18F-AV-1451-A18 SAP v1.0

An Open Label, Multicenter Study Evaluating the Imaging Characteristics of a Follow up 18F-AV-1451 Scan in Subjects That Participated in the Confirmatory Cohort of 18F-AV-1451-A05

NCT02795780

Approval date: 11 Jan 2018

STATISTICAL ANALYSIS PLAN

DATE OF PLAN:

11 January 2018

BASED ON:

^{18}F-AV-1451-A18 Protocol, 22 March 2016

STUDY DRUG:

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

PROTOCOL NUMBER:

^{18}F-AV-1451-A18

STUDY TITLE:

An open label, multicenter study evaluating the imaging characteristics of a follow up ^{18}F-AV-1451 scan in subjects that participated in the confirmatory cohort of ^{18}F-AV-1451-A05

SPONSOR:

Avid Radiopharmaceuticals
Philadelphia, Pennsylvania USA
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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
ADAS-Cog11	Alzheimer's Disease Assessment Scale Cog-11
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomic Therapeutic Chemical
bpm	Beats per minute
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CFB	Change from Baseline
cm	centimeter
ECG	Electrocardiogram
kg	Kilogram
max	maximum
MBq	Megabecquerels
MCI	Mild Cognitive Impairment
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
PT	Preferred Term
ρ	Pearson's Correlation Coefficient
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class

SUVr	Standard Uptake Value Ratio
TEAE	Treatment Emergent Adverse Event

1. INTRODUCTION

Flortaucipir has been developed as a positron emitting radiopharmaceutical for in vivo imaging of tau protein aggregates (Xia et al., 2013). Autoradiography results using tissue sections from human brains showed a strong signal in the grey matter of cortical slices from tau positive brains but weak or no binding in tau negative, Aβ positive, or tau and Aβ negative tissue.

The overarching goal of this protocol is to further investigate the spectrum of PET imaging results with flortaucipir in patients with cognitive decline. To accomplish this goal, the protocol will investigate longitudinal flortaucipir results in patients with cognitive complaints ranging from mild cognitive impairment (MCI) to mild and moderate Alzheimer's disease (AD).

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

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objectives of this protocol is to assess longitudinal change of tau deposition as measured by flortaucipir over time.

3. STUDY DESIGN

3.1. Study Design

This is a phase 2 study, open label, multicenter study in subjects that participated in the confirmatory cohort of ^{18}F-AV-1451-A05 evaluating longitudinal change of tau uptake as measured by flortaucipir Standard Uptake Value Ratio (SUVr). As subjects from the 18F-AV-1451-A05 confirmatory cohort complete the 18F-AV-1451-A05 study, they will be presented with the opportunity to participate in this longitudinal study.

All subjects will provide informed consent before starting any study procedures.

3.2. Study Treatments and Assessments

3.2.1. Trial Flow Chart

Evaluations	Screening Visit	MRI Visit	Flortaucipir Imaging Visit	Follow-Up Phone Call
Updated Medical History	X		X	
Updated Concomitant Meds	X		X	
ECG	X			
Vital Signs			X	
Safety Labs[a]	X			
Urine Pregnancy Test			X	
MRI of the Brain		X		
PET Brain Scan			X	
Follow-up Phone Call				X
Evaluation by Physician/Designee	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 ^{18}F-AV-1451 Injection at Imaging Visit

3.3. Randomization and Blinding

This is an open label, non-randomized study. All subjects who qualify for the study and sign informed consent will receive a single IV bolus of flortaucipir.

3.4. Sample Size Justification

This study is estimated to enroll about 100 subjects from A05 confirmatory arm. Current analyses with A05 exploratory arm data showed that for subjects met A05 confirmatory arm enrollment criteria (MCI or demented, Mini Mental State Exam (MMSE) between 20 and 27), flortaucipir SUVr on average changed 0.0527 (SD=0.0970) for amyloid positive subjects at 9 months follow up. Assume a similar amyloid positivity to A05 exploratory arm (~60%), and assume the change of flortaucipir SUVR is linear, this study is expected to have approximately 60 amyloid positive subjects and the mean change of flortaucipir SUVR is expected to be 0.105, with a 95% confidence interval (0.0635, 0.1473).

3.5. Subject Selection Criteria

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

4. CLINICAL AND IMAGING ASSESSMENTS

4.1. Screening and Baseline Clinical Assessments

Screening assessments should take place at the time of the subject's final ^{18}F-AV-1451-A05 study visit. All screening assessments should be performed within 30 days of the initial flortaucipir PET imaging session.

Screening assessments will include:

- Informed consent;
- Blood and urine samples will be collected for safety labs (may be collected any time prior to flortaucipir injection)
- Electrocardiogram (ECG);
- Updated medical history and concomitant medications.

4.2. MRI Visit

MRI should be acquired after subject consent is obtained, prior to the time of Flortaucipir Imaging Visit.

- MRI imaging including standard clinical sequences and volumetric MRI.

4.3. Flortaucipir PET Imaging Visit

It is preferable that the Flortaucipir PET imaging visit is performed within 30 days of the subject's final ^{18}F-AV-1451-A05 study visit, but no later than 3 months from the final ^{18}F-AV-1451-A05 study visit.

Flortaucipir PET 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 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;
- For women of childbearing potential, a negative urine pregnancy test must be obtained;
- Vital signs will be taken at the following time points:
    - immediately prior to administration of flortaucipir injection
    - after completion of the PET scan, prior to discharge;
- Subjects will receive a single IV bolus injection of approximately 370 MBq (10 mCi) +10% of flortaucipir injection followed by a saline flush. At approximately 80 minutes post dose, a continuous 20-minute brain scan (4 acquisitions of 5 minute duration) will be obtained.;
- The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected;

- The subject will be requested to void after completion of the PET scan;
- Adverse events will be continuously monitored during the Flortaucipir Imaging Visit; Subjects who experience an adverse event 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.

4.3.1. Safety Follow-up/Phone Call

Each study subject (or caregiver/informant if applicable) will be contacted 2 or 3 business days after flortaucipir administration, but not prior to 48 hours post-injection, to collect any new adverse events. End of study for the purpose of adverse event reporting and study participation is defined as 48 hours after flortaucipir administration.

5. CHANGES FROM PROTOCOL

The following changes from the protocol are reflected in this SAP.

- With continued development and accumulated knowledge, Multi-Block Barycentric Discriminant Analysis (MUBADA) SUVr instead of Combination ROI, will be used as the global measurement of tau deposition.

6. DEFINITIONS AND CONVENTIONS

6.1. Data Conventions

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

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

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

6.2. Definitions of Baseline and Follow-up

Baseline characteristics and demographics will be gathered from the AV-1451-A05 datasets for confirmatory cohort subjects who participated in AV-1451-A18. All other baseline data (i.e. electrocardiogram, and safety labs) will be reported from data collected from the AV-1451-A18 CRFs.

Efficacy analysis evaluating longitudinal change will require the use of the Baseline flortaucipir SUVr quantitation, and Baseline and 18 Month MMSE from the AV-1451-A05 datasets to calculate change.

Safety analysis involving change from baseline (CFB) calculations for vital signs will consider AV-45-A18 *Prior to Injection* values as baseline and *Prior to Discharge* as follow-up.

7. ANALYSIS POPULATIONS

7.1.1. Enrolled Population

Subjects who participated in the 18F-AV-1451-A05 confirmatory cohort, meet the inclusion/exclusion criteria of 18F-AV-1451-A18, have consented to be enrolled in this study, and have baseline data captured in the AV-1451-A05 eCRF database will consist of the enrolled population.

7.1.2. Safety Analysis Population

The safety analysis population will consist of all enrolled subjects who received at least one injection of flortaucipir under the AV-1451-A18 protocol.

7.1.3. Efficacy Analysis Population

This population includes all subjects in safety population for whom valid image data are available for the AV-45-A18 flortaucipir scan. All primary analyses will be based on this population.

8. DISPOSITION AND WITHDRAWALS

The entire screened population will be represented in the disposition table. The disposition table be broken down by diagnosis groups and include a summary of:

- Total number of enrolled subjects
- Total number of subjects in the safety population
- Number of subjects in the efficacy population
- Number of Completed Subjects
- Number of Discontinued Subjects

The disposition table will also include details on discontinuation reasons:

- Protocol Violation
- Adverse Event
- Physician Decision
- Pregnancy
- Study Terminated by Sponsor
- Lost to Follow-up
- Technical Problems
- Withdrawal by Subject
- Death
- Other

Termination Status (i.e. 'Completed' and 'Discontinued') percentages will be based on the safety population. Percentages outlining discontinuation reasons will be based on the number of discontinued subjects.

Subject disposition will be presented in a listing with the following information.

- Date of Consent
- Date Subject Ended Study
- Did Subject Complete Study? (Yes/No); Reason for Discontinuation, if No

9. BASELINE ANALYSIS

All baseline data will be summarized by diagnosis groups for the Safety Analysis Population.

9.1. Baseline Characteristics and Demographics

All baseline data will be gathered from the AV-1451-A05 datasets for confirmatory cohort subjects who participated in AV-1451-A18.

The following data will be reported in the baseline characteristics and demographics table by diagnosis groups using descriptive statistics, and presented in a listing:

- Age (years)
- Gender
- Race
    - Sub-race (if Asian): Japanese; Other
- Ethnicity
- Highest Level of Education
- Alcohol History
- Smoking History
- Recreational Drug History
- MMSE
- Clinical Dementia Rating-Sum of Boxes (CDR-SB)
- Flortaucipir SUVr (MUBADA)
- Tau status according to visual interpretation (majority reading results from 5 independent readers)
- Florbetapir SUVr

9.1.1. Missing Baseline Data

No imputation will be performed on missing baseline demographic data.

9.2. Electrocardiogram

ECG data will be presented in a listing including the following information

- Was an ECG Collected at Screening? (Yes/No); Explanation, if No
- Collection Date/time

9.3. Safety Labs

Safety Lab data will be presented in a listing including the following information

- Were Clinical Labs Collected? (Yes/No); Explanation, if No
- Collection Date

10. MRI DATA ANALYSIS

MRI volumes will be normalized to the intracranial volume, and summarized in a table by diagnosis groups at each visit and CFB using descriptive statistics for the following brain regions.

- Total Brain Volume (excluding ventricle)
- Left Hippocampal Volume
- Right Hippocampal Volume
- Ventricle Volume

The MRI volumes will be presented in a listing with the following.

- Was MRI Performed? (Yes/No)
- Date of Screening MRI
- Was SWI MRI Sequence Collected? (Yes/No)

11. MEDICAL AND SURGICAL HISTORY

Medical and Surgical History will be coded using MedDRA Version 20.0. Medical and surgical history will be presented in a listing including:

- Subject has Medical/Surgical History? (Yes/No)
- System Organ Class (SOC)
- Condition/Disease
- Start Date
- End Date
- Condition Still Present (Yes/No)

12. CONCOMITANT MEDICATION

Medications will be coded using the WHO-Drug Classic December 2016 dictionary.

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. This will include any medication continuing from the AV-1451-A05 study.

Medications will be presented in a listing including:

- Medication Name/ Preferred term
- Indication
- Dose
- Dose unit
- Frequency
- Route
- Start date
- End date
- Ongoing (Yes/No)
- Used for Adverse Event? (AE)

12.1.1. Missing and Partially Missing Start and Stop Dates

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

13. FLORTAUCIPIR IMAGING DATA

All flortaucipir imaging data will be summarized by diagnosis groups for the Safety Analysis Population.

13.1. Pregnancy Test

Pregnancy testing information will be presented in a listing including:

- Was a Pregnancy Test Performed? (Yes/No/ N/A)
- Date of Collections
- Result

13.2. PET Scan

The PET scan data will be presented in a listing including:

- Date of PET Imaging
- Scan Emission Start/Stop Time
- Were There Any Deviations From the Standard PET Imaging Protocol? (Yes/No); Explanation, if Yes
- Did the Subject Complete the Protocol-required Imaging Session? (Yes/No); Explanation, if No

14. EFFICACY ANALYSIS

All efficacy analysis will be conducted using the Efficacy Analysis Population.

14.1. Efficacy Variable

Flortaucipir uptake CFB as measured by MUBADA SUVr will be the primary variable of interest. MUBADA CFB will be calculated as the difference between SUVr values from AV-1451-A05 Baseline to the Flortaucipir Imaging Visit under the AV-1451-A18 protocol.

MUBADA and all sub-regional SUVr will be presented in a listing.

14.2. Primary Analysis

14.2.1. Longitudinal Analysis

The flortaucipir image data will be analyzed longitudinally for MUBADA SUVr.

The difference in MUBADA SUVr CFB between diagnosis groups will be tested using the following hypothesis:

$$H_0 : LSM\Delta_{AD} = LSM\Delta_{MCI}$$

$$H_A : LSM\Delta_{AD} \neq LSM\Delta_{MCI}$$

The difference in MUBADA SUVr CFB between Amyloid statuses will be tested using the following hypothesis:

$$H_0 : LSM\Delta_{A\beta+} = LSM\Delta_{A\beta-}$$

$$H_A : LSM\Delta_{A\beta+} \neq LSM\Delta_{A\beta-},$$

where $LSM\Delta_*$ is the respective diagnosis or Amyloid group's LS mean change at the follow-up flortaucipir imaging visit.

An analysis of covariance (ANCOVA) model adjusted for baseline SUVr and age, including the interaction term of diagnosis group and Amyloid status. The appropriate contrasts will be set up to test both longitudinal hypotheses as well as look at the differences between amyloid statuses within each diagnosis group.

A separate table summarizing MUBADA SUVr, and the MUBADA SUVr CFB will be created for each hypothesis, including:

- Descriptive statistics by each group
- LS Mean Changes (SE) by group
- Differences between LS Mean Changes (SE) from contrasts
- 95% Confidence Interval around differences between LS Mean Changes
- P-value from respective contrast

14.2.2. Correlation Analysis

A correlation analysis will be performed to investigate the relationship between MUBADA SUVr CFB and cognitive function CFB as measured by MMSE and CDR-SB. Partial's correlation coefficient (ρ) adjusted for age, baseline MUBADA SUVr, and baseline cognitive score will be calculated to assess the association between changes in cognitive function and tau uptake.

Scatter plots will be generated for MMSE change and SUVr change by Amyloid Beta status. Each plot will include:

- Regression line with ρ
- p-value testing the hypothesis $\rho = 0$

14.2.3. Statistical Considerations in Primary Analysis

All hypothesis testing will be run at a two-sided 0.05 level of significance. No correction for multiplicity will be applied to control for alpha.

ANCOVA models will be run separately for each amyloid status if the assumption of independent identically distributed normal variance is not met by a practical margin. Variances between groups separated by a factor of at least 2 will facilitate the need to run separate models.

15. SAFETY AND TOLERABILITY ANALYSIS

The safety analysis population will be used for all safety outcomes. There will be no statistical comparisons between diagnosis or amyloid groups performed among the safety data.

15.1. Exposure to Flortaucipir

The net activity of flortaucipir injected (MBq) will be summarized using descriptive statistics in a table.

All exposure data will be presented in listings by visit to include:

- Date and time of the Injection
- Injection site
- Lot Number
- Total Dose Administered (mCi and MBq)
- Saline Flush Administered? (Yes/No)

15.1.1. Unit Conversion and Volume Calculation

Volume collected in mCi will be converted to MBq as follows:

- $MBq = 37 \times mCi$

15.2. 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, and thus be reported as AEs, if they occur within 48 hours after administration of the 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.

15.2.1. All AEs

All AEs will be coded using MedDRA Version 20.0. A summary of all AEs will be reported in a listing including:

- SOC
- PT
- Start Date/time
- End Date/time

- Severity
- Relationship to Flortaucipir (Yes/No)
- Relationship to Study Procedure (Yes/No)
- Serious? (Yes/No)
- Action Taken
- Event Resolution
- Lead to Death (Yes/No)

15.2.2. All TEAEs

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

- Number of all TEAE
- 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.

15.2.3. Severity

Severity is classed as mild/moderate/severe (increasing severity). TEAEs with a missing severity will be classified as severe. If a subject 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 15.2.2.

15.2.4. Relationship to Flortaucipir

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

TEAE relationship to flortaucipir will be reported in a table in the same manner as outlined in 15.2.2.

15.2.5. 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 subject reports the same AE more than once within that SOC/PT, the AE with the worst case relationship to study procedure will be used in the corresponding relationship summaries.

TEAE relationship to study procedure will be reported in a table in the same manner as outlined in 15.2.2.

15.2.6. Serious Adverse Events

Serious TEAEs will be summarized in a similar manner as described in Section 15.2.2. 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.

15.2.7. Adverse Events Leading to Death

TEAEs leading to death will be summarized in a similar manner as described in Section 15.2.2.

15.2.8. Missing and Partial AE Onset Dates

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

15.3. Vital Signs

The following vital signs are collected at two time points – *Immediately Prior to (within 5 minutes) Flortaucipir Injection* and *Prior to Discharge* - during the Flortaucipir Imaging Visit. *Immediately Prior to Injection* will be considered the baseline value for all vital sign change calculations

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

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

Vital signs and changes (where applicable) will be presented in a listing along with the following information.

- Time point
- Were Vital Signs Collected
- Collection Date/time

15.3.1. Potentially Clinically Significant Vital Sign Changes

Vital sign at visit and CFB will be monitored for potentially clinically significance (PCS). Below are the PCS criteria.

Table 2: 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	

15.4. Follow-up Telephone Contact Data

The follow-up safety data will be presented in a listing and include:

- Was Contact Made? (Yes/No); Explanation, if No
- Date/time of Follow-up Assessment
- Any AE Reported? (Yes/No)

16. 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 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

AE ONSET DATE/TIME	AE STOP DATE/TIME	ACTION
	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 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