Protocol No. ^{18}F-AV-1451-A19

^{18}F-AV-1451 PET Imaging in Subjects with Frontotemporal Dementia

Statistical Analysis Plan

Prepared for:
Avid Radiopharmaceuticals, Inc

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

Aβ	Amyloid-ß
AD	Alzheimer's Disease
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
CRF	Case Report Form
CRO	Contract Research Organization
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FTD	Frontotemporal Dementia
IB	Investigator's Brochure
ICF	Informed Consent Form
IV	Intravenous
MBq	Megabecquerel
mCi	Millicurie
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
N	Number of subjects
PET	Positron Emission Tomography
PT	Preferred Term
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SUVr	Standard Uptake Value Ratio
TEAE	treatment-emergent adverse event
US	United States
WHO	World Health Organization

2 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses to evaluate the imaging characteristics of Flortaucipir F 18 (^{18}F-AV-1451) in Frontotemporal Dementia (FTD) subjects.

Accurate antemortem diagnosis is challenging in FTD considering the clinical and pathologic heterogenicity of the disease. Most cases of FTD can be classified into two major pathologic categories: (1) diseases that involve tau deposition (FTD-tau) and (2) conditions with tau-negative, ubiquitin and TDP43-positive inclusions. Accurately determining the underlying neuropathology during life is a critical need to enhance the development and testing of biologically specific drugs.
In view of this, Flortaucipir F 18 (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. Flortaucipir F 18 may be useful as a marker of tau pathology in patients with Alzheimer's Disease (AD) and other neurodegenerative disorders. Several preliminary studies using Flortaucipir F 18 have been completed. The purpose of the current study is to extend these findings by evaluating the usefulness of Flortaucipir F 18 in FTD and in particular, whether the regional pattern of tau deposition typical of AD is present in FTD cases.

This SAP is prepared based on the following trial documents:

- Protocol No. ^{18}F-AV-1451-A19, Final version, Date 05 May 2016
- Case Report Form (CRF) ^{18}F-AV-1451-A19, Date 28 Mar 2018

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate Flortaucipir F 18 retention in Positron Emission Tomography (PET) scans of Frontotemporal Dementia (FTD) subjects.

3.2 Secondary Objective

The secondary objective of this study is to expand Flortaucipir F 18 safety database.

4 STUDY DESIGN

4.1 General Design

This is a multicenter Phase I study in subjects diagnosed with symptomatic clinical syndromes with expected FTD pathology.

Subjects followed in a referral center research cohort for FTD will be contacted to participate and must provide informed consent before starting ^{18}F-AV-1451-A19 study procedures. Diagnosis will be determined by companion study with detailed characterization provided by enrolling physician.

Screening assessments will be conducted over several days and preferably will be performed within 60 days prior to the Flortaucipir F 18 PET imaging session. The screening assessments will include demographic information, a medical assessment for eligibility, vital signs, ECG, a brief cognitive assessment [e.g. Mini-Mental State Examination (MMSE)], and Florbetapir F 18 Positron PET imaging.

A physician will evaluate the subjects prior to administration of Florbetapir F 18 injection to determine if they are suitable to undergo the scan. Upon confirmation, the subjects will receive a single IV bolus injection of approximately 370 MBq (10 mCi) Florbetapir F 18 followed by a saline flush. A 20-minute continuous, dynamic PET brain scan will begin approximately 50 minutes following the dose administration. The screening Florbetapir F 18 PET scan is performed to assess for evidence of amyloid pathology and should be interpreted by the local reader prior to enrollment. Amyloid scans that have been obtained within 3 years of screening can be submitted for review by the local reader for enrollment criteria. If deemed interpretable, the subject would not need to complete the screening Florbetapir F 18 PET scan.

The Flortaucipir F 18 PET scan should be performed at least 16 hours apart from the Florbetapir F 18 PET scan due to the half-life of fluorine 18. Subjects who qualify for the study will come to the imaging center at a later date and will have a catheter(s) placed for IV administration of Flortaucipir F 18 . Vital signs will be taken in a supine position prior to administration of Flortaucipir F 18 (within 30 minutes prior to injection) and at the completion of imaging prior to subject discharge. Upon confirmation by physician on suitability of subjects to undergo the scan, the subjects will receive a single IV bolus injection of approximately 370 MBq (10 mCi) Flortaucipir F 18 followed by a saline flush. A 30 minute dynamic image will begin approximately 75 minutes following the dose administration.

Adverse events will be continuously monitored during the imaging sessions. Subjects who experience any adverse event will not be discharged until the event has resolved or stabilized. A follow-up phone call to the subject, or designated decision maker, will be conducted within 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. A physician will evaluate the subject's readiness for discharge from the imaging center.

Subjects who meet eligibility criteria will participate in this protocol until they complete their Flortaucipir F 18 PET scan, or they discontinue, withdraw consent, or if the sponsor decides to end this protocol early.

4.2 Discussion of Study Design

This trial is designed to screen subjects via a Florbetapir F18 PET scan, who are diagnosed with symptomatic clinical syndromes with expected FTD pathology. This scan will be performed at screening to assess for evidence of amyloid pathology prior to enrollment.

4.3 Method of Assignment of Subjects to Treatment Groups

The drug products used in this study are following:

Florbetapir F 18: Subjects will receive a single IV bolus administration target dose of 370 MBq (10 mCi) of Florbetapir F 18 injection at screening for Florbetapir F 18 scan.

Flortaucipir F 18: Subjects who qualify for the study will receive a single IV bolus administration of approximately 370 MBq (10 mCi) of Flortaucipir F 18 Injection at imaging visit.

4.4 Blinding

Blinded design is not used for this trial, hence this section is not applicable.

4.5 Determination of Sample Size

This study will enroll up to 25 subjects. This sample size was chosen in order to allow for qualitative and descriptive review of Flortaucipir F 18 binding in subjects with clinically defined FTD. Based on prior studies, 10-15 subjects are typically sufficient for preliminary exploratory analysis. The sample size is slightly larger in order to accommodate the heterogeneous pathology that underlies FTD. Results of the exploratory analysis from this study will permit planning of subsequent, hypothesis-driven studies.

5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

5.1 Changes in the Conduct of the Study

This SAP is prepared based on the study protocol final version dated 05 May, 2016 and there are no planned changes in the conduct of the study at the time of preparing this SAP.

5.2 Changes from the Analyses Planned in the Protocol/CIP

There are no changes from the analyses planned in the Protocol/CIP at the time of preparing this SAP.

6 BASELINE, EFFICACY AND SAFETY EVALUATIONS

6.1 Schedule of Evaluations

The assessments to be conducted at each scheduled visit are displayed in the following table:

Evaluations	Screening Assessments[a]	Screening Florbetapir F 18 PET Scan[h]	Flortaucipir F 18 Imaging Visit
Signed Informed Consent	X		
Demographics	X		
Medical History	X		
Concomitant Medications	X		
ECG	X		
MMSE	X		
MRI	X[n]		
Serum beta-hCG Pregnancy Test	X[b]		
Urine Pregnancy Test		X[c]	X[c]
Vital Signs		X[d,e]	X[d,f]
PET Brain Scan		X[g, h, i]	X[j,k]
Evaluation by a physician	X	X[l]	X[l]
Adverse Events	X	X	X
Serious Adverse Events	X	X	X
Follow-up Phone Call[m]		X	X

a. Screening may take place over several days. All assessments must be performed prior to the Flortaucipir F 18 imaging session.
b. Serum beta-hCG pregnancy test at screening (for females of childbearing potential defined as pre-menopausal or less than 2 years post-menopausal and not surgically sterile).
c. For women of childbearing potential, a negative urine or serum (if required by local site) pregnancy test must be obtained within 24 hours prior to florbetapir F 18 injection and within 24 hours prior to Flortaucipir F 18 injection.
d. Vital signs (pulse, respiratory rate, supine blood pressure) and weight will be taken prior to dose administration.
e. Height will be taken prior to dose administration
f. Vital signs (pulse, respiratory rate, supine blood pressure) will be taken after completion of the PET scan prior to discharge.
g. The screening florbetapir F 18 PET scan is to be performed to assess for evidence of amyloid pathology and should be interpreted by a local reader prior to enrollment.
h. Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of florbetapir F 18 Injection followed by a saline flush.
i. At approximately 50 minutes following florbetapir F18 injection, a continuous 20-minutes brain scan will begin
j. Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of Flortaucipir F 18 Injection followed by a saline flush.
k. At approximately 75 minutes following Flortaucipir F 18 injection, a continuous 30-minute brain scan will begin.
l. A physician (or licensed/credentialed medical professional) must see the subject prior to drug administration and at study end, prior to discharge from the imaging session.
m. A follow-up phone call to the subject, or designated decision maker, will be conducted within 2 or 3 business days of each 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 are not business days, the follow-up phone call can occur the following business day.
n. If a prior MRI is not available for submission to Avid or designated imaging core lab, an MRI may be performed under this protocol if the subject is able to tolerate one.

6.2 Time Point Algorithms

6.2.1 Relative Day

The date of injection of Flortaucipir F 18 at imaging visit will be considered relative day 1, and the day before the injection of Flortaucipir F 18 will be relative day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

Relative Day
- Date of Assessment – Date of injection of Flortaucipir F 18 + 1
  For assessment on or after the day of injection of Flortaucipir F 18 *AV-*
- Date of Assessment – Date of injection of Flortaucipir F 18
  For assessment before the day of injection of Flortaucipir F 18

6.2.2 Windows

Data will be reported as per the scheduled study visits. No window algorithm will be used for this study.

6.3 Screening Assessments

The baseline assessments will be the last assessment performed before the injection of Flortaucipir F 18 . The screening assessments includes the assessment performed during screening period and during the Florbetapir F 18 imaging visit.

The following screening and baseline assessments will be conducted prior to the injection of Flortaucipir F 18 :

- Informed consent;
- Eligibility criteria;
- Demographics (age, birth gender, education, race, ethnicity);
- Height will be collected as part of the ^{18}F-AV-1451 imaging visit;
- Weight will be collected at both imaging visits prior to injection;
- Medical history, concomitant medications;
- Disease history;
- ECG will be performed to assess the subject's cardiac status if not performed within the last 12 months of enrollment;
- Cognitive status interview, including MMSE;
- MRI of the brain will be performed if not performed within one year of enrollment;

- Serum pregnancy test (women of childbearing potential);
- Urine pregnancy test prior to Florbetapir F 18 injection;
- Vital signs (pulse rate, respiratory rate, supine blood pressure) immediately prior to Florbetapir F 18 injection; Prior to the administration of Flortaucipir F 18 injection, and after the completion of Flortaucipir F 18 imaging, prior Flortaucipir F 18 to discharge.
- Florbetapir F 18 PET dose administration;
- Florbetapir F 18 PET scan;
- Follow-up call to confirm subject well-being and to collect any new adverse events.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) v 21.1 or higher to the preferred term (PT) and system organ class (SOC). Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary version WHODrugDDEB2201809.

Weight will be displayed in kilograms (kg), height will be displayed in centimeters (cm). Weights and heights recorded in alternate units will be converted to the units being displayed using standard conversion formulas. Body Mass Index (BMI) will be calculated as:

- BMI (kg/m^2) =Weight (kg)/Height $(m)^2$

Each subject's age (years) will be calculated as the difference of the year of his/her informed consent date and the year of his/her birth.

The MMSE (Folstein et al., 1975) is a brief instrument used to assess cognitive function in elderly subjects. The instrument is divided into two sections:

- The first section measures orientation, memory, and attention. The maximum score for the first section is 21.
- The second section tests the ability of the subject to name objects, follow verbal and written commands, write a sentence, and copy figures. The maximum score for the second section is 9.

The range for the total MMSE score is 0 to 30, the sum of each correct answer, with higher scores indicating better cognition.

6.4 Efficacy Variables

The Flortaucipir F 18 scan will be evaluated by qualitative visual analysis and quantitatively by standard uptake value ratio (SUVr) analysis including regional SUVr.

6.4.1 Qualitative assessment for Flortaucipir F 18 **PET scan** *and Diagnostic Performance*

The *Flortaucipir F 18* PET scan image will be visually interpreted according to the following criteria:

Read Outcome		Objective Image Features
Not consistent with AD pattern (τAD-)		No increased neocortical activity, or increased neocortical activity isolated to the mesial temporal, anterolateral temporal, and/or frontal regions.
AD pattern (τAD)	τAD+	In either hemisphere, increased neocortical activity in the posterolateral temporal (PLT) or occipital region(s).
	τAD++	In either hemisphere, increased neocortical activity in the parietal/precuneus region(s), or frontal region(s) with increased uptake in the PLT, parietal, or occipital region(s).

6.4.2 Quantitative assessment for Flortaucipir F 18 PET scan *(SUVr based)*

For the Flortaucipir F 18 PET scan, standard uptake value ratios (SUVr) will be calculated to estimate tau globally and regionally. For global assessment, a target region derived statistically with a Multiblock Barycentric Discriminant Analysis (MUBADA) method will be used. 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.

Voxels of interest (VOI) determined in the 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, and right temporal will be applied at the individual region level.

MUBADA SUVr will be the variable used in any efficacy analysis that involving flortaucipir quantitation. All regional SUVrs will be presented in listings.

6.5 Drug Concentration Measurements and Pharmacokinetic Parameters

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

The extent of exposure to study drugs will be quantified for dose administered at Florbetapir F 18 PET scan visit and Flortaucipir F 18 imaging visit.

Since in this study subjects will receive a single bolus of study medication, compliance will not be calculated.

All exposure tables will display volume in millicuries (mCi)..

6.6.2 Adverse Events

All adverse events (AEs) occurring after signing the informed consent are to be recorded on the AE pages of the case report form (CRF). Any pre-existing conditions (i.e., undesirable experiences, signs or symptoms that begin prior to the Screening Visit) will be recorded on the medical history eCRF pages. The investigator's verbatim term of AEs will be mapped to SOC and PT using the MedDRA v 21.1 or higher.

Adverse Events:
An AE is any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the study drug. In this study clinically relevant abnormal finding, as well as worsening of any pre-existing condition shall be recorded as an AE. AEs that occur after administration of either drug but outside 48 hour reporting window will not be reported unless those are attributed to the study drug.

Unexpected Adverse Events:
An unexpected adverse event is an adverse event not previously reported or an adverse event that occurs with specificity, severity or frequency that is not consistent with the current Investigator's Brochure (IB).

Serious Adverse Events (SAEs):
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
- 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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

For the summarization of AEs by seriousness, events recorded with missing seriousness will be summarized as serious, following worst case principle.

Trial Emergent Adverse Events:
Trial Emergent AEs are defined as any AEs that occur or worsen (increase in intensity and/or frequency) after the informed consent, and prior to administration of Florbetapir F 18, or between the Florbetapir F 18 injection session and Flortaucipir F 18 injection session but outside the 48 hours window following administration of Florbetapir F 18 or Flortaucipir F 18.

Treatment Emergent Adverse Events (TEAEs):
TEAEs are defined as any AEs that occur or worsen (increase in intensity and/or frequency) after administration of Flortaucipir F 18 or Florbetapir F 18 and until 48 hours post administration.

6.6.2.1 Classifications of Adverse Events

Severity of Adverse Events:
The severity of an AE will be graded as "Mild", "Moderate" or "Severe". AEs events recorded with missing intensity will be summarized as Severe, following worst case principle.

Relationship to study drug/protocol procedure:
An AE will be considered as related to Flortaucipir F 18 if they occur within 48 hours after administration of Flortaucipir F 18 , and will be considered as related to Florbetapir F 18 if they occur within 48 hours after administration of Florbetapir F 18.

In addition, the investigator will assess the relatedness of an AE to protocol procedure.

Any missing relationship of an AE to study drug or protocol procedure will be considered to be related for the analysis, following worst case principle.

6.6.3 Serum and Urine Pregnancy Test

The serum beta hCG qualitative assessment will be performed at screening for females of child bearing potential who are not surgically sterile. A serum pregnancy test may also be performed prior to injection at the imaging visits, if required.

The urine beta hCG test will performed at the Flortaucipir F 18 imaging visit and Florbetapir F 18 imaging visit (except if screening serum pregnancy test obtained within 24 hours prior to injection) prior to injection for females of childbearing potential.

6.6.4 Other Observations Related to Safety

6.6.4.1 Vital Signs

Vital signs assessment includes measurement of pulse rate, respiratory rate, and supine blood pressure and will be taken immediately prior to injection of Florbetapir F 18. The vital signs measurement will also be taken prior to injection of Flortaucipir F 18 and after the completion of Flortaucipir F 18 imaging prior to discharge.

The baseline assessments will be the last assessment performed prior to the injection of Flortaucipir F 18. The change from baseline at post Flortaucipir F 18 injection time point will be defined as the observed value minus the baseline value.

The weight (lightly clothed) will be measured at both the imaging visits prior to injection of Florbetapir F 18 and Flortaucipir F 18.

Height will only be measured at Florbetapir F 18 imaging visit prior to the injection.

6.6.4.2 Electrocardiogram (ECG)

A resting 12-lead electrocardiogram will be recorded at screening, unless an ECG was not performed within twelve months of the screening visit and is available for review.

6.7 Pharmacodynamics Parameters

No pharmacodynamics parameters will be collected during this study.

7 STATISTICAL METHODS

7.1 General Methodology

All statistical analyses will be performed using SAS® version 9.3 or higher.

The study data collected under companion protocol such as but not limited to subjects' demographic and baseline characteristics, history taking, neurological and behavioral evaluations, and MRI will be transferred to Avid for analysis purposes. Amyloid scans used for review of enrollment criteria will also be transferred to Avid if applicable.

All values will be summarized as a single group, "Frontotemporal Dementia". Data will be summarized using descriptive statistics (number of subjects [N], mean, standard deviation [SD], quartiles, median, minimum, and maximum) for continuous variables and using frequency counts and percentage for discrete variables.

For the purpose of display, the summary results will be rounded as follows:

- Min and Max: same number of decimal places as the raw data.
- Mean and Median: one more decimal place than the raw data.
- 25th and 75th Percentile: one more decimal place than the raw data.

- SD: two more decimal places than the raw data.
- Percentages will be displayed with one decimal precision. A zero count will not have the associated percentage presented on the table.

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

Subject listings of all data form the eCRF as well as any derived variables will be presented.

7.2 Adjustments for Covariates

Not applicable for the primary analyses.

7.3 Handling of Dropouts or Missing Data

Subjects who discontinue the study prior to or after the initiation of the study drug will not be replaced in this study and available data of these subjects until the point of discontinuation will be summarized. For situations with no rules for handling missing data, the default will be no imputation.

7.4 Interim Analyses and Data Monitoring

No interim analysis or data monitoring is planned for this study

7.5 Multi-center Studies and Pooling of Centers

This study will be conducted at approximately 3 centers in United States (US). Data from all centers will be pooled and pooled data will be used for summary tables.

7.6 Multiple Comparisons/Multiplicity

No adjustment for multiplicity will be performed in this study, as there is not statistical analysis planned in this study.

7.7 Active-Control Studies Intended to Show Equivalence

Not applicable to this study.

7.8 Examination of Subgroups

No subgroup analysis will be performed.

8 STATISTICAL ANALYSIS

8.1 Analysis Populations

The study will use following analysis populations for data summarization. Frequency count and percentage of subjects in each analysis population will be summarized.

Population	Definition	Displays
Enrolled Population	The Enrolled Population will consist of all subjects who signed inform consent and have data captured in the clinical database.	Disposition information will be summarized using the Enrolled Population.
Safety Population	The Safety Population will include all subjects who received at least one dose of Flortaucipir F 18 or Florbetapir F 18 injection.	All demographic, baseline and safety endpoints will be using the Safety Population.
ITT Population	The ITT Population will include all subjects in safety population, for whom image data are available i.e. who have a valid Flortaucipir F 18 scan assessment [SUVr (quantitative) and/or visual reads (qualitative)].	All analyses involving imaging outcomes will be based on the ITT Population.
Per Protocol Population	The Per Protocol Population will include all subjects in ITT population who were classified on Florbetapir positive (αβ+) by either investigator or Avid.	All analyses involving imaging outcomes will be based on the Per Protocol Population.

8.2 Disposition of Subjects

The frequency count and percentage of subjects enrolled, completed and discontinued during the study, as well as the reasons for discontinuation will be summarized.

A listing of all subjects who discontinued the study will be presented in a listing.

8.3 Protocol Deviations/Violations

The protocol deviations will be identified prior to data base lock. Protocol deviations will be derived from the eCRF data or will be obtained from the clinical monitoring reports. The Avid/contract research organization (CRO) will monitor and approve the final protocol list.

A listing of all protocol deviations will be presented.

8.4 Demographic and Other Baseline Characteristics

All demographic and baseline characteristics will be summarized using the safety population.

Age, height, weight (at Florbetapir F 18 imaging visit prior to dose administration), BMI, MMSE Score and MRI volumetric measurement score will be summarized as continuous variables using descriptive statistics.

Birth gender, race, ethnicity, highest level education, subject amyloid status, alcohol and substance history will be summarized as categorical variables using frequency count and percentage.

All demographic and baseline characteristics data will be presented in listings.

8.5 Family History

Family History data will be presented in a listing for the safety population.

8.6 Disease History

Diagnosis of FTD will be summarize according to symptomatic clinical syndrome associated with expected FTD pathology by frequency counts and percentage. A listing related to diagnosis of FTD will be provided.

Disease history will be summarized using descriptive statistics for the subjects in Safety Population, and will include:

- Number of months since symptom onset
- Number of months since diagnosis

For subjects with dates of diagnosis or symptom onset is available, months will be calculated as:

- Months = (Date of screening - Date of symptom onset/diagnosis)/12

For partial symptom onset/diagnosis date, if only the day is missing, then impute the day as the first day of the month; if both the day and month are missing, then impute it as 01 January of the year.

8.7 Medical/Surgical History and Concurrent Disease

Medical/Surgical History and Concurrent Disease will be presented in a listing for the safety population.

8.8 Concomitant Medications

A concomitant medication is defined as any medication given to the subject starting on or after the date of the screening visit or the medication started prior to the date of the screening visit but is reported as ongoing. A prior medication is any medication with a stop date prior to the date of screening visit.

If the start date of medication is unknown and the end date is known, then the medication will be considered:

- Prior to study medication if the end date is prior to the patient screening visit.
- Concomitant to study medication if the end date is either on the same day or after the screening visit or the end date is unknown.
- If both the start and end dates are unknown, then the medication will be considered as "concomitant medication".

The medication will be summarized using frequency count and percentage for subjects in safety population by active ingredient within each ATC, with ATC and active ingredients sorted by descending frequency.

ATC classification level 4 will be used in summary tables and listings. If the ATC classification level 4 is missing then the ATC classification level 3 will be used. If the ATC classification level 3 is missing, then the ATC classification level 2 will be used. If the ATC classification level 2 is missing, then the ATC classification level 1 will be used.

All prior and concomitant medications will be presented in listing for the safety population.

8.9 Analysis of Efficacy Parameters

The Flortaucipir F 18 PET scan information and Flortaucipir F 18 PET results will be summarized using Efficacy Population. A subject listing will be presented.

8.9.1 Qualitative Assessment of Images

The visual read results will be categorized as Not consistent with AD pattern (τAD-), and AD pattern (τAD) (τAD+, τAD++) for Flortaucipir F 18 PET results. The visual read results will be summarized by frequency count and percentage for the analysis populations (ITT and per protocol)

8.9.2 Quantitative Assessment of Images

The MUBADA SUVr for Flortaucipir F 18 results will be summarized using descriptive statistics for analysis populations (ITT or per protocol). This analysis will be repeated for the following brain regions: temporal, parietal and caudate, and frontal.

8.9.3 Other Efficacy Variables

8.9.3.1 Increased Neocortical Activity by Brain Regions

Increased neocortical Flortaucipir F 18 activity by hemisphere and region, calculated as regional SUVr values will be presented in a listing.

8.10 Analysis of Safety

All safety data will be summarized using the Safety Population.

8.10.1 Extent of Exposure and Compliance to Study Treatment

The total dose administered (mCi) of Florbetapir F 18 or Flortaucipir F 18 will be summarized using descriptive statistics. All exposure data captured on the CRF will be presented in listing.

8.10.2 Adverse Events

All AE summary tables will include only TEAEs, unless otherwise specified.

Adverse events will be summarized by SOC and PT. A subject will only be counted once per SOC and PT.

For AEs by severity grade (mild, moderate, severe), if a subject has multiple events occurring in the same SOC or same PT, then the event with the maximum intensity (i.e. severe) will be counted.

For AEs by relationship to study drug and protocol procedure will be summarized as Related vs. Not Related. If a subject has multiple events occurring in the same SOC or same PT, the event associated with the study drug will be summarized.

AEs will be summarized by descending frequency, then alphabetically by SOC and preferred term.

An overall summary of AEs will be presented and will include:

- Subjects with any Trial Emergent AEs
- Subjects with at least one TEAE
- Subjects with any severe or moderate TEAE
- Subjects with any TEAE related to Florbetapir F 18
- Subjects with any TEAE related to Flortaucipir F 18
- Subjects with any TEAE related to protocol procedure
- Subjects with any serious TEAE
- Subjects with any TEAE resulting in death
- Subjects with any TEAE leading to study discontinuation

The following summary tables will be presented by SOC and PT:

- Trial Emergent AEs
- All TEAEs
- TEAEs by PT
- TEAEs by severity
- TEAEs by relationship to Florbetapir F 18
- TEAEs by relationship to ^{18}F-AV-1451
- TEAEs by relationship to protocol procedure
- Serious TEAEs
- TEAEs resulting in death
- TEAEs leading to study discontinuation

The following listings will be presented by subject:

- All AEs
- Serious TEAEs
- TEAEs leading to study discontinuation
- TEAEs resulting in deaths

8.10.3 Serum and Urine Pregnancy Test

Serum and urine pregnancy data will be presented in a listing for subjects in Safety Population.

8.10.4 Vital Signs

Vital signs (pulse, respiratory rate and supine blood pressure) including body weight will be summarized using descriptive statistics for observed and change from baseline values.

All vital signs data will be presented in the listing.

8.10.5 Electrocardiogram (ECG)

The ECG data collected at screening will be presented in the listing.

8.10.6 Follow-up Telephone Contact

A listing will be provided for information based on Follow-up Telephone Contact.

8.11 Pharmacodynamics

No pharmacodynamics analysis is planned for this study.

9 COMPUTER SOFTWARE

All analyses will be performed by Chiltern using SAS® Version 9.3 or later. All summary tables and data listings will be prepared utilizing SAS® software.

The standard operating procedures (SOPs) of Chiltern will be followed in the creation and quality control of all data displays and analyses.

10 REFERENCES

1. Clinical Study Protocol: ^{18}F-AV-1451 PET Imaging in Subjects with Frontotemporal Dementia. Date and Version: 05May2016, Final