PROTOCOL

Title: Assessment of Brain Tau Burden in Participants with Parkinson's Disease in the PPMI Study (PPMI Tau PET Imaging)

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

Principal Investigator: Kenneth Marek, MD

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Assessment of Brain Tau Burden in Participants with Parkinson's Disease in the PPMI Study

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1. PURPOSE OF STUDY

1.1 Primary Objective

The primary goal of this imaging study is to test whether positron emission tomography (PET) with PI-2620 can visualize *in vivo* brain tau deposition in participants with Parkinson's disease (PD).

1.2 Secondary Objective

The secondary goal is to evaluate tau deposition in PD LRRK2 mutation carriers given recent data that tau pathology may be present in those individuals.

2. STUDY OUTCOMES

The primary study outcome will be the regional brain binding of PI-2620 targeting brain tau assessed with PET imaging.

PI-2620, an ^{18}F-labelled tracer, is proposed for this study due to its demonstrated high affinity for pathological tau conformations, low background signal, and experience at the Institute for Neurodegenerative Disorders (IND) with PI-2620 imaging and analysis. Images will be compared with age-matched and historical healthy volunteer controls. Tau brain binding will be compared with PPMI clinical outcomes including motor and cognitive assessments, DaTscan and MRI imaging, and blood and cerebrospinal fluid (CSF) measures of amyloid, tau, and p-tau.

3. BACKGROUND AND RATIONALE

Intracellular tau deposition has emerged as a common factor in many neurodegenerative conditions, including Alzheimer's disease, frontotemporal lobal degeneration, progressive supranuclear palsy, amyotrophic lateral sclerosis, chronic traumatic encephalopathy, and others. Experimental models suggest that cell-to-cell propagation of tau may be a part of these diseases' processes. A notable exception to this generalization of tau deposition appears to be Parkinson's disease (PD), in which prominent tau deposition is generally not seen in the brain, but alpha-synuclein is thought to subserve those roles in toxicity and propagation, at least in part.

However, evidence for a role for tau-related pathology in PD is emerging from several different research approaches in recent reports, notably from the strong association in GWAS (Genome-wide Association) studies with the tau genetic locus[1], and tau polymorphisms suggesting increased tau expression increases PD risk. Studies have implicated tau and synuclein directly sharing metabolic pathways, such as degradation pathways, but the strongest evidence to date implicates LRRK2 as an intermediary of these interactions (c.f., Taymans, 2010[2], Araki, 2018[3], Dachsel, 2010[4]). Tau pathology is well-known to be capable of inducing dopaminergic cell loss in the substantia nigra (SN), such as in progressive supranuclear palsy (PSP). Tau deposition has been reported in brain tissue from patients with PD[5]. LRRK2 is expressed little, if at all, in SN neurons, but is expressed at a high level in the striatum[6-9]. Autopsy results from patients who died with PD and LRRK2 mutations is mixed, the cases presenting

with or without Lewy bodies[2]. In cases without Lewy bodies, many demonstrate prominent tau and/or TDP43 deposition instead. Mutant (G2019S) LRRK2 can enhance neuronal transmission of pathological tau, perhaps to SN neurons[10]. Tau hyperphosphorylation is a hallmark of tau deposition pathology and LRRK2 is capable of directly phosphorylating tau[11], but, perhaps more importantly, also promotes tau hyperphosphylation via known Tau-kinases GSK3b[12] and CDK5[13]. This, in turn, affects cytoskeletal dynamics, autophagy, Tau trafficking and release, aggregation, etc.[7, 10, 14-19]. This LRRK2, especially when mutated, may drive tau to vulnerable cells in the SN and other brain nuclei, promoting the development of PD.

Little has been done *in vivo* to visualize tau deposition in human participants with PD. What research has been done has generally been performed without regard to genetic status and has not revealed significant tau using existing tau PET tracers, such as flortaucipir. An exception with flortaucipir is a report of tau in posterior cortical areas in diffuse Lewy body disease [20]. Flortaucipir and similar molecules are limited by relative specificity for a subset of tau pathologies and measurable off-target binding, notably to monoamine oxidase-B [21]. Although some of the newer, "second generation," tau PET tracers are structurally similar to flortaucipir and therefore expected to have similar limitations, others are less structurally similar and have relative advantages in term of sensitivity, signal-to-noise, and target specificity. PI-2620 has been validated in AD subjects and demonstrates minimal off-target specific binding with good reliability, radiation dosimetry, and specificity [22-26]. This tau PET tracer, with data suggesting binding to both 3R and 4R tau pathologies, may have additional advantages in targeting tau deposition *in vivo* in PD in general and in particular PD individuals with underlying LRRK2 mutations [27].

4. STUDY DESIGN

A detailed understanding of brain tau deposition as assessed by PI-2620 across the spectrum of clinical PD, including effects of underlying LRRK2 mutation, is the major goal of this study. The study will enroll up to 35 participants recruited at PPMI study sites. It is anticipated that the most or all participants will be enrolled at the Institute for Neurodegenerative Disorders (IND) in New Haven, CT. PPMI participant data including clinical, imaging, genetic and biofluid data will be available for comparison to the tau imaging data acquired within this study.

5. STUDY POPULATION

Approximately 35 participants enrolled in the PPMI study will be recruited, including approximately 10 individuals with LRRK2 mutations (LRRK2, manifest or non-manifest), 20 sporadic PD individuals (across a range of disease duration from newly diagnosed to longstanding PD) and 5 healthy controls.

6. RECRUITMENT METHODS

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

7. PARTICIPANT ELIGIBILITY

7.1 Inclusion Criteria

a) Enrolled in PPMI Clinical protocol
b) Able to provide informed consent
c) Male or Female (Females must meet additional criteria specified below, as applicable)
   - Females must be of *non-childbearing potential* or using a *highly effective method of birth control* 14 days prior to until at least 24 hours after injection of PI-2620.
     - 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.
   - Females of childbearing potential have a negative urine pregnancy test prior to PI-2620 injection on day of PET scan.

7.2 Exclusion Criteria

a) Exposure to an effective radiation dose of 50 mSv, which would be above the acceptable annual limit established by the US Federal Guidelines 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 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 applicable. The signed informed consent may be uploaded to a secure portal for remote monitoring.

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. PARITCIPANT 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

After consenting to PPMI Clinical protocol, participants interested in completing an additional scan under this study will be asked to complete consent and additional assessments as part of this study.

Once consent is obtained, and eligibility is confirmed by the Site Investigator, the participant may be enrolled into the study and will receive PI-2620 PET Imaging. All protocol activities will be completed in combination with the PPMI Clinical protocol activities at the respective visit under which the PET imaging will occur. The combined visit is anticipated to take about 8 hours and could occur over more than one day.

11. CLINICAL ASSESSMENTS

All 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.

12. SAFETY ASSESSMENTS

All applicable safety assessments will be completed under the PPMI Clinical protocol, according to the visit at which the tau PET Imaging is conducted.

13. TAU PET IMAGING

The radiotracer, PI-2620, doses will be produced and distributed by Life Molecular Imaging Technologies, Inc. Since PET imaging with PI-2620 is investigational, it cannot provide definite information about a clinical diagnosis. Participants will be monitored by study personnel for adverse events on the day that a PI-2620 PET scan is obtained. Participants will also be contacted by phone following the injection/scan to assess adverse events. These events will be reported by the Site Investigator to meet any of the site's institutional reporting requirements.

The procedures that will take place for PET imaging is described below.

- Women of childbearing potential must have a urine pregnancy test prior to injection of PI-2620. The result must be confirmed as negative prior to proceeding with the injection.
- Participants will receive a dose of approximately 5 mCi of PI-2620.
- They will then undergo up to 90 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.

The PPMI Imaging Core (Invicro) 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.

14. 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 tau PET Imaging visit are recorded on the study medication log in the PPMI database.

15. RISKS TO PARTICIPANTS

15.1 Imaging radiation exposure

The radiation exposure from PI-2620 is within FDA guidelines, and the cumulative radiation exposure within PPMI will be monitored prior to injection with PI-2620 to ensure that it is within radiation exposure guidelines.

15.2 Risks Specific to PI-2620 PET Imaging

An Investigator's Brochure (IB) has been prepared for PI-2620 that provides detailed information regarding the known risks associated with the product to date. PI-2620 is an experimental imaging agent that will be administered in microdoses (ICH guideline M3(R2)), thus the risk of a pharmacological effect is minimal. However, because PI-2620 is in the early stages of clinical investigation, participants receiving PI-2620 for injection will be followed closely by means of adverse event reporting and vital signs. The primary risk associated with this study involves radiation exposure. While no dose of radiation can be guaranteed to be safe, the levels involved in this study fall within the limits set by guidelines for research participants. The potential for drug-drug interactions is not presently known. There is no data on the effects of 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 PI-2620. PI-2620 must not be administered to females who are pregnant or lactating.

15.2 Unknown Risks

In addition to the known risks listed above, the PET imaging procedures in this study, as with other procedures involving radiation (including X-rays), 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.

16. POTENTIAL BENEFITS TO PARTICIPANTS

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

17. COSTS FOR PARTICIPATION

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

18. PAYMENT FOR PARTICIPATION

Participants will be paid for completing the PET imaging scan activities.

19. PARTICPANT WITHDRAWALS

Study participants will be informed during the consent process that they have the right to withdraw from the study at any time without prejudice and may be withdrawn at the Site Investigator's or Sponsor's discretion at any time. Any information that has already been collected prior to the study participant's withdrawal will not be removed.

20. ADVERSE EVENTS

20.1 Adverse Event Reporting Requirements

Site Investigators and coordinators will be instructed to assess for adverse events at the study visit when PI-2620 PET imaging is conducted, as well as by telephone up to 2 [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, and study specific AE Log documentation, as applicable.

Events occurring outside of the PI-2620 adverse event reporting period defined above will only be documented on the Tau PET Imaging Adverse Event Log (i.e., will not be listed on the PPMI Clinical Adverse Event Log).

Any adverse event ongoing at the 2 [business/working] day reporting telephone visit, should be followed until resolution or stabilization. Adverse events reported following completion of the study visit should be followed not more than 30 days from PI-2620 PET imaging.

Adverse events will be reported by the site as required by the site's institutional reporting requirements.

20.2 Serious Adverse Event Reporting Requirements

Serious adverse events pertaining to the PI-2620 tracer will be reported as follows:

a. Any serious adverse event occurring within 48 hours following the PI-2620 injection will be documented on the Adverse Event Log and reported using the PPMI Tau PET Imaging SAE Report Form, whether assessed as related to PI-2620 tracer or not.

b. Any serious adverse event that occurs following the PI-2620 injection that is assessed as being related to PI-2620 will be documented on the Adverse Event Log and reported using the PPMI Tau PET Imaging SAE Report Form.

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

20.3 Adverse Event Definitions

Adverse Events (AE)

An AE is any undesirable experience occurring to a participant during study participation, whether or not considered related to the PET imaging 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

20.4 Assessing Relationship of Adverse Events

The assessment of the relationship of an AE to the PI-2620 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 imaging 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 or drug 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.

20.5 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.

21. STUDY MONITORING AND SITE MANAGEMENT

The PPMI Steering Committee has the responsibility to monitor all procedures for safety, GCP, and regulatory compliance. The study sites will be managed and overseen in an ongoing manner to verify:

(a) The rights and well-being of human participants are protected.
(b) The reported study data are accurate, complete, and attributable.

(c) The conduct of the study follows the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

22. PRIVACY AND CONFIDENTIALITY

Privacy of participants will be protected in that each person will have the option to voluntarily choose whether to participate in this study. It is the responsibility of the Site Investigator to consider the participant's privacy and confidentiality when completing study visits and related protocol activities.

The Site Investigator must assure that the confidentiality of participants, including their personal identity and personal medical information, will be maintained at all times. U.S. sites have additional confidentiality obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA), as applicable. 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). This shall include all study relevant documentation including participant medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the participant is in the study, and autopsy reports for deaths occurring during the study (when available). In addition, electronic document storage will be maintained with the Florence electronic trial master file. Identifiable participant information may be stored within this system, which has been validated and deemed compatible with 21 CFR Part 11 requirements. Only study staff requiring access to related study documentation will have permission to view identifiable information.

23. DATA SHARING AND STORAGE FOR FUTURE USE

Data collected for this study will be maintained and stored indefinitely at the study Cores on secure, password protected systems. All study information will be accessed only by those who require access as pertains to the individual's role on the study. All organizations responsible for data storage and review will observe the highest precautions to ensure data integrity and security.

Data collected for this study may be transferred and shared across participating PPMI Cores for conducting analyses as pertains to the study including, but not limited to, enrollment, compliance, study outcomes and, in combination from the data received from PPMI program protocols such as PPMI Clinical. All PPMI data will be incorporated to create a fully harmonized PPMI database.

All data obtained during the conduct of this study will be sent to the Laboratory of Neuro Imaging (LONI) in Los Angeles, California to be stored indefinitely for research purposes. Research data will be made available to researchers to conduct analyses related to PD and other disorders. Researchers will be required to comply with the PPMI data

agreement to receive data. All personally identifiable information will be removed before it is shared outside the study.

24. ANALYSIS PLAN

This is an exploratory study and therefore there are no formal sample size estimates are provided.

- Determination of PI-2620 SUVR in brain regions in all participants to enable assessment of the number of participants that demonstrate tau deposition and to enable comparison of groups as below:
    - PD vs Healthy control
    - Sporadic PD vs LRRK2 PD
- Comparison of tau deposition to clinical, imaging, blood and CSF tau already acquired in these PPMI participants.

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26. Appendix 1 – PPMI Tau PET Imaging Schedule of Activities

PPMI Tau PET Imaging Schedule of Activities	
Assessment	**Tau Imaging Visit**
Consent Activities	
Documentation of Informed Consent	I
Informed Consent Tracking Log	X
Tau PET Imaging Activities	
Review Tau PET Inclusion/Exclusion Criteria	I
Urine Pregnancy Test (prior to PI-2620 injection), if applicable	X
PET Imaging[a]	X
Safety and General Health	
[#]Adverse Events	X
Adverse Event Telephone Assessment	X
Report of Pregnancy	As Needed

I = Investigator completed assessment

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

a = Vital signs to be recorded 5-60 minutes Pre and 15-30 minutes Post PI-2620 injection

#Adverse events collected only day of and 2-3 [business/working] days post PI-2620 injection per protocol.