18F-AV-1451-PX01 Protocol v1.0

Evaluation of the relationship between baseline flortaucipir PET signal and cognitive change in subjects with early Alzheimer's disease participating in the I8D-MC-AZES Protocol Addendum D5010C00009 (2.1) (Tau Imaging)

NCT03901105

Approval date: 12 Mar 2019

Protocol Number:

^{18}F-AV-1451-PX01

Evaluation of the relationship between baseline flortaucipir PET signal and cognitive change in subjects with early Alzheimer's disease participating in the I8D-MC-AZES Protocol Addendum D5010C00009 (2.1) (Tau Imaging)

Date and Version:

12MAR2019

Final Protocol v1.0

Name of Compound: Flortaucipir F 18 (^{18}F-AV-1451)

Sponsor:

Avid Radiopharmaceuticals, Inc.

Philadelphia, Pennsylvania USA

TABLE OF CONTENTS

1. RATIONALE/INTRODUCTION

Study PX01 is designed to further evaluate the relationship between flortaucipir uptake as measured by Positron emission tomography (PET) at baseline and the subsequent rate of cognitive decline due to Alzheimer's disease (AD) observed over an 18-month longitudinal follow up by utilizing a therapeutic trial cohort that had flortaucipir PET scans and up to 2 years of cognitive follow-up. The subjects whose scans will be read in study PX01 were recruited to a PET substudy of the I8D-MC-AZES (AZES) therapeutic clinical trial evaluating the BACE (Beta-site amyloid precursor protein-cleaving enzyme 1) inhibitor AZD3293 (LY3314814), also known as lanabecestat, for the treatment of patients with early AD. The AZES study was terminated early after an independent assessment concluded that the trial was not likely to meet the primary endpoint upon completion and therefore, the trial was stopped for futility.

The subjects enrolled in the PET substudy of AZES had flortaucipir PET scans at baseline and at multiple follow-up timepoints. At the time the study was terminated/completed, 205 subjects with a baseline flortaucipir PET scan had completed 18 month cognitive follow-up evaluations. These subjects will be used as the primary efficacy population for study PX01. Although a subset of these subjects (approximately 90 subjects) completed the 24 month follow-up visit, the 24 month change from baseline data were reserved for exploratory analyses, with 18 months primary endpoints used for direct comparison to the A05 Confirmatory Cohort (A05C) Phase 3 study results.

In the present study, readers will visually interpret each baseline flortaucipir PET scan to identify patterns of tracer uptake that predict risk of clinically meaningful deterioration as determined by Clinical Dementia Rating Scale Sum of Box (CDR-SB) value change (1 point or more increase) within 18 months. The approach used is similar to study A05C, which was a confirmatory study for longitudinal progression in subjects with cognitive impairment who had Mild Cognitive Impairment (MCI) or dementia with a suspected neurodegenerative cause and a Mini Mental State Examination (MMSE) score of 20-27 inclusive.

2. STUDY OBJECTIVES

2.1. Primary Objectives

- To assess whether a visual interpretation (τAD++ vs. non τAD++ pattern) of the baseline flortaucipir PET scan can predict the risk of subjects' clinically meaningful cognitive and functional deterioration within 18 months of scan, as measured by the Clinical Dementia Rating Scale Sum of Box (CDR-SB) change from baseline.

2.2. Secondary Objectives

- To assess whether a visual interpretation (τAD++ vs. non τAD++ pattern) of the baseline flortaucipir PET scan can predict the risk of subjects' clinically meaningful cognitive and functional deterioration within 18 months of scan, as measured by Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog11), Pfeffer Functional Activities Questionnaire (FAQ), and CDR Global change from baseline.

- To assess the relationship between visual interpretation (τAD++ vs. non τAD++ pattern) of the baseline flortaucipir PET scan and magnitude of cognitive and functional deterioration within 18 months of scan, as measured by the mean change from baseline of CDR-SB, MMSE, ADAS-Cog11, and FAQ.

- To assess inter-reader reliability of the flortaucipir F 18 PET scan visual interpretation by 5 independent, blinded readers.

2.3. Exploratory Objectives

- To assess whether a visual interpretation (τAD++ vs. non τAD++ pattern) of the baseline flortaucipir PET scan can predict the risk of subjects' clinically meaningful cognitive and functional deterioration within 24 months of scan, as measured by the Clinical Dementia Rating Scale (CDR), MMSE, ADAS-Cog11 and FAQ change from baseline.

- To assess the diagnostic performance of baseline flortaucipir F 18 PET scan in predicting clinically meaningful deterioration at 18 months

3. STUDY DESIGN

All training and reads will be conducted in accordance with the image review charter (IRC). Five imaging physicians will be trained in-person on the flortaucipir F 18 PET scan read methodology using the previously established visual read method (identical to that used for the ^{18}F-AV-1451-A05C Study).

The training will consist of teaching the readers the steps of interpretation, followed by a practice session using a set of demonstration and practice cases. After the training phase is complete, each reader will independently read 205 flortaucipir F18 PET baseline scans from the Study I8D-MC-AZES "A 24-Month, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, Safety, Tolerability, Biomarker, and Pharmacokinetic Study of AZD3293 in Early Alzheimer's Disease (the AMARANTH study)" in a random sequence. For the flortaucipir PET imaging, a 30 minute PET acquisition was conducted approximately 75 min following an i.v. administration of approximately 240 MBq flortaucipir F 18 which is comparable to a 20 minute acquisition conducted approximately 80 minutes following an i.v. administration of approximately 370 MBq flortaucipir F 18 as obtained in studies A16 and A05C.

The study population for study AZES consisted of subjects aged 55 to 85 years with MCI due to AD or probable AD by NIA-Alzheimer's Association criteria (Albert 2011), with MMSE of 20 to 30 inclusive, a CDR global score of 0.5 (MCI), or 0.5 or 1 (AD) with a memory box score ≥ 0.5, and a score of ≤85 on the Delayed Memory Index of the Repeatable Battery for the Assessment of Neuropsychological Status. All subjects were amyloid positive by florbetapir PET or lumbar puncture. Qualified subjects were randomized to receive either 0 (placebo), 20, or 50 mg lanabecestat daily for a planned duration of 2 years. The primary objective of the study was to evaluate the efficacy of AZD3293 on cognitive and functional outcomes in patients with early AD as measured by the CDR-SB. Subjects returned for periodic follow-up visits up to 24 months post baseline, where change from baseline performance was assessed on cognitive and functional scales including the core scales used in other flortaucipir studies (CDR, MMSE, FAQ and ADAS). The study also included a longitudinal sub-study of flortaucipir F 18 PET. Patients who underwent florbetapir F 18 PET scanning at screening in the main AZES study to document the presence of amyloid for the study inclusion and participated in the amyloid PET sub-study were planned to also have a flortaucipir F 18 PET scan performed at baseline, Week 52, and Week 104 at participating sites. 205 subjects completed baseline flortaucipir F 18 PET scans and completed CDR-SB at 18 months, while approximately 90 subjects completed CDR-SB at 24 months. Only the baseline flortaucipir F 18 PET scan is being read in the present study.

4. PROCEDURES AND METHODS

4.1. Selection and Number of Investigators (Readers)

Five qualified physicians will be used to perform the blinded reads. Readers will be selected using the following criteria:

- Board Certified in Radiology or Nuclear Medicine
- Experience interpreting PET scans

4.2. Selection/number of Images:

A total of 205 unique scans will be read for this study in a random sequence. Scans are from a subset of AZES patients who received a baseline flortaucipir F 18 PET scan in a substudy and completed the 18 month AZES CDR assessment.

4.3. Blinded Read Method:

Readers will be blinded to all demographic and clinical data.

All readers will be trained in-person on the steps of image interpretation, using a set of demonstration and practice cases, prior to starting their independent reads. A copy of the training materials will be provided to each reader for reference. The read methodology is briefly outlined below:

After scaling images to the cerebellar reference region and selecting an appropriate color scale, regions of the neocortex (the posterolateral temporal (PLT), occipital, parietal and frontal regions) are evaluated for increased tracer uptake, and scans are interpreted as either not consistent (τAD-), consistent with an AD pattern (τAD+), or consistent with an AD pattern and likely to progress (τAD++) using the criteria shown in Table 1.

Table 1 Clinical Read Method Criteria

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

4.4. Data Collection

Flortaucipir scan read data will be collected using electronic case report forms (eCRFs) designed for this study. All other data including the demographic/baseline characteristics and all cognitive/functional assessments, for subjects included in Study PX01, will be from the locked database of Study AZES. The locked AZES database was accessed by permission of the study sponsor, Eli Lilly and Company.

4.5. Good Clinical Practice and Monitoring

All clinical studies performed under the direction of Avid/CRO will be conducted in accordance with applicable regulatory requirements and International Conference on Harmonization (ICH), Good Clinical Practice (GCP) and Avid/CRO Standard Operating Procedures.

Monitoring of study data will be performed by the Imaging CRO and be performed in accordance with their SOPs.

5. STATISTICAL METHODS

5.1. General Statistical Considerations

All statistical analyses will be performed using SAS® version 9.0 or higher. The specific analyses to address the objectives will be described in the Statistical Analysis Plan (SAP).

5.2. Population for Analysis

Five readers will independently interpret the flortaucipir F 18 PET scans collected from the AZES PET substudy. No new subjects will be enrolled for purposes of this study.

Valid images will be considered unevaluable in the present study only if 3 out of 5 independent readers declare the image unevaluable for the same reason. Subjects with invalid or unevaluable PET data will be excluded from analyses. Criteria for declaring an image invalid or not evaluable will be specified in advance in the Image Review Charter. The majority reads on each flortaucipir F 18 scan (baseline) from these 5 readers will be used to determine the tau status of the corresponding study subject.

The AZES study was terminated early for futility, therefore not all subjects had the opportunity to complete the full term follow up. To avoid bias, it was decided to include only the subjects that had 1) a valid baseline flortaucipir scan (no later than 91 days post randomization, considering that the flortaucipir scans were added to this study after the initiation of AZES); and 2) a CDR assessment at 18 months visit. 205 subjects met these criteria, and approximately 90 of these subjects completed a CDR assessment at the 24 month visit.

5.3. Power Analysis

This study will include up to 205 subjects who have a valid baseline flortaucipir scan, and a change from baseline value of CDR-SB at 18 months. In Study TZAX, which had a similar design and entry criteria, approximately 75% of subjects were rated as τAD++ and 25% were

rated as non-τAD++. Among non- τAD++ subjects (reference group), approximately 40% had an increase of 1 point or more on CDR-SB at 18 months follow up visit. Assuming a distribution of visual reads and CDR-SB change in this study is similar to that for TZAX, a sample of 205 subjects will provide 90% power to detect a risk ratio of 1.65 or larger, under a two-sided type I error rate of 5%.

5.4. Efficacy Analysis

5.4.1. Primary Objective Analysis

The primary analysis for this study will evaluate whether or not the baseline tau status as determined by flortaucipir F 18 scans will predict the risk of subjects' clinically meaningful cognitive and functional deterioration within 18 months of scan. The clinically meaningful deterioration (CMD) for the primary objective analysis is defined as Clinical Dementia Rating Scale Sum of Box (CDR-SB) change from baseline with an increase of 1 point or more.

A Poisson regression model will be used to calculate the ratio of risk for τAD++ subjects over non-τAD++ (τAD+/ τAD-) subjects. The risk ratio, along with a 95% confidence interval and the associated p-value will be provided. CMD as defined in the section above will be used as the dependent variable, and the model will be adjusted for baseline age, CDR-SB score, and therapeutic treatment assignment from AZES study.

5.4.2. Secondary Objective Analysis

5.4.2.1. Clinically Meaningful Deterioration at 18 Months by Tau Status

To fully assess the prognostic value of tau scan, these CMDs will be assessed for the secondary objective analysis:

1) MMSE decreased by 3 points or more;
2) ADAS Cog-11 increased by 4 points or more;
3) FAQ increased by 3 points or more;
4) CDR global with any increase.

The analyses will be identical to what is described in section 5.4.1, with dependent variables 1-4 for CMDs as described above, and the adjustment of corresponding baseline scores.

5.4.2.2. Mean Change of Cognitive/Functional Assessments at 18 Months by flortaucipir PET visual interpretation (τAD++ vs. non-τAD++)

To assess the mean change of CDR-SB, MMSE, ADAS, and FAQ at 18 month by tau status, a mixed model with repeated measures (MMRM) will be used. For each analysis, the change from baseline value from relative measurement will be the dependent variable, and the model will include the fixed effects of tau status (τAD++ or non-τAD++), visit (categorical covariate), tau status-by-visit interaction, and therapeutic treatment assignment from AZES study, as well as corresponding baseline measurement score, and baseline age as continuous covariates. The null hypothesis is that the least squared mean contrast between τAD++ and non-τAD++ groups at month 18 visit equals zero. An unstructured covariance matrix will be used to model the within-

subject variance-covariance. If the unstructured covariance structure matrix results in a lack of convergence, the following tests will be used in sequence: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, and compound symmetry covariance structure. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

5.4.2.3. Inter-reader Reliability

The inter-reader reliability of flortaucipir scan interpretation (τAD++ vs. non-τAD++) across the 5 independent readers will be assessed using a Fleiss' Kappa statistics. The overall percent of agreement, Fleiss' Kappa, and 95% CI around Kappa value will be provided.

5.4.3. Exploratory Analysis

5.4.3.1. Cognitive/Functional Assessments Deterioration at 24 months, by Tau Status

To further evaluate the prognostic value of a flortaucipir scan, analyses described from 5.4.1 – 5.4.2 (except 5.4.2.3) will be repeated using subjects who completed both baseline and 24 month clinical assessments.

5.4.3.2 Clinically Meaningful Deterioration by τAD vs τAD- tau status

In addition, exploratory analyses will be planned to contrast scan visual interpretations of τAD (τAD+/ τAD ++) vs. τAD- , repeating analyses as described from 5.4.1-5.4.2 using both 18 months and 24 months follow-up data. Details will be described in the SAP.

5.4.3.3 Diagnostic Performance of Flortaucipir Scan in Predicting Clinical Deterioration

The diagnostic performance (sensitivity/specificity) will be assessed by using CMD as truth standard (TS) as defined in section 5.4.1 and 5.4.2.1. The 95% CI around the sensitivity/specificity will be calculated using Wilson Score method.

6. STUDY DOCUMENTATION

Avid will be responsible for the submission of the protocol to the Institutional Review Board/Independent Ethics Committee for regulatory approval prior to start of the study.

All data required by the protocol will be recorded in the eCRF. Completed eCRFs may need to be made available for an audit by the United States Food and Drug Administration or other international regulatory authorities at any time. CRFs and all other records will be filed in accordance with applicable laws and regulations.

6.1. Investigators (Readers)

Readers must supply Avid with the following documentation prior to performing any tasks associated with this protocol:

- Signed and dated 1572
- Curriculum vitae
- Medical license
- Financial disclosure form

In order to ensure blinding, readers will not be provided a copy of the protocol for review; therefore, a Protocol Signature Page will not be collected as part of the trial master file (TMF).

6.2. Use of Study Scan Data for Research Purposes

Patients who participated in the AZES study consented to the use of their data (including scans) for future research purposes. All data (scans) will be anonymized and confidential for the purposes of this study. Additional details around the process for anonymizing scans can be found in the IRC.

7. REFERENCES

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement.* 2011;7:270-279.

TZAX (Tau Imaging in H8A-MC-LZAX): A post-hoc evaluation of the relationship between flortaucipir PET signal and cognitive change in subjects with mild Alzheimer's disease participating in the solanezumab Expedition 3 clinical trial tau imaging addendum (Protocol Addendum H8A-MC-LZAX (6.2) (Tau Imaging) Effect of Passive Immunization on the Progression of Mild Alzheimer's disease: Solanezumab (LY2062430) Versus Placebo

Protocol ^{18}F-AV-1451-A05: An open label, multicenter study, evaluating the safety and imaging characteristics of ^{18}F-AV-1451 in cognitively healthy volunteers, subjects with Mild Cognitive Impairment, and subjects with Alzheimer's disease

Protocol ^{18}F-AV-1451-A16: A Clinico-Pathological Study of the Correspondence Between ^{18}F-AV-1451 PET Imaging and Post-Mortem Assessment of Tau Pathology