PROTOCOL

Title: Assessment of [^{18}F] C05-05 PET Imaging in Participants with Parkinson's Disease in the PPMI Study
(PPMI C05-05 PET Imaging)

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

Principal Investigator: Kenneth Marek, MD.

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Assessment of [^{18}F] C05-05 PET Imaging in Participants with Parkinson's Disease in the PPMI Study **(PPMI C05-05 PET Imaging)**

DocuSigned by:
Ken Marek
DA0B7C82E039409...

26-Jan-2024

Kenneth Marek, MD — Date
Principal Investigator

DocuSigned by:
Sohini Chowdhury
C152A26F061C42B...

26-Jan-2024

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

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1. PURPOSE OF STUDY

The overall goal of this protocol is to investigate [^{18}F] C05-05 PET imaging, targeting alpha synuclein, in Parkinson's Disease (PD) participants and healthy volunteers participating in the PPMI study. Participants must meet the following criteria to enroll.

1.1 Primary Objectives

- To compare [^{18}F] C05-05, a PET tracer targeting alpha synuclein, binding in brain regions in PD participants and healthy volunteers.

1.2 Secondary Objectives

- To evaluate the correlation [^{18}F] C05-05 PET and demographic, clinical and biomarker outcomes in PPMI participants.
- To acquire safety data following injection of [^{18}F] C05-05.

2. STUDY OUTCOMES

The primary study outcome will be the regional brain binding of [^{18}F] C05-05 PET imaging assessment of alpha synuclein binding.

[^{18}F] C05-05, an [^{18}F] -labelled tracer, is proposed for this study due to its demonstrated high affinity for alpha synuclein. Images acquired in PD participants will be compared with healthy volunteer controls in the PPMI. [^{18}F] C05-05 brain binding will be compared with PPMI clinical outcomes including motor and cognitive assessments, DaTscan and MRI imaging, and blood and cerebrospinal fluid (CSF) biomarkers including Synuclein Seed amplification, tau, amyloid and NFL.

3. BACKGROUND AND RATIONALE

Identifying reliable and well-validated biomarkers of Parkinson's Disease (PD) progression is crucial to advance research to develop therapeutics that may slow or prevent PD symptoms and pathology. The Parkinson's Progression Marker Initiative (PPMI) is an observational, international, multi-center study designed to establish biomarker defined cohorts and to identify PD progression biomarkers both to improve understanding of disease etiology and disease course and to provide the necessary tools to enhance the likelihood of success of PD disease modifying therapeutic trials (ClinicalTrials.gov Identifier:NCT01141023)(1). PPMI is a collaborative study of PD researchers with expertise in biomarker development, PD clinical study design and implementation, bioinformatics, statistics, and data management. The study is a public-private partnership of academic researchers, sponsored and largely funded by The Michael J Fox Foundation (MJFF) and supported by approximately thirty-five pharmaceutical and biotech industry partners.

Synuclein is the key defining pathology for Parkinson disease and biomarkers of synuclein aggregation are crucial to monitor disease progression and the response to therapeutic interventions (2-3). Recently the CSF synuclein seed amplification assay has been used to identify individuals with synuclein pathology at an early stage of disease (4-5). A synuclein

imaging tracer has the potential to detect participants with early pathology, to identify the brain regions where synuclein in deposited, and to monitor changes in synuclein pathology with disease progression and in response to therapy.

Development of synuclein tracer has been challenging because of the relatively low expression of synuclein compared to other brain aggregated proteins including amyloid and tau. The consensus of the field is that a successful tracer would need to be both very high affinity for alpha synuclein and have robust selectivity for amyloid and tau. Despite the obstacles, recently several researchers have made progress in the development of a potential alpha synuclein tracer. In a recent presentation (AD/PD - March 2022) the human a-syn PET agent, AC-12589, from AC-Immune was presented by Oskar Hansson and colleagues at Lund University, Sweden. These preliminary studies in multiple-system atrophy, PD, and controls demonstrated the expected increased uptake in cerebellar white matter in multiple-system atrophy, but not PD or healthy volunteers (6). Other tracers with good affinity and selectivity profiles developed by researchers at Merck and Modag are similarly planned to be tested in PD and MSA patients during the next several months (7). Yet another approach led by Keqiang Ye, at the Chinese Academy of Sciences in Shenzhen, used cryo-electron microscopy to identify structural details potential synuclein tracer binding and identified 18F-F0502B as another putative tracer (8).

Researchers led by Makotu Higuchi at National Institutes for Quantum Science and Technology, Chiba, Japan have identified two putative synuclein tracers that have preliminary human data. 18F-SPAL06 has shown midbrain signal in MSA patients but has not demonstrated signal in PD patients (9). [^{18}F] C05-05 has shown evidence of possible synuclein binding in PD patients but this requires more extensive imaging with more robust clinical correlation (10). We propose to compare [^{18}F] C05-05 in PD and healthy PPMI participants and correlate the PET signal with the extensive clinical, imaging, and biomarker data available for these individuals.

4. STUDY DESIGN

This is an observational study evaluating the imaging characteristics of [^{18}F] C05-05 in PPMI participants with PD and healthy volunteers. The PD cohort will include individuals who are moderately affected (i.e., >4 years duration). 5 PD participants and 5 healthy participants will be enrolled at up to 3 PPMI sites in the US. Participants can be enrolled at any time during their PPMI participation. All screening and longitudinal clinical activities will be completed at the clinical sites. Data will be reviewed on an ongoing basis by the Investigator and the study team. Initial enrollment will focus on moderate PD participants, but depending on the study data early PD participants may be included.

5. STUDY POPULATION

Approximately 10 participants enrolled in the PPMI study will be recruited, including approximately 5 participants with PD and 5 healthy participants. \

6. RECRUITMENT METHODS

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

7. PARTICIPANT ELIGIBILITY

Participants must meet the following criteria to enroll.

7.1 Inclusion Criteria

a) 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 [^{18}F]C05-05.
     - 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 [^{18}F] C05-05 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 witnessed paper signature or electronic

signature by the Site Investigator or delegated study staff, as applicable. Each participant will sign such an informed consent to document agreement to participate in the study, as well as to document HIPAA authorization, if appropriate. The signed informed consent may be uploaded to a secure portal for remote monitoring, if possible.

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

9. PARTICIPANT ID ASSIGNMENT

All participants will use their assigned PPMI study ID. The PPMI Participant ID number will be used to identify a participant on all study related documentation (e.g., clinical database, imaging data).

10. STUDY PROCEDURES

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 [^{18}F] C05-05 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 applicable clinical assessments will be completed under the PPMI Clinical protocol titled “The Parkinson’s Progression Markers Initiative (PPMI) Clinical - Establishing a Deeply Phenotyped PD Cohort” for which all participants are required to be enrolled per the inclusion criteria (11). Information collected from those assessments will be combined with the imaging data and any additional information collected for this protocol.

12. SAFETY ASSESSMENTS

All safety assessments will be completed under the PPMI Clinical protocol (11). Information collected from those assessments will be combined with the imaging data and any additional information collected for this protocol.

12.1 Clinical Safety Laboratory Tests

Routine clinical safety laboratory tests indicated in the table below will be performed pre and post injection of [^{18}F]C05-05 and post injection of [^{18}F]C05-05. A central laboratory will be implemented in order to conduct identical analysis methods and utilize consistent normal ranges and thus common interpretation of laboratory changes.

If not stated otherwise, venous whole blood will be collected in blood collection tubes (vacutainers). All samples for laboratory analysis must be collected, prepared, labelled, and shipped according to the laboratory's requirement as detailed in the lab manual. The total amount of blood needed for the clinical safety lab tests will be no more than 5 ml. No more than 10 ml will be drawn at either the pre or post injection safety lab blood samples.

CENTRAL LAB TESTS	
METABOLIC PANEL	**COMPLETE BLOOD COUNT**
Sodium (Na) Potassium (K) Chloride (Cl) Carbon Dioxide (CO2) Blood Urea Nitrogen (BUN) Glucose Calcium (Ca) Creatinine (Crn) Bilirubin Total Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline Phosphatase (ALKP)	White Blood Cell Count (WBC) Red Blood Cell Count (RBC) Hemoglobin (Hb) Hematocrit (HCT) Platelet Count (PLT)

***If clinical safety lab blood samples have been collected for a participant completed under the PPMI Clinical protocol (11) within 14 days of injection of [^{18}F]C05-05 the values from this report will be used for the C05-05 PET imaging pre-study drug administration safety assessment.**

13. PET IMAGING WITH [^{18}F] C05-05

[^{18}F] C05-05 GMP production will be managed by Invicro under an Invicro IND. Invicro will produce and distribute, provide quality control and conduct the analysis. All imaging data will undergo quality control analysis at Invicro's core imaging laboratory in New Haven, CT. Quantitative outcomes will be acquired for all images. Since PET imaging with [^{18}F] C05-05 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 C05-05 PET scan is obtained. Participants will also be contacted by phone 2 to 3 [business/working] days following the injection/scan to assess adverse events. These events will be reported by the Site Investigator as required to the site's Institutional Review/Ethics Boards and to his/her Radiation Safety Committee.

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 [^{18}F]C05-05. The result must be confirmed as negative prior to proceeding with the injection.
- Participants will receive a dose of no more than 6 mCi of [^{18}F] C05-05.
- They will then undergo up to 120 minutes of dynamic PET image acquisition, starting at post-injection.
- Safety and tolerability will be assessed throughout the imaging visit, including

appropriate vital signs pre and post injection, and upon completion of PET imaging, and 12-lead EKGs 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 C05-05 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 [^{18}F]C05-05 is within FDA guidelines, and the cumulative radiation exposure within PPMI will be monitored prior to injection with [^{18}F]C05-05 to ensure that it is within radiation exposure guidelines.

15.2 Risks Specific to C05-05 PET Imaging

[^{18}F]C0505 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 C05-05 is in the early stages of clinical investigation, participants receiving [^{18}F]C05-05 for injection will be followed closely by means of adverse event reporting, vital signs, laboratory blood testing, and EKGs. 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 [^{18}F]C05-05 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]C05-05. [^{18}F]C05-05 must not be administered to females who are pregnant or lactating.

15.3 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. Female participants or a female partner of a male subject who report a pregnancy within 30 days of [^{18}F]C05-05 injection will be asked to have a urine pregnancy test.

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 at no cost to the study participant.

18. PAYMENT FOR PARTICIPATION

Participants will receive a stipend of $200 for completing PET imaging scan visit.

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 C05-05 PET imaging is conducted, as well as by telephone 2 to 3 [business/working] days following such activity. Adverse experiences, whether observed by the Site Investigator, or elicited from or volunteered by the participant, should be recorded on the Adverse Event Log. Events occurring outside of the study procedure adverse event reporting period defined above do not require documentation for study purposes (i.e., will not be listed on the Adverse Event Log).

Any adverse event ongoing at the 2 to 3 [business/working] day reporting telephone visit, should be followed until resolution or stabilization. Adverse events reported following a premature withdrawal or conclusion of participation visit should be followed not more than 30 days from C05-05 PET imaging.

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

20.2 Serious Adverse Event Reporting Requirements

Serious adverse events pertaining to C05-05 PET imaging will be reported as follows:

a. Any serious adverse event occurring within 24 hours following the [^{18}F]C05-05 injection will be documented on the Adverse Event Log and reported using the C05-05 PET Imaging SAE Report Form, whether assessed as related to administration of [^{18}F]C05-05 or not.

b. Any serious adverse event occurring more than 24 hours following the [^{18}F]C05-05 injection that is assessed as being related to the [^{18}F]C05-05 injection will be documented on the Adverse Event Log and reported using the C05-05 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 study procedure.

Serious Adverse Event (SAE)

An SAE is an AE that is fatal or life-threatening, or results in hospitalization, prolongation of hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. A life-threatening AE is an AE that, in the view of the Site Investigator, places the participant at immediate risk of death from the reaction, as it occurred. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Inpatient admission in the absence of a precipitating, treatment emergent, clinical adverse event is not participant to immediate reporting. For example:

- Admission for treatment of a pre-existing condition not associated with the development of a new adverse event.
- Social admission (e.g., participant has no place to sleep).
- Protocol specific admission during a clinical study (e.g., for a procedure required by another study protocol).
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery).

Inpatient admission does not include the following:

- Emergency Room/Accident and Emergency/Casualty Department visits
- Outpatient/same day/ambulatory procedures
- Observation/short stay units
- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Custodial care facilities

20.4 Assessing Relationship of Adverse Events

The assessment of the relationship of an AE to the C05-05 PET imaging procedure and/or PET tracer is a clinical decision based on all available information at the time the event is being documented. The following definitions of the relationship between the AE (including SAEs) and the study procedure should be considered:

- Unrelated - No possible relationship
  The temporal relationship between study procedure or drug and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study procedure is implausible.
- Unlikely - Not reasonably related, although a causal relationship cannot be ruled out. While the temporal relationship between study procedure or drug and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study procedure or drug.

- Possible - Causal relationship is uncertain
  The temporal relationship between study procedure or drug and the adverse event onset/course is reasonable or unknown, and while other potential causes may not exist, a causal relationship to the study procedure or drug does not appear probable.

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

- Definite - Causal relationship is certain
  The temporal relationship between study procedure or drug and the adverse event onset/course is reasonable and other causes have been eliminated.

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

The Site Investigator will permit the study monitor or designated Site Management Core (SMC) representative to review signed informed consent(s) and that portion of the participant's medical record that is directly related to the study (or provide certified copies of source documentation upon request, if possible and consistent with site policies and procedures). This shall include all study relevant documentation including participant medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the participant is in the study, and autopsy reports for deaths occurring during the study (when available). In addition, electronic document storage will be maintained with the Florence electronic trial master file, as consistent with the site's internal policies. Identifiable participant information may be stored within this system, which has been validated and deemed compatible with 21 CFR Part 11 requirements. Only study staff requiring access to related study documentation will have permission to view identifiable information.

23. DATA SHARING AND STORAGE FOR FUTURE USE

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

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

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

24. ANALYSIS PLAN

This is an exploratory study and therefore no formal sample size estimates are provided. All PET scans will be analyzed using to assess regional C05-05 specific binding. It is likely that the target regions will be compared to a white matter reference but given that these data are exploratory several reference regions may be explored.

Based on prior C05-05 studies and other exploratory PET imaging studies it is very likely that regional comparison of five PD and 5 healthy participants will enable proof of concept for synuclein binding

Additional analysis will compare C05-05 binding and clinical and biomarker outcomes.

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26. Appendix 1 – PPMI C05-05 PET Imaging Schedule of Activities

PPMI C05-05 PET Imaging Schedule of Activities^	
Assessment	**C05-05 Imaging Visit**
Consent Activities	
C05-05 Documentation of Informed Consent	X
C05-05 Informed Consent Tracking Log	X
PET Imaging Activities	
Review C05-05 PET Imaging Inclusion/Exclusion Criteria	I
C05-05 Urine Pregnancy Test (prior to [^{18}F]C05-05 injection), if applicable	X
C05-05 PET Imaging[a]	X
Safety and General Health	
[#]C05-05 Adverse Events- In-Clinic Assessment	X
C05-05 Adverse Event Telephone Assessment	X
C05-05 Report of Pregnancy	As needed
General Activities	
C05-05 Conclusion of Study Participation	X

I = Investigator completed assessment

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

^= Additional Clinical assessments (i.e. medical conditions review, physical and neurological examination, vital signs, weight, height, and routine clinical safety laboratory tests (metabolic panel and complete blood count).11. CLINICAL ASSESSMENTS

a = Vital signs to be recorded 5-60 minutes Pre and 15-30 minutes Post [^{18}F]C05-05 injection, and within 15 minutes upon completion of PET imaging. A 12-lead EKG to be recorded 5-60 minutes Pre and 15-30 minutes Post [^{18}F]C05-05 injection. Clinical safety labs pre- and post [^{18}F]C05-05 injection.

#Adverse events collected only day of and 2-3 [business/working] days post [^{18}F] C05-05 injection per protocol.