18F-AV-1451-FR01 Protocol Amendment 1

A Reader Study to Assess Accuracy and Reliability of Flortaucipir F 18 PET Scan Interpretation

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TABLE OF CONTENTS

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1. Rationale/Introduction

In prior clinical studies supporting accuracy and reliability of flortaucipir F 18 positron emission tomography (PET) scans, interpretation has been shown to have acceptable performance when compared to the autopsy truth standard (TS).

This study is designed to further evaluate the accuracy and reliability of multiple readers' interpretations of flortaucipir F 18 PET scans, not only from those subjects who came to autopsy, but also in the intended population for clinical use.

2. Study Objectives

2.1. Primary Objectives

- Test the relationship between ante-mortem flortaucipir F 18 PET imaging and tau neurofibrillary pathology associated with Alzheimer's disease (AD), as measured at autopsy.

- Assess inter-reader reliability.

2.2. Secondary Objectives

- Test the relationship between ante-mortem flortaucipir F 18 PET imaging of an AD pattern with uptake beyond the temporal/occipital regions (i.e., τAD++; see Table 1) and tau neurofibrillary pathology associated with AD, as measured at autopsy.

- Assess inter-reader reliability for scans with an AD pattern that is beyond the temporal/occipital regions (i.e., τAD++; see Table 1).

- Assess agreement among readers of flortaucipir F 18 PET scans in subjects known to be from the intended population (interpretation of scans from Avid Study ^{18}F-AV-1451-A05 [A05]).

- Assess intra-reader reliability for scans read twice by each reader.

3. Study Design

All training and reads will be conducted by an imaging contract research organization (CRO) as described in the imaging review charter (IRC). Five readers will be trained in-person on the flortaucipir F 18 PET scan read methodology using the previously developed read method. 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, readers will then independently read 262 scans; 83 from Study ^{18}F-AV-1451-A16 (A16) and 159 from Study A05.

The study population for Study A16 (^{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) consisted of subjects at the end of life, who were imaged with flortaucipir F 18 and came to autopsy. Subjects were enrolled in the study with the intent of capturing a range of tau neurofibrillary pathology in AD.

The study population for Study A05 confirmatory cohort (^{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) consisted of 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. Subjects were imaged with flortaucipir F 18 and followed longitudinally for 18 months to assess the subsequent rate of cognitive decline.

4. Procedures and Methods

4.1. Selection and Number of Investigators (Readers)

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

- Board Certified in radiology or nuclear medicine
- Experience interpreting PET scans
- Have not received training on the Avid flortaucipir F 18 read methodology

4.2. Selection/Number of Images

Two hundred and forty-two unique scans will be read for this study, comprised of the following:

- All 83 subjects from Study A16 (primary and supplemental) who have a valid scan and autopsy

- All 159 subjects from the Study A05 confirmatory cohort who have a valid scan

- In addition, a sub-set of 20 randomly selected cases will be used for intra-reader reliability purposes for a total of 262 scan reads

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

Data will be collected using electronic case report forms (eCRFs).

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, Good Clinical Practice, and Avid/CRO Standard Operating Procedures. Monitoring of study data will be performed by the Imaging CRO and will be performed in accordance with their standard operating procedures.

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.

5.2. Population for Analysis

Five readers will independently interpret the flortaucipir F 18 PET scans collected from 2 completed Avid Studies, A16 and A05. No new subjects will be enrolled for purposes of this study. All 83 autopsy scans were collected from Study A16 (67 from main study and 16 from supplementary autopsy cohort (SAC)). All 159 scans from Study A05 confirmatory cohort will be included.

Valid images will be considered unevaluable 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 IRC.

5.2.1. Analysis Population for Scan Accuracy Assessment

Flortaucipir F 18 scan accuracy (sensitivity and specificity) will be assessed using all 83 cases from Study A16 that had an autopsy diagnosis by pathologist panel, including:

- 3 front-runners
- 64 main study autopsy cases
- 16 autopsy cases collected under SAC

5.2.2. Analysis Population for Scan Interpretation Precision Assessment

The precision of flortaucipir F 18 PET scan interpretation will be assessed in 2 ways: inter-reader (i.e., reader-to-reader) reliability, and intra-reader reliability (i.e., agreement between the repeated reads on same scan from same reader). The inter-reader reliability will be assessed using all 242 scans included for this study (83 Study A16 scans and 159 Study A05 scans). The inter-reader reliability will also be assessed separately on the 159 Study A05 scans (i.e., the targeted population for clinical usage), and on the 83 Study A16 scans. Twenty scans will be randomly selected and will be read twice by the 5 readers in a randomized sequence, along with all the other scans. The repeated reads on these 20 scans will be used to assess the intra-reader reliability.

5.3. Power Analysis

Assuming 80% sensitivity and 80% specificity, 14 TS positive or TS negative cases will be needed to show the lower bounds of 95% confidence interval (CI; 2-sided) greater than 50%, for

either sensitivity or specificity, with a Wilson score method to calculate the 95% CI. Out of the 83 Study A16 cases with autopsy results, 47 were neurofibrillary tangle (NFT) stage B3 per pathologist's panel diagnosis (TS positive for primary analysis 1), and 36 were NFT stage B2 or lower (TS negative for primary analysis 1); 41 were high AD neuropathologic change (ADNC) according to panel diagnosis (TS positive for primary analysis 2), and 42 were low to intermediate ADNC (TS negative for primary analysis 2). Therefore, this sample size provides adequate power to assess the accuracy of flortaucipir F 18 PET scan in detecting underlying pathological changes.

Fleiss' Kappa will be used to assess the reader-to-reader consistency in flortaucipir F 18 scan visual interpretation. Five independent qualified physicians will read 242 unique scans (83 autopsy scans from Study A16 and 159 scans from Study A05). Assuming the Fleiss' Kappa is expected to be 0.7, this sample size provides over 90% power in detecting a kappa value greater than 0.6, under a two-sided type I error rate of 0.05.

5.4. Efficacy Analysis.

5.4.1. Primary Analyses

The primary objectives for this study are to assess both the accuracy and precision of flortaucipir F 18 PET imaging to detect tau neurofibrillary pathology associated with (AD).

5.4.1.1. Assessing the Accuracy of Flortaucipir F 18 PET Scan

Analyses for Primary Objective 1:

For the first primary objective, 2 analyses will be planned to assess the accuracy of flortaucipir F 18 PET imaging in detecting tau pathology, as measured at autopsy.

Primary Analysis 1

The diagnostic performance (sensitivity/specificity) of 5 independent readers' interpretations of ante-mortem flortaucipir F 18 PET imaging for detection of a pattern of flortaucipir F 18 neocortical uptake that corresponds to NFT Score of B3 (Hyman et al. 2012; Montine et al. 2012) at autopsy will be evaluated; and

Primary Analysis 2

The diagnostic performance (sensitivity/specificity) of 5 independent readers' interpretations of ante-mortem flortaucipir F 18 PET imaging for detection of a pattern of flortaucipir F 18 neocortical uptake that corresponds to high levels of AD neuropathologic change as defined by National Institute on Aging-Alzheimer's Association (NIA-AA) criteria (Hyman et al. 2012) will be evaluated. For individuals with cognitive impairment, high levels of AD neuropathologic change are considered adequate to explain cognitive impairment or dementia symptoms.

For Primary Analysis 1, the hypothesis to be tested is that for the same 3 out of 5 independent readers; the lower bound of the two-sided 95% CI for both sensitivity and the specificity of flortaucipir F 18 PET reading results will be ≥50%. As detailed in Section 5.4.1, Table 2, NFT scores for autopsy cases will be categorized as either B0/B1/B2 or B3 level; and will serve as the NFT Score TS for this analysis. Flortaucipir F 18 PET imaging will be classified by each reader

as either neocortical uptake not consistent with AD (τAD-), or neocortical uptake consistent with AD (τAD+) or neocortical uptake consistent with AD and likely to progress (τAD++). Sensitivity and specificity will be calculated for each reader as the proportions of true positive (TP) and true negative (TN) cases correctly identified as such, according to Table 2 below:

Table 2. **Primary Objective 1 Analysis 1: Diagnostic Performance Calculations for flortaucipir F 18 PET Scan Reader Interpretation vs. Autopsy NFT Score Truth Standard**

	Autopsy NFT Score TS	
Physician Reader Interpretation	**NFT Score B3** **[Truth Positive]**	**NFT Score B0–B2** **[Truth Negative]**
Flortaucipir F 18 neocortical uptake; AD pattern (τAD+/τAD++)	True Positive (TP)	False Positive (FP)
Flortaucipir F 18 neocortical uptake not consistent with AD (τAD-)	False Negative (FN)	True Negative (TN)

Two-sided 95% CIs for sensitivity and specificity will be calculated using the Wilson score method. The first primary endpoint is considered to be met if for the same 3 out of 5 readers, the lower bound of the 95% CIs for both sensitivity and specificity are ≥50% (i.e., statistically significant at two-sided significance level of 0.05).

Like Primary Analysis 1, the hypothesis to be tested for Primary Analysis 2 is that for the same 3 out of 5 readers, the lower bound of the 95% CIs for both sensitivity and the specificity will be ≥50%. For Primary Analysis 2, autopsy cases will be categorized as either not, low, or intermediate versus high level of AD neuropathologic change according to NIA-AA criteria, considering Braak stage, Thal plaque score, and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) amyloid neuritic plaque score, and this level of AD neuropathologic change will be used as the NIA-AA autopsy diagnosis TS as detailed in Section 5.4.1 Table 3. Flortaucipir F 18 PET images will be interpreted by visual examination as either τAD- or τAD+/τAD++ as for Primary Analysis 1. Sensitivity and specificity will then be calculated for each reader as the proportions of TP and TN cases correctly identified as such, according to Table 3 below:

Table 3. **Primary Objective 1 Analysis 2: Diagnostic Performance Calculations for Flortaucipir F 18 PET Scan Reader Interpretation vs. NIA-AA Autopsy Diagnosis Truth Standard**

	NIA-AA Autopsy Diagnosis TS	
Physician Reader Interpretation	**High AD Neuropathologic Change** **[Truth Positive]**	**Not, Low, or Intermediate AD Neuropathologic Change** **[Truth Negative]**
Flortaucipir F 18 neocortical uptake; AD pattern (τAD+, τAD++)	True Positive (TP)	False Positive (FP)
Flortaucipir F 18 neocortical uptake; not consistent with AD pattern (τAD-)	False Negative (FN)	True Negative (TN)

Two-sided 95% CIs will be calculated using the Wilson score method. The second primary endpoint is met if for the same 3 out of 5 readers, the lower bounds of the 95% CIs for both sensitivity and specificity are ≥50%.

The pathological diagnosis (for both NFT score TS and NIA-AA autopsy diagnosis TS) for Study A16 SAC cases were based on tissue samplings from 1 side of brain. Therefore, the reads from the corresponding hemisphere upon which the pathological diagnosis was based on will be used for primary analyses 1 and 2.

5.4.1.2. Assessing the Precision of Flortaucipir F 18 PET Scan Reads

The second primary objective will assess inter-reader reliability.

Primary Objective Analysis 2

The inter-reader reliability of flortaucipir F 18 PET scan visual interpretation will be assessed using kappa statistics. Fleiss' Kappa and the associated 95% CI will be calculated based on 5 readers' visual interpretations on the 242 scans (comprised of 83 scans from Study A16 autopsy cases, and 159 cases from Study A05). The p-value will be calculated using normal approximation method. The lower bound of the 95% CI for Fleiss' Kappa must be greater than or equal to 0.6 to meet the inter-reader reliability criterion. If the scan is selected (by random) to be read twice for the intra-reader reliability assessment, the first read will be used for the second primary objective analysis; for Study A16 SAC cases; the overall reads (using both hemispheres) from each reader will be used for the second primary objective analysis.

5.4.2. Secondary Analyses

Four secondary objectives/analyses will further evaluate the precision of flortaucipir PET scan results.

5.4.2.1. Analyses for Secondary Objective 1

With the same TS as used in primary analyses 1 and 2, these secondary analyses will assess the diagnostic performance (sensitivity/specificity) of a τAD++ pattern found on flortaucipir PET scan interpretation as below:

Table 4. **Secondary Objective 1 Analysis 1: Diagnostic Performance Calculations for Flortaucipir F 18 PET Scan Reader Interpretation vs. Autopsy NFT Score Truth Standard**

	Autopsy NFT Score TS	
Physician Reader Interpretation	**NFT Score B3** **[Truth Positive]**	**NFT Score B0–B2** **[Truth Negative]**
Flortaucipir F 18 neocortical uptake; τAD++ pattern	True Positive (TP)	False Positive (FP)
Flortaucipir F 18 neocortical uptake; non-τAD++ pattern (τAD- or τAD+)	False Negative (FN)	True Negative (TN)

Table 5. **Secondary Objective 1 Analysis 2: Diagnostic Performance Calculations for Flortaucipir F 18 PET Scan Reader Interpretation vs. NIA-AA Autopsy Diagnosis Truth Standard**

	NIA-AA Autopsy Diagnosis TS	
Physician Reader Interpretation	**High AD Neuropathologic Change** **[Truth Positive]**	**Not, Low, or Intermediate AD Neuropathologic Change** **[Truth Negative]**
Flortaucipir F 18 neocortical uptake; τAD++ pattern	True Positive (TP)	False Positive (FP)
Flortaucipir F 18 neocortical uptake; non-τAD++ pattern (τAD- or τAD+)	False Negative (FN)	True Negative (TN)

Two-sided 95% CIs will be calculated using the Wilson score method. The second primary endpoint is met if for the same 3 out of 5 readers, the lower bounds of the 95% CIs for both sensitivity and specificity are ≥50%.

The pathological diagnosis (for both NFT score TS and NIA-AA autopsy diagnosis TS) for Study A16 SAC cases were based on tissue samplings from 1 side of the brain. Therefore, the

reads from the corresponding hemisphere upon which the pathological diagnosis was based on will be used for secondary objective 1, analyses 1 and 2.

For both analyses as listed above, the hypotheses for testing are that for the same 3 out of 5 readers, the lower bound of the 95% CIs for both sensitivity and the specificity will be ≥50%.

5.4.2.2. Analysis for Secondary Objective 2

Like the analysis for primary objective 2, kappa statistics will be used to assess inter-reader reliability of flortaucipir F 18 PET scan visual interpretation with a τAD++ pattern. Fleiss' Kappa and the associated 95% CI will be calculated based on 5 readers' visual interpretations on the 242 scans (comprised of 83 scans from Study A16 autopsy cases, and 159 cases from Study A05). The p-value will be calculated using a normal approximation method. The lower bound of the 95% CI for Fleiss' Kappa must be greater than or equal to 0.6 to meet the inter-reader reliability criterion. If the scan is selected (by random) to be read twice for the intra-reader reliability assessment, the first read will be used for this analysis; for Study A16 SAC cases, the overall reads (using both hemispheres) from each reader will be used for this analysis.

5.4.2.3. Analysis for Secondary Objective 3

For this objective, inter-reader reliability of flortaucipir F 18 PET scan visual interpretation in the Study A05 scans, a population similar to the intended population for clinical use will be assessed similar to the second primary objective analysis except that the Fleiss' Kappa will be calculated based on 5 readers' visual interpretations on the 159 scans from Study A05. If any of the scans are selected (by random) to be read twice for the intra-reader reliability assessment, the first read will be used for this analysis. As an exploratory analysis, a similar analysis will be conducted using Study A16 scans.

5.4.2.4. Analysis for Secondary Objective 4

Twenty scans will be randomly selected for this analysis, and the 5 readers will read them in random sequence along with other scans. Cohen's Kappa will be calculated for each of these 5 readers, based on these 20 scans read repeatedly to assess the intra-reader reliability of flortaucipir F 18 PET scan visual interpretation. The 95% CI as well as p-values will be calculated using normal approximation method.

6. Study Documentation

Avid will be responsible for the submission of the protocol to the Instututional 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. The eCRFs 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

- Signed and dated 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.

6.2. Use of Study Scan Data for Research Purposes

Patients who participated in the parent Studies A16 and A05 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

Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Thies B, Trojanowski JQ, Vinters HV, Montine TJ. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of alzheimer's disease. *Alzheimers Dement.* 2012;8(1):1-13.

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