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Longitudinal [18F]SynVesT-1 PET targeting SV2A in PPMI (PPMI SV2A PET Imaging)

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Abstract

This protocol details the longitudinal [^{18}F]SynVesT-1 PET targeting SV2A in PPMI (PPMI SV2A PET Imaging).

Guidelines

Appendix 1 – PPMI SV2A PET Imaging Schedule of Activities

	A	B	C	D
	PPMI SV2A PET Imaging Schedule of Activities			
	Visit Number	BL	V01	V02
	Assessment	SV2A PET Imaging Baseline Visita	SV2A PET Imaging 12 Month Visit (±45 days)	SV2A PET Imaging 24 Month Visitc (±45 days)
	Consent Activities			
	Documentation of Informed Consent	X		
	Informed Consent Tracking Log	X		
	Tau PET Imaging Activities			
	Review SV2A PET Imaging Inclusion/Exclusion Criteria	I		
	Urine Pregnancy Test (prior to [18F]SynVesT-1 injection), if applicable	X	X	X
	PET Imagingb	X	X	X
	Safety and General Health			
	#Adverse Events	X	X	X
	Adverse Event Telephone Assessment	X	X	X
	Report of Pregnancy	As needed	As needed	As Needed
	General Activities			
	Conclusion of Study Participation			X

I = Investigator completed assessment
X = Investigator or Coordinator completed assessment (or as otherwise delegated)
a = Informed Consent and Eligibility review can be completed prior to Baseline Visit for SV2A PET imaging
b = Vital signs to be recorded 5-60 minutes Pre and 15-30 minutes Post [^{18}F]SynVesT-1 injection
c= To be completed at 24 month visit once all requirements for the study have been met, unless the participant withdraws prior to 24 month visit
#Adverse events collected only day of and 2-3 [business/working] days post [^{18}F]SynVesT-1 injection per protocol.

PURPOSE OF STUDY

1 The overall goal of this protocol is to investigate [^{18}F]SynVesT-1 binding in prodromal and manifest Parkinson's Disease (PD) and to determine the change in [^{18}F]SynVesT-1 binding in PD participants during a 24-month interval.

2 **Primary Objectives**

2.1 To compare [^{18}F]SynVesT-1 binding in prodromal and manifest PD and healthy volunteers.

2.2 To determine the longitudinal change in [^{18}F]SynVesT-1 during a 24-month interval for prodromal, newly enrolled, early untreated and moderately affected, >5years duration, PD participants.

3 **Secondary Objectives**

3.1 To evaluate the correlation between baseline [^{18}F]SynVesT-1 and PPMI clinical and biomarker outcomes.

3.2 To evaluate the correlation between the longitudinal change of [^{18}F]SynVesT-1 and PPMI clinical and biomarker outcomes.

3.3 To acquire safety data following injection of [^{18}F]SynVesT-1.

STUDY OUTCOMES

4 The primary study outcome will be the regional brain binding of [^{18}F]SynVesT-1 PET imaging assessment of brain synaptic density at baseline and annually for 24 months.

5 [^{18}F]SynVesT-1, an ^{18}F-labelled tracer, is proposed for this study due to its demonstrated high affinity for the synaptic vesicle membrane glycoprotein, SV2A, low background signal, and experience at the Institute for Neurodegenerative Disorders (IND) with [^{18}F]SynVesT-1 imaging and analysis. Images will be compared with age-matched and historical healthy volunteer controls. SV2A brain binding will be compared with PPMI clinical outcomes including motor and cognitive assessments, DaTscan and MRI imaging, and blood and cerebrospinal fluid (CSF).

BACKGROUND AND RATIONALE

6 Identifying reliable and well-validated biomarkers for Parkinson's Disease (PD) progression are crucial to advance research to develop therapeutics that may slow or prevent PD symptoms and pathology. The Parkinson's Progression Marker Initiative (PPMI) is an observational, international, multi-center study designed to establish biomarker defined cohorts and to identify PD progression biomarkers 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). 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.

7 Loss in synaptic density is an early step in most neurodegenerative disorders, often preceding frank neuronal loss. Synapse loss is thought to exceed cell loss in neurodegenerative diseases such as Parkinson disease or Huntington disease (Burke and O'Malley 2013; Adalbert and Coleman 2013; Jenner 2008). In Alzheimer disease, synapse loss correlates strongly with cognitive status, and may be due directly to the presence of A-beta oligomers (Wu et al. 2010; Boros et al. 2017). Measurement of brain synaptic density may be an early and quantitative measure of neurodegeneration in diseases like Parkinson disease. On the other hand, increases in synaptic density may underlie phenomena like the sensitization to dopamine in the striatum that occurs with motor fluctuation in the striatum (Suarez et al. 2014; Villalba and Smith 2018). Therefore, assessment of striatal synaptic density may be an early and/or quantitative biomarker of late complications in Parkinson disease.

8 Synaptic vesicle proteins 2 (SV2) are a family of 12-transmembrane glycoproteins present in synaptic vesicles of neural and endocrine cells. SV2A is the most widely expressed SV2 isoform. SV2A protein is involved in synaptic vesicle exocytosis and neurotransmitter release and can act as a modulator of vesicle fusion (Bajjalieh et al. 1993; Bajjalieh et al.1994). Furthermore, SV2A has been considered as a non-invasive biomarker of synaptic density that can be used for monitoring neurodegenerative diseases (Stockburger et al.2016; Finnema et al. 2016). PET imaging with SV2A specific tracers offers the potential for a better understanding of the role and function of this target in neurodegenerative conditions such as Parkinson disease in vivo.

9 The carbon-11 labeled [^{11}C]UCB-J has been extensively studied and characterized in both preclinical and clinical studies. These studies have demonstrated its specificity for SV2A and its excellent PET imaging characteristics (Nabulsi et al. 2016; Finnema et al. 2016; Finnema et al. 2017). Recent studies with [^{11}C]UCB-J have shown that loss of synaptic density in both Parkinson and Alzheimer disease subjects can be quantified in vivo (Cai et al. 2014; Matuskey et al. 2020; Mansur et al. 2020). [^{18}F]SynVesT-1, is an ^{18}F analog of [^{11}C]UCB-J for imaging SV2A. This tracer, previously known as [^{18}F]MNI-1126 was developed independently from [^{18}F]SDM-8 (Li et al. 2019), although sharing the same molecular structure. SynVesT-1 name was mutually agreed between the two research groups. [^{18}F]SynVesT-1 was previously tested in non-human

primates and demonstrated specificity for SV2A and comparable imaging characteristics with [^{11}C]UCB-J (Constantinescu et al. 2019). A parallel study showed similar in vitro affinity for SV2A to [^{11}C]UCB-J (Patel et al. 2019). In a pilot study, in PD, region-level analysis suggested reductions in binding in caudate nucleus, thalamus, and hippocampus, although no region reached statistical significance, likely due to small sample size.

10 We propose to investigate [^{18}F]SynVesT-1 binding in prodromal and manifest PD and to determine the change in [^{18}F]SynVesT-1 binding in PD participants during a 24-month interval. We plan to take advantage of the PPMI clinical study infrastructure to conduct the study. As detailed below, the planned study will include prodromal, participants with manifest PD, and healthy volunteers. Participants will be enrolled at existing PPMI sites using PPMI eligibility criteria. Additionally, early treated PD participants may be included based on emerging data.

STUDY DESIGN

11 This is a longitudinal observational study evaluating the imaging characteristics of the [^{18}F]SynVesT-1 in PPMI participants with prodromal and manifest PD, and healthy volunteers. The manifest PD cohort will include individuals who are untreated for PD, as well as individuals who are moderately affected (i.e., >5 years duration). Up to 50 PD participants and 10 healthy participants will be enrolled at PPMI sites in the US. All screening and longitudinal clinical activities, including, will be completed at the clinical sites. Data will be reviewed on an ongoing basis by the Investigator and the study team. Enrollment for subsets of participants with PD (i.e., prodromal, early untreated, moderately affected) will be flexible and continuously monitored. It is anticipated the size of each subcohort will ultimately be similar but may be shifted based on emerging data. Initial enrollment will focus on moderate PD participants and will not include prodromal participants. Initial data from moderately affected and healthy volunteers will be reviewed by the study team prior to initiating enrollment of prodromal participants.

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

	A	B	C	D	E
		Consent	Baseline (BL)	12 month	24 month
			within 60 days of Informed Consent and eligibility review	12 mo (±45 days)	24 mo (±45 days)
	Performed at Clinical Sites	Informed Consent discussion and eligibility review	[18F]SynVesT-1 PET	[18F]SynVes T-1 PET	[18F]SynVes T-1 PET

Note

*Note that Healthy Volunteers annual imaging may be discontinued if no change in signal is detected between BL and 12 months.

STUDY POPULATION

13 Participants will be recruited until a total of up to 50 Prodromal and manifest (PD) participants, and 10 healthy participants have completed an evaluable baseline [^{18}F]SynVesT-1 imaging. Note that the baseline [^{18}F]SynVesT-1 may occur at any PPMI study visit.

RECRUITMENT METHODS

14 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.

PARTICIPANT ELIGIBILITY

15 Participants must meet the following criteria to enroll.

16 Inclusion Criteria

16.1 A PD and healthy participant consented to PPMI Clinical, or a prodromal participant confirmed eligible to proceed to PPMI Clinical Baseline visit.

16.2 Able to provide informed consent.

16.3 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]SynVesT-1

a) 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).
b) 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]SynVesT-1 injection on day of PET scan.

17 Exclusion Criteria

17.1 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.

17.2 Any other medical or psychiatric condition or lab abnormality, which in the opinion of the Site Investigator might preclude participation.

OBTAINING INFORMED CONSENT

18 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.

19 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.

PARTICIPANT ID ASSIGNMENT

20 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).

STUDY PROCEDURES

21 Assessments for this study will be performed as described below and in the PPMI SV2A PET Imaging Schedule of Activities.

22 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.

23 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]SynVesT-1 PET Imaging at Baseline (BL) visit, 12 month visit, and 24 month visit. Any activities required for this protocol will be completed in combination with the PPMI Clinical protocol visit activities. The combined visit is anticipated to take about 8 hours and could occur over more than one day.

CLINICAL ASSESSMENTS

24 All applicable clinical assessments will be completed under the PPMI Clinical protocol. Information collected from those assessments will be combined with the imaging data and any additional information collected for this protocol.

SAFETY ASSESSMENTS

25 All applicable safety assessments will be completed under the PPMI Clinical protocol, according to the visit at which the SV2A PET Imaging is conducted.

SV2A PET IMAGING

26 [^{18}F]SynVesT-1 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]SynVesT-1 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 [^{18}F]SynVesT-1 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.

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

- Women of childbearing potential must have a urine pregnancy test prior to injection of [^{18}F]SynVesT-1 . 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]SynVesT-1 .
- They will then undergo up to 60 minutes of dynamic PET image acquisition,starting at 60 minutes post-injection.
- Safety and tolerability will be assessed throughout the imaging visit, including appropriate vital signs pre and post injection. Adverse events will be recorded in the Adverse Event Log.

28 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.

CONCOMITANT MEDICATIONS

29 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 SV2A PET Imaging visit are recorded on the study medication log in the PPMI database.

RISKS TO PARTICIPANTS

30 **Imaging radiation exposure**

The radiation exposure from [^{18}F]SynVesT-1 is within FDA guidelines, and the cumulative radiation exposure within PPMI will be monitored prior to injection with [^{18}F]SynVesT-1 to ensure that it is within radiation exposure guidelines.

31 **Risks Specific to [^{18}F]SynVesT-1 PET Imaging**

[^{18}F]SynVesT-1 is an experimental imaging agent that will be used at relatively low (tracer) doses. However, because [^{18}F]SynVesT-1 is in the early stages of clinical investigation, participants receiving [^{18}F]SynVesT-1 for injection will be followed closely by means of adverse event reporting and vital signs. The potential for drug-drug interactions is not presently known. There have been no serious events attributed with the use of the tracer. There is no data on the effects of [^{18}F]SynVesT-1 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]SynVesT-1 . [^{18}F]SynVesT1 must not be administered to females who are pregnant or lactating.

32 **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]SynVesT-1 injection will be asked to have a urine pregnancy test.

POTENTIAL BENEFITS TO PARTICIPANTS

33 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.

COSTS FOR PARTICIPATION

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

PAYMENT FOR PARTICIPATION

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

PARTICPANT WITHDRAWALS

36 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.

ADVERSE EVENTS

37 Adverse Event Reporting Requirements

37.1 Site Investigators and coordinators will be instructed to assess for adverse events at the study visit when [^{18}F]SynVesT-1 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).

37.2 Any adverse event ongoing at the 2 to 3 [business/working] day reporting telephone visit, should be followed until resolution or stabilization. Adverse events reported following a premature withdrawal or conclusion of participation visit should be followed not more than 30 days from [^{18}F]SynVesT-1 PET imaging.

37.3 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.

38 Serious Adverse Event Reporting Requirements

Serious adverse events pertaining to [^{18}F]SynVesT-1 PET imaging will be reported as follows:

38.1 Any serious adverse event occurring within 24 hours following the [^{18}F]SynVesT1 injection will be documented on the Adverse Event Log and reported using the PPMI SV2A PET Imaging SAE Report Form, whether assessed as related to administration of [^{18}F]SynVesT-1 or not.

38.2 Any serious adverse event occurring more than 24 hours following the [18F]SynVesT-1 injection that is assessed as being related to the [^{18}F]SynVesT-1 injection will be documented on the Adverse Event Log and reported using the PPMI SV2A PET Imaging SAE Report Form.

38.3 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.

39 Adverse Event Definitions

39.1 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.

39.2 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

40 Assessing Relationship of Adverse Events

The assessment of the relationship of an AE to the [^{18}F]SynVesT-1 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:

40.1 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.

40.2 Unlikely - Not reasonably related, although a causal relationship cannot be ruledout. 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.

40.3 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.

40.4 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.

40.5 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.

41 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:

41.1 Mild:
A mild AE is an AE, usually transient in nature and generally not interfering with normal activities.

41.2 Moderate:
A moderate AE is an AE that is sufficiently discomforting to interfere with normal activities.

41.3 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.

STUDY MONITORING AND SITE MANAGEMENT

42 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:

42.1 The rights and well-being of human participants are protected.

42.2 The reported study data are accurate, complete, and attributable.

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

PRIVACY AND CONFIDENTIALITY

43 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.

44 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.

45 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.

DATA SHARING AND STORAGE FOR FUTURE USE

46 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.

47 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.

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

ANALYSIS PLAN

49 This is an exploratory study and therefore no formal sample size estimates are provided. The baseline regional [^{18}F]SynVesT-1 binding will be compared between prodromal, and manifest PD (which will include individuals who are untreated for PD, as well as individuals who are moderately affected (i.e., >5 years duration). Each cohort will also be compared with healthy participants. The regional change in binding from baseline to each follow-up visit will be measured and compared. The study and sample size estimates are exploratory. Additional analysis will compare [^{18}F]SynVesT-1 binding and clinical and biomarker outcomes.

Protocol references

REFERENCES

1. Burke, R. E., and K. O'Malley. 2013. 'Axon degeneration in Parkinson's disease', Exp Neurol, 246: 72-83.
2. Adalbert, R., and M. P. Coleman. 2013. 'Review: Axon pathology in age-related neurodegenerative disorders', Neuropathol Appl Neurobiol, 39: 90-108.
3. Jenner, P. 2008. 'Molecular mechanisms of L-DOPA-induced dyskinesia', Nat Rev Neurosci, 9: 665-77.
4. Wu, H. Y., E. Hudry, T. Hashimoto, K. Kuchibhotla, A. Rozkalne, Z. Fan, T. SpiresJones, H. Xie, M. Arbel-Ornath, C. L. Grosskreutz, B. J. Bacskai, and B. T. Hyman. 2010. 'Amyloid beta induces the morphological neurodegenerative triad of spine loss, dendritic simplification, and neuritic dystrophies through calcineurin activation', J Neurosci, 30: 2636-49
5. Boros, B. D., K. M. Greathouse, E. G. Gentry, K. A. Curtis, E. L. Birchall, M. Gearing, and J. H. Herskowitz. 2017. 'Dendritic spines provide cognitive resilience against Alzheimer's disease', Ann Neurol, 82: 602-14.
6. Suarez, L. M., O. Solis, J. M. Carames, I. R. Taravini, J. M. Solis, M. G. Murer, and R. Moratalla. 2014. 'L-DOPA treatment selectively restores spine density in dopamine receptor D2-expressing projection neurons in dyskinetic mice', Biol Psychiatry, 75: 711-22.
7. Villalba, R. M., and Y. Smith. 2018. 'Loss and remodeling of striatal dendritic spines in Parkinson's disease: from homeostasis to maladaptive plasticity?', J Neural Transm (Vienna), 125: 431-47.
8. Bajjalieh, S. M., G. D. Frantz, J. M. Weimann, S. K. McConnell, and R. H. Scheller. 1994. 'Differential expression of synaptic vesicle protein 2 (SV2) isoforms', J Neurosci, 14: 5223-35.
9. Bajjalieh, S. M., K. Peterson, M. Linial, and R. H. Scheller. 1993. 'Brain contains two forms of synaptic vesicle protein 2', Proc Natl Acad Sci U S A, 90: 2150-4.
10. Finnema, S. J., N. B. Nabulsi, T. Eid, K. Detyniecki, S. F. Lin, M. K. Chen, R. Dhaher, D. Matuskey, E. Baum, D. Holden, D. D. Spencer, J. Mercier, J. Hannestad, Y. Huang, and R. E. Carson. 2016. 'Imaging synaptic density in the living human brain', Sci Transl Med, 8: 348ra96.
11. Finnema, S.J., N.B. Nabulsi, J. Mercier, S.F. Lin, M.K. Chen, D. Matuskey, J.D. Gallezot, S. Henry, J. Hannestad, Y. Huang, and R.E. Carson. 2017. 'Kinetic evaluation and test-retest reproducibility of [11C]UCB-J, a novel radioligand for positron emission tomography imaging of synaptic vesicle glycoprotein 2A in humans', J Cereb Blood Flow Metab: 271678X17724947-.
12. Stockburger, C., D. Miano, M. Baeumlisberger, T. Pallas, T. N. Arrey, M. Karas, K. Friedland, and W. E. Muller. 2016. 'A Mitochondrial Role of SV2a Protein in Aging and Alzheimer's Disease: Studies with Levetiracetam', J Alzheimers Dis, 50: 201-15.
13. Li, S., Z. Cai, X. Wu, D. Holden, R. Pracitto, M. Kapinos, H. Gao, D. Labaree, N. Nabulsi, R. E. Carson, and Y. Huang. 2019. 'Synthesis and in Vivo Evaluation of a Novel PET Radiotracer for Imaging of Synaptic Vesicle Glycoprotein 2A (SV2A) in Nonhuman Primates', ACS Chem Neurosci, 10: 1544-54.
14. Cai, H., T. J. Mangner, O. Muzik, M. W. Wang, D. C. Chugani, and H. T. Chugani. 2014. 'Radiosynthesis of (11)C-Levetiracetam: A Potential Marker for PET Imaging of SV2A Expression', ACS Med Chem Lett, 5: 1152-5.