PROTOCOL

Title:	Evaluation of [^{18}F]MODAG-009 PET Imaging in Synucleinopathies
Study number:	MODAG-009-P1-01
Sponsor:	MODAG GmbH
Co- Sponsor:	The Michael J. Fox Foundation for Parkinson's Research
Principal Investigator:	Neha Prakash, MBBS
Protocol Number:	XI-005
PPMI Protocol Number:	035
Date of Protocol:	20 Apr 2026
Final Version:	2.0

PROTOCOL SIGNATURE PAGE

Version 2.0 dated 20Apr2026

MODAG-009-P1-01

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Signing Time: 2026-Apr-24 | 8:21:09 AM EDT
A9B30A9B5657A40BB03691410E994828

2026-Apr-24

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B68E9EE01CA243DB883A885DB8BFCFFF

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C152A26F061C42B488544D2CCD297564

2026-Apr-24

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6CA78C1DDD7F4B03B03DD649CE2BE6D1

2026-Apr-24

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AE425FA717B24D7381B5E1E129D6F5D1

2026-Apr-24

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1. Protocol Synopsis

Study title: Evaluation of [^{18}F]MODAG-009 PET Imaging in Synucleinopathies

Study number: MODAG-009-P1-01

PPMI protocol number: 035

Protocol number: XI-005

Sponsor: MODAG GmbH

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

Principal Investigator: Neha Prakash, MBBS (Institute for Neurodegenerative Disorders, New Haven, CT, USA)

Study centers: Single center (Institute for Neurodegenerative Disorders and XingImaging, New Haven, CT, USA)

Study type: Single-center, open-label, single-tracer, proof-of-concept PET imaging study

Investigational product: [^{18}F]MODAG-009 PET tracer

Dose and route of administration: Single intravenous (IV) bolus injection of up to ≤ 8 mCi [^{18}F]MODAG-009. The estimated whole-body effective radiation dose from administration of up to 8 mCi of [18F]MODAG-009, including attenuation correction CT, is approximately 9–10 mSv, which is comparable to approximately 3 years of natural background radiation exposure.

Study population
Adults with:
• Parkinson's disease (PD) enrolled in the PPMI-002 Clinical study
• Healthy controls (HC) enrolled in the PPMI-002 Clinical study
• Multiple system atrophy (MSA) recruited from the general population

Number of participants
Approximately 13 participants:
• ~5 PD
• ~5 HC
• ~3 MSA

Study duration per participant
PPMI participants:
• Single MODAG PET imaging visit (approximately 3–5 hours) that may be combined with, or occur within ±45 days of, the most recent PPMI-002 annual visit, plus a safety follow-up phone call 2–3 business days after tracer injection.

Non-PPMI (MSA) participants:
• Screening period of up to 8 weeks, a Baseline/Imaging visit (approximately 6–8 hours, potentially over more than one day), and a safety follow-up phone call 2–3 business days after tracer injection.

Primary objective and endpoint
Objective:
To characterize brain uptake and signal characteristics of [^{18}F]MODAG-009 in participants with Parkinson's disease (PD), multiple system atrophy (MSA), and healthy controls (HC).

Primary endpoint:
To compare Standard Uptake Value Ratios (SUVR) in brain regions from [^{18}F]MODAG-009 in PD, MSA, and HC participants.

Secondary objectives and key endpoints
Objectives:
1.To evaluate the safety, tolerability, and feasibility of administering a single intravenous dose of [^{18}F]MODAG-009 tracer in PD, MSA, and HC participants.
2.To determine regional brain uptake and binding patterns associated with α-synuclein pathology.

Key endpoints:
1. To assess the number and severity of adverse events, vital signs, physical examinations, clinical laboratory results, 12-lead ECGs and drop-out/early discontinuation following administration of [^{18}F]MODAG-009 tracer in human participants.
2. To evaluate the regional distribution of [^{18}F]MODAG-009 uptake, expressed as SUVR in brain regions typically affected by α-synuclein pathology in PD and MSA compared to HC.

Exploratory objectives and endpoints

Objectives:

1. To explore potential associations between tracer uptake and clinical measures of disease severity (e.g., MDS-UPDRS, UMSARS, MoCA).

2. To inform the design of a potential future studies in the development of [^{18}F]MODAG-009

Endpoints:
1. To explore association between [^{18}F]MODAG-009 binding and clinical measures of disease severity including motor and cognitive rating scales (MDS-UPDRS, MoCA, UMSARS).
2. To explore association between [^{18}F]MODAG-009 binding and biomarker measures where available (e.g. CSF α-synuclein seed amplification assay, CSF amyloid-β and tau species, plasma pTau217, neurofilament light chain).

Study design and procedures
Single-center, open-label PET imaging study. All eligible participants receive a single IV injection of [^{18}F]MODAG-009 followed by dynamic PET imaging using the United Imaging NeuroEXPLORER (NX) brain PET scanner for up to 3 hours post-injection, according to an Image Acquisition Plan (IAP). Structural MRI (obtained under PPMI-002 or as part of routine care/screening) is used for anatomical localization and region-of-interest definition. Safety assessments include physical examination, vital signs, ECG, safety laboratory tests, and AE

monitoring on the imaging day and at a follow-up contact 2–3 business days after tracer injection. Blood sampling is performed for radiometabolite analysis and to support quantitative interpretation of PET data, as specified in the IAP.

Key inclusion criteria (summary)
• Participation in the PPMI-002 Clinical study with appropriate diagnostic classification (for PD and HC cohorts), or clinical diagnosis of probable MSA according to the consensus criteria of the Movement Disorders Society (Wenning et al., Movement Disorders 2022, (for the MSA cohort).
• Availability of required clinical characterization, imaging (e.g. MRI and/or DaTscan), and fluid biomarker data (including α-synuclein seed amplification assay and core CSF/plasma biomarkers) as specified in the protocol and Schedule of Activities.
• Ability to undergo PET imaging with the NX scanner and to comply with study procedures.
• Written informed consent provided prior to any study-specific procedures.

Key exclusion criteria (summary)
• Clinically significant, unstable medical, neurological, or psychiatric conditions that, in the opinion of the investigator, could confound interpretation of imaging or pose unacceptable risk.
• Contraindications to MRI or PET imaging, including inability to tolerate required positioning.
• Pregnancy or lactation.
• Prior or planned participation in research studies resulting in cumulative radiation exposure above institutional or regulatory limits.
• Any other condition that, in the opinion of the investigator, would make the participant unsuitable for the study.

2. PURPOSE OF STUDY

The purpose of this single-tracer, proof-of-concept clinical single-center study is to evaluate the in-vivo imaging characteristics, safety, and tolerability of the [^{18}F]MODAG-009 PET tracer in participants with Parkinson's disease (PD), multiple system atrophy (MSA) and in healthy controls (HC). The tracer is designed to bind to aggregated α-synuclein, a hallmark of PD and related synucleinopathies. The PD and HC study participants will be enrolled from the ongoing Parkinson Progression Marker Initiative (PPMI), a longitudinal study designed to identify biomarkers of disease, and the MSA participants will be enrolled from the general population.

PPMI participants, including symptomatic PD and prodromal synucleinopathy cohorts, now characterized as Neuronal Synuclein Disease (NSD), a category defined by biological biomarkers combined with clinical phenotype criteria, will be enrolled (Marek et al., 2018; Simuni et al., 2018), (ClinicalTrials.gov Identifier: NCT04477785).

This study aims to determine whether the tracer demonstrates favorable brain uptake, distribution, and specific binding in regions affected by α-synuclein pathology compared with healthy controls.

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

Findings from this study will inform dosimetry studies and the subsequent development of [^{18}F]MODAG-009.

2.1 Primary Objectives

1. To characterize brain uptake and signal characteristics of [^{18}F]MODAG-009 tracer in participants with PD, MSA and HC.

2.2 Secondary Objectives

Secondary Objectives include:

1. To evaluate the safety, tolerability, and feasibility of administering a single intravenous dose of [^{18}F]MODAG-009 tracer in PD, MSA and HC participants.
2. To determine regional brain uptake and binding patterns associated with α-synuclein pathology.

2.3 Exploratory Objectives

1. To explore potential associations between tracer uptake and clinical measures of disease severity (e.g., MDS-UPDRS, UMSARS, MoCA).
2. To inform the design of potential future studies in the development of [^{18}F]MODAG-009.

3. STUDY OUTCOMES

3.1 Primary Outcomes

- To evaluate Standard Uptake Value Ratios (SUVR) in brain regions from [^{18}F]MODAG-009 in PD, MSA, and HC participants.

3.2 Secondary Outcomes

- To assess the number and severity of adverse events, vital signs, physical examinations, clinical laboratory results, 12-lead ECGs and drop-out/early discontinuation following administration of [^{18}F]MODAG-009 tracer in human participants.
- To evaluate the regional distribution of [^{18}F]MODAG-009 uptake, expressed as SUVR in brain regions typically affected by α-synuclein pathology in PD and MSA compared to HC.

3.3 Exploratory Outcomes

- To explore association between [^{18}F]MODAG-009 binding and clinical measures of disease severity including motor and cognitive rating scales (MDS-UPDRS, MoCA, UMSARS).
- To explore association between [^{18}F]MODAG-009 binding and biomarker measures where available (e.g. CSF α-synuclein seed amplification assay, CSF amyloid-β and tau species, plasma pTau217, neurofilament light chain).

4. BACKGROUND AND RATIONALE

Synucleinopathies are a heterogenous group of neurodegenerative disorders characterized by accumulation of misfolded and aggregated alpha-synuclein (α-syn) which is considered its major pathological hallmark (Galvin et al. 2001). Parkinson's disease (PD) is the most common synucleinopathy and others include disorders such as dementia with Lewy body (DLB), and multiple system atrophy (MSA) (Braak et al., 2003; McCann et al., 2014). Although α-syn misfolding and aggregation is the underlying pathology across all synucleinopathies, the diseases exhibit distinct clinical and pathological characteristics. For instance, PD is a slowly progressive neurodegenerative disorder characterized by development of motor and nonmotor symptoms over time. Pathologically, PD and DLB are defined by presence of intraneuronal aggregates of α-syn in form of lewy bodies and lewy neurites.In contrast, MSA is a rapidly progressive synucleinopathy clinically characterized by predominance of autonomic dysfunction along with Parkinsonism and/or cerebellar syndrome (Wenning et al., 2022). Pathologically, MSA is characterized by α-syn aggregation in form of oligodendroglial and neuronal inclusions. Additionally, the regional distribution of α-syn in MSA varies based on the MSA clinical subtype and is considered to be more widespread than PD (Brettschneider et al., 2017; Dickson et al., 1999; Galvin et al., 2001). Currently, PD and MSA diagnoses are made primarily based on the clinical features and utilization of diagnostic tools which demonstrate dopaminergic degeneration.

Diagnostic tools that help detect α-syn can enrich the clinical and research landscape. Not only can such tools help with early diagnosis and diagnostic accuracy, but they could also enhance our understanding of the pathological localization and progression of α-syn pathology across the prodromal and disease stages. Diagnostic α-syn tools could also help enrich the inclusion of appropriate participants in interventional drug trials. The current landscape of α-syn diagnostic tool is limited to biological samples such as cerebrospinal fluid or skin (Gibbons et al., 2024; Kannarkat et al., 2025; Parnetti et al., 2025). Although CSF and other peripheral biomarker tests

allow for α-syn detection, they do not provide information about the regional localization or spatial progression of pathology. A PET tracer targeting pathological α-syn aggregates would uniquely enable in-vivo mapping of α-syn pathology across brain regions and disease stages, allowing for more accurate quantification of α-syn pathology and tracking brain α-syn pathology longitudinally (Xiang et al., 2025).

The [^{18}F]MODAG-009 PET tracer is an investigational fluorine-18–labeled radioligand designed to selectively bind pathologically aggregated α-synuclein. Preclinical studies have demonstrated high affinity for aggregated α-synuclein, favorable brain penetration, and low off-target binding to amyloid-β and tau species, supporting advancement of [^{18}F]MODAG-009 to early human evaluation.

MODAG-009 shows specific binding in (micro)autoradiography in human brain tissue, specific target binding *in vivo*, a high brain uptake, fast wash-out, and preferable signal-to-noise-ratio *in vitro* and *in vivo*. IND-enabling studies comprising secondary pharmacology screenings, a GLP-toxicology study in rats, and a preclinical imaging study in non-human primates show no safety issues, a rapid brain uptake of [^{18}F]MODAG-009, a homogenous distribution and reversible kinetics. No acute toxicity and no ^{18}F-defluorination of the tracer were observed.
Based on individual indication and in accordance with AMG § 13(2b) of the German Medicinal Products Act (*Arzneimittelgesetz*, AMG), 14 patients with parkinsonian syndromes received single i.v. administrations of [^{18}F]MODAG-009 followed by PET/CT imaging. PET imaging was successfully applied in all patients, and no side-effects (e.g., changes in blood pressure, pulse, temperature, well-being) and no evidence of allergic reactions were observed in any of the patients. In conclusion, intravenous injection of a mean radioactive dose of 295 MBq (range 166 – 334 MBq) and a minimum molar activity of at least 203 GBq/µmol of [^{18}F]MODAG-009 appeared to be safe.

This study will evaluate whether [^{18}F]MODAG-009 demonstrates sufficient brain uptake, target engagement, and regional contrast to warrant further clinical development. Results will provide human data to determine whether the [^{18}F]MODAG-009 tracer shows sufficient uptake and regional contrast to warrant further clinical development.

5. STUDY DESIGN

This is a single-center, open-label clinical study designed to evaluate the imaging characteristics and safety of [^{18}F]MODAG-009 in participants with PD, MSA, and HC.

Each participant will receive a single intravenous injection of [^{18}F]MODAG-009, followed by PET imaging using the investigational United Imaging NeuroEXPLORER (NX) camera. The NX PET scanner used in this study is considered a non-significant risk device. It is an investigational non-invasive imaging system not an implant and is not used to diagnose or treat medical conditions.

Imaging data will be evaluated to characterize tracer regional uptake and image quality. Safety and tolerability will be assessed throughout participation, including vital signs and adverse event monitoring. As this is an exploratory proof-of-concept study, analyses are primarily descriptive and hypothesis-generating rather than powered for formal hypothesis testing.
The study and all imaging will be conducted at the Institute for Neurodegenerative Disorders

(INDD) and XingImaging, LLC in New Haven, CT. Clinical and biological biomarker data already collected under the Parkinson's Progression Markers Initiative (PPMI) parent study may be leveraged for the PD and HC cohorts to minimize participant burden and support analysis of imaging outcomes in relation to clinical measures. Clinical and biological biomarkers will be collected for the MSA cohort according to the schedule of activities (SOA) and will be processed for biomarkers including but not limited to cerebrospinal fluid (CSF) SAA and amyloid-beta peptides 1-40 and 1-42, as well as plasma pTau217. Pseudonymized samples may be used for future biomarker evaluation such as Neurofilament light chain (NfL). Amprion's validated SAAMplify aSyn-CSF and RUA assay with expanded, qualitative aSyn-SAA will be used for detecting presence or absence of type-1 and type-2 seeds for inclusion criteria. The SAA results available through the PPMI biomarkers program will be utilized for the inclusion of the PPMI cohort.

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]MODAG-009 and clinical assessments (conducted under the PPMI 002 Clinical study for PPMI participants and per the SOA for non-PPMI participants). Data will be collected under uniformly established protocols. Data will be stored and analyzed at designated core facilities.

6. STUDY POPULATION

Approximately 13 participants will be enrolled in this study. The target enrollment is approximately 5 PD, 5 HC participants, and 3 MSA participants.

All PD and HC participants will be enrolled from the ongoing PPMI 002 Clinical study at the INDD site. Leveraging the existing PPMI cohort allows use of previously collected clinical and biomarker data, thereby minimizing participant burden and ensuring alignment with established study assessments. The MSA cohort will be enrolled from the general population.

7. RECRUITMENT METHODS

PPMI 002 Clinical study participants who are potentially eligible will be provided with information regarding this study and invited to participate. For non-PPMI participants, IRB-approved language and flyers will be used to share information about the study with the public and healthcare community. Recruitment efforts will include, but are not limited to, digital outreach/advertisement, local recruitment database, healthcare referral network, patient support organization, community outreach, and community engagement events.

8. PARTICIPANT ELIGIBILITY

8.1 Inclusion Criteria (all cohorts):

General inclusion criteria include the following:

a) Able and willing to provide informed consent.
b) Ability and willingness to comply with all study procedures and requirements.
c) Male or Female (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]MODAG-009.
    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. Males with female partners of childbearing potential must use adequate contraceptive methods and refrain from sperm donation for at least 90 days after injection of [^{18}F]MODAG-009.

Healthy Controls inclusion criteria:

a) Enrolled in the PPMI 002 Clinical study as a healthy control participant
b) Any gender aged 50 to 75 years of age
c) Negative CSF α-synuclein seed amplification assay (SAA)
d) Previously acquired (since inclusion in PPMI) brain MRI without evidence of significant neurological pathology.
e) Movement Disorders Society- Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) score of <6 at the last PPMI annual visit which is within the past 18 months.
f) Cognitively intact with Montreal Cognitive Assessment (MoCA) ≥26 at the last PPMI annual visit which was within the past 18 months.

Parkinson's Disease and Prodromal PD inclusion criteria:

a) Enrolled in the PPMI 002 Clinical study as a Parkinson's Disease (PD) or Prodromal participant
b) Any gender aged 50 to 80 years of age
c) Positive CSF SAA
d) A current or previously acquired brain MRI (since the onset of motor symptoms for PD or since enrolled in PPMI for the prodromal PD) without evidence of significant neurological pathology other than changes expected for PD.

e) Montreal Cognitive Assessment (MoCA) ≥24 at the last PPMI annual visit which was within the past 18 months.

Multiple System Atrophy (MSA) inclusion criteria:

a) Any gender aged 50 to 75 years of age
b) Clinically established MSA or Clinically Probable MSA according to the Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy (Wenning et al., 2022)
c) Positive CSF SAA
d) A current or previously acquired brain MRI (since the onset of motor symptoms attributed to MSA) without evidence of significant neurological pathology other than the pathology expected for MSA.
e) Evidence of nigrostriatal degeneration on DaTscan obtained at screening or on previously acquired imaging since the onset of the motor symptoms attributed to MSA.

8.2 Exclusion Criteria (all cohorts):

a) Clinical evidence of other neurodegenerative diseases, such as Alzheimer's disease
b) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
c) Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide, lithium and reserpine, within 6 months of Baseline Visit.
d) Any other reason that in the opinion of the investigator, including abnormal labs, that could interfere with the safety with radiotracer injection, would render the participant unsuitable for the study enrollment.
e) Participation in an investigational drug trial targeting α-synuclein within the past 6 months prior to enrollment.
f) Currently being treated with and unable to safely hold antiplatelets (other than low dose aspirin up to 100mg/day) or anticoagulants prior to the procedure that might preclude safe attempt of Lumbar puncture, if applicable.
g) Condition that precludes the safe performance of routine lumbar puncture, if applicable, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant and uncorrected coagulopathy or thrombocytopenia.
h) Conditions or medications that preclude safe performance of imaging procedures (MRI or DaTscan), including but not limited to severe claustrophobia, MRI-incompatible metal implants, or known hypersensitivity to imaging agents.
i) Known hypersensitivity to DaTscan or iodine-containing compounds used as premedication for DaTscan. Participants with iodine sensitivity may still complete the imaging without iodine premedication at the investigator's discretion.
j) Use of medications known to interfere with DaTscan imaging (e.g., bupropion, amphetamines, methylphenidate, modafinil, alpha-methyldopa), unless the participant is

willing and medically able to hold the medication for at least 5 half-lives or specified duration per investigators judgement prior to imaging.

9. OBTAINING INFORMED CONSENT

As part of the consenting process, each potential participant will be explained the procedures and requirements of the study, together with any potential hazards/risks, and the freedom to withdraw from participation in the study at any time. The consent process will take place in a space that allows for privacy and confidentiality and should allow for enough time for the individual to consider participation and ask any questions. Consent will be obtained by the study Investigator or delegated study staff, as applicable. Each participant will sign such an informed consent to document agreement to participate in the study, as well as to document HIPAA authorization. The signed informed consent will be uploaded to a secure portal for remote monitoring, if possible.

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

10. 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.

11. STUDY PROCEDURES

The study visits may occur over a period of more than one day due to the complexity of visits and resources required at the site.The date each assessment is completed will be documented in source records and the EDC, allowing visit windows to be confirmed regardless of whether procedures span multiple days.

11.1 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 providing informed consent for the MODAG-009-P1-01study, non-PPMI participants will complete the clinical assessments and screening procedures outlined in the SOA. Due to the complexity of these procedures, Screening may occur over multiple days. Out of window visits can be accommodated for reasonable reasons and will not be considered as protocol deviations.

The Screening period may extend up to 8 weeks prior to the Baseline visit. Out-of-window Screening assessments may be permitted for reasonable scheduling or participant-burden considerations and will be documented in source but not considered protocol deviations.

11.2 Baseline Visit

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

PPMI Participants

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

Eligible participants consented for the PPMI 002 Clinical study interested in completing additional scans under this study will be asked to complete the MODAG-009-P1-01study informed consent form and complete any additional assessments as part of the study.

Once the Investigator determines that all eligibility criteria have been met, the participant may be considered enrolled in the MODAG-009-P1-01 PET study. The study activities are anticipated to take about 3-5 hours. The MODAG-009-P1-01 study PET imaging visit may be combined with the PPMI 002 Clinical visit when feasible. If not combined, the MODAG-009-P1-01 study PET visit may occur within ±45 days of the most recent PPMI 002 Clinical study annual visit. An out of window visit will be noted in the source document but will not be considered as a protocol deviation.

Non-PPMI participants

Once all Screening activities for this protocol have been completed and the Investigator determines that all eligibility criteria have been met, the participant may be considered enrolled in the MODAG-009-P1-01 study. 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. The study activities are anticipated to take 6-8 hours.

11.3 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 the withdrawal reason.

12. CLINICAL ASSESSMENTS

PPMI Participants

For PPMI participants, all applicable clinical assessments required for study participation are performed under the PPMI 002 Clinical study and will not be duplicated for this study. These PPMI 002 clinical study assessments (e.g., motor, cognitive, and other standardized clinical measures) will be used to support clinical characterization and exploratory analyses in the MODAG-009-P1-01 study.

Non-PPMI (MSA) Participants

For non-PPMI participants, all clinical assessments outlined in the Schedule of Activities (SOA) will be completed as part of this protocol. Information collected from these assessments will be combined with the imaging data and any additional information collected for this study.

For non-PPMI participants, cerebrospinal fluid (CSF) testing will be performed as part of the lumbar puncture (LP) procedure. Routine CSF laboratory analyses will be processed at the local laboratory and will include CSF protein, glucose, and cell count with differential. CSF send-out analyses will include a tau profile, amyloid peptides, and a-synuclein seed amplification assay.

Plasma samples for additional biomarkers such as pTau217 and NfL will be collected.

13. SAFETY ASSESSMENTS

PPMI Participants
For PPMI participants, all routine clinical safety laboratory tests required for study participation are conducted under the PPMI 002 Clinical study and will not be duplicated for this study.

On the day of [^{18}F]MODAG-009 tracer administration, PPMI participants will undergo study-specific safety assessments described below, which apply to all participants.

Non-PPMI (MSA) Participants
For non-PPMI participants, all screening safety assessments will be completed at the Screening visit according to the SOA.

Non-PPMI participants will undergo the same study-specific pre- and post-injection safety assessments on the day of imaging as PPMI participants.

Study-Specific Imaging Day Safety Assessments(Applies to All Participants)
On the day of [^{18}F]MODAG-009 tracer administration, all participants (PPMI and non-PPMI) will undergo study-specific pre- and post-imaging safety assessments as outlined in the SOA and Image Acquisition Plan (IAP).

Study-specific safety assessments on the imaging day will include the following:

Vital Sign Assessments

- Vital Signs will include the following and will be measured at defined times points per the SOA and IAP:
- Body weight: measured at the defined time points and day of imaging.
- Body temperature: If possible, parameter will be measured at the same location throughout the study. The temperature will be taken pre and post imaging. However, it will not be measured while the imaging is occurring to avoid head movements.
- Supine blood pressure and heart rate: If possible, both parameters will be measured on the same arm throughout the study (non-dominant arm preferred) after 5 minutes of supine rest.

Vitals signs will be collected at the following time points during the Imaging visit:

- Pre-injection vital signs [completed within 5-60 minutes prior to injection]
- Post-injection vitals signs [completed 30min +/-5 min post injection]
- Post-imaging vital signs [completed within 30 min after completion of imaging scan]

Results along with collection parameters will be documented in the source document. Clinically significant out of range values will be documented as adverse events.

Electrocardiogram (ECG)
A 12-lead ECG (QT interval corrected by Fridericia's formula) will be performed after 5 minutes of supine rest at defined timepoints pre and post injection;

- Pre-injection ECG will be completed 5-60 minutes prior to injection.
- Post-injection ECG will be completed within 30 minutes after completion of imaging scan.

Clinically significant events will be recorded as adverse events.

Safety Laboratory Testing

Following safety laboratory testing will be completed pre and post injection as outlined in the SOA

- Complete Blood Count (CBC)
- Comprehensive Metabolic Panel (CMP)
- Urinalysis
- Pre-injection safety labs can be drawn any time on the day of the imaging prior to injection.
- Post-injection safety labs will be drawn within 30 minutes after completion of imaging scan.

Clinically significant out of range lab values will be recorded as adverse events.

For women of childbearing potential, a urine pregnancy test must be performed on the day of [^{18}F]MODAG-009 injection and confirmed negative prior to administration of the tracer.

Radiometabolite Sampling (For analysis and imaging data interpretation)

Blood samples for radiometabolite analysis will be collected at specified timepoints before, during and/or after PET acquisition, analyzed and the data will be stored, all in accordance with the Image Acquisition Plan (IAP).

Total Blood Volume

Combined blood draws for safety labs and radiometabolite sampling will total approximately **60 mL** per participant per tracer administration.

14. MODAG PET IMAGING

The radiotracer, [^{18}F]MODAG-009, will be produced and distributed by XingImaging. Each participant will receive a single intravenous (IV) dose of up to ≤8 mCi [^{18}F]MODAG-009, administered prior to PET imaging.

All participants will undergo [^{18}F]MODAG-009 PET imaging of the brain using the NeuroEXPLORER (NX) camera. The NX PET scanner is a non-invasive investigational imaging device and does not present a significant risk to participants.

Because [^{18}F]MODAG-009 imaging is investigational, imaging results will not be used for diagnostic or clinical decision-making. Participants will be monitored for adverse events during the imaging visit. A safety follow-up will be conducted by phone (or in person) 2–3 business days after injection to assess for adverse events. All adverse events will be documented in the EDC and reported to the IRB, Radiation Safety Committee, FDA, and Sponsor as applicable.

The imaging procedures are summarized below and fully detailed in the IAP.

14.1 [^{18}F]MODAG-009 Imaging Procedures

- All women of childbearing potential must have a urine pregnancy test prior to injection of [^{18}F]MODAG-009. The result must be confirmed as negative prior to proceeding with the injection. Pregnant and lactating individuals are excluded from the study.
- Participants will receive a single I.V. administration of up to ≤8 mCi of [^{18}F]MODAG-009.
- Participants will undergo PET image acquisition using the NX camera for up to 3 hours following [^{18}F]MODAG-009 injection, in accordance with the Image Acquisition Plan (IAP).
- Study-specific safety assessments (CBC, CMP, urinalysis, and ECG) will be completed before and after tracer administration upon completion of the imaging for all participants. Pre- and post-injection safety evaluations will be completed as outlined in the SOA.
- Blood samples for radiometabolite correction (approximately 40 mL) will be collected from all participants (PPMI and non-PPMI) during imaging at time points specified in the IAP and analyzed accordingly.
- Vital signs (supine heart rate and supine blood pressure) will be assessed 5-60 minutes prior to tracer administration, repeated within 30 minutes (±5 minutes) after injection, and again within 30 minutes after completion of imaging. Any clinically significant changes will be reviewed by the Investigator prior to discharge.
- Safety and tolerability will be assessed throughout the imaging visit. Adverse events will be recorded in the adverse events log in the EDC database.
- XingImaging will be responsible for imaging site training, oversight of imaging procedures including radiometabolite analysis, data quality, and data analysis. The data and quality assurance procedures to be employed in this study are described in the IAP.
- Participant will be monitored for at least 30 minutes post completion of imaging before being discharged.

15. 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 002 Clinical study for PPMI participants. This includes medications known to be associated with drug-induced parkinsonism which are not allowed for 6 months prior to screening for the PPMI 002 clinical study and for the duration of the study (dopamine receptor blockers, metoclopramide, and reserpine). All concomitant medications reported at the time of the MODAG-009-P1-01 study PET Imaging visit are recorded on the study medication log in the respective clinical databases.

Certain medications are known to interfere with DaTscan imaging, such as alpha-methyldopa, bupropion, methylphenidate, modafinil, amphetamine derivatives and other CNS stimulants. Participants taking such medications may be required to temporarily discontinue them prior to imaging, if it is medically safe to do so. The appropriate washout period (e.g., at least 5 half-lives) will be determined by the investigator based on the specific medication and participant's safety.

16. PARTICIPATION IN CLINICAL TRIALS

It is preferred that participants do not participate in investigational clinical trials of study drugs during participation in this study or within 6 months prior to enrolment. 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.

17. RISKS TO PARTICIPANTS

17.1 Imaging Radiation Exposure

The radiation exposure from [^{18}F]MODAG-009 is expected to be within FDA guidelines.
Prior to [^{18}F]MODAG-009 injection, each participant's cumulative radiation exposure will be reviewed according to local imaging radiation exposure guidelines to ensure it remains within allowable limits. The estimated effective radiation dose from [^{18}F]MODAG-009 PET imaging, including attenuation correction CT, is estimated to be approximately 9–10 mSv, considered equivalent to 3 years of natural background radiation while living in the United States.

For PPMI participants, this cumulative review will also include radiation exposure from prior imaging procedures performed under the PPMI 002 Clinical study, such as DaTscan.

For non-PPMI participants (MSA cohort), cumulative radiation exposure will include any imaging procedure (like screening DaTscan) performed for this protocol in addition to the radiation from [^{18}F]MODAG-009 PET imaging.

The estimated cumulative effective radiation dose from [^{18}F]MODAG-009 PET imaging, including attenuation correction CT, and DaTscan is estimated to be approximately 13-14 mSv, considered equivalent to ~4 years of natural background radiation while living in the United States.

The site's Radiation Safety Officer (RSO) or designated reviewer will confirm that each participant's cumulative exposure is within institutional and federal research radiation guidelines prior to administering [^{18}F]MODAG-009.

17.2 Risks Specific to [^{18}F]MODAG-009

[^{18}F]MODAG-009 is an investigational imaging agent that will be used at low mass dose with minimal potential pharmacological risks. To dateno clinical studies have been performed. In a limited number of cases with the use of [^{18}F]MODAG-009 for individual diagnostic use in Germany under the local regulations (Arzneimittelgesetz §13.2b), good tolerability and no safety incidents for this tracer have been reported. Pre-IND studies have shown a favorable safety profile for this tracer. However, because [^{18}F]MODAG-009 is in the very early stages of clinical investigation, participants receiving [^{18}F]MODAG-009 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]MODAG-009 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]MODAG-009. [^{18}F]MODAG-009 injection must not be administered to females who are pregnant or lactating. Males with female partners of childbearing potential must use adequate contraceptive methods and refrain from sperm donation for at least 90 days after injection of [^{18}F]MODAG-009.

17.3 Blood Sampling
Risks associated with venous blood draw include pain and bruising at the site where the blood is taken. Sometimes people can feel lightheaded or even faint after having blood drawn. Very rarely, blood draw can lead to nerve damage.

17.4 MRI
Participants should notify the study doctor if they suffer from claustrophobia because they may become anxious while in the magnetic resonance scanner.The investigator may treat the participant for anxiety if indicated. There may be loud noises such as knocking or hammering that occur while the MRI is being conducted. Participants should also inform the study doctor if they have a pacemaker or metal implants (screws, plates or clips) because this may preclude MR evaluation.

Participants with contraindications to MRI (e.g., certain implanted metal devices or severe claustrophobia) will not undergo MRI procedures.

17.5 DaTscan Imaging
DaTscan imaging, when performed, will utilize a standard clinically approved dose of I-123 ioflupane (approximately 3–5 mCi). DaTscan is administered at radiotracer doses and is not expected to have any pharmacological or toxicological effects. DaTscan binds to the dopamine and serotonin transporter. At pharmacologic doses DaTscan might be expected to have stimulant-like effects and affect cardiovascular responses. However, in the proposed study the estimated mass dose of DaTscan is very low (<30/pmol kg). More than 500,000 doses of the radiotracer have been administered to human participants.

Iodine: Prior to each injection, participants will be pretreated with Lugol's (or similar) solution, 10 drops of a saturated solution of potassium iodide, to reduce thyroid uptake of the radioactive agent. Participants may experience a metallic or bitter taste in their mouths from the iodine. Participants with allergies to iodine might get itching, a rash, bloating, severe blood pressure changes (shock), and death if given iodine. Participants who are allergic to iodine may be imaged without Lugol's or if available may be administered potassium perchlorate rather than Lugol's.

17.6 Lumbar Puncture
The most common risks of a lumbar puncture are pain at the procedure site and a temporary headache usually due to a small amount of CSF leakage around the needle insertion site.The headache is usually mild and self-resolves in few days. Lying flat, drinking water and caffeinated drinks, and analgesics can relieve the headache. There is a slight risk of infection because the needle breaks the skin's surface, providing a possible portal of entry for bacteria. A temporary numbness to the legs or lower back pain may be experienced. There is a small risk of bleeding in the spinal canal. Participants will have blood drawn at the Screening or Baseline visit to test for coagulopathies.

17.7 Risks Specific to Clinical assessments
The clinical assessments will be conducted in a private room. Participants may be asked to move to the examination table or sit in a chair. The neurological exam will also include assessments of walking. These assessments pose a very small risk of fall or inconvenience. The study staff are highly trained and have worked with elderly population and with individuals with

neurodegenerative diseases. The study team will use appropriate measures to minimize any potential adverse event related to these assessments. Cognitive assessments will require participants to perform cognitive tasks with use of paper and pencil. The assessments may make some of the participants feel uncomfortable. The study staff will make participants as comfortable as possible. Participants will be informed that they do not have to answer any questions they choose not to answer. Completing all the assessments may lead to physical, mental, or emotional fatigue. Study staff can space out assessments to minimize these effects if needed. Participants will be informed that they can take breaks anytime.

17.8 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 female participants are encouraged to use reliable form of contraception 14 days prior to until at least 24 hours after injection of the radiotracer. Males with female partners of childbearing potential must use adequate contraceptive methods and refrain from sperm donation for at least 90 days after injection of [^{18}F]MODAG-009.

The device (NX PET camera) is not an implant, is not used to support or sustain human life, is not used for a purpose of substantial importance in diagnosing, curing, mitigating, or treating disease or preventing impairment of human health, and does not otherwise present a potential for serious risk to the health, safety, or welfare of participants.

18. 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 and multiple system atrophy.

19. COSTS FOR PARTICIPATION

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

20. PAYMENT FOR PARTICIPATION

All participants will receive a stipend of $200.00 for completing each PET scan visit. Non-PPMI participants will receive $100 for completing the Screening visit.

21. PARTICIPANT 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.

Withdrawal from the study will not impact any participant's interaction with the study team or

participation in any other ongoing studies at the site. Any information that has already been collected prior to the study participant's withdrawal will not be removed.

22. ADVERSE EVENTS

22.1 Adverse Event Reporting Requirements

Site investigators and coordinators will be instructed to assess for adverse events at the study visit when [^{18}F]MODAG-009 PET imaging is conducted (or other study procedures like DaTscan, and LP, if applicable), as well as by telephone (or in person) 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 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 day reporting period should be followed until resolution or stabilization or a clinically acceptable endpoint but not beyond 30 days from [^{18}F]MODAG-009 PET imaging (or DaTscan or lumbar puncture, if applicable), unless continued follow-up is considered clinically indicated by the investigator. Adverse events reported following a premature withdrawal or conclusion of participation visit should be followed not more than 30 days from [^{18}F]MODAG-009 PET imaging, DaTscan imaging, and/or LP.

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.

22.2 Serious Adverse Event Reporting Requirements

Serious adverse events pertaining to [^{18}F]MODAG-009 PET imaging, DaTscan Imaging, and LP will be reported as follows:

a) Any serious and unexpected adverse event occurring within 48 hours following [^{18}F]MODAG-009 or DaTscan injection, and LP, regardless of relatedness to study procedures or investigational agent, will be documented on the Adverse Event Log within the EDC and reported by the site to the site management core (SMC), using the PPMI 035 MODAG SAE Report Form.

b) The SMC will notify the appropriate responsible person(s) to report any serious and unexpected adverse events to the respective Health Authority as soon as possible, but no later than within 15 calendar days of first being notified of the event, as well as additional regulatory and Sponsor entities per respective reporting requirements.

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

22.3 Adverse Event Definitions

Adverse Events (AE)

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

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

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

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

Inpatient admission does not include the following:

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

Unexpected Adverse Event
For FDA reporting purposes, an unexpected AE is an AE not previously reported or an AE that occurs with specificity, severity or frequency that is not consistent with the current investigator's brochure.

22.4 Assessing Relationship of Adverse Events
The assessment of the relationship of an AE to the imaging procedure is a clinical decision based on all available information at the time the event is being documented. The following definitions of the relationship between the AE (including SAEs) and the study procedure should be considered:

- Unrelated - No possible relationship
  The temporal relationship between study procedure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study procedure is implausible.

- Unlikely - Not reasonably related, although a causal relationship cannot be ruled out.
  While the temporal relationship between study procedure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study procedure.

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

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

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

22.5 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.

22.6 Study Stopping Criteria

In the event of a serious adverse event (SAE) that is determined by the Investigator and Sponsor to be related to administration of [^{18}F]MODAG-009, enrollment and further administration of [^{18}F]MODAG-009 will be temporarily suspended. The Sponsor and study team will conduct a review of the SAE to determine causality and assess participant safety prior to resuming study procedures or additional tracer administrations. Any decision to restart study enrollment and administration of [^{18}F]MODAG-009 will be made collaboratively by the Principal Investigator, Sponsor, and as appropriate, regulatory authorities.

Progression to subsequent study phases (dosimetry, test–retest, and clinical validation studies) will be contingent upon completion of a Sponsor-led safety and data review confirming acceptable tolerability, image quality, and tracer performance in the PoC study. Each phase will require separate IRB/IEC and regulatory authorization prior to activation.

23. 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 as described in the monitoring plan. 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).

24. 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, the 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 within the Florence electronic trial master file for both PPMI and Non-PPMI participants. 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.

25. 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 in the study. All organizations responsible for data storage and review will observe the highest precautions to ensure data integrity and security.

Data collected for this study for PPMI participants may be transferred and shared across participating PPMI Cores including the Clinical Trials Statistical and Data Management Core (CTSDMC) at the University of Iowa, Indiana University PPMI Cores (Indianapolis, IN), the Site Management Core (SMC) and Data Systems and Technology Operations at the Institute for

Neurodegenerative Disorders (New Haven, CT) for conducting operations and analyses as pertains to the study including, but not limited to, enrollment, compliance, and study outcomes. Additionally, data collected for this study for PPMI participants may be shared with the study sponsor MODAG GmbH (Germany) and the Michael J Fox Foundation (New York, NY) . All PPMI data will be incorporated into the PPMI database to create a fully harmonized PPMI database and transferred to the Sponsor, MODAG (outside the United States), for the purpose of further developing [^{18}F]MODAG-009, and for research and participant contact information will not be sold.

The data for non-PPMI participants may be 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 MODAG GmbH (Germany), as necessary to support study conduct, data analysis, and regulatory obligations, and transferred to the Sponsor, MODAG (outside the United States), for the purpose of further developing [^{18}F]MODAG-009 and for research and participant contact information will not be sold.

Data obtained during the conduct of this study will be transferred to secure data repositories designated by the study Cores for long-term storage and research use. PPMI participant data will be sent to the Laboratory of Neuro Imaging (LONI) in Los Angeles, California to be stored indefinitely for research purposes. De-identified research data may be made available to qualified researchers in accordance with applicable PPMI data access procedures and data use agreements. All personally identifiable information will be removed before data are shared outside the study team.

26. ANALYSIS PLAN

Analysis populations:
For this exploratory proof-of-concept study, three analysis populations are defined. The Full Analysis Set (FAS) will comprise all participants who meet all inclusion and none of the exclusion criteria, are enrolled into the study, and for whom at least one evaluable [^{18}F]MODAG-009 PET imaging dataset and corresponding minimum clinical data are available. The Safety Analysis Set (SAS) will include all participants who receive any amount of [^{18}F]MODAG-009; all safety analyses (including adverse events, vital signs, safety laboratory parameters, and ECGs) will be performed on the SAS. The Per-Protocol Set (PPS) will be a subset of the SAS and will consist of participants who complete the imaging procedures as planned and who do not have major protocol deviations considered to affect interpretation of imaging or safety outcomes (e.g., key eligibility violations, incomplete imaging acquisition, or substantial deviations from the imaging methodology). The primary and secondary imaging outcome analyses will be conducted primarily on the FAS, with sensitivity analyses performed on the PPS, while safety analyses will be conducted on the SAS.

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

- Determination of [^{18}F]MODAG-009 SUVR in brain regions in all participants to assess tracer binding across study cohorts.

- Analysis of variance (ANOVA) on a voxel-wise level with group (PD vs MSA vs HC) as the main factor to evaluate potential differences in tracer uptake.
- Comparison of [^{18}F]MODAG-009 binding with clinical assessments, CSF α-synuclein seed amplification, and other biomarker assays to determine the relationship of tracer signal to underlying pathology.
- Determination of incidence, relatedness and severity of adverse events.

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28 Appendix 1- PPMI MODAG-009 Imaging Study - Schedule of Activities

Visit Number	Baseline (BL)	Follow up
Assessments	**D0**	**D2-D3**
MODAG-009 **study** ***Consent Activities***		
Informed Consent Documentation	X	
Informed Consent Tracking Log	X	
Additional MODAG-009 **study** ***Activities***		
Inclusion/Exclusion Criteria	I	
Urine Pregnancy Test (prior to tracer injection), if applicable [a]	X	
Screen Fail	As Needed	
Conclusion of Study Participation	As Needed	
MODAG-009 **study** ***PET Imaging***		
Pre-injection vitals signs[b]	X	
ECG[c]	X	
Pre-injection safety labs[c]	X	
MODAG-009 PET Imaging injection	X	
MODAG-009 PET Imaging	X	
Post-injection vital signs[b]	X	
Venous sampling for radiometabolite analysis[d]	X	
Post-imaging vital signs[b]	X	
ECG[c]	X	
Post injection safety labs[c]	X	
MODAG-009 **study** ***Safety and General Health***		
[#] Adverse Event In-Clinic Assessment	X	
[#]Adverse Event Telephone Assessment		X
Report of Pregnancy	As Needed	

**Window of ±45 days either side of Target Visit Date
I = Investigator (or trained designee) completed assessment
X = Investigator or Coordinator completed assessment (or as otherwise delegated)
a = Urine pregnancy test required for women for childbearing potential. Must be completed on the day of [^{18}F]MODAG-009 injection and confirmed negative prior to administering tracer.
b = Vital signs (body temperature, supine heart rate and supine blood pressure) will be assessed approximately 5-60 min prior to [^{18}F]MODAG-009 administration. Vitals signs will be repeated within 30 minutes (± 5 minutes) post [^{18}F] MODAG-009 injection. and within 30 minutes post completion of imaging. Body temperature will not be completed at the 30+/-5 min post-injection timepoint to avoid head movements and interference with imaging.

c = Safety assessments (CBC, CMP, urinalysis, ECG) will be completed before and after [^{18}F]MODAG-009 injection as specified in the protocol and/or IAP.
d = Blood samples for radiometabolite correction will be collected during imaging at time points defined in the IAP.
# Adverse events will be collected on the day of [^{18}F]MODAG-009 imaging during the visit and again via telephone 2–3 business days following injection.

29 Appendix 2- Non-PPMI MODAG-009 PET Imaging Schedule of Activities

Visit Number	Screening (SC)	Baseline (BL)	Follow-up
Assessments	**Upto -8 weeks**	**D0**	D2-D3
MODAG-009 Consent Activities			
Documentation of Informed Consent	X		
Informed Consent Tracking Log	X	X	
Additional MODAG Activities			
Inclusion/Exclusion Criteria	I	I	
Demographics	X		
Medical History and Concomitant Medications Review	X		
Vital signs including body weight and height	X		
Safety assessments[a]	X		
Complete Physical exam	I		
Full Neurological Exam	I		
MoCA		X	
Unified Multiple System Atrophy Rating Scale		I	
MDS-UPDRS (III)[b]		I	
Lumbar Puncture[c]	X		
Plasma biomarkers		X	
Screening DaTscan, if applicable	X		
Screening MRI Brain, if applicable	X		
Serum or Urine Pregnancy Test (prior to tracer injection), if applicable [d]	X	X	
Imaging Screen Fail	As Needed		
Conclusion of Study Participation	As Needed		
MODAG-009 PET Imaging			
Pre-injection vital signs[e]		X	
ECG[f]		X	
Pre-injection safety labs[f]		X	

MODAG-009 PET Imaging injection		X	
MODAG-009 PET Imaging		X	
Post-injection vital signs[e]		X	
Venous sampling for radiometabolite analysis[g]		X	
Post-imaging vital signs[e]		X	
ECG[f]		X	
Post-injection safety labs[f]		X	
MODAG-009 Safety and General Health			
[#] Adverse Event In-Clinic Assessment		X	
[#]Adverse Event Telephone Assessment			X
Report of Pregnancy	As Needed		

**Window of ±45 days either side of Target Visit Date
I = Investigator (or trained designee) completed assessment
X = Investigator or Coordinator completed assessment (or as otherwise delegated)
a = Screening safety assessments will include lab tests [CBC, CMP, coagulation labs, urinalysis] and ECG
b = MDS-UPDRS III must be performed in the defined "OFF" state, which is achieved by withholding Levodopa (and other short-acting dopaminergic medications, if applicable) for at least 10 hours prior to the examination.
c = CSF routine labs include CSF protein, glucose, and cell count with differential (processed locally). CSF send-out assays include tau profile, amyloid peptides, and α-synuclein seed amplification assay.
d = For women of childbearing potential, serum pregnancy test will be completed at the time of screening visit. Urine pregnancy test will be completed prior to injection on day of DAT SPECT or [18F]MODAG-009 PET imaging.
e = Vital signs (body temperature, supine heart rate and supine blood pressure) will be assessed approximately 5-60 min prior to [^{18}F]MODAG-009 administration. Vitals signs will be repeated within 30 minutes (± 5 minutes) post [^{18}F] MODAG-009 injection and within 30 minutes post completion of imaging. Body temperature will not be completed at the 30+/-5 min post-injection timepoint to avoid head movements and interference with imaging.
f = Safety assessments (CBC, CMP, urinalysis, ECG) will be completed before and after [^{18}F]MODAG-009 injection as specified in the protocol and/or IAP.
g = Blood samples for radiometabolite correction will be collected during imaging at time points defined in the IAP.
#Adverse events collected day of and 2-3 business days post [18F]MODAG injection per protocol.