Protocol No. 18F-AV-1451-A08

^{18}F-AV-1451 PET Imaging in the Preclinical, Prodromal and Dementia Phases of Alzheimer's Disease

Statistical Analysis Plan

Prepared by:
Avid Radiopharmaceuticals, Inc

Final Version 1.0
13 June 2018

Revision History

Version	Date	Revision Author	Comments
0.1	10 May 2018	[redacted]	Initial Draft
0.2	24 May 2018	[redacted]	• Updated Introduction • Updated language to primary objective • Added inferior temporal SUVr as a key ROI in efficacy analysis • Updated exploratory analysis to only include MUBADA SUVr when assessing tau quantitation • Updated primary analysis to include amygdala, precuneus, PLT, lateral parietal, occipital, frontal, medial temporal, MUBADA and inferior temporal SUVr • Added Clinically Meaningful Progress Section • Included risk ratio as an exploratory endpoint for MMSE and CDR-SB clinically meaningful progress

			• Updated instances of 'tau' to 'flortaucipir' as not to equate the two • Updated 'Non-SMC' to HC • Updated MedDRA dictionary version • Updated WHODrug dictionary • Updated Changes to Planned Analysis excluding CVLT, D-KEFS, Boston Naming, and Complex Figures tests from any analysis • Removed CVLT, D-KEFS, Boston Naming, and Complex Figures from Additional Efficacy Variables section • Removed bulleted lists of table/listing outputs • Updated language describing hypothesis tests in contexts of the alternative conclusion.
0.3	12 June 2018	[redacted]	• Changed HC to CN • Added section outlining presentation of MRI data • Updated efficacy SUVr regions of interest to MUBADA • Included Fisher's exact test contingency when evaluating Relationship of Qualitative Flortaucipir Uptake and Cognitive Status • Updated exploratory SUVR regions of interest to 'all other • Minor update to "Qualitative Analysis of Flortaucipir Section • Removed ANCOVA analysis evaluating MUBADA change across tau groups • Removed years of education as a covariate in SUVr CFB analysis • Removed correlation analysis between MUBADA and MRI brain volumes • Added paired t-test analysis on SUVr CFB across amyloid groups

			• Moved comparison of SMC and HC group SUVr to primary as third hypothesis
1.0	13 June 2018	[redacted]	• Finalized document

SIGNATURE PAGE

Author:

[redacted]

Approved by:

[redacted]

Avid Radiopharmaceuticals, Inc.

[redacted]

Avid Radiopharmaceuticals, Inc.

[redacted]

Avid Radiopharmaceuticals, Inc.

Table of Contents

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS **8**

1 INTRODUCTION **9**

2 STUDY OBJECTIVES **9**

3 STUDY DESIGN **9**

3.1 GENERAL DESIGN **9**

3.1.1 Screening Visit *11*
3.1.2 MRI Visit *11*
3.1.3 Flortaucipir PET Imaging Visits *11*
3.1.3.1 Dosage and Administration 11
3.1.3.2 Initial flortaucipir PET Imaging Visit 11
3.1.3.3 Follow-up flortaucipir PET Imaging Visit 11

3.2 BLINDING **12**

3.3 DETERMINATION OF SAMPLE SIZE **12**

4 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES **12**

4.1 CHANGES IN THE CONDUCT OF THE STUDY **12**

4.2 CHANGES FROM THE ANALYSES PLANNED IN THE PROTOCOL **12**

5 BASELINE, EFFICACY AND SAFETY EVALUATIONS **13**

5.1 SCREENING ASSESSMENTS **13**

5.2 EFFICACY VARIABLES **13**

5.2.4 Primary Efficacy Variable(s) *13*
5.2.4.1 Quantitative Analysis of Flortaucipir Scan 13
5.2.4.2 Qualitative Analysis of Flortaucipir Scan 13
5.2.5 Additional Efficacy Variables *13*
5.2.5.1 Mini-Mental State Examination (MMSE) 14
5.2.5.2 Clinical Dementia Rating (CDR) Scale (Berg, 1988) 14
5.2.5.3 Clinically Meaningful Progress 14

5.3 SAFETY ASSESSMENTS **14**

5.3.1 Adverse Events *14*
5.3.2 Vital Signs *15*

6 STATISTICAL METHODS **15**

6.1 GENERAL METHODOLOGY AND CONVENTIONS **15**

6.2 DEFINITIONS OF BASELINE AND FOLLOW-UP **16**

6.3 WINDOWS **16**

6.4 CALCULATING AGE **16**

6.5 CALCULATING YEARS OF EDUCATION **16**

6.6 CALCULATING BMI **16**

6.7 TIME POINT ALGORITHMS **17**

6.8 ADJUSTMENTS FOR COVARIATES 17
6.9 HANDLING OF DROPOUTS OR MISSING DATA 17
6.10 MULTI-CENTER STUDIES AND POOLING OF CENTERS 17
6.11 MULTIPLE COMPARISONS/MULTIPLICITY 17
7 STATISTICAL ANALYSIS 17
7.1 ANALYSIS POPULATIONS 17
7.1.1 Enrolled Population 17
7.1.2 Safety Population 18
7.1.3 Efficacy Population 18
7.2 DISPOSITION OF SUBJECTS 19
7.3 ANALYSIS OF SCREENING AND BASELINE ASSESSMENTS 19
7.3.1 Demographic and Other Baseline Characteristics 19
7.3.2 Medical and Surgical History 19
7.3.3 Concomitant Therapy 19
7.3.4 Physical Examination 19
7.3.5 Neurological Examination 20
7.3.6 History of Cognitive Decline 20
7.3.7 Family History of Dementing Disorder 20
7.3.8 Electrocardiogram (ECG) 20
7.3.9 Safety Labs 20
7.3.10 MRI Visit 20
7.4 ANALYSIS OF EFFICACY PARAMETERS 20
7.4.1 Primary Efficacy Analysis 20
7.4.1.1 Two-way Analysis of Variance for Comparison of MUBADA SUVr across Cognitive Groups 20
7.4.1.2 Relationship of Qualitative Flortaucipir Uptake and Cognitive Status 21
7.4.2 Exploratory Analysis 22
7.4.2.1 Two-way ANOVA for Comparison of MUBADA SUVr between Amyloid Groups 22
7.4.2.2 ANCOVA for Comparison of MMSE CFB as a Function of Tau Scan Visual Interpretation 22
7.4.2.3 ANCOVA for Comparison of CDR-SB CFB as a Function of Tau Scan Visual Interpretation 22
7.4.2.4 ANCOVA for Comparison of MMSE CFB as a Function of Cognitive Status 23
7.4.2.5 ANCOVA for Comparison of CDR-SB CFB as a Function of Cognitive Status 23
7.4.2.6 Risk Ratio of AD++ vs. Non-AD++ Subjects in Progression to Clinically Meaningful Changes Evaluated by MMSE 23
7.4.2.7 Risk Ratio of AD++ vs. Non-AD++ Subjects in Progression to Clinically Meaningful Changes Evaluated by CDR-SB 23
7.4.2.8 Relationship between Baseline MUBADA SUVr and Cognitive Change 23
7.4.2.9 Relationship between MUBADA SUVr Change and Cognitive Change 24
7.4.2.10 Comparison of MUBADA SUVr CFB as a Function of Amyloid Status 24
7.5 ANALYSIS OF SAFETY 24
7.5.1 Exposure 24
7.5.1.1 Unit Conversion and Volume Calculation 24
7.5.2 Flortaucipir PET Scan 24
7.5.3 Treatment Emergent Adverse Events 24
7.5.4 Severity 25
7.5.5 Serious Adverse Events 25
7.5.6 Adverse Events Leading to Study Discontinuation 25
7.5.7 Adverse Events Leading to Death 26
7.5.8 Missing and Partial AE Onset Dates 26

7.5.9 Analysis of Vital Signs *26*
7.5.10 Potentially Clinically Significant Vital Sign Changes *26*
7.5.11 Follow-up Telephone Contact Data *27*

APPENDIX I: ALGORITHMS TO HANDLE MISSING AND PARTIAL DATES **28**

1.1. MISSING AND PARTIAL AE ONSET AND END DATES 28

LIST OF TABLES

Table 1: Abbreviations and Definitions of Terms 8
Table 2: Trial Flow Chart 10
Table 3: Potentially Clinical Significant Criteria 26

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

Aβ	Amyloid Beta
AD	Alzheimer's Disease
AE	Adverse event
AIBL	Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CFB	Change from baseline
CMH	Cochran Mantel Haenszel
CN	Cognitive normal
CRF	Case report form
CVLT-II	California Verbal Learning Test-II
D-KEFS	Delis-Kaplan Executive Function System
ECG	Electrocardiogram
LSM	Least squares mean
MBq	Megabecquerel
mCi	millicurie
MCI	Mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Exam
MRI	Magnetic resonance imaging
MUBADA	Multi-Block Barycentric Discriminant Analysis
PCS	Potentially clinically significant
PERSI	Parametric estimated signal reference intensity
PET	Positron Emission Tomography
PT	Preferred term
ρ	correlation coefficient
SMC	Subject memory complaints
SOC	System organ class
SUVr	Standard Uptake Value ratio
TEAE	Treatment emergent adverse events

1 INTRODUCTION

The goal of this protocol is to further investigate the positron emission tomography (PET) imaging results with flortaucipir in patients across the Alzheimer's Disease (AD) spectrum from individuals with subjective memory complaints (SMC) to those with dementia. To accomplish this goal, the protocol will investigate flortaucipir Standard Uptake Value Ratios (SUVr) in older cognitively unimpaired individuals and across a spectrum of participants who may have a range of brain tau deposition, including; a) cognitive normal subjects (CN), b) individuals with SMC, and patients with a clinical diagnosis of c) mild cognitive impairment (MCI) and d) AD. The findings will be analyzed in relationship to brain amyloid status, magnetic resonance imaging (MRI) scans and cognitive assessments performed in the same Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) participants.

The purpose of this statistical analysis plan (SAP) is to describe the statistical analyses for the protocol. The SAP should be read in conjunction with the protocol.

2 STUDY OBJECTIVES

The primary objective of this study is:

- To compare the density and distribution of flortaucipir uptake among men and women aged over 60 years with objective cognitive impairment (MCI and AD) and without objective cognitive impairment (CN and subjects with SMC).

The exploratory objectives of this study are:

- To determine the prevalence and distribution of brain tau in men and women aged over 60 years with and without subjective cognitive complaints.

- To relate the regional distribution of brain tau deposits to the presence of brain amyloid, current cognitive and brain function as well as brain atrophy.

- To relate the change over time in the levels of regional brain tau to baseline brain tau, baseline brain amyloid and change over time in cognition and function, and brain volume.

- To expand the flortaucipir safety database.

3 STUDY DESIGN

3.1 GENERAL DESIGN

This is a phase I study that will evaluate imaging characteristics of flortaucipir in the preclinical, prodromal and dementia phases of AD.

AIBL subjects who have previously had beta-amyloid imaging in the form of florbetapir PET imaging will be contacted to participate and must provide informed consent before starting any 18F-AV-1451-A08 study procedures. In addition to consenting to study procedures, participants will consent to have amyloid PET images and data, MRI images and data, and cognitive data made available to this study to allow analysis and comparison. Other AIBL participants who have had other types of amyloid imaging will be recruited when required to reach the study target enrollment numbers. Screening assessments may take place over several days and will include demographic information and safety assessments.

Subjects who qualify for the study will return to the clinic at a later date for a flortaucipir PET scan. To optimally compare to the AIBL cognitive evaluation, the flortaucipir scan will be obtained within +/- 2 months of the planned (or obtained) cognitive evaluation in AIBL.

Subjects will have a follow-up flortaucipir PET scan at 12 (+/- 3) months following the initial flortaucipir scan. A brief cognitive evaluation will be performed on the day of the follow-up flortaucipir scan or on a separate visit within 2 months of the follow-up scan.

Table 2: Trial Flow Chart

Evaluations	Screening Visit	MRI Visit	Flortaucipir Imaging Visit	Follow-up Flortaucipir Imaging Visit	Follow-Up Phone Call
Demographics	X				
Medical History	X				
Concomitant Medications	X				X
Physical Examination	X				
Neurological Examination	X				
ECG	X				
Safety Labs[a]	X				
Vital Signs	X		X	X	
Neurological Testing			X	X	
MRI of the Brain		X			
PET Brain Scan			X		
Follow-up Phone Call					X
Evaluation by Physician/Designee	X		X	X	
Adverse Events	X	X	X		X
Serious Adverse Events	X	X	X		X

[a]Safety labs to be collected any time between consent and flortaucipir Injection at Imaging Visit

3.1.1 Screening Visit

Subjects enrolled in the AIBL (previously had amyloid imaging in the form of flotbetapir PET imaging) study were contacted to participate. Screening may take place over several days. All screening assessments were performed within 60 days of the initial flortaucipir PET imaging session.

3.1.2 MRI Visit

MRI was acquired within 6 months, either prior to or after, the initial flortaucipir PET scan. The subject's AIBL MRI scan could have been used as long as it was obtained within this timeframe.

3.1.3 Flortaucipir PET Imaging Visits

3.1.3.1 Dosage and Administration

All subjects received a single IV bolus administration of approximately 240 MBq +/- 10% of flortaucipir injection at both the initial and follow-up flortaucipir imaging visit.

3.1.3.2 Initial flortaucipir PET Imaging Visit

The initial flortaucipir PET scan was obtained within +/- 2 months of the planned (or obtained) cognitive evaluation in AIBL.

A physician must have seen the subject prior to the administration of the flortaucipir injection to determine if they were suitable to undergo the scan, and again prior to discharge from the imaging center to evaluate the subject's readiness for discharge. Vital signs were taken (pulse rate, respiratory rate, and supine blood pressures) immediately prior to the administration of flortaucipir and prior to discharge. Weight was also collected, prior to injection.

A 5 minute brain scan began immediately following the administration of flortaucipir, and another continuous 30-minute brain scan approximately 75 minutes after injection.

Adverse events were continuously monitored during the flortaucipir PET imaging visit. A follow-up phone call to the subject, or designated decision maker, was 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.

3.1.3.3 Follow-up flortaucipir PET Imaging Visit

The follow-up flortaucipir imaging visit was obtained 12 (+/-3) months following the initial flortaucipir scan, and followed the same procedures outlined in section 4.1.3.2.

In addition, a brief cognitive evaluation was performed on the day of, or within 2 months of the follow-up flortaucipir scan. This consisted of the Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR) scale, the alternative forms of California Verbal Learning Test-II (CVLT-II), Delis-Kaplan Executive Function System (D-KEFS) verbal fluency (letter and category), Boston Naming Test 30 Item, (Taylor) Complex Figure Test and Logical Memory – Wechsler Memory Scale – Revised.

3.2 BLINDING

In regards to flortaucipir scan, a blinded design was not used because all subjects received the same medication.

3.3 DETERMINATION OF SAMPLE SIZE

Due to the exploratory purpose of this study, the sample size was determined outside statistical consideration.

4 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

4.1 CHANGES IN THE CONDUCT OF THE STUDY

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

4.2 CHANGES FROM THE ANALYSES PLANNED IN THE PROTOCOL

There were no changes in the analyses planned from the protocol to those described in this SAP. However, CVLT, D-KEFS, Boston Naming and Complex Figure tests, which are collected as part of AIBL, were not analyzed for this study as there are no comparable assessments in other Avid studies. Additionally, the method for quantitatively estimating flortaucipir PET signal was modified to focus on the cortical target region (MUBADA) and parametric estimated signal reference intensity (PERSI) that is the current standard at Avid. In addition, planned exploratory analyses involving partial volume correction and analyses of regional distribution during the 5 minutes immediate post dose imaging have not been performed and will not be included in this Clinical Study Report. Finally, analyses of tau visual reads (AD++ vs. Non-AD++) have been added to assess the relationship of tau and other biomarkers at a categorical level.

5 BASELINE, EFFICACY AND SAFETY EVALUATIONS

5.1 SCREENING ASSESSMENTS

Screening assessments included informed consent, demographics, medical history and concomitant medications, physical and neurological examination, disease history for cognitively impaired subjects, a family history of neurologic disease, vital signs, electrocardiogram (ECG), safety labs, and a physician having seen the subject during the screening visit.

5.2 EFFICACY VARIABLES

5.2.4 Primary Efficacy Variable(s)

5.2.4.1 Quantitative Analysis of Flortaucipir Scan

Voxels of interest from the AAL atlas masked to exclude white matter and CSF will be extracted for amygdala, anterior hippocampus, posterior hippocampus, anterior parahippocampus, posterior parahippocampus, anterior fusiform, posterior fusiform, caudate, left putamen, right putamen, temporal, left temporal, right temporal, occipital, left occipital, right occipital, parietal, left parietal, right parietal, precuneus, frontal, left frontal, and right frontal.

SUVr will be calculated to estimate global tau load and in individual regions from flortaucipir images from both baseline and follow up visits. The MUBADA SUVr will be used for the global measurement. A selected white matter region derived using the PERSI method will be used as reference region for all SUVr calculations.

MUBADA will be the variable used in all efficacy analysis involving flortaucipir quantitation. All regional and MUBADA SUVrs will be presented in listings.

5.2.4.2 Qualitative Analysis of Flortaucipir Scan

Baseline flortaucipir images will be visually assessed independently by two expert readers at Avid who will be blinded to any clinical information of the subjects. For any discrepant reads, a consensus discussion will take place and a final read will be recorded. The images will be classified as either AD++ (AD pattern, likely to progress), AD + (AD pattern, but unlikely to progress; tau limited to temporal/occipital lobe) or AD- (Inconsistent with an AD pattern), following the pre-specified read method (see imaging read manual for details). For the purposes of study analyses images will be considered positive for progression if they are rated AD ++ and negative for progression if they are rated non-AD++ (AD- or AD+ but not AD++).

5.2.5 Additional Efficacy Variables

5.2.5.1 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. MMSE was collected at baseline under the AIBL protocol and at 12 months under the AV-1451-A08 protocol.

5.2.5.2 Clinical Dementia Rating (CDR) Scale (Berg, 1988)

The CDR examines 6 categories of cognitive functioning domains. Each domain is scored on a scale ranging from 0 to 3 (including 0.5). A CDR Sum of Boxes (CDR-SB) will be generated as the sum of the values in each of the six domains. The CDR-SB sum scores ranges from 0-18, where higher scores indicate greater cognitive impairment. CDR will be collected at baseline under the AIBL protocol and at 12 months under the AV-1451-A08 protocol.

5.2.5.3 Clinically Meaningful Progress

The MMSE and CDR-SB assessments will be dichotomized, to allow for the assessment of risk to progress to a clinically significant change. Subjects will be categorized to these groups by the criteria accordingly.

- MMSE: clinically significant progress is defined as MMSE has a 3 points or more decrease from baseline.

- CDR-SB: clinically significant progress is defined as CDR-SB has a 1 point or more increase from baseline.

5.3 SAFETY ASSESSMENTS

5.3.1 Adverse Events

An adverse event (AE) is any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the study drug. 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, whether or not considered drug related. 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 using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0.

Severity is classified as mild/moderate/severe (increasing severity). If a subject reports a TEAE more than once within that SOC/preferred term (PT), the TEAE with the worst case severity will be used in the corresponding severity summaries.

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

5.3.2 Vital Signs

Supine blood pressure, pulse rate, and respiratory rate are collected at Screening and two time points – Immediately Prior to (within 5 minutes) Flortaucipir Injection and Prior to Discharge - during the flortaucipir imaging visits. In addition, height is captured at screening, and weight is collected at both Screening and prior to each injection of flortaucipir.

6 STATISTICAL METHODS

6.1 GENERAL METHODOLOGY AND CONVENTIONS

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

Continuous data will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum (min), and maximum (max)). Frequency counts and percentages will be used to summarize 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 the listings with maximum two digits per level (e.g., Table XX.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.

6.2 DEFINITIONS OF BASELINE AND FOLLOW-UP

Baseline cognitive scores will be collected under the AIBL protocol, outside the AV-1451-A08 electronic data capture (EDC) system. All other baseline data (e.g. demographics) will be reported from data collected from the AV-1451-A08 EDC. All follow-up cognitive scores for the calculation of change from baseline (CFB) are collected under the AV-1451-A08 protocol.

Safety analysis involving CFB calculations for vital signs will consider *Prior to Injection* values as baseline and *Prior to Discharge* as follow-up for each scan session.

6.3 WINDOWS

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

6.4 CALCULATING AGE

Age will be derived in years as the difference between the year of informed consent and year of birth.

6.5 CALCULATING YEARS OF EDUCATION

Years of education will be derived using the following mapping based on the 'Highest Level of Education' collected on the demographics case report form (CRF).

- Elementary School = 6
- Middle School = 8
- High school = 12
- College/University = 16
- Post Graduate School = 18

Any 'Other' response clarified in the CRF where a definitive number of years can be determined (e.g. '2 years of college' or '14 years') will be mapped accordingly based on the definitions bulleted above. Otherwise, 'Other' will be mapped to the mean value of available data based on the aforementioned mapping.

6.6 CALCULATING BMI

Body Mass Index (BMI) will be calculated using the following formula.

$$BMI = \frac{weight\ (kg)}{height^2 (m^2)}$$

6.7 TIME POINT ALGORITHMS

The date of first dose of flortaucipir will be considered relative day 1, and the day before the first dose of study drug 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):

For days on or after the first dose of study drug:
Date of Assessment – Date of First Dose of Study Drug + 1.

For days before the first dose of study drug:
Date of Assessment – Date of First Dose of Study Drug.

6.8 ADJUSTMENTS FOR COVARIATES

Analysis of Covariance (ANCOVA) models evaluating cognitive change in the exploratory analyses will be adjusted for the baseline value of the cognitive score, age, and years of education. Log-linear models estimating risk ratios in the exploratory analyses will be adjusted for the baseline value of the cognitive score, age, and years of education. ANCOVA models evaluating SUVr CFB in the exploratory analysis will be adjusted for baseline SUVr and age.

6.9 HANDLING OF DROPOUTS OR MISSING DATA

Dropout subjects will not be replaced in this study. The missing data will not be imputed.

6.10 MULTI-CENTER STUDIES AND POOLING OF CENTERS

The data from all centers will be pooled. The pooled data will be analyzed and presented.

6.11 MULTIPLE COMPARISONS/MULTIPLICITY

No multiple comparisons/multiplicity adjustment is planned. Unless otherwise specified, hypothesis testing will be two-sided with type I error rate of 0.05.

7 STATISTICAL ANALYSIS

7.1 ANALYSIS POPULATIONS

7.1.1 Enrolled Population

The enrolled population will consist of all enrolled AIBL subjects who have baseline cognitive assessments captured in the AIBL clinical database, and who signed informed consent for the AV-1451-A08 protocol. Disposition information will be summarized using the enrolled population.

7.1.2 Safety Population

The safety population will consist of all subjects that received an injection of flortaucipir. All baseline information and safety endpoints will be reported on using the safety population.

7.1.3 Efficacy Population

The efficacy population used in the primary analysis will include all subjects in the safety population with a valid interpretable baseline PET image (SUVr and/or visual read) available. The exploratory efficacy population will include all subjects with available SUVr, flortaucipir visual read, and the relevant clinical/cognitive assessment.

7.2 DISPOSITION OF SUBJECTS

The enrolled population will be represented in the disposition table. The disposition table will be broken down by diagnosis (AD, MCI, CN and SMC) and include a summary of the analysis populations, number of completed and discontinued subjects, and the reasons for discontinuation.

Disposition data will be presented in a listing.

7.3 ANALYSIS OF SCREENING AND BASELINE ASSESSMENTS

7.3.1 Demographic and Other Baseline Characteristics

All baseline summaries will be based on the safety population. Age (years), gender, amyloid status (Aβ+, Aβ-), tau status (AD-, AD+, AD++), race, ethnicity, height (cm), weight (kg), BMI, years of education, substance use (alcohol, smoking, and recreational drug history), MMSE, CDR-SB will all be reported in the demographics table using descriptive statistics.

All baseline cognitive scores are collected in the AIBL database. Baseline height and weight are the measurements collected on the AV-1451-A08 CRF.

7.3.2 Medical and Surgical History

Medical and surgical histories were coded using MedDRA version 17.0. Medical and surgical history will be defined in the same manner as in the protocol. Medical and surgical history will be presented for the safety population in a listing.

7.3.3 Concomitant Therapy

Concomitant therapies were coded using WHODRUG V20140601. Concomitant medications are medications that started prior to, on or after the informed consent date *and* ended on or after the date of the flortaucipir injection or were ongoing at the end of the study. Concomitant medications will be presented for the safety population in a listing.

7.3.4 Physical Examination

Physical examination will be summarized for the safety population. Each assessment of the physical examination – general appearance, skin, HEENT, respiratory, cardiovascular, gastrointestinal, musculoskeletal – will be summarized in a table in aggregate and by diagnosis.

Individual subject assessments will be presented in a listing, including any abnormalities noted on the CRF.

7.3.5 Neurological Examination

Neurological examination will be summarized using the safety population. Each assessment of the neurological examination – level of consciousness, mood and affect, cranial nerves, motor function, fundoscopy, sensory function, gait cerebellar, reflexes – will be summarized in a table in aggregate and by diagnosis.

Individual subject assessments will be presented in a listing, including any abnormalities noted on the CRF.

7.3.6 History of Cognitive Decline

History of cognitive decline will be presented in a listing for the safety population.

7.3.7 Family History of Dementing Disorder

Family history of dementing disorders will be presented in a listing for the safety population.

7.3.8 Electrocardiogram (ECG)

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

7.3.9 Safety Labs

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

7.3.10 MRI Visit

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

7.4 ANALYSIS OF EFFICACY PARAMETERS

7.4.1 Primary Efficacy Analysis

The primary analysis will be analyzed in both the quantitative (MUBADA SUVr) and qualitative (the visual interpretation of the baseline flortaucipir scan) measures of brain flortaucipir accumulation.

7.4.1.1 Two-way Analysis of Variance for Comparison of MUBADA SUVr across Cognitive Groups

The first hypothesis for testing is whether MUBADA SUVr is the same or different between subjects with objective cognitive impairment (AD and MCI) and subjects without objective cognitive impairment (CN and SMC) at baseline.

The second hypothesis for testing is whether MUBADA SUVr is the same or differs between subjects with objective cognitive impairment (AD and MCI) and SMC subjects at baseline.

The third hypothesis for testing is whether MUBADA SUVr is the same or differs between SMC and CN subjects at baseline.

Depending on available data, a two-way analysis of variance (ANOVA) model will be used to test all three hypotheses. Baseline MUBADA SUVr will be the dependent variable, with cognitive group (AD, MCI, CN and SMC) and amyloid status (Aβ+ and Aβ-) as the fixed effects. The appropriate contrast will be set up to test each hypothesis.

Descriptive summary statistics along with least squares means (LSM) for SUVr at baseline will be summarized for all subjects by cognitive group (AD, MCI, SMC, CN). The difference in LSM between groups and p-values from each ANOVA contrast will be included in the table.

Box-and-whisker plots will be generated to visualize SUVr distribution across cognitive groups.

7.4.1.2 Relationship of Qualitative Flortaucipir Uptake and Cognitive Status

The first hypothesis will test whether a relationship exists between the subjects who exhibit an AD pattern likely to progress and those who do not (AD++ vs. Non-AD++), as determined by the visual interpretation of the baseline flortaucipir scan, and cognitive status (AD, MCI, CN, SMC), while controlling for amyloid status.

The second hypothesis will test whether a relationship exists between all subjects with an AD pattern (AD+ and AD++ vs. AD-), and cognitive status, while controlling for amyloid.

Depending on available data, Cochran Mantel Haenszel's (CMH) test for general association will be used to test both of these hypotheses. Further, Pearsons's chi-square test of association will be used to test this hypothesis within each amyloid group separately. Fisher's exact test will be used in the event that at least one expected cell count is less than 5. The joint distributions (frequency and percentages) from each amyloid group, along with the p-values from the CMH and Pearson chi-square (or Fisher's exact) tests from each hypothesis will be summarized in a unique table.

7.4.2 Exploratory Analysis

All exploratory analysis involving flortaucipir quantitation will be run with MUBADA SUVr only.

7.4.2.1 Two-way ANOVA for Comparison of MUBADA SUVr between Amyloid Groups

Depending on available data, the same analyses as described in Section 7.4.1.1 will be performed with the substitution of comparing MUBADA SUVr between amyloid groups (Aβ+ vs. Aβ-) rather than cognitive groups, via properly set up contrasts.

7.4.2.2 ANCOVA for Comparison of MMSE CFB as a Function of Tau Scan Visual Interpretation

The objective of this analysis is to determine if baseline tau status will predict subjects' cognitive deterioration.

The first hypothesis will test whether a difference in MMSE CFB exists between AD++ and Non-AD++ (AD- and AD+ only) subjects at 12 month follow-up visit.

The second hypothesis will test whether a difference in MMSE CFB exists between subjects with AD pattern (AD+ and AD++) and AD- subjects.

The third hypothesis will test whether a difference in MMSE CFB exists between AD++ and AD- subjects.

Depending on available data, an ANCOVA model with MMSE CFB at 12 months as the dependent variable, adjusted for baseline MMSE, age, cognitive group, level of education, and the interaction of cognitive group and tau status will be used to test these hypotheses. The appropriate contrasts will be set up to test each hypothesis.

Descriptive summary statistics for MMSE at baseline, 12 months and CFB will be summarized for all subjects by tau status (AD-, AD+, AD++). Group LSM, the difference in LSM between groups, and the p-values from each ANCOVA contrast will be included in the table.

A scatter plot will be created to display the relationship between MMSE CFB and baseline MUBADA SUVr across each tau group.

7.4.2.3 ANCOVA for Comparison of CDR-SB CFB as a Function of Tau Scan Visual Interpretation

The same analyses as described in Section 7.4.2.2 will be performed with the substitution of CDR-SB for MMSE.

7.4.2.4 ANCOVA for Comparison of MMSE CFB as a Function of Cognitive Status

This analysis will test the hypothesis whether there is a difference between subjects with objective cognitive impairment (AD and MCI) and SMC subjects. The same analyses as described in Section 7.4.2.2 will be performed with the substitution of impairment group (AD and MCI vs. SMC) for tau status, via properly set up contrasts.

7.4.2.5 ANCOVA for Comparison of CDR-SB CFB as a Function of Cognitive Status

The same analyses as described in Section 7.4.2.4 will be performed with the substitution of CDR-SB for MMSE.

7.4.2.6 Risk Ratio of AD++ vs. Non-AD++ Subjects in Progression to Clinically Meaningful Changes Evaluated by MMSE

The specific hypothesis for testing is the risk of progressing to a clinically meaningful event ($\leq$ -3 change) as determined by MMSE value change within 12 months will be significantly greater for subjects in the AD++ group as compared to those in the non-AD++ group (otherwise, including AD- and AD+ only but not AD++ reading).

As described in section 5.2.5.3, the MMSE CFB will be the dichotomized (3 point or more decrease vs. otherwise). Depending on available data, incidence of this clinically meaningful event by tau visual read groups will be compared using a log-linear model adjusted for baseline age, years of education, and baseline MMSE score. The Poisson distribution will be chosen for the dependent variable and a log link function will be used to model for the risk ratio.

The risk ratio of AD++ rated subjects progressing to the event over non-AD++ rated subjects along with the 95% confidence interval will be provided.

7.4.2.7 Risk Ratio of AD++ vs. Non-AD++ Subjects in Progression to Clinically Meaningful Changes Evaluated by CDR-SB

The same analyses as described in Section 7.4.2.6 will be performed with the substitution of CDR-SB clinically meaningful progression ($\geq$ 1 point change) for MMSE clinically meaningful progression.

7.4.2.8 Relationship between Baseline MUBADA SUVr and Cognitive Change

This exploratory analysis will test whether a relationship exists between baseline MUBADA SUVr and cognitive CFB, as measure by both MMSE and CDR-SB.

Partial correlation coefficient (ρ) adjusted for age and baseline cognitive score, will be calculated to assess the relationship between baseline MUBADA SUVr and each

cognitive score CFB. The results will be summarized in a table along with p-values associated with the hypothesis that $\rho = 0$.

7.4.2.9 Relationship between MUBADA SUVr Change and Cognitive Change

Based on data availability, the same analyses as described in Section 7.4.2.9 will be performed with the addition of partial ρ being adjusted for age.

7.4.2.10 Comparison of MUBADA SUVr CFB as a Function of Amyloid Status

The hypothesis for testing is whether MUBADA CFB within each amyloid group (AB+ and AB-) is equal to 0.

Descriptive summary statistics for MUBADA SUVr at baseline, 12 months and CFB will be summarized for all subjects by amyloid status (Aβ+ and Aβ-). Paired t-tests will be run for each group separately and the p-values from each test will be included in the table.

Box-and-whisker plots will be generated to visualize MUBADA CFB across amyloid groups.

7.5 ANALYSIS OF SAFETY

7.5.1 Exposure

The total dose administered of flortaucipir will be summarized using megabecquerels (MBq) in a table using descriptive statistics by imaging visits and collectively. Exposure data captured on the CRF will be presented in a listing.

7.5.1.1 Unit Conversion and Volume Calculation

All exposure tables will display volume in MBq. Radioactive dose collected in millcuries (mCi) will be converted to MBq as follows:

$$MBq = 37 \times mCi$$

7.5.2 Flortaucipir PET Scan

Imaging information captured on the CRF during the flortaucipir imaging visits will be presented in a listing for the safety population.

7.5.3 Treatment Emergent Adverse Events

A summary of TEAEs will be reported in the tables including number of all TEAE and number of subjects with 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 TEAEs will be presented in a listing for the safety population.

7.5.4 Severity

TEAE severity will be reported in a table in the same manner as outlined in 7.5.3. If a subject reported more than one TEAE with the same SOC or PT, the highest severity level will used.

7.5.5 Serious Adverse Events

Serious TEAEs will be summarized in a similar manner as described in Section 7.5.3. If a subject reported more than one serious TEAE with the same SOC or PT, the TEAE will be counted only once in that SOC or PT.

7.5.6 Adverse Events Leading to Study Discontinuation

TEAEs leading to study discontinuation will be summarized in a similar manner as described in section 7.5.3.

7.5.7 Adverse Events Leading to Death

TEAEs leading to death will be summarized in a similar manner as described in section 7.5.3.

7.5.8 Missing and Partial AE Onset Dates

See appendix 1.1 for specific algorithms to impute missing start and stop dates.

7.5.9 Analysis of Vital Signs

Supine blood pressure, pulse rate, and respiratory rate will be monitored for significant changes at the flortaucipir imaging visits.

Immediately Prior to Injection (within 5 minutes) will be considered the baseline value for all change calculations of systolic and diastolic blood pressures, pulse rate, and respiratory rate.

The data from each visit (Screening, Initial Flortaucipir Imaging, and 12 Month Flortaucipir Imaging) along with calculated CFB, defined as the difference from the *Prior to Injection* to *Prior to Discharge* values at the each imaging visits, will be summarized in aggregate. A paired t-test will be performed of each vital sign to assess if any significant changes occurred.

Vital signs and changes (where applicable) will be presented in a listing for the safety population.

7.5.10 Potentially Clinically Significant Vital Sign Changes

Vital signs will be monitored for potentially clinical significance (PCS). Below are the PCS criteria.

Table 3: Potentially Clinical Significant Criteria

Vital Sign		PCS Criteria	
		Low	High
Systolic blood pressure	mmHg	≤ 90 and ≥ 20 decrease	≥ 180 and ≥ 20 increase
Diastolic blood pressure	mmHg	≤ 50 and ≥ 15 decrease	≥105 and ≥ 15 increase
Pulse rate	bpm	≤ 50 and ≥ 15 decrease	≥ 120 and ≥ 15 increase

Respiration rate	Breaths/min	≤ 10	

7.5.11 Follow-up Telephone Contact Data

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

APPENDIX I: ALGORITHMS TO HANDLE MISSING AND PARTIAL DATES

1.1. MISSING AND PARTIAL AE ONSET AND END 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:

AE ONSET DATE/TIME	AE STOP DATE/TIME	ACTION
Partial, but known components show that it cannot be on or after an injection date/time and within 48 hours post-injection	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after an injection date/time and within 48 hours post-injection	Known	If stop date/time < flortaucipir injection date/time, then not TEAE If stop date/time >= flortaucipir injection date/time, then TEAE
	Partial	Impute stop date as latest possible date (i.e. 59 if minutes unknown or 23:59 if hours and minutes unknown; last day of month if day unknown or 31st December if day and month unknown), then: If stop date/time < flortaucipir injection date/time, then not TEAE If stop date/time >= flortaucipir injection date/time, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date/time < flortaucipir injection date/time, then not TEAE If stop date/time >= flortaucipir injection date/time, then TEAE
	Partial	Impute stop date as latest possible date (i.e. 59 if minutes unknown or 23:59 if hours and minutes unknown; last day of month if day unknown or 31st

AE ONSET DATE/TIME	AE STOP DATE/TIME	ACTION
		December if day and month unknown), then: If stop date/time < flortaucipir injection date/time, then not TEAE If stop date/time >= flortaucipir injection date/time, then TEAE
	Missing	Assumed TEAE

For the summarization of TEAEs by intensity, events recorded with missing intensity will be summarized as Severe.
For the summarization of TEAEs by seriousness, events recorded with missing seriousness will be summarized as Serious.
For the summarization of TEAEs by relationship to study drug or protocol procedure, events recorded with missing relationship will be summarized as Related.