Protocol No. ^{18}F-AV-1451-A14

Clinical Evaluation of ^{18}F-AV-1451

Statistical Analysis Plan

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations

AAL	Automated anatomical labeling
Amyloid beta	Aβ
AD	Alzheimer's disease
AE	adverse event
ANCOVA	Analysis of covariance
CFB	change from baseline
C.I.	Confidence interval
CI	cognitively impaired
CN	cognitively normal
CRF	Case report form
CSF	cerebrospinal fluid
CSR	clinical study report
DBP	diastolic blood pressure
ECG	electrocardiogram
IV	intravenous
LSM	Least squares mean
Max	maximum
MBq	Megabecquerel
mCi	Millicurie
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MMSE	Mini-Mental State Examination
MUBADA	Multiblock Barycentric Discriminant Analysis
N	Sample size
ODD	Other Dementing Disease
OND	Other Neurological Disorder
OSU-TBI	Ohio State University – Traumatic Brain Injury
PCS	Potential clinically significant
PD	Psychiatric Disorder
PERSI	parametric estimated signal reference intensity
PET	positron emission tomography
PLT	Posterolateral Temporal
PR	Pulse rate
PT	preferred term
RR	Respiratory rate
SAE	Serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SBP	Systolic blood pressure
SD	Standard deviation

SE	Standard error
SOC	system organ class
SUVr	standardized uptake value ratio
TEAE	treatment-emergent adverse event
WHO	World Health Organization

2 INTRODUCTION

^{18}F-AV-1451 (originally named [F-18]T807 by Siemens Molecular Imaging Biomarker Research group) has been developed as a positron emitting radiopharmaceutical for *in vivo* imaging of tau protein aggregates (Xia et al., 2013). Autoradiography results using tissue sections from human brains showed a strong signal in the grey matter of cortical slices from tau positive brains but weak or no binding in tau negative, amyloid-beta (Aβ) positive, or tau and Aβ negative tissue

AV-1451 was assessed in competitive binding assays against a panel of 72 of the most common central nervous system (CNS) targets and no clinically relevant inhibition was seen. AV-1451 was positive in the i*n vitro* hERG assay, albeit at a concentration more than 40-fold the maximum theoretical AV-1451 plasma concentration. Additionally, *in vivo* cardiovascular safety pharmacology assessments in dogs showed no evidence of QT prolongation at doses up to 50x the intended maximum human dose (MHD). Nonetheless, until sufficient human cardiovascular safety data are available, initial clinical studies will exclude subjects with a history of risk factors for Torsades de Pointes and subjects taking drugs known to prolong the QT interval.

In vivo safety pharmacology studies were also conducted in rats to determine potential effects on the CNS and respiratory systems. In these studies no clinically relevant effects were reported at doses exceeding 100x the intended MHD. Additionally, non-radioactive AV-1451 has been tested in single and repeat dose toxicology studies in rat and dog species. In each of these studies the no observable adverse effect levels (NOAELs) were the highest doses tested (150x MHD for single, 50x MHD for repeat).

Potential genotoxicity of non-radioactive AV-1451 was tested in both *in vitro* and *in vivo* assays. In the *in vitro* assays, AV-1451 tested positive for potential genotoxicity. However, in the *in vivo* rat micronucleus assay at doses up to 750x MHD (scaled allometrically), AV-1451 showed no evidence of genotoxicity. The different results in the *in vitro* genotoxicity assays and the *in vivo* micronucleus study are likely related to differences in the exposure conditions encountered by the target cells in the different test systems. *In vivo*, AV-1451 is cleared rapidly; however, the *in vitro* experiments employ static, prolonged exposure of cells to high concentrations of the test article. While the *in vitro* data show the potential for genotoxicity, the *in vivo* data provide assurance that genotoxicity is unlikely to occur at clinically-relevant doses for human diagnostic studies.

Human dosimetry has been obtained in nine subjects. Generally, the radiotracer distribution was consistent among the subjects and showed rapid hepatobiliary clearance. There were three organs that received estimated doses higher than 0.05 mSv/MBq. The organ that received the largest estimated dose was the upper large intestinal wall (0.0962 ± 0.0134 mSv/MBq), followed by the small intestine and the liver. The Effective Dose was 0.0241 ± 0.0016 mSv/MBq. This results in an estimated Effective Dose of 8.92 mSv for an anticipated 370 MBq (10 mCi) injection and is comparable to the effective dose of approved ^{18}F-labeled compounds such as fluorodeoxyglucose (FDG) and florbetapir F 18 injection.

The present study is designed to expand the database of ^{18}F-AV-1451 safety and tau binding as measured by PET imaging, and to provide standardized conditions for tau use, data collection, and analysis to facilitate companion studies including, but not limited to, longitudinal studies of aging, depression, and traumatic brain injury.

The purpose of this statistical analysis plan (SAP) is to describe the statistical analyses for study ^{18}F-AV-1451-A14. This SAP should be read in conjunction with the A14 protocol.

3 STUDY OBJECTIVES

The primary objectives of this study are:

- to provide standardized conditions for flortaucipir use, data collection, and analysis to facilitate evaluation of subjects' tau burden.
- To expand the flortaucipir safety database.

4 STUDY DESIGN

4.1 General Design

This is a phase II, multicenter study that will expand the flortaucipir safety database and explore tau binding as measured by PET imaging, and will provide standardized conditions for the use, data collection and analysis of flortaucipir to facilitate companion studies looking at tauopathies.

4.1.1 Screening Visit

Screening assessment may have taken place over several days and included collection of demographic information, medical assessment for eligibility, electrocardiogram (ECG), a brief cognitive assessment (i.e. Mini-mental State Exam [MMSE]), and a traumatic brain injury questionnaire (i.e. Ohio State University Traumatic Brain Injury [OSU-TBI]).

4.1.2 Flortaucipir PET Imaging Visit

For the flortaucipir PET imaging session, an intravenous (IV) catheter was placed for administration of flortaucipir injection. Subjects received a single IV bolus injection target dose of 240 megabecquerel (MBq) (6.49 millicuries (mCi)) or 370 MBq (10 mCi) of flortaucipir injection. Vital signs were taken in a supine position immediately prior to (within 30 minutes of) flortaucipir injection and at the completion of imaging prior to subject discharge. At approximately 80 minutes post injection, a 20-minute dynamic brain scan was obtained. Sites may have elected to use an alternative imaging protocol (i.e. different scan duration or scan start time) with additional time points with sponsor approval. All datasets were submitted to the sponsor for analysis.

Adverse events (AE) were continuously monitored during the imaging visit (see section 6.6.2). Any subject who experienced an adverse event was not discharged until the event had resolved or stabilized.

4.1.3 Follow-Up Phone Call

A follow-up phone call to the subject, or designated decision maker, was conducted between 2 and 3 business days after imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days were not business days, the follow-up phone call occurred the following business day.

4.1.4 Repeat Imaging

Longitudinal imaging studies may have been conducted under protocol ^{18}F-AV-1451-A14 with prior sponsor approval. In these studies, subjects may have had up to two imaging sessions within a 12-month time-frame. If the second scan was obtained more than 3 months after the previous scan, then the MMSE was repeated and updated OSU-TBI, medical history, and concomitant medications information was collected. Procedures for each the repeat imaging were identical to those described above.

4.2 Method of Assignment of Subjects to Treatment and Diagnosis Groups

Subjects who qualified for the study received a single IV bolus injection with a target dose of 240 (6.49 mCi) or 370 MBq (10 mCi) of flortaucipir (^{18}F) injection.

Subjects will be classified into diagnosis groups (Alzheimer's disease AD [AD], mild cognitive impairment [MCI], control subject [CN], other dementing disorder [ODD], other neurological disorder [OND], psychiatric disorder [PD]) as outlined by pre-specified criteria (see protocol amendment 1, appendix 11.3 for details), however there was no design (adaptive or otherwise) to stratify an equal number of subjects in each diagnosis group. Diagnosis groups will be consolidated in the following way in the result summaries.

Table 2: Consolidation of Diagnosis Groups for Presentation of Results

Diagnosis Group	Presentation Group
AD	Cognitively Impaired (CI)
MCI	
ODD	
OND	
PD	
CN	Cognitively Normal (CN)

4.3 Blinding

This was a phase II open-label study of approximately 179 subjects including healthy controls and subjects at risk for tau accumulation as defined by the sites' companion protocols. No blinding to flortaucipir treatment was required since all study participants received a single IV bolus injection of ~240 or 370 MBq (6.49 or 10 mCi) of flortaucipir (^{18}F).

4.4 Determination of Sample Size

No power or sample size calculation was done for this study as there was no hypothesis for testing per study objectives. Approximately 179 subjects including healthy controls and subjects at risk for tau accumulation as defined by the sites' companion protocols were dosed with flortaucipir and underwent a PET scan.

5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

5.1 Changes in the Conduct of the Study

There were no changes in the conduct of the study at the time of preparing this SAP.

6 BASELINE, EFFICACY AND SAFETY EVALUATIONS

6.1 Schedule of Evaluations

Table 3: Schedule of Evaluations

Evaluations	Screen	Pre-dose	Dose	PET Imaging	End of Imaging	2 – 3 days post injection
Signed Consent	X					
Medical / Disease History	X					
Concomitant Meds	X	X				
ECG	X					
MMSE	X					
Physician Visit	X	X			X	
OSU TBI-ID	X					
Vital Signs[2]		X			X	
Pregnancy Test	X	X				
^{18}F-AV-1451 Administration			X			
PET Imaging[1]				Continuous 20 minute scan		
Follow-up Phone Call						X
Adverse Event Assessment	X	X	X	X	X	X

[1]Sites may elect to perform additional imaging time points with prior sponsor approval.

[2]Height and weight will be measured prior to injection on imaging day.

6.2 Time Point Algorithms

6.2.5 Windows

For all analyses, results will be summarized at the planned study visit they were obtained.

6.3 Screening and Baseline Assessments

Screening assessments may take place over several days, preferably within 30 days prior to the flortaucipir PET scan, and will include collection of demographics, a medical assessment for eligibility, ECG, a brief cognitive assessment, and a traumatic brain injury questionnaire.

6.4 Efficacy Variables

6.4.1 Primary Efficacy Variable

6.4.1.1 Flortaucipir Quantitation

Standard uptake value ratios (SUVr) will be calculated to estimate tau load globally and in individual regions for the flortaucipir images. A target region derived statistically with a Multiblock Barycentric Discriminant Analysis (MUBADA) method will be used for the global measurement.

Voxels of interest determined in the automated anatomical labeling (AAL) atlas masked to exclude white matter and CSF for amygdala, anterior fusiform, posterior fusiform, anterior hippocampus, posterior hippocampus, anterior parahippocampus, posterior parahippocampus, caudate, frontal, parietal, precuneus, temporal, occipital, left frontal, right frontal, left occipital, right occipital, left parietal, right parietal, left putamen, right putamen, left temporal, right temporal will be applied at the individual region level. A selected white matter region derived using a parametric estimated signal reference intensity (PERSI) method will be used as reference region for all SUVr calculations.

MUBADA SUVr will be the variable used in in the primary efficacy analysis.

6.4.2 Additional Variables

6.4.2.1 Mini-Mental State Examination (MMSE)

The MMSE (Folstein et al., 1975) is a brief instrument used to assess cognitive function in elderly patients. The range for the total MMSE score is 0 to 30, the sum of each correct answer, with higher scores indicating better cognition. The score on a continuous scale will be used for primary objective analysis.

6.4.2.2 Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID)

The OSU TBI-ID (Corrigan and Bogner, 2007) short version was used to screen for a history of traumatic brain injury. It is the briefest version that still provides several summary indices on which the original version was validated. To shorten the instrument, TBIs resulting in loss of consciousness are emphasized over less severe injuries.

6.5 Drug Concentration Measurements and Pharmacokinetic Parameters

6.5.1 Handling of Pharmacokinetic Parameter Outliers

No pharmacokinetic parameters or drug concentration measurements will be collected during this study.

6.6 Safety Assessments

6.6.1 Extent of Exposure and Compliance to Study Treatment

During the flortaucipir imaging sessions, all subjects received a single IV bolus administration target dose of 240 (6.49 mCi) or 370 MBq (10 mCi) of flortaucipir injection.

6.6.2 Adverse Events

An AE is any undesirable experience occurring to a subject during a clinical trial, whether considered related to the study drug or not. AEs are classed by severity and seriousness.

Treatment-emergent adverse events (TEAE) are any untoward medical occurrences associated with the use of a drug in humans. For the purposes of this study, untoward medical occurrences will be considered associated with the use of flortaucipir, and thus be reported as TEAEs, if they occur within 48 hours after administration of the PET tracer. The end of study for the purpose of AE reporting is defined as 48 hours after the administration of flortaucipir injection.

The investigator's verbatim term of both serious and non-AEs will be mapped to system organ class (SOC) and preferred terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.1.

Investigators will be instructed to report their assessment of the potential relatedness of each AE to protocol procedure and flortaucipir. The assessment of the relationship of an AE to the administration of the flortaucipir is a clinical decision based on all available information at the time of the completion of the eCRF.

Investigators will also assess the severity of AE. Severity is classified as mild/moderate/severe (increasing severity).

Serious AEs (SAEs) are events that result in one of the following outcomes or constitute one of the following events:

- Death
- Initial or prolonged hospitalization (other than that required by protocol; "social hospitalization" or any hospitalization for non-medical reasons does not constitute an SAE)
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason

7 STATISTICAL METHODS

7.1 Definitions and Conventions

7.1.1 Analysis Programming Platform

All analysis will be performed using SAS version 9.2 or higher.

7.1.2 Reporting Conventions

Data will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]) for continuous variables and using frequency count and percentage for discrete variables. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.

The tables and listings will be numbered using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with maximum two digits per level (e.g., Table XX.YY.ZZ…). Tables will be numbered as 14.YY.ZZ. Baseline analysis will be reported in table series 14.1, efficacy analysis in series 14.2, and safety analysis in series 14.3. Listings will be numbered as 16.YY.ZZ.

7.1.3 Type I Error

Unless otherwise specified, hypothesis testing will be two-sided with type I error rate of 0.05.

7.1.4 Definition of Baseline

Baseline summaries will include all available data from the screening time point (i.e. MMSE, OSU TBI-ID, family and neurologic disease histories, etc.). For the purposes of safety analysis involving change calculations (e.g. vital signs), baseline will be defined as the measurement immediately prior to flortaucipir injection. All efficacy variables to be tested will be based on the initial imaging visit.

7.1.5 Age Calculation

Subjects' ages (in years) will be calculated as the difference between their year of birth and their year of informed consent into the study.

7.2 Handling of Dropouts or Missing Data

Dropout subjects will not be replaced in this study. For situations with no rules for handling missing data the default will be no imputation.

7.3 Interim Analyses and Data Monitoring

No interim analysis or data monitoring is planned for this study.

7.4 Multi-center Studies and Pooling of Centers

This is a multi-center study. Data from all sites will be pooled for the analysis outlined in this SAP.

7.5 Multiple Comparisons/Multiplicity

No multiple comparisons/multiplicity adjustment is planned.

7.6 Examination of Subgroups

No subgroup analysis will be conducted for this study.

8 STATISTICAL ANALYSIS

8.1 Analysis Populations

8.1.1 Enrolled Population

The enrolled population will consist of all subjects who have signed the consent form and for whom data exists in the electronic data capture. The enrolled population will not include screen failures. Disposition will be summarized using the enrolled population.

8.1.2 Safety Population

The safety population will consist of all subjects who received at least one injection of flortaucipir. All baseline and safety data will be summarized using the safety population.

8.1.3 Efficacy Population

The efficacy population will include all subjects with a valid quantitated PET image (available SUVr). All efficacy endpoints will be summarized using the efficacy population.

8.2 Disposition and Withdraws

The enrolled population will be represented in the disposition table. The disposition table will summarize the analysis populations in section 8.1, as well as completed and discontinued subjects.

Discontinued subjects will be defined as any safety subject who fail to complete the 48-hour safety follow-up. Termination status (i.e. ‘Completed’ and ‘Discontinued’) and reasons for discontinuation percentages will be based on the safety population. Screen failures will not be included in the summary of disposition.

8.3 Baseline Subject Data

8.3.1 Demographic and Other Baseline Characteristics

All baseline summaries will be based on the safety population. Age (years), gender, race, ethnicity, education, and MMSE will all be summarized in a table and presented in a listing.

8.3.2 Medical and Surgical History

Medical and surgical histories were coded using MedDRA version 17.1 and will be presented in a listing for the safety population.

8.3.3 Concomitant Therapy

Concomitant therapies were coded using WHODRUG Sep 2014 and will be presented in a listing for the safety population.

8.3.4 Neurologic Disease History

Neurologic disease information captured on the case report form (CRF) will be presented in a listing for the safety population.

8.3.5 Pregnancy Test

Pregnancy testing information captured on the CRF will be presented in a listing for the safety population.

8.3.6 Family History

Family history information captured on the CRF will be presented in a listing for the safety population.

8.3.7 Electrocardiogram

ECG data captured on the CRF will be presented in a listing for the safety population.

8.3.8 MMSE & OSU TBI-ID

MMSE and OSU TBI-ID information captured on the CRF will be presented in listing.

8.4 Analysis of Efficacy Parameters

8.4.1 Analysis of Primary Efficacy Variable

8.4.1.1 Quantitative Assessment of Images

The MUBADA SUVr (as described in section 6.4.1.1) from the available imaging visits will be summarized using descriptive statistics (n, mean, SD, min, max, and median) for the efficacy population by cognitive groups (CI and CN). An analysis of covariance (ANCOVA) model will be used to test significant differences in baseline MUBADA SUVr between the two cognitive groups adjusted for age. All descriptive statistics, including LSM (+/- SE), LSM differences (95% C.I.), and p-values will be reported in a table.

MUBADA SUVr will also be presented in a scatter plot by clinical group.

8.4.1.2 Correlation between MMSE and MUBADA SUVr

Depending on available data, Spearman's correlation coefficient will be used to measure the relationship between MMSE and MUBADA SUVr at baseline. This relationship will also be presented in a scatter plot.

8.5 Analysis of Safety

8.5.1 Exposure

The total dose administered (MBq) of flortaucipir will be summarized for each visit in a table using descriptive statistics and presented in a listing.

8.5.1.1 Dose Unit Conversion

All exposure tables and listings will display dose administered in MBq. Dose recorded in mCi will be converted to MBq as follows:

$$MBq = 37 \times mCi$$

8.5.2 Treatment Emergent Adverse Events

A summary of TEAEs will be reported in the tables including number of all TEAEs and number of subjects who experienced at least one TEAE. The summary of TEAEs will be broken down further in descending frequency by SOC and PT, and by PT only in separate tables. A subject will be counted once if the subject reported one or more events in a given level of summarization.

All AEs (regardless of treatment emergence) will be presented in a listing.

8.5.2.1 Severity

TEAE severity will be reported in a table in the same manner as outlined in 8.5.2.
Events recorded with missing intensity will be summarized as 'Severe'. If the same TEAE is reported more than once for a subject within an SOC/PT, the TEAE with the worst severity will be summarized in the table.

8.5.2.2 Relationship to Flortaucipir

TEAE relationship to flortaucipir will be reported in a table in the same manner as outlined in 8.5.2. TEAEs with a missing relationship to flortaucipir will be summarized as 'Related' to flortaucipir. If the same TEAE is reported more than once for a subject within an SOC/PT, the TEAE most related to flortaucipir will summarized in the table.

8.5.2.3 Relationship to Study Procedure

TEAE relationship to study procedure will be reported in a table in the same manner as outlined in 8.5.2. TEAEs recorded with a missing relationship to study procedure will be regarded as

related to study procedure. If the same TEAE is reported more than once for a subject within that SOC/PT, the TEAE most related to study procedure will summarized in the table.

8.5.2.4 Serious Adverse Events

Serious TEAEs will be summarized in a similar manner as described in Section 8.5.2. TEAEs recorded with a missing seriousness will be summarized as 'Serious'. If more than one serious TEAE was reported for a subject with the same SOC or PT, the TEAE will be counted only once in that SOC or PT.

8.5.2.5 Adverse Events Leading to Study Discontinuation

TEAEs leading to study discontinuation will be summarized in a similar manner as described in section 8.5.2.

8.5.2.6 Adverse Events Leading to Death

TEAEs leading to death will be summarized in a similar manner as described in section 8.5.2.

8.5.2.7 Missing and Partial AE Onset Dates

If the AE onset dates are missing, then the most conservative approach will be used to decide if the AE is TEAE or not, as detailed in the table below:

Table 4: Imputation Algorithm for Missing AE Date/Time

Scenario	Imputation
Missing AE start date/time	if AE stop date is missing or after injection date, then TEAE ='Y'. If AE stop date is prior to the injection date, then TEAE=N'
Missing AE start time	Impute time as 23:59, and follow TEAE definition in section 6.6.2
Partial Date	If AE start day is missing then: • If AE start month and year are the same as injection date month and year then TEAE='Y', otherwise impute missing days as the first day of the respective AE start month, and follow TEAE definition in section 6.6.2 If AE start month is missing then: • If AE start year is the same as injection year then TEAE='Y', otherwise TEAE = 'N'

8.5.3 Vital Signs

Systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), pulse rate (PR) (bpm), and respiratory rate (RR) (breaths/min) were collected *Immediately Prior to (within 30 minutes) Flortaucipir Injection* and *Prior to Discharge* during the Flortaucipir Imaging Visit. *Immediately Prior to Injection* will be considered the baseline value for all vital sign change from baseline (CFB) calculations.

The data from each available visit and time point, along with calculated CFB, as defined as the difference from the *Prior to Injection* to *Prior to Discharge* values will be summarized by diagnosis groups in a table using descriptive statistics. A paired t-test will be performed on the aggregate data of each vital sign to assess if any significant changes occurred.

Vital signs and changes (where applicable) will be presented in a listing.

8.5.3.1 Potentially Clinically Significant Vital Sign Changes

Vital sign at visit and CFB will be monitored for potentially clinically significance (PCS) using the following criteria:

Table 5: Potentially Clinically Significant Criteria

Vital Sign	PCS Criteria	
	Low	High
SBP	≤ 90 and ≥ 20 decrease	≥ 180 and ≥ 20 increase
DBP	≤ 50 and ≥ 15 decrease	≥105 and ≥ 15 increase
PR	≤ 50 and ≥ 15 decrease	≥ 120 and ≥ 15 increase
RR	≤ 10	

8.5.4 Follow-up Contact Data

The follow-up contact information captured on the CRF will be presented in a listing for the safety population.

9 APPENDICES

9.1 References

Xia, C.F., et al. "[18F]T807, a novel tau positron emission tomography imaging agent for Alzheimer's disease," Alzheimers Dement. 2013, 1-11.

Corrigan, J.D., & Bogner, J. (2007). Initial reliability and validity of the Ohio State University TBI identification method. Journal of Head Trauma Rehabilitation, 22, 318 – 329.

Folstein, M.R., Folstein, S.E., and McHugh, P.R. "Mini Mental State: A practical method for grading the cognitive status of patients for the clinician." Journal of Psychiatric Research, 12: 189-198, 1975.

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