STATISTICAL ANALYSIS PLAN

DATE OF PLAN:

09-June-2017

BASED ON:

^{18}F-AV-1451-A11 Protocol 13 July 2015, Amendment 1

STUDY DRUG:

^{18}F-AV-1451 ([F-18]T807)

PROTOCOL NUMBER:

^{18}F-AV-1451-A11

STUDY TITLE:

^{18}F-AV-1451 PET Imaging in Professional Fighters

SPONSOR:

Avid Radiopharmaceuticals
Philadelphia, Pennsylvania USA
215-298-0700

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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Table 1: List of Abbreviations

Abbreviation	Term
AD	Alzheimer's Disease
AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomic Therapeutic Chemical
bpm	Beats per minute
cm	centimeter
CTE	Chronic Traumatic Encephalopathy
ECG	Electrocardiogram
kg	Kilogram
max	maximum
MBq	Megabecquerels
mCi	Millicurie
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
mmHg	Millimeters of Mercury
MMSE	Mini Mental State Exam
MRI	Magnetic Resonance Imaging
MUBADA	Multi-Block Barycentric Discriminant Analysis
n	Number of subjects
PCS	Potentially Clinically Significant
PET	Positron Emission Tomography
PFBHS	Professional Fighters Brain Health Study
PT	Preferred Term
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
SUVr	Standard Uptake Value Ratio
TBI	Traumatic Brain Injury
TEAE	Treatment Emergent Adverse Event

1. INTRODUCTION

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease marked by widespread accumulation of hyperphosphorylated tau (p-tau), predominantly as neurofibrillary and astrocytic tangles. CTE has been found most often in professional athletes involved in contact sports (e.g. boxing, American football) who have been subjected to repetitive brain trauma, including mild traumatic brain injury (TBI) or even asymptomatic, subconcussive trauma.

The Professional Fighters Brain Health Study (PFBHS) being conducted at the Cleveland Clinic Lou Ruvo Center for Brain Health is a longitudinal study that focuses on a sample of active and retired professional fighters, and compares them with a control cohort matched for age and level of education. The primary objective of the PFBHS is to determine the relationship between measures of head trauma exposure and other potential modifiers and changes in brain imaging, neurological and behavioral function over time. In this context, the addition of an imaging biomarker that could identify the presence of underlying tau pathology might be useful in understanding the etiology and evolution of chronic traumatic encephalopathy (CTE), and could potentially identify cases at risk for subsequent neurodegeneration or other clinically important outcomes with implications for management of CTE and/or TBI cases.

Flortaucipir (^{18}F-AV-1451) 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 have been completed (e.g., Chien et al., 2013). Based on this rationale, the goal of this protocol is to perform flortaucipir PET imaging on active and retired professional fighters enrolled in the PFBHS protocol and explore its potential as a biomarker for CTE.

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

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objectives of this study are:

- To explore the use of flortaucipir as a biomarker for brain injury related to repetitive head trauma; and
- To examine the relationship between clinical presentation and tau deposition as measure by flortaucipir uptake in active and retired professional fighters.

2.2. Secondary Objective

The secondary objective of this study is to expand the flortaucipir and florbetapir safety databases.

3. STUDY DESIGN

3.1. Overview

This is a phase I study that will evaluate imaging characteristics of flortaucipir in active and retired professional fighters enrolled in the PFBHS.

Subjects enrolled in the PFBHS will be contacted to participate and must provide informed consent before starting any ^{18}F-AV-1451-A11 study procedures. In addition to consenting to study procedures, participants will consent to have Magnetic Resonance Imaging (MRI) images/data, including volumetric, functional and standard clinical sequences, and cognitive/behavioral data as part of the PFBHS made available to this study to allow for analysis and comparison. Screening assessments may take place over several days, within 90 days of the flortaucipir Positron Emission Tomography (PET) scan, and will include demographic information, cognitive testing and safety assessments. Subjects may be permitted to return for the flortaucipir PET scan after the 90 day window with sponsor approval if the investigator does not recognize any significant medical changes. If a volumetric MRI has not been performed as part of PFBHS within six months of the flortaucipir PET imaging visit, a volumetric MRI is to be performed as part of this study's screening assessments.

Subjects who qualify for the study will return to the clinic at a later date for the flortaucipir PET imaging visit. For the flortaucipir PET imaging visit, an intravenous catheter will be placed for IV administration of flortaucipir Injection. Subjects will receive a single IV bolus injection with a target dose of 370 MBq (10 mCi) of flortaucipir Injection followed by a saline flush. At approximately 75 minutes following injection, a continuous 30-minute brain scan will begin. Adverse events (AE) will be monitored continuously during the imaging session. A physician or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to injection and prior to discharge from the imaging center. If a designee performs this activity, a physician must be available to provide medical consultation.

All professional fighters > 50 years of age and other participants in whom, and in the opinion of the investigator, the clinical presentation suggests a possible diagnosis of AD will return to the clinic for a florbetapir PET imaging visit. The PET imaging visits must be performed no more than 60 days apart. For the florbetapir PET imaging visit, an intravenous catheter will be placed for IV administration of florbetapir. Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of florbetapir (Florbetapir Injection) followed by a saline flush. At approximately 50 minutes following injection, a continuous 10-minute brain scan will begin. AE will be monitored continuously during the imaging session. A physician, or physician designee, must evaluate the subject for AE prior to injection and prior to discharge from the imaging center.

A follow-up phone call to the subject, or informant where applicable, will be conducted between 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.

3.2. Sample Size Justification

No formal sample size calculation was performed. The study will stop enrolling subjects according to administrative consideration and decisions.

3.3. Patient Selection Criteria

Subjects who currently consented and enrolled in the PFBHS protocol, can tolerate PET scan procedures, and have the ablility to provide informed consent for study procedures will be provided opportunity to participate this study.

Refer to Protocol Section 5.3, Selection of Subjects, for the detail of inclusion/exclusion details.

4. STUDY DURATION AND VISIT SCHEDULE

The study participants will have a screening visit and two imaging visits. The details of these visits are shown below.

Table 2: Visit Schedule

Evaluations	Screening Assessments[a]	Flortaucipir Imaging Visit	End of Flortaucipir Imaging (prior to discharge)	Follow-up Phone Call[b]	Florbetapir Imaging Visit[c]	End of Florbetapir Imaging (prior to discharge)	Follow-up Phone Call[b]
Signed Informed Consent	X						
Demographics	X						
Medical History	X						
Concomitant Medications	X						
Vital Signs	X[d]	X[e, f]	X[g]		X[e]		
Clinical Lab Tests	X[h]						
ECG	X[i]						
MMSE, Beck Depression Inventory II, Digit span forward/backward	X						
MRI	X[j]						
PET Brain Scan		X[k, l]			X[m, n]		
Evaluation by a physician	X	X[o]	X[o]		X[p]	X[p]	
Adverse Events	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X

a. Screening may take place over several days. All assessments must be performed within 90 days prior to the ^{18}F-AV-1451 imaging session. Subjects may be permitted to return for the ^{18}F-AV-1451 PET scan after the 90 day window with sponsor approval if the investigator does not recognize any significant medical changes.
b. A follow-up phone call to the subject, or information where applicable, 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.
c. For all professional fighters $\geq$ 50 years of age and other participants in whom, and in the opinion of the investigator, the clinical presentation suggests a possible diagnosis of AD.
d. Screening vital signs include pulse rate, respiratory rate, supine blood pressure, height and weight.
e. Vital signs (pulse, respiratory rate, supine blood pressure) and weight will be taken prior to dose administration.
f. Vital signs (pulse, respiratory rate, supine blood pressure) will be taken within 5 minutes after completion of injection of dose administration.
g. Vital signs (pulse, respiratory rate, supine blood pressure) will be taken after completion of the PET scan prior to discharge.
h. Safety labs to include hematology, chemistry and urinalysis including plasma thiamine (vitamin B1) level.
i. ECG (with results reviewed prior to ^{18}F-AV-1451 administration).
j. If a volumetric MRI has not been performed as part of PFBHS within six monthsof the ^{18}F-AV-1451 PET imaging visit, a volumetric MRI is to be performed as part of this study's screening assessments.
k. Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of ^{18}F-AV-1451 Injection followed by a saline flush.
l. At approximately 75 minutes following ^{18}F-AV-1451 injection, a continuous 30-minute brain scan will begin.
m. Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of florbetapir followed by a saline flush.
n. At approximately 50 minutes following florbetapir injection, a continuous 10-minute brain scan will begin.
o. Or a licensed/credentialed medical professional (i.e. PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator. If a designee performs this activity, the physician must be available to provide medical consultation.
p. Or physician designee.

5. CLINICAL AND IMAGING ASSESSMENTS

5.1. Screening and Baseline Clinical Assessments

Subjects currently enrolled in the PFBHS protocol will be contacted to participate. Screening assessments may take place over several days, within 90 days of the flortaucipir PET scan, and will include:

- Informed Consent will take place before any ^{18}F-AV-1451-A11 study procedures;
- Demographics (birth year, gender, race, ethnicity, education, alcohol, drug use and smoking);
- Medical history and concomitant medications;
- Safety assessments: Vital signs (pulse rate, respiratory rate, supine blood pressure, height and weight), electrocardiogram (ECG) (with results reviewed prior to flortaucipir administration), and safety labs (hematology, chemistry and urinalysis) including plasma thiamine (vitamin B1) level;
- Mini-Mental State Examination (MMSE);
- Digit span forward and backward;
- Beck Depression Inventory II;
- If a volumetric MRI has not been performed as part of PFBHS within six months of the flortaucipir PET imaging visit, a volumetric MRI is to be performed as part of this study's screening assessments; and
- A physician will see the subject during the screening assessments.

5.2. Imaging Assessments

5.2.1. Flortaucipir PET Imaging Visit

Subjects who qualify for the study will return to the clinic at a later date for the flortaucipir PET imaging visit. For the flortaucipir PET imaging visit, an intravenous catheter will be placed for IV administration of flortaucipir Injection.

- A physician or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to administration of Flortaucipir Injection to determine if they are still suitable to undergo the scan. If a designee performs this activity, a physician must be available to provide medical consultation;
- Vital signs will be taken (pulse rate, respiratory rate, supine blood pressure) at the following time points:
    - Prior to administration of Flortaucipir Injection (weight will also be collected)
    - Within 5 minutes after completion of injection of Flortaucipir Injection
    - After completion of the PET scan prior to discharge;
- Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of flortaucipir Injection followed by a saline flush.
- At approximately 75 minutes following injection, a continuous 30-minute brain scan will begin;
- The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected;

- AEs will be continuously monitored during the flortaucipir PET imaging visit. Subjects who experience an AE will not be discharged from the imaging center until the event has resolved or stabilized;
- A physician or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge. If a designee performs this activity, a physician must be available to provide medical consultation; and
- A follow-up phone call to the subject, or informant where applicable, 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 AEs. If both of these days are not business days, the follow-up phone call can occur the following business day.

5.2.2. Florbetapir PET Imaging Visit

All professional fighters > 50 years of age and other participants in whom, and in the opinion of the investigator, the clinical presentation suggests a possible diagnosis of AD will return to the clinic for a florbetapir PET imaging visit. The PET imaging visits must be performed no more than 60 days apart.

- A physician, or physician designee, must see the subject prior to administration of Florbetapir Injection to determine if they are still suitable to undergo the scan;
- Vital signs will be taken (pulse rate, respiratory rate, supine blood pressure and weight) immediately prior to injection of florbetapir;
- Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of florbetapir followed by a saline flush;
- At approximately 50 minutes following injection, a continuous 10-minute brain scan will begin;
- AEs will be continuously monitored during the florbetapir PET imaging visit. Subjects who experience an AE will not be discharged from the imaging center until the event has resolved or stabilized;
- A physician, or physician designee, will see the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge; and
- A follow-up phone call to the subject, or informant where applicable, 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 AEs. If both of these days are not business days, the follow-up phone call can occur the following business day.

5.3. Post-Baseline Assessments

Besides the clinical assessments at screening visit and relative imaging assessments, there will be no post-baseline assessments in this study.

5.4. Final Evaluation or Premature Termination Visit

There will be only one clinical and imaging assessment visit in this study, and will not include any premature termination visit.

6. DEFINITIONS AND CONVENTIONS

6.1. Data 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.

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

6.2. General Summary Table and Individual Patient Data Listing Considerations

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 two digits per level (e.g., Table XX.YY.ZZ…). Tables will be presented starting with 14 and individual patient data listings are presented starting with 16.

6.3. Calculations Using Dates

The date of study drug (flortaucipir) administration in this study will be considered relative day 1, and the day before the 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: (Assessment Date – Exposure Date) + 1.
- For days before the first dose of study drug: Assessment Date – Exposure Date

6.4. Visit Windows Relative to the First Dose of Study Medication

No visit windowing will be performed for this study.

7. ANALYSIS POPULATIONS

7.1.1. Enrolled Population

All subjects who meet the inclusion/exclusion criteria and have consented to be enrolled in this study, and have baseline data captured in the eCRF database will consist of the enrolled population.

7.1.2. Safety Analysis Population

The safety analysis population will consist of all subjects who received at least one injection of flortaucipir or florbetapir.

7.1.3. Efficacy Analysis Population

This population includes all subjects in safety population for whom valid image data are available for the flortaucipir visit(s). All primary and exploratory analyses will be based on this population.

8. DISPOSITION AND WITHDRAWALS

The entire enrollment population will be represented in the disposition table. The disposition table be reported overall and broken down by enrolling diagnosis and include a summary of:

- Total number of enrolled patients
- Total number of patients in safety population
- Number and percentage of completed patients (defined as completing scan procedure and receiving follow-up safety phone call)
- Number and percentage of patients in efficacy population
- Number and percentage of discontinued patients

The disposition table will also include details on discontinuation reasons:

- Adverse Event
- Death
- Lost to Follow-up
- Other
- Physician Decision
- Protocol Violation
- Study Terminated by Sponsors
- Technical Problems
- Withdraw by Subject

Efficacy, completed and discontinued percentages will be based on the safety population. Percentages outlining discontinuation reasons will be based on the number of discontinued subjects. Discontinued reasons will be presented in a table by descending total frequency.

9. BASELINE PATIENT DATA

9.1. Baseline Demographics and Characteristics

Demographic data and other baseline characteristics will be presented for the flortaucipir safety analysis population in a table.

The most recent value prior to a subject's initial injection of flortaucipir will be considered the baseline value, and will be reported in the demographics table. The following data from the will be reported in the baseline and demographics table:

- Age (years)
- Gender
- Race
- Ethnicity
- Highest Level of Education
- Alcohol use
- Tobacco use
- Recreational Drug Use
- Height (cm)
- Weight (kg)
- MMSE
- Beck Depression Inventory II
- Digit span forward/backward

9.1.1. Missing Baseline Data

No imputation will be performed on missing baseline demographic data.

9.2. Medical and Surgical History

Medical and Surgical History information will be presented for the safety analysis population. Medical and Surgical History will be coded using MedDRA Version 17. Medical History findings are defined as those conditions which stop prior to or at Screening.

Medical and surgical history will be presented in a listing including:

- System Organ Class (SOC)
- Condition/Disease
- Start Date
- End Date
- Condition Still Present (Y/N)

Medical and Surgical History data will be presented by System Organ Class (SOC) and Preferred Term (PT), sorted in descending frequency.

9.3. Prior and Concomitant Medication

Medications will be presented for the safety analysis population and coded using WHODRUG V2014Q1 or higher. Preferred Anatomic Therapeutic Chemical (ATC) coding will be applied. Medications will be presented by ATC Level 1, ATC Level 4.

'Prior' medications are medications which started and stopped prior to the flortaucipir injection. 'Concomitant' medications are medications that started prior to, on or after the flortaucipir injection *and* ended on or after the date of the flortaucipir injection or were ongoing at the end of the study.

Prior and concomitant medications will be presented in a listing including:

- Preferred term
- Indication
- Total daily dose
- Dose unit
- Frequency
- Route
- Start date
- End date
- Ongoing (Y/N)
- Used for AE (Y/N)

For table summaries, the ATC Level 1s will be sorted by descending frequency of the total number of subjects with at least one medication. Within each ATC Level 1, the ATC Level 4s will be sorted by descending frequency of the total number of patients with at least one medication in each category.

9.3.1. Missing and Partially Missing Start and Stop Dates

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

9.4. Electrocardiogram & Routine Laboratory Data

A resting 12-lead ECG and clinical laboratory evaluations will be performed at screening.

Safety labs performed at screening will include hematology, chemistry and urinalysis including plasma thiamine (vitamin B1) level.

This ECG and laboratory data will be summarized in listing with the following information for the safety analysis population:

- Collected at Screening (Y/N)

- Collection Date
- Collection Time

9.5. MRI

If a volumetric MRI has not been performed as part of PFBHS within six months days of the flortaucipir PET imaging visit, a volumetric MRI is to be performed as part of this study's screening assessments.

MRI data will be summarized in a listing and table for the following regions (normalized to intracranial volume)

- Whole Brain Volume
- Total Gray Volume
- Hippocampal Volume
- Ventricle Volume

9.5.1. Missing and Partially Missing Start and Stop Dates

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

9.6. Baseline Vital Signs

Baseline vital signs will be presented in a listing, and will include:

- Pulse rate (bpm)
- Respiratory rate (breaths/minute)
- Supine blood pressure (mmHg)
- Height (cm)
- Weight (kg)

9.6.1. Imputation for Missing Scale Items

No imputation method will be used for missing baseline vital sign data.

10. EFFICACY ANALYSIS

10.1. Primary Efficacy Analysis

10.1.1. Efficacy Variable

The relationship of flortaucipir uptake will be evaluated both quantitatively (SUVr) and qualitatively using assessments from a visual read of the signals from images, classifying scans as 'No uptake', 'Mild uptake', 'Moderate uptake', and 'Intense uptake'.

The flortaucipir PET SUVr will be generated as an average SUVr across selected AAL defined regions and a weighted average (MUBADA) SUVr based on regions used in other studies to discriminate among AD and control groups.

Efficacy analyses will be conducted separately on these two sets of SUVr and the qualitative read.

10.1.2. Hypothesis Tests

There are no formal hypothesis testing planned for this study. All the statistical hypothesis testing described below are for exploratory purpose only.

10.1.2.1. Hypothesis #1: Difference in Quantitative Flortaucipir Uptake Between Cognitive Groups

The mean flortaucipir SUVr difference between cognitive statuses (cognitively impaired vs without cognitive or behavioural complaint) will be tested with the following hypothesis.

$$H_0 : \mu_{CI} = \mu_{CN}$$

$$H_A : \mu_{CI} \neq \mu_{CN} \ ,$$

Where:

- μ_{CI} is the mean flortaucipir SUVr in the cognitively impaired group
- μ_{CN} is the mean flortaucipir SUVr in the cognitive normal group

10.1.2.2. Hypothesis #2: Difference in Quantitative Flortaucipir Uptake Between Fighter Groups

The mean flortaucipir SUVr difference between fighting groups (active vs retired) will be tested with the following hypothesis.

$$H_0 : \mu_{Act} = \mu_{Ret}$$

$$H_A : \mu_{Act} \neq \mu_{Ret} \ ,$$

Where:

- μ_{Act} is the mean flortaucipir SUVr in the active fighters
- μ_{Ret} is the mean flortaucipir SUVr in retired fighters

10.1.2.3. Hypothesis #3: Association of Qualitative Flortaucipir Uptake and Cognition

The association of flortaucipir uptake ('No uptake', 'Mild uptake', 'Moderate uptake', 'Intense uptake') and cognitive status ('Cognitively Impaired', 'Cognitive Normal') will be tested with the following hypothesis.

H_0: Cognitive status and qualitative flortaucipir uptake are independent

H_A: Cognitive status and qualitative flortaucipir uptake are not independent

10.1.2.4. Hypothesis #4: Association of Qualitative Flortaucipir Uptake and Fighter Status

The association of flortaucipir uptake ('No uptake', 'Mild uptake', 'Moderate uptake', 'Intense uptake') and fighter status ('Retired', 'Active') will be tested with the following hypothesis.

H_0: Fighter status and qualitative flortaucipir uptake are independent

H_A: Fighter status and qualitative flortaucipir uptake are not independent

10.1.3. Primary Analysis

Descriptive statistics for flortaucipir SUVr will be reported overall and by each enrolment group. Box-and-whisker plots of flortaucipir SUVr will be created to visually display tau distribution across these groups.

Hypotheses 1 and 2 will be tested using a two-way ANOVA, with fighters status (active or retired) and cognitive status (impaired or normal) as two main factors. The comparisons of mean SUVr values will be compared through setting up proper contrasts.

The descriptive statistics and ANOVA analysis will be summarized in a table and include the following:

- n
- Mean (SD)
- Median
- Min, Max
- Overall P-value from ANOVA
- P-values from each contrast

Hypotheses 3 and 4 will be tested using Fisher's exact test. The distributions for each enrollment group will be presented in a 4x2 contingency table along with the p-values from each test.

10.1.3.1. Statistical Considerations in Primary Analysis

All hypothesis testing will be run at the 0.05 level of significance. Because this is a Phase I study, no correction for multiplicity will be applied to control for alpha.

10.1.4. Exploratory Analysis

A correlation analysis will be performed to investigate the relationship between flortaucipir SUVr and:

- MMSE
- Beck Depression Inventory II
- Digit span forward/backward
- MRI brain volumes (normalized to intracranial volume)
    - Whole brain volume
    - Gray volume
    - Hippocampal volume
    - Ventricle volume

Contingent on a trending significance in the primary analysis ($p \leq 0.1500$ for contrasts), more correlation analysis will be performed to investigate the relationship between tau deposition as measured by flortaucipir SUVr and:

- Years of fighting
- Age when fighting began
- Number of bouts
- Number of losses
- Number of wins
- Number of draws
- Number of knockouts

A multivariate model may also be derived assuming strong relationships found in the primary and correlation analyses.

10.1.4.1. Subgroup Analysis

All correlation analysis conducted will be performed for each cognitive group separately, and results will be provided in a table.

11. SAFETY AND TOLERABILITY

The safety analysis population will be used for all safety outcomes. There will be no statistical comparisons performed among the safety data.

All safety analysis will be conducted separately for flortaucipir and florbetapir injections.

11.1. Exposure to Study Drugs

Exposure to study medication will be presented for the safety analysis population. All exposure data will be presented in listings by visit to include:

- Injection site (Left Arm, Left Hand, Right Arm, Right Hand, Unknown)
- Net activity administered (MBq)
- Date and time of the Injection
- Saline flush administered (Y/N)

The actual dose (MBq) of flortaucipir and florbetapir received will be summarized by enrolling diagnosis using descriptive statistics (n, mean, SD, median, min, and max) in a table.

11.1.1. Unit Conversion and Volume Calculation

All exposure tables and listings will display volume in MBq. Volume collected in mCi will be converted to MBq as follows:

- $MBq = 37 \times mCi$

11.2. 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.

Treatment-emergent adverse events (TEAE) are any untoward medical occurrence 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 or florbetapir, and thus be reported as AEs, if they occur within 48 hours after administration of the respective PET tracer. AE that occur after the administration of study drug but outside the 48 hour reporting window will not be reported unless the investigator believes they are attributable to the drug.

The end of study for the purpose of AE reporting is defined as 48 hours after the administration of flortaucipir injection or florbetapir injection (whichever occurs last).

11.2.1. All AEs

A summary of all AEs will be reported in a listing including:

- SOC
- PT
- Start Date/time

- End Date/time
- Severity
- Relationship to Medication (Y/N)
- Relationship to Study Procedure (Y/N)
- Seriousness (Y/N)
- Lead to Death (Y/N)

11.2.2. All TEAEs

A summary of TEAEs will be reported in the tables including:

- Number of all TEAE
- Number of patients with at least one TEAE

The summary of TEAEs will be broken down further in descending frequency by SOC and PT. A subject will be counted once if the subject reported one or more events in a given level of summarization.

11.2.3. Severity

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

TEAE severity will be reported in a table in the same manner as outlined in 11.2.2.

11.2.4. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as related or unrelated to study medication. TEAEs with a missing relationship to study medication will be regarded as related to study medication. If a patient reports the same AE more than once within that SOC/PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

TEAE relationship to medication will be reported in a table in the same manner as outlined in 11.2.2.

11.2.5. Relationship to Study Procedure

Relationship, as indicated by the Investigator, is classed as related or unrelated to protocol procedure. TEAEs with a missing relationship to study procedure will be regarded as related to study procedure. If a patient reports the same AE more than once within that SOC/PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

TEAE relationship to medication will be reported in a table in the same manner as outlined in 11.2.2.

11.2.6. Serious Adverse Events

Serious TEAEs will be summarized in a similar manner as described in Section 11.2.2. If a patient reported more than one serious TEAE with the same SOC or PT, the TEAE will be counted only once in that SOC or PT.

11.2.7. Adverse Events Leading to Death

TEAEs leading to death will be summarized in a similar manner as described in Section 11.2.2.

11.2.8. Missing and Partial AE Onset Dates

See appendix 1.2 for specific algorithms to impute missing start and stop dates

11.3. Vital Signs

The following Vital Signs measurements will be reported for this study:

- Supine Systolic Blood Pressure (mmHg)
- Supine Diastolic Blood Pressure (mmHg)
- Supine Pulse Rate (bpm)
- Respiratory Rate (breaths/min)

Vital signs data will be summarized at screening, and [when applicable] at each imaging visit prior to the administration of injection (florbetapir or flortaucipir), within 5 minutes after completion of injection, and at the completion of the imaging visit prior to discharge. Changes from baseline (prior to injection) to each follow-up will be calculated. All vital sign data will be summarized by enrolling diagnosis in a table, and listing for the Safety population.

11.4. Potentially Clinically Significant Results

Changes from baseline to all follow-ups in vital signs will be monitored for potentially clinically significance (PCS). Below are the criteria for PCS vital sign results.

Table 3: Potentially Clinically Significant Criteria

Parameter		Potentially Clinically Significant Criteria	
Vital Sign		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	

12. INTERIM ANALYSES

There is no interim analysis planned for this study.

APPENDIX I: ALGORITHMS TO HANDLE MISSING AND PARTIAL DATES

1.1. MISSING AND PARTIAL CONCOMITANT AND OTHER MEDICATION START AND STOP DATES

CONMED START DATE	CONMED STOP DATE	ACTION
Known	Known	If stop date < study med date, assign as prior If stop date ≥ study med date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med date, assign as prior If stop date ≥ study med date and start date, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med date, assign as prior If stop date ≥ study med date and start date, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med date, assign as prior If stop date ≥ study med date and start date, assign as concomitant
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication
Missing	Known	If stop date < study med start date, assign as prior If stop date ≥ study med start date, assign as concomitant

CONMED START DATE	CONMED STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med date, assign as prior If stop date ≥ study med date, assign as concomitant
	Missing	Assign as concomitant

1.2. 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:

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 (or florbetapir) injection date/time, then not TEAE If stop date/time >= flortaucipir (or florbetapir) 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 (or florbetapir) injection date/time, then not TEAE If stop date/time >= flortaucipir (or florbetapir) injection date/time, then TEAE

AE ONSET DATE/TIME	AE STOP DATE/TIME	ACTION
	Missing	Assumed TEAE
Missing	Known	If stop date/time < flortaucipir (or florbetapir) injection date/time, then not TEAE If stop date/time >= flortaucipir (or florbetapir) 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 (or florbetapir) injection date/time, then not TEAE If stop date/time >= flortaucipir (or florbetapir) 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.

APPENDIX II: SAS CODE TEMPLATE FOR ANALYSIS

1.1. SAMPLE CODE FOR EFFICACY ANALYSIS

1.1.1. DESCRIPTIVE STATISTICS

```
PROC MEANS data = <data>; class COGGRP;
output out= summ n=n_ mean=mean std=std median=median min=min max=max;
RUN;
QUIT;

PROC MEANS data = <data>; class FIGHTGRP;
output out= summ n=n_ mean=mean std=std median=median min=min max=max;
RUN;
QUIT;
```

1.1.2. HYPOTHESIS #1 AND #2

```
ods output contrasts=contrasts;
PROC GLM data = <data>;
class FIGHTGRP COGGRP;
model SUVR = FIGHTGRP COGGRP FIGHTGRP*COGGRP;
contrast "Active vs. Retired"     FIGHTGRP 1 -1;
contrast "CI vs. CN"              COGGRP   1 -1;
RUN;
QUIT;
```

1.1.3. HYPOTHESIS #3

```
PROC FREQ data = <data>;
table VISREAD*COGGRP /  fisher;
RUN;
```

1.1.4. HYPOTHESIS #4

```
PROC FREQ data = <data>;
table VISREAD*FIGHTGRP /  fisher;
RUN;
```

1.2. SAMPLE CODE FOR EXPLORATORY ENDPOINT

```
ods output PearsonCorr=corr;
PROC CORR data = <data> pearsons;
var <variable list>;
RUN;
```

1.3. SAMPLE CODE FOR TEAE TABLES BY DESCENDING FREQUENCY

```
ods output crosstabfreqs=xtab;
PROC FREQ data = <data> order=freq;
table <SOC variable>*<Preferred Term variable>;
RUN;
```