safety profile for this tracer. However, because [^{18}F] FD4 is in the very early stages of clinical investigation, participants receiving [^{18}F]FD4 for injection will be monitored closely by means of adverse event reporting and vital signs. The potential for drug-drug interactions is presently unknown. There is no data on the effects of [^{18}F]FD4 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]FD4. [^{18}F]FD4 injection must not be administered to females who are pregnant or lactating.

16.3 Risks of blood draw

Blood draws may cause pain and bruising at the site where the blood is taken.

16.4 Risks of Electrocardiogram (ECG)

ECGs may cause minor discomfort from the placement or removal of adhesive electrodes, such as temporary skin irritation, redness, or itching.

16.5 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. Confirmation of negative pregnancy test is required for participation in the study. All participants are encouraged to use reliable form of contraception 14 days prior to until at least 24 hours after injection of the radiotracer.

17. POTENTIAL BENEFITS TO PARTICIPANTS

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

18. COSTS FOR PARTICIPATION

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

19. PAYMENT FOR PARTICIPATION

All participants will receive a stipend of $200.00 for completing each PET scan visit (i.e., Day 1 PET imaging, Day 2 PET imaging, as applicable).

20. 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. PPMI 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.

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]FD4 PET imaging is conducted, as well as by telephone (or in person) 1 to 3 business days following such activity as outlined in the SOA. 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 1 to 3 business day reporting period 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]FD4 PET imaging.

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

21.2 Serious Adverse Event Reporting Requirements

Serious adverse events pertaining to [^{18}F]FD4 PET imaging will be reported as follows:

a) Any serious and unexpected adverse event occurring within 48 hours following [^{18}F]FD4 injection, regardless of relatedness to FD4, will be documented on the Adverse Event Log within the EDC and reported by the site-to-site management core (SMC), using the PPMI 032 FD4 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/Independent Review Board (IRB)/Ethics Board, 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 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 does not require 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.

21.4 Assessing Relationship of Adverse Events

The assessment of the relationship of an AE to the imaging procedure 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.

21.5 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.

21.6 Study Stopping Criteria

In the event of a serious adverse event (SAE) that is determined by the Investigator and Sponsor to be related to administration of [^{18}F]FD4, enrollment and further administration of [^{18}F]FD4 will be temporarily suspended. The study team will conduct a review of the SAE to determine causality and assess participant safety prior to resuming study procedures or additional tracer administrations. Any decision to restart study enrollment and administration of [^{18}F]FD4 will be made collaboratively by the Principal Investigator, Sponsor, and as appropriate, regulatory authorities.

22. STUDY MONITORING AND SITE MANAGEMENT

The Institute for Neurodegenerative Disorders and XingImaging have the responsibility to monitor all procedures for safety, GCP, and regulatory compliance. The study site will be managed and overseen in an ongoing manner by the PPMI Site Management Core 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. As a U.S. site, there is additional confidentiality obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA), as applicable. Participants will be identified by participant ID numbers on data forms and other study materials. For PPMI participants, PPMI assigned ID number will be utilized.

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, if applicable, 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 for PPMI participants. 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 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 for PPMI participants 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 (SMC) and Data Systems and Technology Operations at the Institute for Neurodegenerative Disorders (New Haven, CT) for conducting operations and analyses as pertains to the study including, but not limited to, enrollment, compliance, and study outcomes. All PPMI data will be incorporated into the PPMI database to create a fully harmonized PPMI database.

All data obtained from the PPMI participants 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.

25. ANALYSIS PLAN

Given this is an exploratory study, no formal sample estimates are provided. The following analysis pathways will be utilized:

- Determination of [^{18}F]FD4 SUVR in brain regions in all participants to compare [^{18}F]FD4-R (XI-0002) and [^{18}F]FD4-S (XI-0004) enantiomers binding across study cohorts.
- Analysis of variance (ANOVA) on a voxel-wise level with group as the main factor will be performed to evaluate potential differences between people with PD and unaffected healthy controls.
- Compare [^{18}F]FD4 binding with clinical assessments, CSF Synuclein Seed Amplification and other biomarker assay to determine the relationship of pathology to these biomarkers.
- Determination of incidence and severity of adverse events.
- To compare performance of the selected [^{18}F]FD4 enantiomer's SUVR in brain regions in participants using NX and Standard PET camera.

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26. Appendix 1- Schedule of Activities

Assessment	Baseline Visit Day 1	Baseline Visit Day 2*
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Urine pregnancy test[b]	X	X
[^{18}F]FD4 Imaging		
[^{18}F]FD4 injection (including pre and post injection vital signs)	X [a]	X[a]
NX PET Scan Imaging (includes vital signs, as applicable)	X	X
Standard PET Scan Imaging[c] (includes vital signs, as applicable)	X	
Adverse Event In Clinic	X	X
[#]Adverse Event Telephone Assessment	X	X
Imaging Screen Fail	As Needed	As Needed
Conclusion of Study Participation	As Needed	As Needed
Report of Pregnancy	As Needed	As Needed

X = Investigator or Coordinator completed assessment (or as otherwise delegated)
a= Blood collection, Urine sample, and ECG for safety monitoring and radiometabolite correction will be collected before and after injection as detailed in the IAP. b = Urine pregnancy test prior to injection on day of scan for women of childbearing potential. c = Second scan on the standard PET scanner will be completed on a subset of newly enrolled participants on Baseline visit Day 1.
#Adverse events collected by phone (or in person) 1-3 business days post [^{18}F]FD4 injection per protocol. Adverse events will be monitored for both enantiomers separately, when applicable. * Optional: participants will be asked to return a second day if they agree to receiving both enantiomers.