PROTOCOL

Title:	Evaluation of Tau-Pathology in Sporadic and LRRK2 Parkinson's Disease Using [^{18}F]PI-2620: A High-resolution PET Imaging Study Using NeuroEXPLORER (NX PI-2160 in PD)
Sponsor:	The Michael J Fox Foundation for Parkinson's Research
Principal Investigator:	Neha Prakash, MBBS
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NX PI-2160 in PD

Neha Prakash, MBBS — Date
Principal Investigator

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

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

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1. PURPOSE OF STUDY

The study aims to utilize a second-generation tau radioligand, [^{18}F]PI-2620, using a high resolution NeuroEXPLORER (NX) positron emission tomography (PET) camera to visualize and better understand the role of tau pathology in synucleinopathies such as sporadic and LRRK2 Parkinson's Disease (PD). We hypothesize that NX PET imaging is well suited to capture the heterogeneity of tau accumulation in a diverse clinical population of sporadic and LRRK2 PD compared to conventional PET cameras. We further speculate that the amount of measured tau pathology may increase as cognitive decline progresses in the clinical patient population. We hypothesize that tau pathology may play an important role in describing the pathological profile and that the combination of NeuroEXPLORER PET in conjunction with [^{18}F]PI-2620 will provide quantifiable data on tau pathology in PD participants without presence of CSF alpha synuclein. We also expect that NX PET imaging could help detect change in tau deposition in diseased cohorts over time.

1.1 Primary Objectives

Primary objective is to investigate in vivo tau deposition in sporadic and LRRK2 Parkinson's disease (PD) compared to taupathies and healthy individuals using the NeuroEXPLORER (NX) positron emission tomography (PET) and [18F]PI-2620.

1.2 Secondary Objectives

Secondary Objectives include:

- To assess tau burden in regions of interest in sporadic and LRRK2 PD compared to diseased and healthy controls using NX.
- To compare quality of tau visualization across the cohorts between NX and conventional PET camera.
- To understand the relationship between clinical and biological biomarkers with tau deposition across the cohorts.
- To compare the longitudinal change of tau imaging outcomes across the cohorts over a period of 12 months.

2. STUDY OUTCOMES

2.1 Primary Outcomes

- Determination of [^{18}F]PI-2620 binding in brain regions in all participants with NX acquired images to compare tau binding between study cohorts.

2.2 Secondary Outcomes

- To compare [^{18}F]PI-2620 binding with clinical assessments including motor and cognitive rating scale.
- To compare [^{18}F]PI-2620 binding with CSF Synuclein Seed Amplification status
- To compare [^{18}F]PI-2620 binding with plasma phosphoTau217
- To compare the tau binding in all participants between the NX and conventional PET scanner (Siemens Biograph mCT).
- To compare longitudinal change in [^{18}F]PI-2620 binding over a period of 12 months across all cohorts.

3. BACKGROUND AND RATIONALE

Parkinson's Disease (PD) is a progressive neurodegenerative disease characterized by alpha-synuclein accumulation that has downstream negative effect on the dopamine-producing neurons in the substantia nigra. It is characterized clinically as a constellation of motor symptoms, such as tremor, bradykinesia, rigidity, and postural instability, and nonmotor symptoms, such as cognitive decline, depression or other mood disorders, sleep disturbances and autonomic dysfunction. Abnormal alpha-synuclein has been identified as the pathology in PD. Recently, biologic frameworks of PD diagnosis incorporating the alpha synuclein presence have been proposed, with or without associated clinical symptoms (Simuni et al., 2024). These frameworks aid in the diagnosis of PD based on a positive biomarker profile (Höglinger et al., 2024; Simuni et al., 2024).

Akin to synucleinopathies, tauopathies are a group of neurodegenerative diseases that share the pathological hallmark of tau protein aggregation in the brain (Goedert et al., 2017). These disorders include Alzheimer's disease (AD), chronic traumatic encephalopathy, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Pick's disease. Interestingly, in predominant alpha-synucleinopathies, the additional co-pathology of tau tangles has been observed at autopsy, suggesting that tau pathology in these conditions may be a contributing factor towards clinical symptomatology (Colloby et al., 2012; Henderson et al., 2019). Additionally, genome-wide association studies have suggested that increased tau expression increases PD risk (Simón-Sánchez et al., 2009). There has been increased interest in understanding the role of tau in PD, particularly those with LRRK2 mutation or with negative Lewy bodies. LRRK2 has been implicated to phosphorylate tau and alluded to playing an intermediary role between tau and synuclein interactions (Araki et al., 2018; Lubben et al., 2024; Taymans & Cookson, 2010). Neuropathological studies have reported not only on the presence of tau in majority of the LRRK2 PD, but also to have positive correlation with alpha synuclein pathology burden highlighting the complex interaction between the two proteins (Henderson et al., 2019). As such, there is an increased interest for in vivo visualization of tau burden in LRRK2 PD. However, imaging tau aggregation, particularly in non-AD tauopathies and synucleinopathies, has remained a challenge (Bischof et al., 2017; Leuzy et al., 2019; J. Zhang et al., 2023).

Limited research has been conducted utilizing the available tau radioligands in PD (J. Zhang et al., 2023). Few studies utilizing Flortaupicir, [18F]AV-1451, a first-generation tau radioligand in PD have demonstrated decreased nigral uptake than healthy controls consistent with nigral loss in PD (Hansen et al., 2016). However, no expected loss of nigral signals were noted over two years follow up (Hansen et al., 2020). Additionally, the studies failed to demonstrate tau deposits elsewhere regardless of the cognitive status. A major limitation of Flortaucipir and similar molecules are measurable off-target binding in the basal ganglia, mainly attributed to MAO-B binding (Murugan et al., 2019).

[18F]-PI-2620 is one of the second-generation tau radioligand with higher selectivity for tau binding with favorable off-target profile, and lower affinity for MAO-B (Murugan et al., 2019). Preclinical studies have shown its binding to both 3-repeat (3R) and 4-repeat (4R) tau isoforms. Clinical studies of [18F]-PI-2620 till date have been concluded in AD and taupathies such as PSP and Corticobasal syndrome (CBS) demonstrating higher image

quality and low signal-to-noise ratio (Messerschmidt et al., 2022; Mueller et al., 2020; Palleis et al., 2021). In 4R tauopathies like PSP and CBD, [^{18}F]PI-2620 binds to tau structures in the basal ganglia and midbrain, with significant activity observed in regions such as the globus pallidus internus, subthalamic nucleus, putamen, and dentate nucleus (Bischof et al., 2024; Brendel et al., 2020). [18F]PI-2620 has been granted fast-track designation by the FDA for AD, PSP, and CBD, and orphan designations for PSP and CBD from both the FDA and EMA.

The Parkinson's Progression Marker Initiative (PPMI) is an observational, international, multi-center study designed to identify PD progression biomarkers both to improve understanding of disease etiology and course and to provide the necessary tools to enhance the likelihood of success of therapeutics studies to slow PD progression (ClinicalTrials.gov Identifier: NCT01141023). A small sub study of PPMI was completed utilizing [18F]PI-2620 in 35 participants to detect tau burden. The study did not identify significant tau binding in PD or LRRK2 individuals regardless of the cognitive status (Marek et al., unpublished). It's lack thereof could be either due to the relatively low levels of tau, the difficulty in visualizing tau in small brain structures with conventional PET cameras, or the different microstructural folding characteristics of tau in these diseases compared to AD, PSP, and CBD (Falcon et al., 2019; Fitzpatrick et al., 2017; W. Zhang et al., 2020).

NeuroEXPLORER (NX) is a dedicated head-only high-resolution PET scanner or camera developed by United Imaging Healthcare in collaboration with Yale University and the University of California, Davis (Omidvari et al., 2025). The camera is built in with various technical advances leading to higher sensitivity and higher spatial resolution of 1.4mm (Li et al., 2024). Compared to conventional PET scanners, NX has demonstrated higher quality images (Carson et al., 2023; Li et al., 2024). A high-resolution camera such as the NX could facilitate better visualization of smaller nuclei, focal tracer uptake within nuclei, and/or potentially improve sensitivity to detect target binding. The NX could offer huge advantage in visualizing the tau aggregation in diseases with potentially low level of tau burden.

The current study aims to:

1. Investigate the ability of [^{18}F]PI-2620 to detect tau binding in sporadic and LRRK2 PD with taupathies (PSP, CBS) as disease control compared to healthy individuals using the NX scanner.
    a. Evaluate whether the NX's higher resolution improves the visualization of tau in taupathies and in synucleinopathies with low or less distinct tau deposition.
2. Evaluate whether tau binding varies according to the clinical, cognitive, CSF-SAA and plasma phosphoTau217 status across the cohorts.
3. Compare the findings obtained from the NX with data from conventional lower-resolution PET imaging system.
4. Evaluate longitudinal change in tau pathology in diseased cohorts using the NX.

4. STUDY DESIGN

This is a single-center study being conducted to gain understanding of tau pathology in people with PD comparing it to diseased and healthy controls. The study will be conducted at the Institute for Neurodegenerative Disorders and XingImaging, LLC clinic and imaging site based in New Haven, CT. The study is planned to be conducted over a period of two years. The study aims to assess the tau burden in PD compared to diseased and healthy controls with PET imaging using [^{18}F]PI-2620 and utilizing the new NX PET camera. The study will include subjects already enrolled in the PPMI study to enable efficient enrollment. The study will utilize clinical and imaging assessments obtained during the PPMI study visit to reduce the subject burden and enable longitudinal PPMI study data used in the study analysis.

In the first year, half of the cohort will be recruited including 10 sporadic PD, 10 LRKK2 PD, 5 PSP/CBS, and 5 Healthy controls. The first-year cohorts, may be scanned on both the NX and the conventional PET camera to allow for comparison of tau deposits visualization between the two camera systems.

During the second year, remaining cohorts will be recruited to acquire the [^{18}F]PI-2620 image using the NX PET camera. In order to investigate the temporal change in tau pathology in PD, participants recruited in the first year will be followed up at 12 months with repeat imaging with NX.

Participants will be comprehensively assessed at baseline and follow up, if applicable, according to the Schedule of Activities (SOA). Participants will undergo imaging assessments with [^{18}F]PI-2620 and clinical assessments (conducted under the PPMI Clinical protocol for PPMI participants and per SOA for non-PPMI participants). Data will be collected under uniformly established protocols. Data will be stored and analyzed at designated core facilities.

5. STUDY POPULATION

Approximately 60 participants will be enrolled into the study. Around 20 sporadic PD, 20 LRRK2 PD, and 10 healthy control participants will be enrolled from the PPMI clinical study. Around 10 participants with either PSP or CBS will be enrolled from the general population.

6. RECRUITMENT METHODS

PPMI clinical participants who are potentially eligible will be provided information regarding this study and invited to participate. Non-PPMI participants will be recruited via the local recruitment channels including digital outreach, local recruitment database, healthcare referral network, patient support organization, and community engagement events.

7. PARTICIPANT ELIGIBILITY

7.1 Inclusion Criteria:

General inclusion criteria include the following:

a) Ability to comply with the study procedures and attend follow-up visits.
b) Written informed consent from the participant or legal guardian.

c) Male or Female between 45 years and 85 years of age (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]PI-2620 or DaTscan.
        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.
    c. Non PPMI participant females of childbearing potential must have a negative serum pregnancy test at Screening and all females of childbearing potential must have negative urine pregnancy test prior to [^{18}F]PI-2620 injection on day of Baseline PET scan.
    d. Non PPMI participant females of childbearing potential must have a negative urine pregnancy test prior to Screening Visit DaTscan injection.

Healthy Controls:

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

Disease specific inclusion criteria:

a) Parkinson's disease
    a. Enrolled in the PPMI study as a sporadic PD or LRRK2 PD participant.
    b. Known CSF alpha synuclein seeding amplification assay status.

b) Progressive Supranuclear Palsy (PSP):
    a. Diagnosis of progressive supranuclear palsy (PSP) based on the Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria (Höglinger et al., 2017).
    b. Symptom onset within 2-5 years prior to screening.

c. Progressive motor symptoms including vertical supranuclear gaze palsy, postural instability, and other signs of parkinsonism.
d. Evidence of striatal degeneration in form of abnormal DaTscan (previously obtained DaTscan since onset of motor symptoms may be used).

c) Corticobasal Syndrome (CBS):
   a. Diagnosis of corticobasal syndrome (CBS) based on clinical criteria, with asymmetric motor and cognitive dysfunction (Armstrong et al., 2013).
   b. Presence of limb apraxia, dystonia, alien limb phenomenon, and/or parkinsonism (e.g., rigidity, bradykinesia).
   c. Cognitive decline as indicated by impairment in attention, executive function, or memory.
   d. Evidence of striatal degeneration in form of abnormal DaTscan (previously obtained DaTscan since onset of motor symptoms may be used).

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. For those receiving Screening DaTscan:
   - Received any of the following medications that could interfere with the imaging and unwilling or medically unable to hold them for five half-lives before SPECT imaging: alpha methyldopa, methylphenidate, amphetamine derivatives or modafinil, bupropion, phentermine, phencyclidine, fentanyl, or medication commonly considered to interfere with Ioflupane binding per standard clinical practice.
c. Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine, within 6 months of Screening Visit for non-PPMI participants or within 6 months of Baseline Visit for PPMI participants.
d. 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).
e. 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 and compliance with GDPR regulation, as applicable. The signed informed consent will be uploaded to a secure portal for remote monitoring, if possible.

It is the responsibility of the Investigator (or as delegated to the person obtaining consent) to make sure that the participant understands what she/he is agreeing to, and that written informed consent is obtained before the participant is involved in any protocol-defined procedures. Each participant will be provided a copy of the consent form.

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). Non-PPMI participants will be assigned a study ID using internal protocol which will be used to identify the participant across all study documents including clinical and imaging data.

10. STUDY PROCEDURES

Study visits may occur over a 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. Screening visits for non-PPMI participants can be completed according to the schedule of activities up to 8 weeks prior to the baseline visit. Assessments are to be completed by the Investigator or trained designee as indicated on the schedule of activities.

10.1 Screening Visit (Non PPMI Participants Only):
Refer to the Schedule of Activities (see Appendix) for the activities to be conducted at the Screening visit.

After consenting to the tau PET imaging study, participants will complete the clinical protocol activities as outlined in the schedule of activities. Given the complexity of the procedures, the visit could occur over more than one day.

10.2 Baseline Visit (Day 0):
Refer to the Schedule of Activities (see Appendix) for the activities to be conducted at the Baseline visit.

PPMI participants
Eligible participants consented for the PPMI Clinical protocol interested in completing additional scans under this study will be asked to complete the tau 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 into the PET study. The combined visit is anticipated to take about 8 hours and

given the complexity of the visit could occur over more than one day. For PPMI participants, the Tau PET imaging visit could be combined with the PPMI Clinical visits or completed within 45 days of it.

Non-PPMI participants

Participants will complete the clinical protocol activities as outlined in the schedule of activities for the Baseline visit. Given the complexity of the procedures, the visit could occur over more than one day.

10.3 Follow Up Visit- 12 Months

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

All participants evaluated in Year 1 will undergo a second PET imaging visit after 12 months. Participants recruited during Year 2 of the study will not undergo an annual follow-up visit. The annual visit could be completed +/- 45 days of the target visit day and could occur over more than one day. Out of window visits will not be considered protocol deviation but will be monitored and noted by the study monitoring team. A follow-up visit will be completed in combination with participant's PPMI Clinical protocol activities for PPMI participants and according to the SOA for the non-PPMI participants. For PPMI participants, the Tau PET imaging visit could be combined with the PPMI Clinical visits or completed within 45 days of it.

10.4 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 Clinical protocol. For non-PPMI participants, clinical assessments as outlined in the schedule of activities (SOA) will be completed. Information collected from those assessments will be combined with the imaging data and any additional information collected for this protocol.

12. SAFETY ASSESSMENTS

All applicable safety assessments, including the routine clinical lab tests, will be completed for enrolled PPMI participants under the PPMI Clinical protocol. For non-PPMI participants, safety labs and post imaging safety follow up will be completed per the SOA. Safety labs completed for non-PPMI participants include a minimum of Complete Blood Count (CBC) and Comprehensive Metabolic Panel (CMP). Labs to confirm coagulopathy status including Partial Thromboplastin Time (ptt), Prothrombin time test/ International Normalized Ratio (PT/INR), platelet count will be completed for participants undergoing Lumbar Puncture, as appropriate per investigator. Standard clinical practice, per investigator's opinion, for safety with Lumbar Puncture procedure will be utilized.

13. TAU PET IMAGING

The tau radiotracer, [^{18}F]PI-2620, will be produced and distributed by Life Molecular Imaging Technologies, Inc. In clinical studies [^{18}F]PI-2620 has shown increased uptake in Alzheimer's disease and taupathies such as Progressive Supranuclear Palsy with low background signals in controls.

Participants will undergo [^{18}F]PI-2620 PET imaging using the NX camera. Year 1 participants will also be scanned using the conventional PET camera (Siemens Biograph mCT PET/CT).

Since [^{18}F]PI-2620 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]PI-2620 PET scan is obtained. A safety follow-up will also be conducted where the participants will be contacted by phone 2 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]PI-2620 injection are described below and detailed in the Image Acquisition Plan (IAP).

13.1 [18F] PI-2620 Imaging Procedures

- All women of childbearing potential must have a urine pregnancy test prior to injection of [^{18}F]PI-2620. 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 approximately 5 to 10mCi of [^{18}F]PI-2620, prior to PET imaging scan.
- Participants will undergo PET image acquisition within 90 minutes after the radiotracer injection. The images will be acquired using the NX PET camera, in accordance with the Image Acquisition Protocol (IAP). Participants may be asked to also undergo imaging on the Biograph PET camera. Participants will be imaged for up to 90 minutes in total.
- Safety and tolerability will be assessed throughout the imaging visit. Vital signs will be monitored pre and post injection. Adverse events will be recorded in the adverse events log in each respective clinical 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 Image Acquisition Protocol (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 tau

PET Imaging visit are recorded on the study medication log in the PPMI and non-PPMI clinical databases.

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]PI-2620 is within FDA guidelines, and the cumulative radiation exposure for PPMI and non-PPMI participants will be monitored prior to injection with [^{18}F]PI-2620 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]PI-2620

Risks of [^{18}F]PI-2620: The most up-to-date and complete information regarding the use of [^{18}F]PI-2620 can be found in the investigator's brochure. [^{18}F]PI-2620 is an experimental imaging agent that will be used at relatively low (tracer) doses with minimal potential pharmacological risks. To date clinical studies have shown a favorable safety profile for this tracer. However, because [^{18}F] PI-2620 is in the early stages of clinical investigation, subjects receiving [^{18}F]PI-2620 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]PI-2620 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]PI-2620. [^{18}F]PI-2620 injection 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. 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 the Baseline and 12-month study visit. Non-PPMI participants will receive $50 for the Screening visit.

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. Non-PPMI participants who withdraw can continue to participate in other studies at the site, if they are already doing so. 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]PI-2620 PET imaging is conducted (and DaTscan, if applicable), as well as by telephone 2 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 Tau PET imaging Adverse Event Log located within the clinical databases. Events occurring outside of the imaging 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 reported adverse event deemed ongoing at the 2 to 3 business day reporting telephone visit, should be followed until resolution or stabilization. Adverse events reported following a premature withdrawal or completion of participation visit should be followed not more than 30 days from [^{18}F]PI-2620 PET or DaTscan 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. All Adverse Events will be reported to the Institute for Neurodegenerative Disorders for reporting to the FDA, as required.

21.2 Serious Adverse Event Reporting Requirements

Serious adverse events pertaining to [^{18}F]PI-2620 PET imaging and DaTscan SPECT imaging will be reported as follows:

a. Any serious adverse event occurring within 48 hours following [^{18}F]PI-2620 or DaTscan injection will be documented on the Adverse Event Log within the clinical databases and reported by the site to XingImaging and the Institute for Neurodegenerative Disorders (INDD), using the Tau PET Imaging SAE Report Form, regardless of causal relationship to [^{18}F]PI-2620 or DaTscan tracer.

b. Notwithstanding the estimated data availability timeframe, XingImaging will report to INDD and the tracer manufacturer within 24 hours of notification from the clinical site of an

occurrence of any SAE occurring within 48 hours post [^{18}F]PI-2620 or DaTscan injection. INDD will facilitate expedited safety reporting to FDA, when required.

c. The Investigator will comply with the study Institutional/Independent Review Board (IRB), 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 considered related to the study procedure or not.

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 [^{18}F]PI-2620 PET imaging procedure and/or [^{18}F]PI-2620 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 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.

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. For non-PPMI participants, unique study assigned ID 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. For non-PPMI participants, site assigned electronic data management and storage will be utilized. 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, study outcomes. All PPMI data will be incorporated into the PPMI database to create a fully harmonized PPMI database. Similarly, the data for non-PPMI participants will be stored securely and shared with the study teams/cores including Institute for Neurodegenerative Disorders (New Haven, CT), XingImaging (New Haven, CT), the Michael J Fox Foundation (New York, NY) and Life Molecular Imaging (Germany).

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]PI-2620 SUVR in brain regions in all participants to compare [^{18}F]PI-2620 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 sporadic and LRRK2 PD patients, taupathies and unaffected healthy controls.
- Compare [^{18}F]PI-2620 binding with clinical assessments, CSF Synuclein Seed Amplification assay and plasma phosphoTau217 to determine the relationship of tau pathology to these biomarkers.
- Compare the tau binding pattern in all participants between the NX and Biograph mCT.
- Comparison of longitudinal change in all imaging end points. The analyses will examine the change during 12 months in [^{18}F]PI-2620 SUVR across all cohorts and compared to clinical, DAT imaging, biofluid outcomes to better assess relationship of change to these biomarkers.

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27. Appendix 1- Schedule of Activities (Taupathy Non-PPMI Participants)

Visit Number		Screening (SC)	Baseline (BL)	Year 1 Follow-Up (conditional)
Assessment	**Timepoint**	**Up to - 8 weeks**	**0**	**12 months[e] +/- 45 days**
Informed Consent		X		
Inclusion/Exclusion Criteria		X	X	
Demographics		X		
Medical History and Concomitant Medications Review		X		X
Vital Signs		X		
Physical Exam		X		X
Neurological Exam - Full		X		X
MoCA		X		X
Serum Pregnancy test for women of childbearing age		X		
PSPRS[a]			X	X
Safety labs		X		
Lumbar Puncture[b]			X	
CSF Routine Test (including send out labs[c])			X	
Plasma phosphoTau217			X	X
Screening DaTscan[d], if applicable		X		
Screening Brain MRI, if applicable		X		
[^{18}F]PI-2620 Imaging[d] (including pre and post injection vital signs)			X	X
	NeuroEXPLORER		X	X[e]
	Conventional PET		X	
[#]Adverse Events		X	X	X
[#]Adverse Event Telephone Assessment		X	X	X
Imaging Screen Fail		As Needed		
Conclusion of Study Participation			As Needed	
Report of Pregnancy		As Needed		

X = Investigator or Coordinator completed assessment (or as otherwise delegated)
a= Progressive Supranuclear Palsy Rating Scale (PSPRS) will be administered for Progressive Supranuclear Palsy (PSP), and Corticobasal Syndrome (CBS) participants b= Lumbar Puncture is optional for PSP and CBS c= CSF send out labs will include CSF tau profile, amyloid peptides, synuclein amplification assay d = Urine pregnancy test prior to injection on day of DaTscan or [18F] PI-2620 for women of childbearing potential. e= For 12-month follow-up, repeat scan using NX camera will be performed on those scanned during Year 1 f = Safety labs include Complete Blood Count (CBC) and Comprehensive Metabolic Panel (CMP). Labs to confirm coagulopathy status including Partial Thromboplastin Time (ptt), Prothrombin time test/ International Normalized Ratio (PT/INR), and platelet count will be completed for participants undergoing Lumbar Puncture, as appropriate per investigator.
#Adverse events collected day of and 2-3 business days post DaTscan (if applicable) and [^{18}F]PI-2620 injection, per protocol.

28. Appendix 2- Schedule of Activities (PPMI Participants)

		Visit Number	**Baseline (BL)**	**Year 1 Follow-Up (conditional)**
Assessment		**Timepoint**	**0**	**12 months[b] +/- 45 days**
Informed Consent			X	
Inclusion/Exclusion Criteria			X	
[^{18}F]PI-2620 Imaging[a] (including pre and post injection vital signs)				
		NeuroEXPLORER	X	X[b]
		Conventional PET	X	
[#]Adverse Events			X	X
[#]Adverse Event Telephone Assessment			X	X
Imaging Screen Fail			As Needed	
Conclusion of Study Participation			As Needed	
Report of Pregnancy			As Needed	

X = Investigator or Coordinator completed assessment (or as otherwise delegated)
a = Urine pregnancy test prior to injection on day of scan for women of childbearing potential. b = For 12-month follow-up, repeat scan using NX camera will be performed on those scanned during Year 1
#Adverse events collected day of and 2-3 business days post [^{18}F]PI-2620 injection per protocol.