CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212123Orig1s000

INTEGRATED REVIEW

Executive Summary
Interdisciplinary Assessment
Appendices

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	212123
Priority or standard	Priority
Submit date(s)	9/30/2019
Received date(s)	9/30/2019
PDUFA goal date	5/29/2020
Division/office	Division of Imaging and Radiation Medicine (DIRM)
Review completion date	5/27/2020
Established name	Flortaucipir F 18
(Proposed) trade name	Tauvid
Pharmacologic class	Radioactive diagnostic agent (for PET imaging)
Code name	F18-AV-1451, F18-T807, LSN3182568
Applicant	Avid Radiopharmaceuticals Inc
Dose form/formulation(s)	Injection
Dosing regimen	370 MBq (10 mCi), administered as a bolus intravenous injection
Applicant proposed indication(s)/population(s)	For positron emission tomography (PET) imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles (NFTs) (b) (4) in (b) (4) adult patients who are being evaluated for AD (b) (4)
Proposed SNOMED indication	(b) (4)
Regulatory action	Approval
Approved indication(s)/population(s) (if applicable)	Tauvid is indicated for use with PET imaging of the brain to estimate the density and distribution of aggregated tau NFTs in adult patients with cognitive impairment who are being evaluated for AD. Limitations of Use: Tauvid is not indicated for use in the evaluation of patients for chronic traumatic encephalopathy (CTE)
Approved SNOMED indication	386806002 | Impaired cognition (finding)

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(b) (4)

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Glossary

AD	Alzheimer's disease
ADAS	Alzheimer's Disease Assessment Scale
ADAS-Cog	Alzheimer's Disease Assessment Scale–Cognitive Subscale
ADNC	Alzheimer's Disease Neuropathological Change
AE	adverse event
ANART	American National Adult Reading Test
CBD	corticobasal degeneration
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDR-SB	Clinical Dementia Rating Scale Sum of Box
CERAD	Consortium to Establish Registry for Alzheimer's Disease
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CRF	case report form
CSF	cerebrospinal fluid
CTE	chronic traumatic encephalopathy
ECG	electrocardiogram
FAQ	Pfeffer Functional Activities Questionnaire
FBP	florbetapir F 18
FDA	U.S Food and Drug Administration
FDG	fluorodeoxyglucose F 18
FEH	fluoroethyl harmol
FTP	flortaucipir F 18
GLP	good laboratory practice
HR	hazard ratios
IC_{50}	half maximal inhibitory concentration
ICC	intraclass correlation
IHC	immunohistochemistry
IND	investigational new drug
IP	investigational product
IR	information request
Kd	dissociation constant
LR	likelihood ratio
LS	least square
MAO	monoamine oxidase
MBq	megabecquerel
MCI	mild cognitive impairment
MDCK	Madin-Darby canine kidney
MedDRA	Medical Dictionary for Regulatory Activities
MHD	maximum human dose
MMRM	mixed model with repeated measures
MMSE	Mini-Mental State Examination

MRI	magnetic resonance imaging
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide
MUBADA	multiblock-barycentric-discriminant-analysis
NDA	new drug application
NFT	neurofibrillary tangle
NIA-AA	National Institute on Aging Alzheimer's Association
NOAEL	no observed adverse effect level
NPV	negative predictive value
OCN	old cognitively normal
PET	positron emission tomography
PHF	paired helical filament
PI	prescribing information
PiD	Pick's disease
PK	pharmacokinetics
PLT	posterolateral temporal
PPV	positive predictive value
PSP	progressive supranuclear palsy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SUVr	standard uptake value ratio
QT-IRT	QT Interdisciplinary Review Team
Tdp	Torsade de pointes
TEAE	treatment-emergent adverse event
TS	truth standard
YCN	young cognitively normal

Note for the purpose of this review: *"FTP" may be used for readability to refer to flortaucipir containing the isotope fluorine 18, the new drug under review in this application. In submitted or referenced source material or as otherwise necessary in context, the isotope fluorine 18 may be variously abbreviated, including: "F 18," "F18," "[F-18]," "18F," and "^{18}F." Manufacturer code names for flortaucipir include "AV-1451" and "T807." Therefore, "FTP" and "F18-AV-1451," "F18-T807," "flortaucipir F 18," et cetera, may be used interchangeably. In nonimaging contexts where it may be appropriate to distinguish FTP from the manufactured or decayed drug containing the stable isotope fluorine 19, the following terms may be used: "flortaucipir," "AV-1451," and "T807," without adjacent reference to fluorine 18 or with the term "cold" added for emphasis. The tradename "Tauvid" and "TAUVID" may be used in reference to the to-be-marketed product and prescribing information, respectively.*

I. Executive Summary

1. Summary of Regulatory Action

The Applicant (Avid Radiopharmaceuticals) is seeking U.S Food and Drug Administration (FDA) authorization to market Tauvid in the United States per authority granted under Section 505(b)(1) of the Food, Drug, and Cosmetic Act. The drug substance in Tauvid is flortaucipir F 18 (FTP), a benzimidazole-pyrimidine derivative new small molecule labelled with fluorine 18 for imaging. After Tauvid is administered intravenously, FTP crosses the blood brain barrier and concentrates at binding sites containing beta sheet structures associated with tau protein misfolding and Alzheimer's disease (AD) pathology. From these and other sites of off-target binding or biodistribution, fluorine 18 decay leads to release of positrons and emission of dual 511 keV photons that can be imaged.

After multidisciplinary review, the team has found that there is substantial evidence to support the safety and effectiveness of Tauvid to estimate the density and distribution of aggregated tau neurofibrillary tangles (NFTs) in adult patients with cognitive impairment who are being evaluated for AD.

For efficacy, the team relied on evidence consistent with FDA regulation at 21 CFR 314.126 and 21 CFR 315.5(a)(5). There were two phase 3 studies. Study 1 (NCT02516046) compared the performance of blinded image readers to detect individuals with tau pathology from among patients who were terminally ill with life expectancy ≤9 months at the time of FTP administration. Per prespecified methods for interpreting each patient as positive versus negative, reader performance was determined by comparison with pathological assessment at autopsy. The performance of the five FTP readers for sensitivity (95% confidence interval (CI)) ranged from 92% (80, 97) to 100% (91, 100) and for specificity (95% CI) ranged from 52% (34, 70) to 92% (75, 98). The number of readers for whom the lower bound of 95% CIs exceeded prespecified coprimary thresholds for sensitivity and specificity was 3, equal to the prespecified minimum the review division agreed was adequate to support efficacy during study planning meetings under investigational new drug (IND) 119863.

Study 2 (NCT03901092) was a prospectively designed substudy with five new blinded readers. The Applicant designed Study 2 after analyzing results from Study 1 and another phase 3 study in the indicated patient population. Study 2 readers reread a combined set of FTP images previously acquired under both Study 1 and under the indicated population study, which lacked autopsy or other reliable standard against which to quantify reader performance for tau pathology detection. The team found that Study 2 results provided confirmatory evidence for the primary Study 1 efficacy findings, since, across the combined image set, Fleiss' kappa statistic (95% CI) was 0.87 (0.83, 0.91), demonstrating that Study 2 readers in comparison to one another distinguished positive from negative FTP scans with consistency exceeding the agreed prespecified threshold. In addition, for the images from Study 1 that were reread, Study 2 and Study 1 reader performance was similar when estimated against autopsy.

For safety, the team relied on evidence from 1921 study subjects exposed to FTP. To mitigate risk, the Applicant agreed to accept addition of a Limitations to Use in prescribing information (PI). This limitation emphasizes that Tauvid is not indicated for evaluation of patients for chronic traumatic encephalopathy (CTE) and cross-references an added Warning and Precaution under the heading "Risk of Chronic Traumatic Encephalopathy Misdiagnosis." The Applicant also agreed to the team's recommendation for addition of a Warning and Precaution under the heading "Risk of Misdiagnosis in Patients Evaluated for Alzheimer's disease." This warning includes the precaution for risk mitigation that patients with a negative Tauvid scan should consider additional evaluation to confirm absence of AD pathology.

Overall, multidisciplinary reviewers from each discipline represented on the team, including consulted subject matter experts, found that benefit-risk was favorable and recommend an approval action for Tauvid when used per agreed labeling for estimating the density and distribution of aggregated NFTs in adult patients with cognitive impairment who are being evaluated for AD.

Within this patient population, the available options for tau pathology detection rely on in vitro testing of samples from autopsy or invasive brain surgery, leaving unmet a clear medical need for more accessible products such as Tauvid. Another disadvantage of pathological testing is that it limits understanding of biological change within individuals over time, so longitudinal imaging and follow-up to investigate the spatiotemporal course of tau pathology, as well as its prognostic or other clinical value, is an area of evolving knowledge. On the other hand, pathologists can detect amyloid and tau and other clinically meaningful pathologies from one sample source, an advantage compared to imaging for one pathology at a time, particularly since detection together of tau and amyloid pathology is required for AD diagnosis.

(b) (4)

On April 14, 2020, since the Applicant formally withdrew these claims, FDA announced that the Medical Imaging Drugs Advisory Committee meeting that had been scheduled for April 23, 2020, was cancelled because the issues for which FDA was seeking the scientific input of the Committee had been resolved.

During late-cycle discussion, the team sought comment from the Applicant regarding (b) (4)

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Alzheimer's disease (AD) is the most common neurodegenerative disease and ranks as the sixth most common cause of death in the United States (Alzheimer's 2015). It is characterized by a gradual and progressive decline in cognitive and functional status of the afflicted individuals. • There are approximately 5.7 million people with AD within the United States and 46 million worldwide. These numbers are projected to triple by the year 2030 (Alzheimer's 2015). • The current economic burden of this devastating disorder within the US is about 290 billion dollars per year. This is projected to increase to beyond $1 trillion per year (Hurd et al. 2013). • Clinical diagnosis of probable AD is based on medical history, clinical examination, neuropsychological assessment, and laboratory tests. Diagnosis of definite AD requires documentation of the presence of beta-amyloid plaques and neurofibrillary tangles (NFTs), the two hallmark pathological lesions of AD, through postmortem examination (Apostolova 2016). • The clinical syndrome of AD is considered to be a continuum consisting of preclinical, prodromal (mild cognitive impairment, MCI) and dementia stages (Petersen 2018). • Patients in the preclinical stage harbor the underlying pathological features of amyloid deposition, tau pathology and neurodegeneration but are clinically unimpaired. In the prodromal or MCI state, patients present with subtle decline in cognition but are functional in their daily activities (Petersen 2018). • Current thinking in the field proposes that by the time patients experience clinical symptoms and signs the damage in the brain may be irreversible (Sperling et al. 2011; Petersen 2018). Therefore, early identification of the disease processes in the AD continuum may be necessary to initiate more timely intervention with therapies to decrease or eliminate further damage to the central nervous system (CNS).	AD is an important global and domestic public health concern. AD has a major impact on patients, families, society, and the health care economy. Accurate diagnosis and staging of patients is essential for optimal management of patients and families. To this end, imaging of one of the neuropathological hallmarks of the disease, NFTs, can add important new information to the clinical assessment of patients undergoing evaluation for AD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• The accuracy of a clinical diagnosis of AD by dementia experts is modest when compared to postmortem diagnosis (Beach et al. 2012). • Increasing diagnostic performance can help the patient and family anticipate future needs including periodic monitoring for progression and safety,and functional assessment. • In vivo assessment of fibrillary Aβ deposition, tau pathology and neurodegeneration can provide a measure of the underlying pathophysiology in living persons (Jack et al. 2018). • Assessments of amyloid by themselves cannot confirm a diagnosis of AD. Amyloid positron emission tomography (PET) tracers, also bind to Aβ deposits in vessel walls decreasing their specificity (Jack et al. 2016). Increased amyloid PET tracer binding has also been found following acute traumatic brain injury (Hong et al. 2014). Up to 30% of elderly asymptomatic individuals demonstrate accumulation of amyloid (Bennett et al. 2006; Mufson et al. 2016). Further, cerebrospinal fluid (CSF) Aβ is found in some non-AD conditions such as HIV encephalitis (Krut et al. 2013) and multiple-system atrophy (Holmberg et al. 2003; Leuzy et al. 2016). • Measures of neurodegeneration (atrophy as measured by structural magnetic resonance imaging (MRI) and hypometabolism as measured by fluorodeoxyglucose F 18 (FDG) PET in AD-specific brain regions) are relatively nonspecific and can occur in a variety of disorders (Fotuhi et al. 2012; Crary et al. 2014). • In vitro diagnostic assays to detect pathological amyloid and tau aggregates in CSF are under investigation (Shaw et al. 2018; Doecke et al. 2020). However,these tests do not provide information on the spatial distribution of the pathology - a characteristic that can be helpful in the differential diagnosis of tau-related neurodegenerative disorders. Lack of standardization across tests is also a concern. • In summary, there is an unmet need for reliable, sensitive and noninvasive/minimally invasive tests that can aid in the evaluation of the AD continuum to facilitate timely and effective intervention before irreversible neuropathological changes occur.	In conjunction with other diagnostic evaluations, a tau PET tracer that can image and estimate the density and distribution of tau-NFTs of AD can be helpful in the assessment of patients being evaluated for AD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The ability to image and estimate the density and distribution of NFTs, one of the two pathological hallmarks of AD, has important implications for patients afflicted with or at risk for developing this devastating disorder (Jack et al. 2018). Data from the truth standard A16 study show that advanced (B3) level of tau-NFT pathology can be reliably detected with Tauvid. • However, limitations apply to patients in the earlier phases of the AD continuum. Reported off-target binding in brain regions such as the choroid plexus can interfere with quantification of Tauvid uptake in the hippocampaus and neighboring mesial temporal lobe structures (Marquie et al. 2015; Lowe et al. 2016; Scholl et al. 2019). Therefore, the ability of Tauvid to reliably detect tau pathology in these regions representing earlier Braak stages I and II is limited. • (b) (4) [redacted]	The Applicant presents data from phase 3 trials supporting the ability of Tauvid to identify a B3 level of NFT pathology reflecting an advanced stage of the disease in the AD continuum. Such information can be helpful in evaluating patients presenting with cognitive and behavioral changes consistent with AD who also show amyloid positivity. (b) (4) [redacted] A negative scan result does not preclude the presence of B2 or lower NFTs or amyloid pathology. In cases of a negative scan result, further testing to determine earlier AD neuropathology (e.g., presence of B2 tau pathology and the presence of amyloid) or other causes of cognitive decline may be necessary.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• There were no serious adverse events deemed related to FTP administration. The incidence of mild to moderate adverse reactions was low with a frequency <3%. Among these adverse reactions, headache, injection site pain and increased blood pressure were the most common with a frequency of >0.5%. • FTP binds to monoamine oxidase (MAO)-A, MAO-B and tau-NFTs with nanomolar affinities. This high affinity binding of FTP to MAO-A and MAO-B could potentially affect the interpretation of Tauvid PET images. • In 785 patients administered FTP (majority without history of cardiac rhythm disturbances or QT prolonging medications), singlet ECG recordings pre and post FTP administration showed that the mean increase in QTcF was 5.1 msec, around the borderline for concern, when measured approximately 2 hours following FTP administration. There was no parallel control arm for comparison of this finding, though earlier measurements around the time of peak FTP concentration were reassuring. With respect to the 5.1 msec estimate, the upper limit of the 90% confidence interval (equivalent to a one-sided 95% confidence interval) did not approach the 10 msec threshold for concern. There were no patients who demonstrated a concerning QTcB or QTcF interval >500 msec or marked increase of 60 msec or greater above predose values. In the overall clinical trials safety database comprising 1921 individuals, no treatment-emergent adverse events related to QT interval prolongation or ventricular arrhythmias were identified. Safety hERG preclinical studies showed a large exposure margin given the low mass dose of FTP administered clinically. • Diagnostic radiopharmaceuticals, including Tauvid, expose patients to radiation; the estimated whole body radiation absorbed dose of 8.7 mSV for a 370 megabecquerel (MBq) dose is comparable to the absorbed radiation dose of approved F 18 labeled compounds such as FDG and and florbetapir F 18. • Potential off-label use of Tauvid in chronic traumatic encephalopathy (CTE) and other tau-related neurodegenerative disorders is a concern because preliminary nonclinical and clinical investigations suggest differences in tau conformation and distribution may limit FTP binding in CTE.	• Overall Tauvid was well tolerated. The mild to moderate adverse reactions experienced were of low frequency (<3%). • There is no evidence among the substantial nonclinical and clinical safety evidence submitted to support a clinically meaningful risk of QT prolongation caused by Tauvid. • To alert the prescribing clinician of the issue related to MAO clinical pharmacology, the following language will be included in Section 12.2 of the prescribing information (PI): Effect of MAO Inhibitors on Flortaucipir Binding in AD Patients - TAUVID PET signal was slightly reduced by rasagiline, a MAO-B inhibitor, in vivo in low tau, high MAO-B areas of the brain such as the nucleus accumbens, putamen, and caudate. However, there is little potential for MAO binding to affect TAUVID scan interpretation in neocortical areas." • The potential off-label use of Tauvid in CTE will be addressed in the Indications and Usage Section of the PI as a Limitiation of Use and in the Warnings and Precautions section as a risk for CTE misdiagnsosis.

Conclusions Regarding Benefit-Risk

AD is a significant public health concern worldwide. Accurate and early assessment of the different stages in AD continuum is critical for timely intervention with therapies and counseling of the patient and families. A definitive diagnosis of AD can only be established by the demonstration of the two pathological hallmarks, namely the presence of amyloid plaques and tau-based NFTs. Tauvid represents a new molecular entity designed to image and estimate the density and distribution of NFTs in the brain.

The data submitted by the Applicant supports Tauvid's ability to reliably estimate only B3 level of tau pathology. Due to off-target binding in several brain regions including the medial temporal lobe structures, Tauvid does not reliably detect tau pathology in these regions.

The limitation of Tauvid's utility to reliably detect only advanced levels of NFT pathology is addressed in labeling. (b) (4)

Evaluation of the safety profile raised issues of image misinterpretation, potential interaction of Tauvid with MAO inhibitors, and potential off-label use of Tauvid in CTE and other tau-related neurodegenerative disorders. Each of these risks has been addressed through labeling.

With all factors considered, together with its acceptable safety profile, Tauvid offers clinicians an option to reliably detect B3 level of tau pathology.

II. Interdisciplinary Assessment

3. Introduction

The Applicant (Avid) submitted this new drug application (NDA) for Tauvid, a fluorine-18-labeled diagnostic positron emission tomography (PET) radiopharmaceutical, to image aggregated tau–neurofibrillary tangles (NFTs) (b) (4) of patients (b) (4) who are being evaluated for AD (b) (4)

AD is a devastating disorder and ranked as the sixth most common cause of death in the United States (Alzheimer's 2015). The clinical syndrome of AD is considered to be a continuum and evidence suggests that there is irreversible brain damage by the time patients manifest clinical symptoms and signs (Sperling et al. 2011; Petersen 2018). Therefore, early diagnosis and intervention are needed to decrease further damage to the central nervous system (CNS) (Sperling et al. 2011; Petersen 2018). The accuracy of clinical diagnosis of AD by dementia experts is modest when compared to postmortem diagnosis (Beach et al. 2012). An in vivo definitive diagnosis of AD is possible by the demonstration of Aβ amyloid plaques and intraneuronal tau NFT aggregation, the two pathological hallmarks of the disease (Hyman et al. 2012; Montine et al. 2012), in the brains of patients presenting with cognitive and memory disturbances (Marquez and Yassa 2019).

Tau is a microtubule stabilizing phosphoprotein with six isoforms that are categorized into two functional groups based on whether there are three (3R) or four (4R) repeats of the microtubule-binding domain (Villemagne et al. 2015; Hall et al. 2017; Leuzy et al. 2019; Scholl et al. 2019). Hyperphosphorylation of tau leads to its abnormal aggregation into protofibril assemblies that are classified into straight, twisted or paired helical filaments (PHF) based on the presence or absence of periodicity of twists. The abnormal aggregation of these protofibril assemblies forms the NFTs. The NFTs in AD typically exist as PHFs and their deposition follows a distinct spatiotemporal pattern (Braak and Braak 1997).

In addition to AD, tau NFT deposition is a key pathological component in other neurodegenerative disorders collectively called tauopathies and include Down's syndrome, chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), Picks disease, frontotemporal dementia, Lewy body disease and progressive supranuclear palsy (PSP) (Hyman et al. 2012; Montine et al. 2012). The isoform composition and the distinct neuroanatomical spatial pattern of the intracellular tau inclusions vary across these different tauopathies (Hyman et al. 2012; Montine et al. 2012). While both 3R and 4R groups that include all six isoforms of tau are found in AD and CTE, in PSP and CBD there is a relative overexpression of the 4R tau isoforms (Dickson 1999; Williams et al. 2007). In AD, NFT aggregation starts in the transentorhinal cortex before spreading to the medial and inferior temporal lobe, the parietal-occipital regions and the posterior cingulate cortex (Braak and Braak 1997; Hyman et al. 2012; Montine et al. 2012). This hierarchical spatial topography of tau NFT accumulation in AD is markedly distinct from the midbrain and frontostriatal accumulation in PSP and CBD,

respectively (Dickson 1999; Williams et al. 2007; Hyman et al. 2012; Montine et al. 2012). In CTE, tau aggregates have been found in neurons, astrocytes and cell processes around small vessels in the depths of cortical sulci (McKee et al. 2016).

Similar to how the development of techniques to measure and map Aβ has transformed translational and clinical research in AD (Apostolova et al. 2016; Jack et al. 2018; Rabinovici et al. 2019), the development of techniques to measure and map tau pathology can further this transformation even more. Over the last 2 decades, the in vivo assessment of tau through assays that measure total (T-tau) and phosphorylated tau (P-tau) in the cerebrospinal fluid has become possible (Blennow et al. 1995). While assays to measure tau proteins in blood have also been developed in recent years, the importance of tau-related changes in the blood is still not completely understood (Scholl et al. 2019).

Though cerebrospinal fluid (CSF) tau assays have been available for several years they are limited by the invasiveness of the required lumbar puncture procedure and its associated side effects of back discomfort, headache, and in rare cases iatrogenic meningitis. Further, the assays report a single absolute value reflecting the degree of abnormality but do not indicate the topographic extent of tau pathology, the knowledge of which can be helpful in the differential diagnosis of tauopathies. On the other hand, selective in vivo tau imaging is relatively noninvasive and has the ability to measure the spatio-temporal distribution of tau deposition (Villemagne et al. 2015; Hall et al. 2017; Leuzy et al. 2019; Scholl et al. 2019).

Over the last few years, there have been significant efforts to develop PET imaging ligands that bind to tau with high affinity and enable the visualization, mapping, and quantification of tau in the living brain (Villemagne et al. 2015; Hall et al. 2017; Leuzy et al. 2019; Scholl et al. 2019). Among these, flortaucipir F 18 (FTP) is a new molecular entity designed to estimate the density and characterize the distribution and spatial extent of the aggregated intracellular tau-NFTs. FTP binds to intracellular, phosphorylated, paired helical filamental tau that is specific for AD (Lowe et al. 2016). Currently, there are no approved PET imaging tracers for estimating the density and distribution of tau-NFTs.

The phase 3 program for FTP consisted of four studies to evaluate its diagnostic (Studies A16 and FR01) and (b) (4) (Studies A05C and PX01) in patients with AD. The Applicant initially submitted an original investigational new drug (IND) application 114102 in December 2011 (b) (4) . In 2013, the Applicant inactivated IND 114102 and submitted IND 119863 to continue further work on FTP. The clinical development of FTP included work to evaluate test-retest reproducibility for brain imaging of tau in healthy volunteers and subjects with cognitive impairment. This was followed by a submission of an amendment to Study A05 (November 2014) to add a phase 3 confirmatory arm and a Type C meeting with the U.S. Food and Drug Administration (FDA) to discuss proposed indication and phase 3 study designs.

The protocol for Study A16 was submitted in June 2015 followed by a Type C meeting with FDA in October 2016 to discuss analysis plans for this study. In August 2017, at a Type B meeting with the FDA, confirmatory study analysis plans and read methods for A16 and A05 were discussed. This was followed by the submission of the final A05 confirmatory phase blinded read manual and imaging review charter in December 2017.

The Applicant then submitted the final A05 confirmatory phase statistical analysis plan in January 2018 and the final A16 statistical analysis plan, neuropathology analysis plan, image review charter, and blinded read manual on August 30, 2018. In November 2018, a pre-NDA Type B meeting was held. Refer to Summary of Regulatory History (Section 12).

Issues Relevant to Evaluation of Benefit

The team identified the following issues relevant to the evaluation of benefit (see Section 6.4):

- User Guide for Tauvid PET Image Display (see Section 6.4.1)
- Limitations of Efficacy Evidence for Tau Pathology Detection (see Section 6.4.2)
- (b) (4)

Issues Relevant to Evaluation of Risk and Risk Management

The team identified the following issues relevant to the evaluation of risk and risk management (Section 7.7):

- CTE Misdiagnosis (see Section 7.7.1)
- Effect of MAO Inhibitors on FTP Binding (see Section 7.7.2)
- QT Interval Prolongation (see Section 7.7.3)

As AD is a serious and fatal disease, and a radiopharmaceutical for imaging aggregated tau pathology in the brain has the potential to contribute to the assessment of this debilitating disorder, this NDA was assigned a priority review.

3.1. Approach to the Review

The development of FTP included 23 completed trials. Table 3 (copied from the Applicant's NDA submission) provides an overview of these trials. In summary, these trials include

- Two phase 3 trials, Study 18F-AV-1451-A16 (A16) and the reader performance study, Study 18F-AV-1451-FR01 (FR01), to estimate the sensitivity and specificity of FTP to detect patients with B3 NFT pathology and high Alzheimer's Disease Neuropathological Change (ADNC) (as per National Institute on Aging Alzheimer's Association (NIA-AA) postmortem classification)
- Two phase 3 trials, Study 18F-AV-1451-A05 (A05C) and Study 18F-AV-1451-PX01 (PX01) (scan interpretation and analysis of cases that received FTP PET scans in therapeutic Study I8D-MC-AZES), to address the relationship between baseline FTP PET estimate of tau burden and 18-month decline in cognitive performance
- Additional completed supportive trials included the following:
  - Two trials, Study 18F-AV-1451-A05E (A05E) and Study 18F-AV-1451-TZAX (TZAX), to assess relationship between FTP PET signal and 18-month cognitive decline
  - Ten trials (T807000, 18F-AV-1451-A01, 18F-AV-1451-A03, 18F-AV-1451-A07, 18F-AV-1451-A09, 18F-AV-1451-A10, 18F-AV-1451-A11, 18F-AV-1451-A13, 18F-AV-1451-A15, 18F-AV-1451-A18) to assess tracer performance

- Two supportive longitudinal trials (18F-AV-1451-A04 and 18F-AV-1451-A08) to assess relationships between baseline FTP PET signal and longitudinal cognitive change; however, these trials differed from the two phase 3 trials A05C and PX01 in the duration of follow-up and the cognitive test procedures used to assess cognitive decline
- Five trials of investigational therapeutic drugs, H8A-MC-LZBE, I7X-MC-LLCF, I8D-MC-AZES, I8D-MC-AZET, and I8D-MC-AZED, which included FTP PET imaging

The team evaluated and analyzed all data related to the efficacy claims and safety of Tauvid. Based on the indications outlined in the proposed label on the (b) (4) the team primarily focused on the two trials submitted to support (b) (4) (A16 and FR01) (b) (4) The review included data verification and analysis of the primary and secondary endpoints.

- For the assessment of safety, the team conducted a detailed evaluation of the trial design, submitted data, and inferred conclusions. Data were assessed from all 23 trials submitted in the NDA. A total of 1,921 subjects received at least one dose of FTP. Dr. Jun Zhu and Dr. Jinzhong Liu from the clinical data scientist group at the FDA, provided verification and analyses of the raw safety data.
- For the assessment of efficacy, the team evaluated the following:
  - Design of the trials
  - Diagnostic performance (sensitivity and specificity) of two sets of five independent readers (Studies A16 and FR01) to interpret antemortem FTP PET scan images and detect a pattern of neocortical uptake that corresponds to NFT score B2 and B3 at autopsy
  - Performance (sensitivity and specificity) of an additional two separate sets of five independent readers (for Studies A05C and PX01) to assess whether the baseline FTP PET signal (specifically an "advanced AD" (τAD++, according to the objective image features described below) pattern) predicted a higher risk of subjects' clinically meaningful cognitive and functional deterioration within 18 months of the PET scan, as measured by a change in the Clinical Dementia Rating Scale Sum of Box (CDR-SB) scores from baseline
    Objective image features - FTP PET scans were interpreted as either "not consistent with an AD pattern" (τAD-); or "consistent with an AD pattern" (τAD+, τAD++) as follows:
    1. 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
    2. AD pattern (τAD)
       - τAD+: Increased neocortical activity in the PLT or occipital region(s) in either hemisphere
       - τAD++: Increased neocortical activity in the parietal/precuneus region(s), or frontal region(s) with increased uptake in the PLT, parietal, or occipital region(s) in either hemisphere
  - Inter-reader reliability

- For the assessment of image interpretation, the team, including experts from the Center for Devices and Radiological Health (CDRH), viewed a set of images from the pivotal studies provided by the Applicant as reviewer aids, reviewed and tested the instructions in the proposed prescribing information (PI) to image readers for Tauvid image interpretation.

Table 3. Summary of Completed Studies

Protocol No. Study Start – Stop Date	Study Drug Dose, Route & Frequency	Study Objective	No. of Subjects
Pivotal trials: Relationship between flortaucipir PET signal and pattern and distribution of tau at autopsy			
^{18}F-AV-1451-A16	370 MBq, IV	Relationship ante-mortem flortaucipir imaging and postmortem tau NFT and AD Neuropathic change	Scanned 156; Autopsy: 67 Supplemental Academic Autopsies: 16
^{18}F-AV-1451-FR01	No new doses	Relationship ante-mortem flortaucipir imaging and postmortem tau NFT and AD Neuropathic change Assess Inter-reader reliability	Autopsy cohort: 83 cases from Study A16 Target Population Cohort: 159 MCI and AD from Study A05C
Pivotal trials: Relationship between flortaucipir PET signal and 18-month cognitive decline			
^{18}F-AV-1451-A05C	370 MBq, IV	Relationship between flortaucipir PET Visual Interpretation and 18-month cognitive deterioration.	Enrolled 160 Scanned 159 97 MCI; 62 AD
^{18}F-AV-1451-PX01	No new doses 240 MBq, IV in AZES	Visual interpretation of flortaucipir PET and risk of meaningful deterioration on the CDR-SB in I8D-MC-AZES	205 141 AD, 64 MCI
Supportive trials: Relationship between flortaucipir PET signal and 18-month cognitive decline			
^{18}F-AV-1451-A05E	370 MBq, IV	Flortaucipir PET in AD, MCI, CN Longitudinal change in flortaucipir Preliminary relationship between flortaucipir signal and longitudinal cognitive change	Enrolled 223 Scanned 222 51 AD, 98 MCI, 58 OCN (≥50); 16 YCN (≥20 to ≤40 years of age) 1 MCI did not get scanned
^{18}F-AV-1451-TZAX	240 MBq, IV Baseline, 9 and 18 months	Visual interpretation of flortaucipir PET and risk of meaningful deterioration on the CDR-SB in study H8A-MC-LZAX Phase 3 solanezumab treatment study	206 AD 204 evaluable images
Other Supportive Longitudinal Trials			
^{18}F-AV-1451-A04	370 MBq, IV	Longitudinal change in flortaucipir PET signal	Enrolled 44 Scanned 37 (5 AD, 10 MCI, 1 ODD, 28 CN)
^{18}F-AV-1451-A08	240 MBq, IV at baseline and 12 months	Flortaucipir PET signal in subjects with MCI, AD, subjective memory complainers (SMC), and CN	Enrolled 89 Scanned 86 (5 AD, 11 MCI 45 SMC, 25 CN)

Protocol No. Study Start – Stop Date	Study Drug Dose, Route & Frequency	Study Objective	No. of Subjects
Phase I and II: Tracer Performance			
T807000	370 MBq, IV	Biodistribution and dosimetry Brain distribution and retention Safety	Enrolled 16 Scanned 10 3 low probability AD 7 high probability AD 1 high probability AD did not complete the scan
^{18}F-AV-1451-A01	370 MBq, IV	Brain uptake and retention relative to amyloid status and cognitive function Dosimetry Safety.	Enrolled 36 Cohort 1: 4 AD, 3 MCI, 4 OCN, 4 YCN, Cohort 2: 9 CN dosimetry Cohort 3 (florbetapir/MRI): N=7: 6 High Prob AD, 1 YCN
^{18}F-AV-1451-A03	370 MBq, IV Two sessions within 4 weeks	Test-retest reproducibility	Enrolled/Scanned 24 10 AD, 8 MCI, 6 CN
^{18}F-AV-1451-A07	370 MBq, IV	Flortaucipir as a biomarker for CTE (NFL players); Relationship between clinical presentation and flortaucipir	Enrolled 41 Scanned 39 28 CTE, 11 CN
^{18}F-AV-1451-A09	370 MBq, IV At baseline and (for CBD and PSP subjects) at 9 months	To evaluate flortaucipir for brain imaging of tau in subjects with PSP, CBD, and CN subjects	Enrolled/Scanned 29 20 PSP, 6 CBD, 3 CN
^{18}F-AV-1451-A10	240 MBq, IV at baseline. 10 subjects received a second dose at 1 year.	Kinetic modelling in patients in Alzheimer's disease and healthy controls.	Enrolled/Scanned 22 12 AD, 10 CN
^{18}F-AV-1451-A11	370 MBq, IV	Flortaucipir as a biomarker for repetitive head trauma (fighters) Relationship between clinical presentation and flortaucipir signal	Enrolled/Scanned 35 21 Impaired, 14 CN
^{18}F-AV-1451-A13	370 MBq, IV	Voxel wise comparison of flortaucipir PET signal and tau immunohistochemistry	Enrolled/Scanned 3 1 AD, 1 CN, 1 ODD
^{18}F-AV-1451-A15	No new doses	Urinary excretion data from subjects who were administered flortaucipir in Study A05	Enrolled 6 5 MCI, 1 OCN
^{18}F-AV-1451-A18	370 MBq, IV	Longitudinal change in flortaucipir PET in Study A05C subjects	Enrolled/Scanned 79 25 AD, 54 MCI
H8A-MC-LZBE	240 MBq, IV for each scan session	Biomarker for solanezumab efficacy	9 prodromal AD
I7X-MC-LLCF	240 MBq, IV for each scan session	Biomarker for LY3202626 efficacy	316 AD
I8D-MC-AZES	240 MBq, IV for each scan session	Biomarker for lanabecestat efficacy	Enrolled/Scanned 484 308 AD, 176 MCI 205 completed 18-month follow-up and were analyzed in study PX01
I8D-MC-AZET	240 MBq, IV for each scan session	Biomarker for lanabecestat efficacy	157 AD Scanned
I8D-MC-AZFD	240 MBq, IV for each scan session	Biomarker for lanabecestat efficacy	7 6 AD, 1 MCI

Source: Table 2.5.1.1 from the Applicant's NDA submission
Abbreviations: AD, Alzheimer's disease; CBD, corticobasal degeneration; CDR-SB, Clinical Dementia Rating Scale Sum of Box; CN, cognitively normal; CTE, chronic traumatic encephalopathy; IV, intravenous; MBq, megabecquerel; MC, multicenter; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NFT, neurofibrillary tangle; NFL, National Football League; OCN, old cognitively normal; ODD, orphan drug designation; PET, positron emission tomography; PSP, progressive supranuclear palsy; SMC, subjective memory complainers; YCN, young cognitively normal

Table 4. Clinical Trials Submitted[1] in Support of Safety

Parameter	Trial Population	Trial Design	Drug, Dose, Number Treated, Follow-Up Period	Number of Subjects Enrolled	Number of Centers and Countries
Summary	ISS, safety population	Open-label, single arm	FTP, 240/370 MBq, 1,921, 48 hours	1,921	322 centers; 8 countries
Trial identifiers	18F-AV-1451-A01 (A01); 18F-AV-1451-A03 (A03); 18F-AV-1451-A04 (A04); 18F-AV-1451-A05 (A05); 18F-AV-1451-A07 (A07); 18F-AV-1451-A08 (A08); 18F-AV-1451-A09 (A09); 18F-AV-1451-A10 (A10); 18F-AV-1451-A11 (A11); 18F-AV-1451-A13 (A13); 18F-AV-1451-A16 (A16); 18F-AV-1451-A18 (A18); T807000 (T807); H8A-MC-LZBE (LZBE); I7X-MC-LLCF (LLCF); I8D-MC-AZES (AZES); I8D-MC-AZET (AZET); I8D-MC-AZFD (AZFD); H8A-MC-LZAX (TZAX)				

Source: CSR and adsl.xpt
Calculations in the following tables are based on the 1,921 unique subjects from the 19 listed clinical studies.
[1] Includes all submitted clinical trials.
Abbreviations: FTP, flortaucipir F 18; ISS, integrated summary of safety; MBq, megabecquerel

4. Patient Experience Data

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Tau is a microtubule associated protein that promotes microtubule assembly and function. In disease, tau protein becomes hyperphosphorylated and forms misfolded aggregates that accumulate to form NFTs associated with neurodegeneration. Tau misfolding and aggregation occurs in several neurodegenerative diseases, the most common of which is AD. AD is defined pathologically by accumulated NFTs and the presence of beta-amyloid plaques.

The pharmacology of FTP was assessed in in vitro experiments that determined the binding affinity and selectivity for tau protein aggregates in purified human tau aggregates and postmortem human brain sections (Table 6). The dissociation constant (Kd) of FTP was determined on PHFs, an aggregated fibrillar form of tau, one of the defining neuropathologies of AD, extracted from human AD brain. A Kd of 0.68nM was determined for FTP by homologous competition. A Kd of 0.57nM was measured by saturation binding. These studies indicate that FTP binds potently to tau from human AD brain.

H3-AV-1451 (tritiated flortaucipir) binds with nanomolar affinities in brain homogenates and to tau fibrils isolated from patients with Alzheimer's disease or PSP. Tritiated flortaucipir also binds with similarly high affinities in brain homogenates devoid of tau pathology. This unexpected binding was demonstrated to be due to nanomolar affinities of tritiated flortaucipir for monoamine oxidase A and B enzymes.

Tritiated flortaucipir binds to recombinant human MAO-A protein with a single, high-affinity, and reversible binding site with a Kd of 1.6±0.4nM and a dissociation off rate $t_{1/2}$ of about 25 minutes.

Similarly, tritiated flortaucipir binds reversibly to human recombinant MAO-B at a single site with a Kd of 21±9nM. H3-AV-1451 high-affinity binding to human recombinant enzymes MAO-A and MAO-B was displaced by cold FTP itself with a Ki of 2.4nM and 45nM, respectively, in line with the Kd values measured with tritiated flortaucipir (Vermeiren et al. 2018).

After intravenous (IV) injection, FTP was rapidly eliminated from blood. Plasma radioactivity (including parent FTP and all its metabolites) fell below 10% of the theoretical maximum concentration by 5 minutes postdose. Parent FTP accounted for approximately 86% of plasma radioactivity at 5 minutes postdose, approximately 34% at 80 minutes postdose, and approximately 22% at 130 minutes postdose. Polar fractions 1 and 2 plus activity retained on the chromatography cartridge accounted for <10% of radioactivity in the 5-minute sample but >40% of activity at the final sampling time point (130 minutes). Additionally, two metabolites were detected in high-performance liquid chromatography/methanol soluble Fraction 3 and accounted for 30% to 35% of plasma radioactivity at ≥80 minutes postdose. The identity of the metabolites and their pharmacologic activity was not determined by the Applicant.

Exposure-response relationships for FTP have not been studied systematically. However, FTP was administered at 370 megabecquerel (MBq) (10 mCi) with a 20-minute image acquisition period in most Applicant-sponsored FTP studies, and at 240 MBq (6.5 mCi) with a 30-minute image acquisition period in studies where FTP was used for evaluation of AD disease progression. These doses and acquisition periods achieved the same count density.

Study A01 performed radiation dosimetry assessment in nine HV >50 years of age who received whole-body PET scans over approximately 6 hours after administration of 370 MBq (10 mCi) FTP. Following completion of Study A01 procedures, urinary excretion data were collected from six additional subjects in Study A15 to include assessment of the impact of urinary retention/excretion on radiation dosimetry.

The radiotracer biodistribution among subjects was consistent and showed rapid hepatobiliary clearance. Three organs received the highest estimated doses: upper large intestinal wall (0.0955±0.0134 mSv/MBq), small intestine (0.0845±0.0118 mSv/MBq), and liver (0.0572±0.00803 mSv/MBq). The effective dose was 0.0235±0.0016 mSv/MBq, which results in an estimated effective dose of 8.70 mSv for an anticipated 370 MBq (10 mCi) injection. This dose is comparable to the effective dose of approved 18F-labeled compounds such as fluorodeoxyglucose F 18 (FDG) and florbetapir F 18 (FBP).

Flortaucipir is metabolized by CYP1A2 and CYP2C8 and CYP3A4. In vitro data suggest that FTP would not be expected to cause clinically significant inhibition of the clearance of drugs metabolized by these CYP enzymes. The potential for flortaucipir to inhibit P-gp was evaluated in vitro using Madin-Darby canine kidney (MDCK)-MDR1 cells. Calcein-AM was utilized as a probe for P-gp transport, which was challenged with two different concentrations of flortaucipir (5μM and 25μM) to evaluate the potential for flortaucipir to inhibit P-gp. Neither 5μM nor 25μM flortaucipir resulted in appreciable inhibition of the bidirectional efflux of calcein-AM. Taken together, this demonstrates that P-gp inhibition by flortaucipir is unlikely.

Study A03 was designed to evaluate test-retest reproducibility of FTP for imaging of aggregated tau. HV and subjects with cognitive impairment underwent two FTP imaging sessions not <48 hours and not more than 4 weeks apart. A total of 24 subjects (10 AD, 8 mild cognitive impairment (MCI), 6 CN) enrolled in the study. Analysis of the primary outcome variable—test-retest reproducibility of FTP using intraclass correlation (ICC)—showed high test-retest agreement (ICC >0.9) for the whole cohort and across diagnostic groups for most individual brain regions and for the composite region of interest at 80–100 minutes postinjection. Similar results were obtained for scans at 110 minutes postinjection.

MAO Drug Interaction

FTP binds to MAO-A, MAO-B, and tau-NFTs with low nanomolar affinities. This binding of FTP to MAO-A and MAO-B could potentially affect the interpretation of FTP PET images.

MAO-A

Due to the structural similarity between FTP and MAO-A ligands such as harmine and F18-fluoroethyl harmol (FEH), the binding of FTP to MAO-A was evaluated in both in vitro and in vivo experiments. The Applicant determined that FTP binds to recombinant human MAO-A with a Kd of 2.0nM, a value similar to the value reported in the literature (Vermeiren et al. 2018).

The Applicant has provided clinical data from one unpublished study to demonstrate how MAO-A inhibitors may or may not affect the ability of FTP to reliably identify tau-NFT in brain areas afflicted by tau pathology in patients with MCI and AD.

MAO-B

The Applicant summarized the rationale for evaluating binding of flortaucipir to MAO-B as follows:

> *MAO-B is expressed by reactive astrocytes (Saura et al. 1994; Ekblom et al. 1994; Scholl et al. 2015; Rodriguez-Vieitez et al. 2016). In AD brain, reactive astrocytes are found in high tau regions, typically in association with neuritic plaques (Gulyas et al., 2011). Thus, the distribution of the PET signal for a tracer that binds MAO-B might overlap the distribution of a tracer that binds to tau. This was recently shown to be the case for 18F-THK-5351, which is known to bind to both NFT tau and to MAO-B (Harada et al., 2018). Although 18F-THK-5351 shows increased retention in cortex of patients with amyloid positive AD by comparison to controls (Harada et al., 2016), 10 mg selegiline, given p.o. 1 hour prior to scan, substantially reduced 18F-THK-5351 PET signal (36.7 to 51.8% regional reduction relative to baseline scan) (Ng et al., 2017).*

The Applicant did not observe binding of flortaucipir to recombinant MAO-B using conditions in which the MAO-B inhibitor safinamide bound to MAO-B with a Kd of 57nM and F18-THK-5351 had a Kd of 37nM. When the Applicant evaluated binding to commercial protein preparations with and without MAO-B, over a flortaucipir concentration range of 1nM up to 15μM, no significant binding of flortaucipir to MAO-B was observed.

In contrast to the Applicant's data, Vermeiren et al. reported a 21nM Kd for FTP binding to MAO-B by a filtration radioligand binding assay. The difference between the Applicant's data and Vermeiren et al.'s data may be due to assay design. When the Applicant performed the assay in a similar format as described in Vermeiren et al. using cold flortaucipir, results similar to those of Vermeiren et al. (apparent Kd of 28nM) were observed (Vermeiren et al. 2018).

Clinical MAO Inhibitor Effect on FTP Binding

The Applicant summarized their assessment of a prospective, randomized study by Matthews et al. reported on December 2019 at a Clinical Trials on Alzheimer's Disease, CTAD conference. In this study 50 patients with AD received flortaucipir scans before and after 6 months of treatment with the MAO-B inhibitor rasagiline or placebo.

Patients had a clinical diagnosis of probable AD supported by FDG PET at screening and a Mini-Mental State Examination (MMSE) of 11 to 26. Although the primary outcome variable was change in FDG PET, an exploratory evaluation compared flortaucipir scans at baseline and endpoint. The flortaucipir results are shown in Figure 1, illustrating the expected increase in tau over time.

In both the rasagiline and placebo groups, FTP uptake was stable or slightly increased from baseline to post-treatment in cortical regions. However, mean FTP uptake was decreased in some subcortical regions, most notably nucleus accumbens, putamen, and caudate.

In conclusion, FTP binds in vitro to both MAO-A and MAO-B. The distribution of the PET signal for a putative tau tracer that binds to MAO-B might overlap the distribution of a tracer that binds to tau-NFT because MAO-B is expressed by reactive astrocytes, which often colocalize with NFTs. In a clinical study in patients with AD, FTP PET signal was slightly reduced by the

MAO-B inhibitor rasagiline in vivo in low tau, high MAO-B areas such as nucleus accumbens, putamen, and caudate.

Thus, the preliminary (unpublished) clinical data cited by the Applicant demonstrates that FTP binding affinities to either MAO-A or MAO-B are generally low and occur in areas not involved in visual determination of AD diagnosis or prognosis by FTP. Further, MAO inhibitors have little or no effect on in vivo uptake of FTP. Therefore, it appears that there is little potential for MAO binding to affect Tauvid PET image interpretation. The language in the proposed label Image Interpretation (2.4) and Warnings and Precautions (5.1) sections states that "only uptake in neocortex should contribute to the interpretation of a positive Tauvid scan" would be adequate to mitigate any putative effect of MAO inhibitors on scan interpretation.

In addition to the amyloid-associated neocortical retention attributed to binding to AD NFTs, age-related retention of flortaucipir was seen in amyloid negative normal controls (Study A05E) in some mesial temporal lobe structures, specifically anterior and posterior hippocampus and amygdala. It is possible that some of this signal, particularly in hippocampus, could represent spill out from flortaucipir binding in the choroid plexus. This choroid plexus signal may represent binding to aggregated tau protein, but it could also reflect off-target binding. Alternatively, the elevated signal in the hippocampus/choroid plexus ROI may reflect age-related aggregation of tau independent of choroid plexus signal.

Presumed off-target elevations of FTP PET signal have also been observed in older Aβ-subjects in the midbrain (striatum) and in structures rich in neuromelanin including neurons in substantia nigra and subpial melanin-containing structures. Although potentially important for research purposes, these regions are outside of the proposed AD-associated neocortical areas examined for visual interpretation, and thus, the observed activity may or may not have impact on ability to visually interpret Tauvid PET scans.

The off-target binding potential of Tauvid to MAO-A and MAO-B has been described in Section 12 of the Tauvid prescribing information.

QTc Prolongation

The Applicant reported small but statistically significant increases in QTcB and QTcF intervals around 2 hours following IV administration of FTP when compared to baseline predose measurements.

A formal QT assessment was not conducted by the Applicant. In the clinical studies, singlet electrocardiogram measurements were conducted prior to FTP dose, immediately postdose (0 to 5 minutes postinfusion), and at the end of scan (approximately 90 to 120 minutes postinfusion). In the pooled safety analysis, there were small, statistically significant increases in QTcB and QTcF at the end of scan time point at each imaging visit that were not considered to be clinically significant. The mean change from predose in QT interval duration (Fredericia correction method; QTcF) of 5.14 msec (±12.09 msec; standard deviation (SD)) at approximately 90 to 120 minutes postinfusion was observed for 785 measurements. The absence of placebo- or active-compound comparator groups limits interpretation of these findings. The mean 5.14 msec increase in QTcF approximates the regulatory threshold of concern (5 msec); however, the upper limit of the 90% CI (equivalent to a one-sided 95% CI) was 5.85 msec, which is well below the 10 msec threshold of concern.

No subjects demonstrated an increase in QTcF >60 msec above baseline values. Only one subject had a >60 msec (61.5 msec) increase in QTcB from baseline to end of scan. The generally accepted upper limits of normal for QTc intervals in adult men and women is 450 ms and 460 ms, respectively. Both QT interval as well as the magnitude of increase in QT duration have been shown to predict the risk for developing Torsade de pointes (Tdp) and fatal arrythmias. A 10 ms increase in QTc has been shown to be associated with a 5 to 7% increase in the risk of developing Tdp. The risk of Tdp is also considered to markedly increase when the absolute QTc is >500 ms. The threshold for regulatory concern for QTc interval is >500 ms and for an increase in QTc interval is around 5 msec with the upper bound of the 95% CI being 10 ms.

The increases in QTcB and QTcF intervals around 2 hours following intravenous administration of FTP when compared to baseline predose measurements were statistically significant. However, these increases are deemed to be of no clinical significance for the following reasons:

- No subjects demonstrated a QTcB or QTcF interval >500 msec or an increase of 60 msec or greater above predose values.
- While the mean 5.14 msec increase in QTcF at the end of scan is close to the threshold of concern (5 msec), the upper limit of the 90% CI (equivalent to a one-sided 95% CI) was 5.85 msec, which is well below the 10 msec threshold of concern. Additionally, this was not observed immediately postinfusion of FTP when the maximum plasma concentration of FTP is highest, suggesting that it is unlikely to be related to FTP administration.
- No reported treatment-emergent adverse events were related to QT interval prolongation or ventricular arrhythmias in the pooled safety database.
- Flortaucipir was positive in the hERG assay, with a half maximal inhibitory concentration (IC_{50}) of 0.610μM. Based on a maximum 20 μg dose, the theoretical dose (5.2 L human blood) would be 3.8 ng/mL. According to the Applicant, "If the flortaucipir hERG channel IC_{50} is converted to a ng/mL concentration (161 ng/mL) and compared to the maximum theoretical flortaucipir peak plasma concentration in a subject given a 20-μg dose

(3.8 ng/mL), the safety margin is at least 42-fold. This calculation assumes a worst-case scenario that 100% of the drug is unbound and that the volume of distribution is restricted to the blood volume (about 5.2 L in an adult human). The safety margin increases to over 900-fold when accounting for plasma protein binding (fuhuman 0.047)." Thus, there is a large safety margin based upon the plasma concentrations of FTP and IC5o for hERG assay.

- The cardiovascular safety testing in dogs did not reveal any flortaucipir-induced adverse effects up to 100x and 50x maximum human dose (MHD) (allometrically scaled). The MHD of flortaucipir is 20 μg or 0.33 μg/kg for a 60 kg human. Thus, nonclinical in vitro cardiac safety hERG studies show a large exposure margin considering the low mass dose of FTP.
- Tauvid PET imaging is performed in a clinical setting and the patient is dosed only once, therefore the risk to patient is minimal.

This issue was also reviewed by QT Interdisciplinary Review Team (QT-IRT) and they concluded that no additional regulatory action was indicated.

Table 6. General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	Diagnostic PET imaging agent
Mechanism of action	The pharmacology of FTP was assessed in a series of in vitro experiments that determined the binding affinity and selectivity for tau protein aggregates in purified human tau aggregates and postmortem human brain sections. The dissociation constant (Kd) of FTP was determined on paired helical filaments, an aggregated fibrillar form of tau pathology which is one of the defining neuropathologies of AD, that were extracted from human AD brain. A Kd of 0.68nM was determined for FTP by homologous competition. A Kd of 0.57nM was measured by saturation binding. These studies indicate that FTP binds potently to tau pathology from human AD brain. H3-AV-1451 binds to multiple sites with nanomolar affinities in brain homogenates and to tau fibrils isolated from patients with Alzheimer's disease or those with PSP. H3-AV-1451 also binds with similarly high affinities in brain homogenates devoid of tau pathology. H3-AV-1451 binds to recombinant human MAO-A protein with a single, high-affinity, and reversible binding site with a Kd of 1.6±0.4nM and a dissociation off rate $t_{1/2}$of about 25 minutes. Similarly, H3-AV-1451 also binds reversibly to human recombinant MAO-B at a single site with a Kd of 21±9nM. H3-AV-1451 high-affinity binding to human recombinant enzymes MAO-A and-MAO-B was displaced by flortaucipir itself with a Ki of 2.4nM and 45nM, respectively, in line with the Kd values measured with H3-AV-1451 (Vermeiren et al. 2018).
Active moieties	
QT prolongation	There were small statistically (but not clinically) significant increases in QTcB and QTcF at the end of scan time point at each imaging visit. Overall, mean increase in QTcB at the end of scan time point was 2.34 msec and 5.14 msec for QTcF. The cognitive impaired group and cognitive normal group showed similar mean changes in QTcB and QTcF at the postdose and end-of scan time points. Mass dose ranged from 0.01 µg to 13 µg. No clinically meaningful or statistically significant correlation was seen between mass dose of FTP and SBP or DBP at either the postdose or end of scan time point.

Characteristic	Drug Information
	General Information
Bioanalysis	Formation of metabolites was estimated using a LC/MS/MS method. All analyses were qualitative and the relative abundance of metabolites was based on LC/MS peak intensity. The method was acceptable.
Healthy subjects versus patients	Whole body biodistribution of FTP appears to be similar in normal adults and patients.
Drug exposure at steady state following therapeutic dosing regimen (or single dose, if more relevant for drug)	Not applicable
Range of effective dose(s) or exposure	240–370 MBq
Maximally tolerated dose or exposure	Not applicable for medical imaging drug
Dose proportionality	Not applicable (drug is used only once)
Accumulation	The dug is administered only once, no accumulation expected
Time to achieve steady-state	Not applicable
Bridge between to-be marketed and clinical trial formulations	Not applicable
	Absorption
Bioavailability	The drug is injected intravenously and is available 100%
T_{max}	
Food effect (fed/fasted); geometric least square mean and 90% CI	Not applicable
	Distribution
Volume of distribution	Not reported
Plasma protein binding	The protein binding of FTP in human plasma was 94.7%. FTP protein binding in normal physiologic solutions of human serum albumin (4%) was 88.8%, which was similar to human plasma protein binding, suggesting that FTP is primarily bound to albumin.
Drug as substrate of transporters	FTP is not a P-gp substrate.

Characteristic	Drug Information
	Elimination
Mass balance results	Mass balance study not performed
Clearance	Not reported
Half-life	2 hours
Metabolic pathway(s)	FTP was rapidly eliminated from blood. Plasma radioactivity (including parent FTP and all its metabolites) fell below 10% of the theoretical maximum concentration by 5 minutes postdose. Parent FTP accounted for approximately 86% of plasma radioactivity at 5 minutes postdose, approximately 34% at 80 minutes postdose, and approximately 22% at 130 minutes postdose. Percent polar fractions 1 and 2 plus activity retained on the chromatography cartridge accounted for <10% of radioactivity in the 5-minute sample but >40% of activity at the final sampling time point (130 minutes). Additionally, two metabolites were detected in HPLC/methanol soluble. Fraction 3 accounted for 30% to 35% of plasma radioactivity at ≥80 minutes postdose. The identities of metabolites are not known.
Primary excretion pathways (% dose)	The drug is excreted by hepatobiliary and renal excretion route. The exact percentage amount excreted is not known.
	Intrinsic Factors and Specific Populations
Body weight	No studies conducted by the Applicant
Age	
Renal impairment	No studies conducted by the Applicant
Hepatic impairment	No studies conducted by the Applicant
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	Flortaucipir is metabolized by CYP1A2 and CYP2C8 and CYP3A4. In vitro data suggest that flortaucipir would not be expected to cause clinically significant inhibition of the clearance of drugs metabolized by these CYP enzymes.
Inhibition/induction of transporter systems	The potential for LSN3182568 (flortaucipir) to inhibit P-gp was evaluated in vitro using MDCK-MDR1 cells. Calcein-AM was utilized as a probe for P-gp transport, which was challenged with two different concentrations of flortaucipir (5μM and 25μM) to evaluate the potential for flortaucipir to inhibit P-gp. Neither 5μM nor 25μM LSN3182568 resulted in appreciable inhibition of the bidirectional efflux of calcein-AM. Taken together, this demonstrates that P-gp inhibition by flortaucipir is unlikely.
	Immunogenicity (for Biologics)
Bioanalysis	Not applicable
Incidence	Not applicable
Clinical impact	Not applicable

Abbreviations: AD, Alzheimer's disease; DBP, diastolic blood pressure; FTP, flortaucipir F 18; HPLC, high-performance liquid chromatography; LC/MS/MS, liquid chromatography-tandem mass spectrometry; MAO, monoamine oxidase; MBq, megabecquerel; MDCK, Madin-Darby canine kidney; P-gp, P-glycoprotein; PET, positron emission tomography; PSP, progressive supranuclear palsy; SBP, systolic blood pressure

5.1. Nonclinical Assessment of Potential Effectiveness

The nonclinical data support the diagnostic efficacy of Tauvid for PET imaging of PHF tau aggregates in AD based on the following findings:

- In vitro binding to native PHF-tau purified from human AD brain with subnanomolar affinity (Kd=0.57nM to 0.68nM)
- Ex vivo binding by autoradiography for native PHF-tau in postmortem human AD brain sections with a Kd of 4.5nM with little or no binding in $tau^{-}/A\beta^{+}$ brain sections
- FTP autoradiography signal strongly correlated with PHF-tau immunohistochemistry (r^2=0.9) on postmortem human AD brain sections and low for $A\beta_{42}$ immunohistochemistry (IHC) (r^2=0.08); >25-fold selectivity toward PHF-tau aggregates over Aβ
- Absence of FTP autoradiography signal from postmortem human brain sections from age-matched decedents
- FTP demonstrated specificity toward PHF-tau aggregates in AD compared to other tauopathies, e.g., PSP, Pick's disease (PiD), and CTE

Mechanism of Action

FTP is a F18-lableled diagnostic radiopharmaceutical for PET imaging that binds to hyperphosphorylated PHF-tau enriched within NFTs. NFTs develop and accumulate in the brain in a defined spatiotemporal manner and Tauvid PET imaging enables an assessment of their density and distribution in patients with cognitive impairment evaluated for AD. FTP is distinct from other approved PET imaging agents for the evaluation of AD due to binding to PHF-tau with no appreciable binding to Aβ.

6. Evidence of Benefit (Assessment of Efficacy)

6.1. Assessment of Dose and Potential Effectiveness

FTP Dose Selection

Studies T807000, A01, A05, and A10 showed FTP was selectively retained in neocortical regions of patients with AD known to accumulate tau-NFTs in the neuropathology literature. The washout of tracer in cognitively normal (CN) and Aβ- cognitively impaired subjects was sufficiently rapid to allow good visual and quantitative discrimination between CN/Aβ- and Aβ+ patients with AD.

As a diagnostic radiopharmaceutical, Tauvid is administered as a microdose of no more than 20 µg. No formal dose finding studies were conducted by the Applicant. The Applicant listed five studies to support clinical pharmacology section of this NDA (see Section 14). One study reported the use of 240 MBq (n=20, 10 HV and 10 patients with AD). All other studies used 370 MBq of FTP given as intravenous bolus injection. FTP was administered at 370 MBq with a 20-minute image acquisition period in most Applicant-sponsored FTP studies, and at 240 MBq with a 30-minute image acquisition period in studies where FTP was used to assess AD disease progression. These doses and acquisition periods achieve the same count density.

Therefore, it appears that both doses of 240 and 370 MBq have the potential of giving similar count density and thus image quality (effectiveness). A longer image acquisition period is necessary for the lower dose (240 MBq). This introduces the likelihood of motion related artefact during image acquisition. Therefore, a dose of 370 MBq (10 mCi) appears acceptable. Furthermore, whole-body effective dose for a FTP dose of 10 mCi (370 MBq) was calculated to be 8.70 mSv. The total effective dose is similar to that of other approved 18F radiopharmaceuticals.

Therefore, the proposed dose of 10 mCi (370 MBq) selected for pivotal trials was acceptable for the general patient population for which the indication is being sought. No bridging study was conducted by the Applicant for formulation. No exposure-response was studied by the Applicant.

6.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

6.2.1. Trial Design

To assess the utility of Tauvid to estimate the density and distribution of aggregated tau NFTs in patients with cognitive impairment being evaluated for AD, the Applicant conducted two neuropathologic correlation studies—the A16 autopsy study and the FR01 reader study. (b) (4) the Applicant conducted two longitudinal phase 3 studies, A05C and PX01.

A16 Autopsy Study *(see also Section 15.2)*

This phase 3 open-label trial was designed to assess the relationship between FTP retention in the brain measured with antemortem FTP PET imaging and postmortem assessment of tau-NFT pathology (Braak stage) (Braak et al. 2006) and associated NIA-AA pathological diagnosis (Hyman et al. 2012) in terminally ill subjects with Alzheimer's disease or MCI and terminally ill subjects who were cognitively normal. Five imaging physicians, blinded to clinical and neuropathological results, independently reviewed the FTP PET scans and opined on whether the images showed an AD tau pattern of FTP retention (τAD) or FTP retention in a non-AD pattern (τAD-). The trial was designed to test the hypotheses that (1) a τAD pattern of FTP retention would correspond to a B3 (Braak V/VI) pattern of tau accumulation at autopsy and (2) a τAD pattern of FTP retention would occur selectively in the presence of high amyloid burden such that cases with a τAD pattern of FTP retention would also meet criteria for high ADNC at autopsy.

The diagnostic performance (sensitivity and specificity) of individual readers (primary objective) or majority reads (secondary objective) for the identification of histopathological status (both tau and AD pathology) through interpretation FTP PET imaging were calculated.

Win criteria for sensitivity and specificity were proposed as a lower bound of the 95% CI ≥50% for the same three out of five individual readers (primary objective) and lower bound of the 95% CI ≥50% for the majority reading result (secondary objective). While an autopsy population is not generalizable to the intended use population, the design used in this trial is the most feasible design to obtain a truth standard (TS).

Study FR01 (FTP Reader 01 Study) *(see also Section 15.3)*

To serve as an additional phase 3 trial supporting NDA approval, following up on the recommendation made by the FDA at the pre-NDA meeting in February 2019, the Applicant conducted the FTP reader study (FR01) to demonstrate that FTP reader performance is generalizable and reproducible in a population of intended use. The overall strategy for this study is similar to that implemented for the approved three amyloid PET agents. The study was designed to evaluate inter- and intrareader reproducibility of FTP PET on both a population that had autopsy TS (A16) and a population of intended use that did not have such a TS (A05).

For this study, five new independent imaging physicians blinded to demographic and clinical data received image reading training similar to the A16 autopsy and A05 studies. After training, all scans were read from the A16 study and a randomly selected subset of scans were read from the (b) (4) A05C study. Additionally, to assess intrareader reliability, a subset of 20 cases that were randomly selected and viewed were reread. The primary endpoints for this study focused on diagnostic performance versus autopsy TS, and on inter-reader reliability across all included cases. Win criteria for diagnosis and characterization of both the primary and secondary endpoints are the same as those established for A16.

For both A16 and FR01, agreement across readers was assessed and the lower bound of the 95% CI for Fleiss' kappa was deemed acceptable if it was ≥0.6.

Study A05C *(see also Section 15.4)*

This is a cross-sectional and longitudinal observational trial designed to confirm the relationship between FTP uptake in the brain as measured using FTP PET brain imaging and the subsequent rate of cognitive and functional decline observed over longitudinal follow-up.

The primary hypothesis of this study was to evaluate, using a Cox proportional hazard model, if the hazard of progressing to a clinically meaningful event of at least a 1 point or more increase in CDR-SB score within 18 months would be significantly greater for subjects with FTP scans rated (by the majority of the five readers) as a τAD++ pattern, as compared to those with scans rated as showing a non-τAD++ (τAD- and τAD+ but not τAD++) pattern.

The key secondary analysis used dichotomized CDR-SB change (1 point or more increase versus otherwise) as a TS to assess the performance (sensitivity and specificity) of baseline τAD++ status (as determined by both the majority and individual readers) for detecting subjects who would experience a 1 point CDR-SB change.

Comment: *During study planning under IND 119863, the review division recommended that this analysis designated as "key secondary" instead serve as a primary basis for experimental testing. The study's success criteria, for both sensitivity and specificity endpoints, would require that at least the same three of five independent readers have lower bounds of two-sided 95% CIs >50%.*

With regard to performance of strictly clinical evaluation at baseline, the clinical evaluators would need to be blinded to FTP PET results to make baseline predictions as to whether or not each A05 subject will meet the same 1-point CDR-SB endpoint at 18 months for clinical deterioration at follow-up. If necessary, these clinical predictions could be obtained retrospectively by presenting clinical evaluators with baseline neuropsychological results and other baseline clinical information.

For the sake of efficient development, the Applicant declined the suggestion for additional investigation under a no-imaging control condition. In the absence of comparative performance data for investigational products (IPs), the following outcome cannot be excluded, a general limitation of against-threshold reader performance studies, including both A16 and A05C: [reader + IP > chance] and [clinician + IP ≤ clinician]. Nevertheless, to the extent reader and clinician performance are established to be high and low, respectively, this possible outcome may be of no concern.

Additional exploratory analyses evaluated the hazard ratios (HRs) and diagnostic performance for FTP PET relative to clinically meaningful change in Clinical Dementia Rating Scale (CDR) global (change >0), MMSE (3 or more points decrease), Pfeffer Functional Activities Questionnaire (FAQ) (3 or more points increase) and Alzheimer's Disease Assessment Scale (ADAS) (4 or more points increase), and also evaluated an alternative threshold for CDR-SB (2.5 points or greater increase). Mixed model with repeated measures (MMRM) analyses also modeled mean change in each cognitive/functional variable as related to majority FTP visual interpretation.

Study PX01 ***(see also Section 15.5)***

As the prespecified success criteria for the above Study A05C were not met, following up on the discussions at the pre-NDA meeting, the Applicant designed this study using scans from placebo subjects in the AZES therapeutic trial. Similar to Study A05C, the primary hypothesis tested in Study PX01 was that the risk of progressing to the clinically meaningful event as determined by CDR-SB value change (1-point or more increase) within 18 months would be significantly greater for subjects with FTP scans rated (by the majority of the five readers) as τAD++, as compared to those with scans rated as non-τAD++ (τAD- and τAD+ but not τAD++). Secondary analyses evaluated the risk ratios for FTP PET relative to clinically meaningful change in CDR Global (change >0), MMSE (3 or more points decrease), FAQ (3 or more points increase) and ADAS (4 or more points increase). MMRM analyses also modeled mean change in each cognitive/functional variable as related to majority FTP visual interpretation.

The inter-reader and intrareader reliability of the PET interpretation across the five independent readers for both A05C and PX01 trials was assessed using Fleiss' kappa statistics. The lower bound of the 95% CI for Fleiss' kappa was deemed acceptable if it was ≥0.6

A detailed summary of the design for A16, FR01, A05C, and PX01 studies is located in Section 15.2.

Comment: *The guidance for industry on developing medical imaging drugs (June 2004) and the Code of Federal Regulations (21CFR 315.5) state that a drug's effectiveness can be evaluated by assessing its ability to provide useful clinical information related to its proposed indication, which includes structure delineation; disease or pathology detection; functional, physiological or biochemical assessment; and diagnostic and therapeutic patient management. The design of Studies A16 and FR01 taken together has the potential to evaluate FTP's ability to detect pathology, tau-NFTs, one of the two pathological hallmarks of AD. However, there is a limitation that arises from the chosen neuropathological threshold of B3 level of NFT pathology to define a positive AD FTP pattern (see Section 6.4 for further details).*

The two longitudinal (b) (4) *trials, A05C and PX01, were designed to evaluate FTP's ability in functional assessment, i.e., predict a change in patient's functional outcome based on the level of NFT pathology detected by FTP. Contrary to the Division's recommended preference at the pre-NDA meeting for prospectively-collected, independent datasets to test hypotheses, the PX01 study included in this NDA is a retrospective analysis of scans from a tau imaging substudy of the AZES therapeutic trial in a population that had higher baseline risk for AD. The limitation of a retrospective analysis in this setting with the exclusion of dropouts imposes a selection bias because of which the results may not be generalizable across a broader population. Further, the amyloid positivity inclusion criterion utilized in this trial reflects a different study population when compared to Study A05, which did not have that subject inclusion criterion.*

6.2.2. Eligibility Criteria

For Study A16, males or females ≥50 years of age who had a projected life expectancy of ≤6 months as determined by the principal investigator were eligible. Patients with suspected encephalopathy, a clinically significant infectious disease or those who were aggressively being treated with life sustaining measures or known to have a structural brain lesion that would interfere either with PET imaging or pathological assessment were ineligible. Subjects with a history of risk factors for Torsades de Pointes or are taking drugs that are known to cause QT were also ineligible. For Study A05C, male or female subjects ≥50 years of age with clinically defined MCI and AD dementia with MMSE between 20 and 27 inclusive were eligible.

No new subjects were enrolled in both FR01 and PX01 studies. For Study FR01, images from the A16 and A05C studies were selected and used to test the reader training and inter/intrareader reliability. While no new subjects were enrolled for PX01, images from a subset of patients who underwent Tau imaging as part of the AZES therapeutic trial were included. The AZES therapeutic trial included males or females, aged 55 to 85 years, with MCI due to AD or with mild AD dementia. Unlike the other three studies (A16, FR01, and A05C), patients for the AZES trial whose images were used in the PX01 study were required to have documented amyloid pathology as measured by Florbetapir F 18 PET or CSF Aβ1-42.

6.2.3. Statistical Analysis Plans

Study A16 (Autopsy)

A Clinico-Pathological Study of the Correspondence Between FTP PET Imaging and Postmortem Assessment of Tau Pathology

Approximately 200 subjects with terminal medical conditions and projected life expectancy of ≤6 months were to be enrolled and imaged with FTP in order to obtain postmortem histological data on approximately 80 subjects. This was to include up to six subjects in a front-runner cohort (unblinded initial autopsy cases for evaluating and refining pathology and FTP PET read methods; they are not included in the primary efficacy analyses) and up to 74 subjects in the primary efficacy analysis cohort).cohort (for exploratory analysis) and up to 74 subjects in the primary efficacy analysis cohort (for confirmatory analysis).

The Applicant was not blinded to the front-runner imaging and pathology results. These results were analyzed on a subject-by-subject basis and were used to refine the PET or autopsy methods (e.g., pathology staining, quantitation methods, etc.). Upon completion of the final front-runner subjects analysis, the final imaging and autopsy methods were specified.

For the primary efficacy analysis, the diagnosis performance (sensitivity, specificity) of five independent readers' interpretation of antemortem FTP PET scan images (τAD++/τAD+ or τAD-) for detection of a pattern of neocortical uptake that corresponds to NFT score B3 at autopsy were to be evaluated.

The sensitivity and specificity along with their 95% CIs based on the Wilson score method were to be calculated for each of the five readers. The first primary hypothesis was to be considered

met if the lower bounds of sensitivity and specificity were ≥50% for at least three of the five readers.

The Efficacy Analysis Set 1 was to include all safety analysis set subjects (provided informed consent and received study drug) recruited under this protocol who fulfilled all of the following:

- Came to autopsy *after* the front-runner cohort (i.e., excluding the first three subjects who came to autopsy)
- Had valid and evaluable PET data
- Had valid and interpretable autopsy specimens, where interpretability was to be assessed for the Braak stage

Primary efficacy analysis hypothesis 2 would be the same as the first primary hypothesis except that the NIA-AA autopsy criteria would be used to define the TS. Both primary hypothesis 1 and primary hypothesis 2 would need to be significant at the two-sided 0.05 significance level for the study to be considered positive.

Study FR01

The objective of this reader study was to assess the accuracy and reliability of FTP PET scan interpretation. After training, readers were to independently read 241 scans: 82 from Study A16 and 159 from Study A05C. Fleiss' kappa was to be used to assess the inter-reader reliability in FTP visual scan interpretation.

Study A05C

The exploratory (first) phase of this study (Study A05E) identified a pattern of FTP retention that (1) is unique to amyloid-positive subjects, (2) is consistent with the expected pattern of tau distribution in AD, and (3) increases in density and extent with disease severity. Moreover, within the τAD pattern subjects it would be possible to identify a group (τAD++) that appeared to have an increased risk for worsening of cognitive impairment over 18 months. The confirmatory phase was, thus, informed by the exploratory phase, and was designed to test the exploratory phase findings in an independent subject population.

Approximately 150 subjects were to be enrolled in the confirmatory (second) phase of the study. The efficacy population was to include all subjects with a valid and interpretable PET image and at least one clinical/cognitive assessment.

The primary efficacy variable in Study A05C was a dichotomized CDR-SB score change from baseline (1 point or more increase versus otherwise). Time to first occurrence of this clinically meaningful event was to be modeled using a Cox proportional hazard model by baseline tau status as determined by majority FTP scan visual reading results from five independent imaging physicians. Then the hazard ratio of τAD++ rated subjects progressing to the event when compared to non-τAD++ rated subjects along with the 95% CI was to be calculated. The Cox proportional hazard model was to be adjusted for baseline age, American National Adult Reading Test (ANART) scores, and baseline CDR-SB scores. The specific hypothesis for testing was that the hazard of progressing to this clinically meaningful event as determined by CDR-SB value change within 18 months would be significantly greater for subjects with FTP scans rated as τAD++, as compared to those with scans rated as non-τAD++ (τAD- and τAD+ pattern).

Secondary Analysis

The secondary analysis of Study A05C was to use dichotomized CDR-SB change at 18 months (1 point or more increase versus otherwise) as a TS to assess the diagnostic performance of baseline tau status as determined by a FTP scan. The assessments were to be conducted for each of the five independent imaging readers. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-) were to be calculated.

The CIs around sensitivity, specificity, accuracy, NPV, and PPV were to be calculated using the Wilson score method. The key secondary hypothesis for testing is that, of the five independent imaging physicians, at least the same three will have the lower bounds of two-sided 95% CIs $\geq$50%, for both sensitivity and specificity.

To control the overall type I error rate at a 2-sided 0.05 level, a gate keeper methodology would be employed. Hypotheses would be tested in the following order:

1. Testing of hypothesis for primary objective analysis
2. Testing of hypothesis for secondary objective analysis

Hypothesis testing would begin testing (1) at the 0.05 level. If the p-value is $\leq$0.05, the second hypothesis would be tested.

Intrareader Agreement

Twenty scans from the confirmatory cohort were randomly selected for the evaluation of intrareader agreement. These 20 scans were then assigned with two unique randomization codes each and randomized into the reading sequence along with all other scans in order to be read twice by the same readers in a random sequence.

Study PX-01

The D5010C00009 (AZES) study was a multicenter, randomized, double-blind placebo-controlled, parallel-group, longitudinal study evaluating the efficacy of an investigational therapeutic drug in subjects with early AD. The primary efficacy measure of the study was Alzheimer's Disease Assessment Scale–Cognitive Subscale 13 (ADAS-Cog13).

Subjects who underwent FBP PET scanning at screening in the main D5010C00009 study to document the presence of amyloid for study inclusion and participated in the longitudinal amyloid PET substudy were also to have an FTP PET scan performed at baseline, Weeks 52 and 104 at the participating sites. Subjects who established eligibility by historical amyloid scan were not eligible to participate in the FTP (tau) addendum unless they also had an optional, subsequent FBP scan as a part of the main D5010C00009 study. To achieve this goal, FTP PET measurements were to be conducted in at least 500 subjects. Once the randomization targets for Addendum 2 had been reached, enrollment was to be considered complete and, at the discretion of the Applicant, enrollment of additional subjects may have been stopped. FTP PET scanning was to be conducted under the management of a central PET vendor.

More than 400 subjects received a bolus injection of FTP and quantitative imaging as part of a tau addendum. However, not all subjects had the opportunity to complete the full-term follow-up.

The Applicant included only the subjects who had (1) a valid baseline FTP scan (no later than 91 days post randomization, considering that the FTP scans were added to this study after the initiation of AZES); and (2) a CDR assessment at 18 months visit. A total of 205 subjects met these criteria, and approximately 90 of these subjects completed a CDR assessment at the 24-month visit.

Five independent radiologists or nuclear medicine physicians visually interpreted the PET scans from the 205 qualified subjects as either τAD++ (a pattern indicating spread of aggregated tau beyond the posterolateral temporal (PLT) or occipital lobe), τAD + (a pattern indicating aggregated tau confined to posterolateral temporal/occipital lobe) or τAD- (inconsistent with an AD pattern). The primary hypothesis tested by this study is that the risk of clinically meaningful cognitive deterioration would vary as a function of FTP PET scan status at baseline.

This analysis was to test the hypothesis that the risk of progressing to a clinically meaningful event (1 point or more increase) as determined by CDR-SB value change at 18 months would be significantly greater for subjects in the τAD++ group as compared to those in the non-τAD++ group (τAD- and τAD+). Since the study goal is to evaluate the risk ratio of τAD++ group versus non-τAD++ group at Month 18 instead of marginal risk ratio by tau status, only Month-18 measurements were to be included for this analysis.

The primary efficacy variable was the dichotomized CDR-SB score change from baseline (CFB) (1 point or more increase versus otherwise). Incidence of this clinically meaningful event by tau visual read groups was to be compared using a log-linear model adjusted for investigational therapeutic drug treatment arm (low dose, high dose, or placebo), baseline age, years of education (categorical), and baseline CDR-SB score. The Poisson distribution was chosen to describe the distribution of the dependent variable and a log link function was to be used to model the risk ratio. To improve the model's stability and reliability, a modified Poisson regression model (Zou 2004) was to be applied using a robust error variance estimation, although there is only one observation per subject. The risk ratio of τAD++ rated subjects progressing to the event over non-τAD++ rated subjects along with the 95% CI was to be provided.

Diagnostic Performance of Baseline Tau Status in Predicting Clinically Meaningful Deterioration Evaluated by CDR-SB

This analysis was to use dichotomized CDR-SB change (1 point or more increase versus otherwise at 18 months) as a TS to assess the diagnostic performance of baseline tau status as determined by FTP scan. Sensitivity, specificity, accuracy, PPV, and NPV were to be presented in a table, along with their respective 95% Wilson score CIs.

6.3. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

In the study [redacted], A05, the study population was appropriate [redacted]. In the autopsy study, A16, the study population is not the intended population [redacted] due to the need for a sufficient number of study subjects to go to autopsy in a feasible timeframe.

Of the 64 subjects in the primary efficacy cohort of A16, 62 subjects (96.9%) were white, and 34 subjects (53.1%) were female. The mean age was 82.5 years (range 55 to 100 years). Among the 49 subjects with dementia, 47 subjects (95.9%) were white and 28 subjects (57.1%) were female. The median and the range of the duration of time (#days) between the FTP PET and autopsy for these 64 subjects was 59.5 days (1 – 264 days). Additional characteristics of the primary A16 cohort are summarized in Table 7.

Table 7. Study A16 Baseline Demographics of Primary Cohort

		Most Recent Neurological Disease Diagnosis[a]			Total (N = 64)
Characteristic Category	Statistic	Normal (N = 14)	Mild Cognitive Impairment (N = 1)	Dementia (N = 49)	
Age (years)	n	14	1	49	64
	Mean	78.6	76.0	83.8	82.5
	SD	12.06	-	8.63	9.59
	Median	78.5	76.0	84.0	83.5
	Min, Max	55, 97	76, 76	59, 100	55, 100
<65 years	n (%)	2 (14.3)	0	1 (2.0)	3 (4.7)
≥65 to <75 years	n (%)	4 (28.6)	0	5 (10.2)	9 (14.1)
≥75 years	n (%)	8 (57.1)	1 (100.0)	43 (87.8)	52 (81.3)
Birth gender					
Male	n (%)	8 (57.1)	1 (100.0)	21 (42.9)	30 (46.9)
Female	n (%)	6 (42.9)	0	28 (57.1)	34 (53.1)
Race					
Asian	n (%)	0	0	1 (2.0)	1 (1.6)
Black or African American	n (%)	0	0	1 (2.0)	1 (1.6)
White	n (%)	14 (100.0)	1 (100.0)	47 (95.9)	62 (96.9)
American Indian or Alaska native	n (%)	0	0	0	0
Native Hawaiian or other Pacific Islander	n (%)	0	0	0	0
Ethnicity					
Hispanic or Latino	n (%)	2 (14.3)	0	1 (2.0)	3 (4.7)
Not Hispanic or Latino	n (%)	12 (85.7)	1 (100.0)	48 (98.0)	61 (95.3)

Source: Page 62 of Applicant's Study Report for Study A16
[a] Most recent neurological diagnosis collected prior to subject's most recent FTP PET scan. Subjects were classified by their neurological history by the referring physician at the time of entry into the study. No formal neurological diagnosis was done as part of the study.
Abbreviations: N, number of subjects in group; n, number of subjects with given characteristic; SD, standard deviation

Subject disposition for all subjects enrolled, defined as subjects who provided informed consent, completed screening evaluations, and received at least one injection of FTP, is summarized in Table 8. The enrolled consisted of 156 subjects: 103 subjects with dementia, three subjects with MCI, and 50 cognitively normal subjects.

Of the 70 subjects who died during the study, three did not come to autopsy. Thus, 67 subjects completed the study, defined as subjects who died and who had a valid FTP PET scan and valid autopsy results: 52 subjects with dementia, 1 subject with MCI, and 14 cognitively normal subjects.

Table 8. Study A16 Patient Disposition

		Most Recent Neurological Disease Diagnosis[A]			
Disposition	Statistic	Normal (N=50)	Mild Cognitive Impairment (N=3)	Dementia (N=103)	Total (N=156)
Received the ^{18}F-AV-1451 Injection	n (%)	50 (100.0)	3 (100.0)	103 (100.0)	156 (100.0)
Completed the Study[B]	n (%)	14 (28.0)	1 (33.3)	52 (50.5)	67 (42.9)
Died during the Course of the Study[C], but Autopsy Not Performed	n (%)	0	0	3 (2.9)	3 (1.9)
Discontinued Early from the Study	n (%)	36 (72.0)	2 (66.7)	48 (46.6)	86 (55.1)
Reason for Early Discontinuation from the Study[D]					
Withdrawal by Subject or Next of Kin	n (%)	2 (5.6)	0	0	2 (2.3)
Invalid Data	n (%)	0	0	1 (2.1)	1 (1.2)
Physician Decision	n (%)	0	0	2 (4.2)	2 (2.3)
Survival Greater than 9 Months Post Most Recent Scan	n (%)	1 (2.8)	2 (100.0)	36 (75.0)	39 (45.3)
Study Terminated by Sponsor	n (%)	30 (83.3)	0	5 (10.4)	35 (40.7)
Lost to Follow-up	n (%)	0	0	1 (2.1)	1 (1.2)
Other	n (%)	3 (8.3)	0	3 (6.3)	6 (7.0)

Source: Page 124 of Applicant's Study Report for Study A16
*Note: Three "frontrunners" excluded from A16 analysis per protocol, as prespecified by the Applicant since this data were unblinded early for the Applicant planning purposes
Note: Percentages are based on the number of enrolled subjects reported in each column
[A] Most recent neurological diagnosis collected prior to subject's most recent FTP PET scan
[B] For the analysis purpose, study completion is defined as having died within 9 months after most recent FTP PET scan for subjects with mild cognitive impairment or dementia and after most recent FTP PET scan, but during the course of the study for cognitively normal subjects and had an autopsy performed
[C] Within 9 months after most recent FTP PET scan for subjects with mild cognitive impairment or dementia and after most recent FTP PET scan, but during the course of the study for cognitively normal subjects
[D] Percentages are based on the number of subjects who discontinued early from the study reported in each column
Abbreviations: N, number of subjects in group; n, number of subjects with disposition

In the primary cohort (N=64) of Study A16, using the prespecified B3 threshold, the lower limit of the 95% CI for sensitivity ranged from 80% to 91% across the five readers, while the lower limit of the 95% CI for specificity ranged from 34% to 75% across the five readers (Table 9). Three of the five readers achieved lower bounds on both sensitivity and specificity that were >50%. For the majority read, sensitivity (95% CI) was 92% (80, 97) and specificity was 80% (61, 91).

Table 9. FTP PET Scan Interpretation (τAD+/++ or τAD-) Versus Autopsy NFT Score Truth Standard (B3 Defines Positive)

Reader	True Positive	True Negative	False Positive	False Negative	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV	NPV
1	38	17	8	1	97 (87, 100)	68 (48, 83)	83	94
2	36	23	2	3	92 (80, 97)	92 (75, 98)	95	88
3	36	22	3	3	92 (80, 97)	88 (70, 96)	92	88
4	36	19	6	3	92 (80, 97)	76 (57, 89)	86	86
5	39	13	12	0	100 (91, 100)	52 (34, 70)	76	100
Majority Read	36	5	3	20	92 (80, 97)	80 (61, 91)	88	87

Abbreviations: AD, Alzheimer's disease; τAD-, neocortical uptake not consistent with AD; τAD+, neocortical uptake consistent with AD; τAD++, neocortical uptake consistent with AD and likely to progress; CI, confidence interval; FTP, flortaucipir F 18; PET, positron emission tomography; NFT, neurofibrillary tangle; PPV, positive predictive value; NPV, negative predictive value

Table 10 shows the patient disposition for the confirmatory phase of Study A05, i.e., A05C. A total of 160 subjects (AD, n=62 and MCI, n=98) were included in the enrolled population of the study. The enrolled population consisted of all subjects who had signed informed consent and had data in the electronic data capture system. The safety population (n=160) consisted of all subjects who received at least one dose injection of either FTP or FBP. The efficacy population (n=159 (AD, n=62 and MCI, n=97)) included all subjects who received an injection of FTP and had valid FTP imaging data available (either visual reads or SUVr). A total of 111 subjects (AD, n=35 and MCI, n=76) completed the confirmatory phase of the study. Forty-nine subjects (AD, n=27 (43.5%) and MCI, n=22 (22.4%)) discontinued from the study.

Table 10. Study A05C Patient Disposition

	AD (N=62)	MCI (N=98)	Total (N=160)
Total Number of Subjects			
All Enrolled Population [a]	62 (100.0%)	98 (100.0%)	160 (100.0%)
Safety Population [b]	62 (100.0%)	98 (100.0%)	160 (100.0%)
Florbetapir Safety Population [c]	62 (100.0%)	98 (100.0%)	160 (100.0%)
Baseline Scan	62 (100.0%)	98 (100.0%)	160 (100.0%)
Flortaucipir Safety Population [d]	62 (100.0%)	98 (100.0%)	160 (100.0%)
Baseline Scan	62 (100.0%)	98 (100.0%)	160 (100.0%)
Efficacy Population [e]	62 (100.0%)	97 (99.0%)	159 (99.4%)
Completed	35 (56.5%)	76 (77.6%)	111 (69.4%)
Terminated	27 (43.5%)	22 (22.4%)	49 (30.6%)

Source: page 81 of Applicant's Study report
Note: Percentages are based on the number of enrolled subjects in each diagnosis group.
[a] The all enrolled population consists of all subjects who signed informed consent and have data in the EDC system.
[b] The safety population consists of all subjects who received at least one dose injection of either Flortaucipir or Florbetapir F 18.
[c] The Florbetapir safety population consists of all subjects who received at least one dose injection of Florbetapir F 18.
[d] The Flortaucipir safety population consists of all subjects who received at least one dose injection of Flortaucipir.
[e] The efficacy population includes all subjects with valid interpretable PET images and at least one clinical/cognitive assessment.
[f] Reason for termination percentages use the safety population as the denominator.
Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; N, number of subjects in group

Baseline demographic characteristics for subjects in the A05C safety population are presented in Table 11. The mean age of the safety population was 72.9 years (range of 50 to 97 years). The mean age of subjects with AD was 73.6 years, compared with 72.5 years for subjects with MCI. The percentage of male and female subjects was 53.8% and 46.3%, respectively. Overall, 96.9% of subjects were Caucasian, followed by African Americans (1.9%) and Asians (1.3%). Most subjects (94.4%) were of non-Hispanic ethnicity.

Mean weight in the overall safety population was 75.63 kg, with a range of 63.7 to 86.1 kg, and a mean height of 168.36 cm (range of 160.0 to 176.3 cm). More than half (53.1%) of the subjects in the overall safety population had completed a college or university education and 23.1% had completed graduate school. (b) (4)

Table 11. Study A05C Baseline Demographics

	AD (N=62)	MCI (N=98)	Total (N=160)
Age (years)			
n	62	98	160
Mean	73.6	72.5	72.9
SD	9.53	9.69	9.61
Median	75.0	73.0	73.5
Min, Max	50, 90	51, 97	50, 97
25th pct, 75th pct	68, 80	68, 79	68, 80
Sex			
Male	32 (51.6%)	54 (55.1%)	86 (53.8%)
Female	30 (48.4%)	44 (44.9%)	74 (46.3%)
Race			
Asian	1 (1.6%)	1 (1.0%)	2 (1.3%)
Black Or African American	0	3 (3.1%)	3 (1.9%)
White	61 (98.4%)	94 (95.9%)	155 (96.9%)
American Indian Or Alaska Native	0	0	0
Native Hawaiian Or Other Pacific Islander	0	0	0
Other	0	0	0
Ethnicity			
Not Hispanic or Latino	58 (93.5%)	93 (94.9%)	151 (94.4%)
Hispanic or Latino	4 (6.5%)	5 (5.1%)	9 (5.6%)

Source: Page 313 of Applicant's Study Report
Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; pct, percentile; N, number of subjects in group; n, number of subjects with characteristic; SD, standard deviation

Study FR01 was a rereading of scans from Studies A16 and A05C by five new readers. Therefore, the subject disposition and demographics for FR01 can be obtained from the same information for Studies A16 and A05C that was presented above.

The team also evaluated FR-01 study, in which the scans from both studies A05-C and A16 were pooled and reread in random order. The overall Fleiss' kappa across the five new readers across all scans was estimated as 0.87 with a 95% CI of (0.83, 0.91). The lower bound of 0.83 exceeded the prespecified success criterion of 0.6. Among the 241 scans that were reread, all five readers agreed on 209 scans, four readers agreed on 19 scans, and three readers agreed on 13 scans.

Table 12 shows the number of FTP positive scans according to the majority of readers, Fleiss' kappa results and distribution of agreement among readers on tau pathology characterization.

Table 12. Fleiss' Kappa Results and Distribution of Agreement for Tau Pathology Characterization

Study	N	Number Designated Positive by Majority Read	Kappa	3 Agree	4 Agree	5 Agree
A16 primary	64	41	0.85 (0.81, 0.89)	9	5	50
A16 including supp	82	46	0.83 (0.79, 0.86)	11	5	66
FR01 ALL	241	141	0.88 (0.86, 0.90)	13	19	209
FR01 (A16, subgroup of patients who are terminally ill)	82	49	0.82 (0.78, 0.86)	6	10	66
[redacted]						

(b) (4)

Source: FDA primary statistical reviewer's analysis
Abbreviations: N, number of subjects in group

6.4. Review Issues Relevant to the Evaluation of Benefit

The team concluded that the results of the submitted phase 3 studies support the efficacy of Tauvid to estimate the density and distribution of aggregated tau-NFTs in the indicated patient population (efficacy for tau pathology detection). The team concluded that [redacted]

(b) (4)

Early in the review cycle, the team communicated to the Applicant that Tauvid was not approvable without development of additional guidance for image display, therefore this issue is discussed first in Section 6.4.1.

The next two efficacy issues were addressed via revision of the proposed indication and other major PI sections. Limitations of the evidence supporting tau pathology detection and the team's rationale [redacted]

(b) (4)

(b) (4)

6.4.1. User Guide for Tauvid PET Image Display

The PI has been revised to provide adequate guidance for users to display Tauvid PET images.

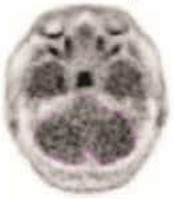
Background

Per standard of care, PET images, including Tauvid PET images, require computer hardware and software for optimal display and manipulation. Instructions for image display (an important step before qualitative image interpretation) are straightforward in many approved imaging agent PIs. In contrast, in the Tauvid PI, instructions for image display are complex as detailed in the following excerpt under the heading "2 DOSAGE AND ADMINISTRATION > 2.4 Image Display > Select and Adjust the Color Scale":

(b) (4)

- Draw a region of interest around the cerebellum in the transverse plane.
- Select the plane to go through the cerebellum at the maximum cross-sectional area of the cerebellum.
- Record the mean activity or cerebellar counts (MCC). The region of interest should be drawn with the scan in gray scale and in the transverse plane as seen in the example in Figure 1.

Example of Cerebellar Region of Interest



- Select a color scale for image display that has a rapid transition between two distinct colors in the general range of 25% to (b) (4) of maximum intensity.
- Set the upper contrast value (UCV) of the color scale. Use the following formula to set the visual threshold of 1.65 x MCC to match the rapid transition in the color scale:

UCV = (MCC x 1.65) x (100% / % level of color transition)

Source: Tauvid prescribing information

Review Team Assessment and Follow Up Work by Applicant

The team, including members from CDRH and DMEPA, assessed that Tauvid readers will need more detailed instructions for image display to supplement the high-level instructions provided in the Tauvid PI. Lack of detailed guidance for optimal Tauvid image display can pose risks during image interpretation that could be mitigated by development of more detailed Tauvid labeling. To address this issue, the team recommended that the Applicant develop a user guide with step by step instructions specific for each of the commonly used image-viewing software platforms. For additional information, refer to image display device expert review in Section 25.

(b) (4)

To facilitate access to these user guides, the Applicant, in consultation with the Agency, added the following language in Section 2.4 (Image Display) of the PI:

> *If additional guidance on image display is needed, refer to the TAUVID User Guide for PET Image Display available by request from the manufacturer.*

In addition, it was agreed that the guide should be considered part of Tauvid labeling subject to postmarketing annual reporting requirements under FDA regulations at 21 CFR 314.70(d) but not subject to electronic structured product labeling requirements under 21 CFR 314.50(l) or 21

CFR 314.81(b). Thus, the Applicant will provide in postmarketing annual reports a summary of any changes to the guide or, if no change, a statement of that fact.

Conclusion

The team concluded that the steps taken by the Applicant are acceptable to ensure proper implementation of the image display and interpretation of Tauvid images in a clinical setting.

6.4.2. Limitations of Efficacy Evidence for Tau Pathology Detection

Issue

In the Applicant's submission, diagnostic performance characteristics were calculated for coprimary endpoints such that a positive FTP scan (Tauvid pattern—moderate or advanced) identified B3 level of NFT pathology (Primary Analysis 1) and high levels of ADNC. This approach may impose limitations on the utility of Tauvid imaging as a subset of patients with B2 level tau pathology could potentially be classified as Negative Tauvid scans (b) (4) while still possessing tissue pathology sufficient for AD diagnosis. In a clinical setting, this may result in decreased performance of Tauvid PET scans in characterizing brain tau pathology in patients with AD.

Also, this autopsy study was conducted in terminally ill patient population which is not the intended patient population. The Applicant submitted another study, FR-01, showing inter-reader agreement in the subgroup of patients in the intended population, which does not have the data about pathological TS.

Background

The 2012 NIA-AA guidelines for pathological diagnosis of Alzheimer's disease (Hyman et al. 2012; Montine et al. 2012), assign "not," "low," "intermediate," or "high" levels of AD neuropathology based on an "ABC" score that is derived from three separate 4-point scales: (A) Aβ/amyloid plaque score (Thal phase); (B) NFT stage (Braak stage); and (C) neuritic plaque score (CERAD) (refer to Table 13).

Table 13. Level of AD Neuropathologic Change

Table 2
Level of AD neuropathologic change

A: Aβ/amyloid plaque score (Thal phases)*	C: Neuritic plaque score (CERAD)†	B: NFT score (Braak stage)‡		
		B0 or B1 (None or I/II)	B2 (III/IV)	B3 (V/VI)
A0 (0)	C0 (none)	Not§	Not§	Not§
A1 (1/2)	C0 or C1(none to sparse)	Low	Low	Low¶
	C2 or C3 (mod. to freq.)**	Low	Intermediate	Intermediate¶
A2 (3)	Any C	Low††	Intermediate	Intermediate¶
A3 (4/5)	C0 or C1 (none to sparse)	Low††	Intermediate	Intermediate¶
	C2 or C3 (mod. to freq.)	Low††	Intermediate	High

Source: (Hyman et al. 2012; Montine et al. 2012)
Note: AD neuropathologic change is evaluated using an "ABC" score that derives from three separate 4-point scales: Aβ/amyloid plaques (A) by the method of Thal phases, NFT stage by the method of Braak (B), and neuritic plaque score by the method of CERAD (C). The combination of A, B, and C scores receives a descriptor of "Not," "Low," "Intermediate," or "High" AD neuropathologic change. "Intermediate" or "High" AD neuropathologic change is considered sufficient explanation for dementia.
*Ab/amyloid plaque score should be determined by the method of Thal et al (Thal et al. 2002).
† Neuritic plaque score should be determined by the method of CERAD (Mirra et al. 1991).
‡ NFT stage should be determined by the method of Braak (Braak and Braak 1991b; Braak et al. 2006).
§ Medial temporal lobe NFTs in the absence of significant Ab or neuritic plaques occur in older people and may be seen in individuals without cognitive impairment, with mild impairment, or with cognitive impairment from causes other than AD (Nelson et al. 2009). Consider other diseases when clinically or pathologically indicated.
¶ Widespread NFTs with some Ab/amyloid plaques or limited neuritic plaques are relatively infrequent, and when they occur, other diseases, particularly tauopathies, should be considered. Such cases may not fit easily into a specific Braak stage, which is intended for categorization of AD-type NFTs.
** Presence of high levels of neuritic plaques in setting of low Thal phase is a rare occurrence and should prompt reconsideration of neuritic versus diffuse plaques, and the possible contribution of other diseases to cognitive impairment or dementia.
†† Higher levels of Ab or neuritic plaques with low Braak stage should prompt consideration of contribution by comorbidities such as vascular brain injury, LBD, or HS. Also, consider additional sections as well as repeat or additional protocols to demonstrate other non-AD lesions.
Abbreviations: AD, Alzheimer's disease; CERAD, Consortium to Establish Registry for Alzheimer's Disease; freq., frequent; mod., moderate; NFT, neurofibrillary tangle; LBD, Lewy body dementia; HS, hippocampal sclerosis

According to these guidelines, an "intermediate" level of ADNC includes B2 level of tau pathology with co-existing Aβ plaques (score A1-3) and neuritic plaques (score C0 to C3). These guidelines also indicate that "intermediate" and "high" levels of AD neuropathology are sufficient to confer a diagnosis of AD in the presence of cognitive symptoms. On the other hand, a designation of "not" and "low" levels of neuropathology indicate that cognitive symptoms are likely due to a diagnosis other than AD. Further, these guidelines suggest that a B3 NFT score and a C2/C3 Consortium to Establish Registry for Alzheimer's disease (CERAD) score can theoretically occur in either high or intermediate overall AD pathology depending on the level of amyloid plaque (Thal phase). These guidelines also state that "widespread NFTs with some Aβ/amyloid plaques or limited neuritic plaques are relatively infrequent, and when they occur, other diseases, particularly tauopathies, should be considered." Further, an NFT score of B3 is unlikely to occur without C2/C3 CERAD score and A3 Aβ/amyloid plaque score.

Assessment

The team assessed that using the Applicant's proposed approach for conducting Tauvid PET diagnostic performance statistics, a scan interpreted as a Negative Tauvid scan could include a considerable number of subjects with B2 NFT and intermediate AD pathology. To illustrate this issue, consider the publication cited by the Applicant for support of the AD neuropathological criteria used in Study A16 (Hyman et al. 2012). The publication reported on 562 patients who came to autopsy between 2005 and 2010 and who had been clinically evaluated in a standardized manner in one of the approximately 30 AD centers located throughout the United States.

The authors found that 134/562 (23%) of the autopsies performed on patients had an NFT score of B2. Among these 134 patients, 93 possessed a CERAD score of C2/3, an intermediate level of AD pathology which in the presence of cognitive symptoms was considered adequate for diagnosis of AD neuropathological change and as an explanation for clinical manifestations. Thus, using the Applicant's B3 threshold and assuming perfect Tauvid performance for B-staging, at least 93/562 (16.5%) of the total patients in the series (Hyman et al. 2012) would be characterized as Negative Tauvid scans (b) (4) while still possessing tissue pathology sufficient for AD diagnosis.

The team performed an additional analysis using the B2 pathological threshold, since it is recommended by Hyman and colleagues (Hyman et al. 2012) and was recommended by the review division under IND 119863. The total number of positive scan reads (TP+FP) and the total number of negative scan reads (TN+FN) was the same in this analysis (Table 14) when compared to the primary B3 analysis (Table 9). In this analysis, the performance of the five readers for sensitivity (95% CI) ranged from 68% (55, 79) to 86% (74, 93) and for specificity (95% CI) ranged from 63% (31, 86) to 100% (68, 100). Four out of the five readers achieved lower bounds on both sensitivity and specificity >50%. Comparing the performance between Table 9 using the B3 pathological threshold and Table 14 using the B2 pathological threshold, the numerical difference in the reported specificities ranged from 0% to 12%, except reader 1 whose difference was 20%. However, the reported sensitivity appears to be different between the two different classifications, the nominal p-value is <0.05 for each of the five readers.

Table 14. FTP PET Scan Interpretation (τAD+/++ or τAD-) Versus Autopsy NFT Score Truth Standard (B2 or B3 Defines Positive)

Reader	True Positive	True Negative	False Positive	False Negative	Sensitivity % (95% CI*)	Specificity % (95% CI)	PPV	NPV
1	45	7	1	11	80 (68, 89)	88 (53, 98)	98	39
2	38	8	0	18	68 (55, 79)	100 (68, 100)	100	31
3	38	7	1	18	68 (55, 79)	88 (53, 98)	97	28
4	41	7	1	15	73 (60, 83)	88 (53, 98)	98	32
5	48	5	3	8	86 (74, 93)	63 (31, 86)	94	38
Majority Read	40	1	16	7	71 (59, 82)	88 (53, 98)	98	30

Abbreviations: AD, Alzheimer's disease; τAD-, neocortical uptake not consistent with AD; τAD+, neocortical uptake consistent with AD; τAD++, neocortical uptake consistent with AD and likely to progress; CI, confidence interval; FTP, flortaucipir F 18; NFT, neurofibrillary tangle; NPV, negative predictive value Conclusion; PET, positron emission tomography; PPV, positive predictive value

Comment: *The number of primary patients in Study A16 with B3 tau pathology (TP+FN in Table 9) was 39 (61% of those studied). The number of patients with B3 or B2 tau pathology (TP+FN in Table 14) was 56 (88% of those studied). These high numbers demonstrate that the spectrum of disease studied in this sample of patients who are terminally ill is weighted toward severe tau pathology.*[1] *In comparison, the spectrum of tau pathology in indicated patients with cognitive impairment being evaluated for AD is almost certain to be weighted more toward*

[1] In addition, only one of the 64 patients who came to autopsy in Study A16 was classified as having mild cognitive impairment on neurological exam around the time of FTP imaging, further supporting this spectrum-associated finding.

earlier stages of the pathological spectrum, since AD is a progressive neurodegenerative disease.[2]

In addition, in the subgroup of 17 patients with B2 tau pathology (27%, 12 of whom were also diagnosed with AD neuropathological change), Reader 4, for example, interpreted the FTP scan as negative in 12 patients (i.e., of 17 patients with B2 tau pathology, FTP imaging lead to the detection of tau pathology in 29%). This result suggests that patients with intermediate tau pathology may be missed more often than detected and that missed detections will be more common than in the studied sample of patients who are terminally ill. It should also be noted that Tauvid scan results are indicative of distribution of brain tau NFT only at the time of image acquisition.

The concern about relying on performance evidence from the patient population studied is somewhat mitigated by Study FR-01, because of reasonable sensitivity and specificity in that limited population and reasonably large value of Fleiss' kappa in a broader patient population, some of which included the intended patient population.

Conclusion

To address this issue, the PI was revised in Section 5 WARNINGS AND PRECAUTIONS to alert the prescribing clinicians of the limitation of a Negative Tauvid scan read by including the following:

5.1 Risk of Misdiagnosis in Patients Evaluated for Alzheimer's disease

TAUVID does not target β-amyloid, one of two required components of the neuropathological diagnosis of AD.

TAUVID performance for detecting tau pathology was assessed in terminally ill patients, the majority of whom had AD dementia with B3 level NFT pathology. TAUVID performance for detecting tau pathology may be lower in patients in earlier stages of the pathological spectrum [see Clinical Studies (14)].

Negative TAUVID Scan
NFTs may be present at levels that qualify for the neuropathological diagnosis of AD (B2 tau stage in the presence of at least moderate levels of cortical amyloid pathology) in patients with a negative TAUVID scan. Consider additional evaluation to confirm the absence of AD pathology in patients with a negative TAUVID scan.

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[2] In the absence of tau pathology data based on different methods of patient sampling, it is easier to infer the direction and harder to estimate the magnitude of spectrum differences between samples based on studying patients who are terminally ill versus the indicated population.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The Tauvid nonclinical safety studies included single-dose toxicity study in rats and repeat-dose toxicity studies in rats and dogs; in vitro and in vivo safety pharmacology and genotoxicity studies. There were no nonclinical safety issues of concern as assessed by the general toxicology studies conducted during the development program. All pertinent studies and findings are summarized in the following section. Full reviews for all nonclinical studies are located in Section 13.1.

Overall, the nonclinical safety assessment for Tauvid as a microdose radiopharmaceutical diagnostic agent was considered acceptable to support marketing approval from a pharmacology/toxicology perspective.

Pharmacology and Pharmacokinetics

Flortaucipir selectivity toward PHF-tau was evaluated by competitive binding and functional assays against a panel of receptors, ion channels, transporters, enzymes, and human tissues. Flortaucipir demonstrated minimal off-target binding for five CNS targets; norepinephrine transporter, monoamine transporter VMAT2, the polyamine site of the glutamate receptor, μ-opiate receptor, and acetylcholinesterase. Binding to MAO-A and MAO-B was evaluated because of the similarity between flortaucipir and reversible MAO ligands (harmine and F18-FEH). FTP bound MAO-A with a Kd of 2nM and little or no specific binding to recombinant MAO-B; flortaucipir weakly inhibited binding in competitive binding assays with the MAO-B ligand safinamide, with an IC_{50} of 1.3μM.

In autoradiography studies with human postmortem tissue, FTP binding was weakly blocked by safinamide and deprenyl ($IC_{50} \geq 10\mu M$). Off-target binding is observed in iron-rich regions, the substantia nigra, calcifications in the choroid plexus, and leptomeningeal melanin (Lowe et al. 2016). Flortaucipir binds to pathologic tau containing 4-repeat (4R) and 3-repeat (3R) isoforms of PHF-tau which is more prevalent in AD (Lebouvier et al. 2017) in contrast to greatly reduced uptake for other tauopathies, e.g., PSP (4R), PiD (3R), and CTE (3R/4R).

Cardiovascular safety pharmacology assessments were conducted in a hERG assay; in a 30-day repeat-dose study in dogs; and as part of a PET imaging dosimetry study in monkeys. Flortaucipir was positive in the hERG assay with an IC_{50} of 0.610μM (≥40x the maximum plasma concentration of 15nM). Transient increases in heart rate (1 through 2.5 hours, postdose) were observed in one of four female dogs at 30 μg/kg/day on Day 29 of the dosing phase; no effect was observed for other cardiovascular parameters (i.e., PR interval, QRS duration, QT or corrected QT interval). No drug-related effects on cardiovascular function were observed in monkeys following a single administration of flortaucipir. Respiratory parameters were evaluated in a rat respiratory function study and neurobehavioral parameters were evaluated in a modified Irwin test in rats. No drug-related findings on these parameters were observed in studies of flortaucipir at up to 200 μg/kg, the highest doses tested.

FTP pharmacokinetics was evaluated in vitro by protein binding and metabolism studies and in vivo in mice, rats, and monkeys for biodistribution, metabolism, and excretion studies. In vitro plasma protein binding for FTP was low (<90%) to moderate across mouse (89%), rat (91%), dog (81%), monkey (90%), and human (95%) species. In vitro metabolism studies identified primary metabolic pathways across rodent (mouse, rat) and nonrodent species (dog, monkey, and human), consistent with oxidation (CYP and non-CYP) and direct glucuronidation with human metabolites present in species selected for the nonclinical safety studies.

In vivo metabolism studies in mice identified the parent compound as the predominant circulating entity in plasma with three additional, smaller and more hydrophilic metabolites; only parent compound was present in brain. In PET imaging study conducted in healthy mice, rats, and monkeys, FTP rapidly distributed to the brain by 5 minutes and underwent moderate clearance within 30 min. In monkeys, FTP displayed 1.5-fold to 2-fold greater uptake across striatum, cortex, and cerebellum compared to white matter. In biodistribution studies in mice and monkeys, greatest accumulation was observed in the kidneys and liver; low levels uptake in bone was attributable to defluorination. FTP is predicted to undergo renal elimination based on biodistribution and dosimetry studies in mice and monkeys.

General Toxicology

Pivotal repeat-dose toxicity studies for FTP included good laboratory practice (GLP) studies of up to 1-month duration in rats and dogs. Rats and dogs were considered appropriate rodent and nonrodent animal models based on PK properties described above. Toxicity studies were conducted with an intravenous formulation that included excipient (b) (4) (absent in the clinical formulation).

In rats, no adverse, drug-related findings were observed up to the highest dose tested in a 14-day extended, single-dose (0.3 mg/kg) toxicity study and a 1-month repeat-dose studies (0.1 mg/kg/day). There were no drug-related effects on clinical or ophthalmological observations, body weight, food consumption, clinical pathology or histopathological observations. Exposure multiples at the no observed adverse effect levels (NOAELs) in the single-dose and 1-month rat studies are 150-fold and 50-fold, respectively.

In dogs, no adverse, drug-related clinical or ophthalmological observations, effects on body weight or food consumption, clinical pathology or histopathological findings were observed at up to the highest dose tested (30 µg/kg/day). A transient increase in heart rate (9 to 30 bpm) from 1 through 2.5 hours, postdose was observed in one of four females (30 µg/kg/day) on dosing Day 29 but not considered clinically relevant for a single-use agent. Exposure multiples at the NOAEL in the 1-month dog study are 50-fold.

Genotoxicology and Carcinogenicity

Flortaucipir was positive for mutagenicity by the in vitro bacterial reverse mutation assay (Ames test) and clastogenicity by the in vitro chromosomal aberration assay. In the Ames test, flortaucipir was positive in TA1535 and TA1537 tester strains in the absence of S9 metabolic activation and positive in four tester strains (TA98, TA100, TA1537, and WP2uvrA) with S9 metabolic activation. In an in vitro mammalian chromosomal aberration assay, flortaucipir produced a dose-dependent increase in clastogenicity that was sensitive to S9 metabolic activation; the number of cells with aberrations was significantly increased at 10.9 and 22.2 µg/mL dose level without S9 and significantly increased at 22.2 and 31.8 µg/mL dose level

with S9. Flortaucipir also produced a dose-dependent increase in the number of cells with aberrations when incubated for 20 hours at 3.74, 5.34, and 7.63 µg/mL dose levels. Flortaucipir was negative for mutagenicity by an in vivo rat micronucleus assay at dose levels up to 1,600 µg/kg/day for 2 days, with a safety margin of 780-fold.

The positive findings from in vitro assays are acceptable for a radioactive diagnostic agent because the radiolabel makes this class of products inherently genotoxic. Furthermore, flortaucipir was negative when tested in an in vivo micronucleus assay.

Carcinogenicity studies were not conducted for FTP because the product is intended for use as a single-use diagnostic radiopharmaceutical.

Reproductive and Developmental Toxicity

Reproductive and developmental toxicology studies were not conducted for FTP. The Applicant requested a waiver for conduct of reproductive and developmental toxicity studies, which was granted based on the proposed single-use indication, target population, and microdose.

Additional Toxicology Studies

Flortaucipir was negative for cytotoxicity at up to 10µM by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay in normal (MRC5 human normal lung fibroblast, AML12 mouse normal liver cell) and tumor (LS174T human colorectal adenocarcinoma, A172 human glioblastoma cell lines) cell lines.

Exposure Multiples

Exposure multiples, based on a proposed human dose of 20 µg, are presented in Table 15.

Table 15. Flortaucipir Exposure Multiples

Study	NOAEL (µg/kg/dose)	Adverse Findings	Exposure Multiple
Single-dose study (intravenous)			
14-day rat	300	None	150
Repeat-dose studies (intravenous)			
1-month rat	100	None	50
1-month dog	30	None	50

Abbreviations: NOAEL, no observed adverse effect level

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Overall, FTP was well tolerated. Treatment-emergent adverse event (TEAEs) were infrequent and mild to moderate in severity. FTP binds with high-affinity binding to MAO-A and MAO-B, which could potentially affect the interpretation of FTP PET images (see Section 7.7.2 for further details).

There was a small but statistically significant increase in QTcB and QTcF intervals around 2 hours following intravenous administration of FTP when compared to baseline predose measurements. These increases were deemed to be of no clinical significance by the Applicant as

well as the FDA QT-IRT (see Sections 7.7.3 and 25 (Cardiac Safety Expert Review) for further details).

In the clinical studies two deaths occurred within 7 days and 14 deaths more than 7 days after FTP administration; these events were considered unrelated to FTP by the site investigator and the Applicant (see Section 7.6.2 for further details). Three additional serious adverse events (SAEs; angina pectoris, myocardial infarction, and transient ischemic attack) were assessed by the Applicant to be unrelated to FTP (see Section 7.6.3 for further details). These reported SAEs do not raise a safety concern.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

The Applicant reports that FTP is not marketed in any country.

7.4. FDA Approach to Safety Review

FTP safety data were pooled across clinical studies completed by June 19, 2019; the studies consist of 13 diagnostic studies and six biomarker studies. While the Applicant reports 2,013 study subjects, 92 of them were included in more than one study. Therefore, the safety database was analyzed using data from 1,921 unique study subjects. Among these subjects, 1,192 received 240 MBq and 729 received 370 MBq of FTP (Table 16). An analysis was performed for the overall number of unique study subjects and separately for those who received 240 MBq versus those who received 370 MBq. Comparisons across groups were based on descriptive analyses.

7.5. Adequacy of the Clinical Safety Database

The safety database presented by the Applicant is comprehensive and adequate to assess the safety of Tauvid. There were no major data quality or integrity issues that precluded a safety review.

There were no major issues related to recording, coding, and categorizing adverse events (AEs). The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for the events reported in all the studies submitted were reviewed and found to be acceptable.

AEs were described by the Applicant as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. As specified in study protocols, untoward medical occurrences were considered associated with the use of FTP, and reported as AEs, if they occurred within 48 hours after FTP administration. Considering the rapid elimination of FTP, 48 hours was determined to be a reasonable period for AEs to be judged as treatment emergent."

Treatment-emergent AEs were defined by the Applicant as "events that started or worsened during or after the administration of study drug and within the protocol-specified follow-up period.

Table 16 presents baseline demographics of the overall study subjects (1,921) and those who received 240 MBq (1,192) and 370 MBq (729) included in the safety analyses.

Table 16. Baseline Demographic and Clinical Characteristics, Safety Population, ISS

Characteristic	ISS Overall N=1,921	ISS 240 MBq N=1,192	ISS 370 MBq N=729
Sex, n (%)			
Female	957 (49.8)	645 (54.1)	312 (42.8)
Male	964 (50.2)	547 (45.9)	417 (57.2)
Age, years			
Mean (SD)	71.9 (10.7)	72.9 (7.5)	70.3 (14.0)
Median (min, max)	73.0 (21.0, 104.0)	74.0 (55.0, 93.0)	72.0 (21.0, 104.0)
Race, n (%)			
White	1654 (86.1)	1016 (85.2)	638 (87.5)
American Indian or Alaska Native	3 (0.2)	1 (0.1)	2 (0.3)
Asian	122 (6.4)	106 (8.9)	16 (2.2)
Black or African American	89 (4.6)	24 (2.0)	65 (8.9)
Multiple	11 (0.6)	11 (0.9)	0 (0.0)
Native Hawaiian or other Pacific Islander	3 (0.2)	2 (0.2)	1 (0.1)
Other	10 (0.5)	3 (0.3)	7 (1.0)
Missing	29 (1.5)	29 (2.4)	0 (0.0)
Ethnicity, n (%)			
Hispanic	98 (5.1)	51 (4.3)	47 (6.4)
Non-Hispanic	1742 (90.7)	1060 (88.9)	682 (93.6)
Not applicable	58 (3.0)	51 (4.3)	47 (6.4)
Not reported	1 (0.1)	1060 (88.9)	682 (93.6)
Missing	22 (1.1)	22 (1.8)	0 (0.0)
Country of participation, n (%)			
USA	1476 (76.8)	752 (63.1)	724 (99.3)
AUS	194 (10.1)	189 (15.9)	5 (0.7)
BEL	14 (0.7)	14 (1.2)	0 (0.0)
CAN	23 (1.2)	23 (1.9)	0 (0.0)
FRA	28 (1.5)	28 (2.3)	0 (0.0)
JPN	99 (5.2)	99 (8.3)	0 (0.0)
NLD	21 (1.1)	21 (1.8)	0 (0.0)
POL	66 (3.4)	66 (5.5)	0 (0.0)

Source: adsl.xpt; Software: Python
Age values are calculated according to the variable AAGE as described in ISS SAP Section 4.4.4.
Abbreviations: ISS, integrated summary of safety; MBq, megabecquerel; N, number of subjects; n, number of subjects with given characteristic; SD, standard deviation

Table 17 shows the "enrolled population" defined by the Applicant as all subjects who satisfied all inclusion and exclusion criteria, agreed to participate in the study, were enrolled to the study, and had data captured in the electronic data capture system, regardless of whether or not they received study medication. The analysis was limited to "unique subjects" defined as those who received at least one injection of FTP.

Table 17. Patient Enrollment, ISS

Screening Disposition	ISS Overall
Patients enrolled	
Study subjects	2,085
Unique subjects	1,985
Patients who received at least 1 dose of FTP	
Study subjects	2,013
Unique subjects	1,921

Source: adds.xpt; Software: Python
"Study subjects" are all patients who participated in any of the listed studies in Table 4 of this review. Of the 2,013 study subjects, 92 were enrolled in more than one study.
Abbreviations: FTP, flortaucipir F 18; ISS, integrated summary of safety

Table 18 shows the disposition of the patients enrolled in the study.

Table 18. Patient Disposition, ISS

Disposition Outcome	ISS Overall N=1,921 n (%)	ISS 240 MBq N=1,192 n (%)	ISS 370 MBq N=729 n (%)
Patients			
Safety population	1,921	1,192	729
Discontinued study	767 (39.9)	568 (47.7)	199 (27.3)
Administrative decision	496 (25.8)	431 (36.2)	65 (8.9)
Adverse event	29 (1.5)	28 (2.3)	1 (0.1)
Consent withdrawn	139 (7.2)	70 (5.9)	69 (9.5)
Death	16 (0.8)	7 (0.6)	9 (1.2)
Lost to follow-up	22 (1.1)	8 (0.7)	14 (1.9)
Protocol deviation	43 (2.2)	3 (0.3)	40 (5.5)
Technical problems	1 (0.1)	9 (0.0)	1 (0.1)
Modified adverse event	2 (0.1)	2 (0.2)	9 (0.0)
Other	19 (1.0)	19 (1.6)	9 (0.0)

Source: adds.xpt; Software: Python
Abbreviations: ISS, integrated summary of safety; MBq, megabecquerel; N, number of subjects in group; n, number of subjects in specified population or group

Table 19 shows the maximal duration of enrollment of the study subjects.

Table 19. Duration of Subject Enrollment, Safety Population, ISS

Variable	ISS Overall N=1,921	ISS 240 MBq N=1,192	ISS 370 MBq N=729
Duration (months)			
Mean (SD)	7.5 (8.1)	8.9 (8.2)	5.0 (7.5)
Median (min, max)	6.7 (0.0, 33.4)	10.4 (0.0, 33.4)	0.0 (0.0, 23.0)
Subjects, by duration, n (%)			
<6 months	948 (49.3)	461 (38.7)	487 (66.8)
≥6 months	973 (50.7)	731 (61.3)	242 (33.2)

Source: adex.xpt; Software: Python
For those subjects who participated in multiple studies, the subject enrollment was calculated as maximal values among studies.
Abbreviations: ISS, integrated summary of safety; MBq, megabecquerel; N, number of subjects in group; n, number of subjects with given duration; SD, standard deviation

7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

The safety data submitted for Tauvid is adequate, and the demonstrated safety profile of Tauvid is acceptable.

Only one patient discontinued from the study due to an adverse event. There was no specific pattern in the reported SAEs that raise a specific safety concern. The most commonly reported treatment-emergent adverse reactions were predominantly mild to moderate in severity and included headache (1.4%), injection site pain (1.2%), and increase in blood pressure (0.8%).

The overall safety assessment is based on the data summarized in the following subsections (see Section 16 for additional detail).

7.6.1. Overall Adverse Event Summary

Approximately 10 percent of subjects experienced one or more TEAE. TEAEs were considered mild to moderate in severity and were numerically more frequent in subjects who received 370 MBq compared to those who received 240 MBq. Importantly, the analyses of AEs in subjects with cognitive impairment, the indicated population of use, showed no clinically significant pattern. The mass dose of FTP administered is similar for the two radioactivity doses—370 MBq and 240 MBq—and the severity of TEAEs was mild, therefore the numerically difference of TEAEs in these patient subgroups is not pharmacologically plausible and has no clinical significance.

Two deaths within 7 days and 14 deaths more than 7 days after FTP administration were considered unrelated to FTP (see Section 7.6.2 for further details). Three additional SAEs (angina pectoris (Study A05), myocardial infarction (Study A16), and transient ischemic attack (Study I7X-MC-LLCF) were reported by the Applicant. The myocardial infarction occurred in a patient enrolled in the A16 autopsy study with <6 months of life expectancy 1 day after FTP administration. This patient had a history of hypertension, coronary artery disease, hypercholesterolemia, and was on hemodialysis and the Applicant assessed the event as unrelated to FTP (see Section 7.6.3 for further details).

An overall summary of TEAEs in the pooled data (1,921) and separately for the two dose groups, 1,192 in the 240 MBq dose group and 729 in the 370 MBq dose group, is presented in Table 20.

Table 20. Overview of Adverse Events,[1] Safety Population, ISS

Event Category	ISS Overall N=1,921 n (%)	ISS 240 MBq N=1,192 n (%)	ISS 370 MBq N=729 n (%)
Any AE	190 (9.9)	90 (7.6)	100 (13.7)
Moderate or severe AEs	41 (2.1)	20 (1.7)	21 (2.9)
SAE	5 (0.3)	1 (0.1)	4 (0.5)
SAEs with fatal outcome	2 (0.1)	0 (0.0)	2 (0.3)
AE leading to discontinuation of study drug	1 (0.1)	0 (0.0)	1 (0.1)
AE leading to dose modification of study drug	1 (0.1)	1 (0.1)	0 (0.0)
AE leading to interruption of study drug	1 (0.1)	1 (0.1)	0 (0.0)
AE leading to reduction of study drug	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to dose delay of study drug	0 (0.0)	0 (0.0)	0 (0.0)

Source: adae.xpt; Software: Python
[1] In this and the following tables, treatment-emergent adverse event defined as undesirable experiences, signs or symptoms that begin or worsen in intensity or frequency ≤48 hours after the FTP dose injection
Abbreviations: AE, adverse event; ISS, integrated summary of safety; MBq, megabecquerel; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event

7.6.2. Deaths

Two deaths, one due to acute kidney injury and the other to malignant neoplasm occurred within 7 days after FTP administration in subjects enrolled in the end-of-life study (Study A16) and were assessed by the Applicant as unrelated to FTP. Fourteen deaths occurred more than 7 days after FTP administration and were also considered to be unrelated to FTP by the site investigator and the Applicant.

7.6.3. Serious Adverse Events

In addition to the two deaths described above, additional SAEs that occurred within 7 days of FTP administration included angina pectoris (Study A05), myocardial infarction (Study A16), and transient ischemic attack (Study I7X-MC-LLCF). The myocardial infarction that occurred 1 day after FTP administration in a patient enrolled in the A16 autopsy study with <6 months of life expectancy was considered unrelated to FTP administration by the Applicant because the patient had a history of hypertension, coronary artery disease, hypercholesterolemia, and was also on hemodialysis.

Angina pectoris that occurred in a patient enrolled in Study A05 was deemed unrelated to FTP administration by the Applicant because it occurred 1 month after FTP administration and is most likely related to patient's history of diabetes, hypertension, hyperlipidemia, and coronary artery disease.

The transient ischemic attack that occurred in a patient enrolled in Study I7X-MC-LLCF on the day of FTP administration was deemed by the Applicant to be unrelated to FTP administration

and most likely related to patient's age and history of hypertension, hyperlipidemia, diabetes mellitus, and tobacco use.

Supraventricular Arrhythmias

The Applicant reports that in one patient enrolled in an independent investigator-sponsored study (b) (4) (not part of the pooled safety population used for the analyses reported in this application), atrial fibrillation with rapid ventricular response was diagnosed on the day of FTP administration. The Applicant assessed that this event is not possibly related to FTP administration given the patients advanced age of 90 years and that the event can have multiple causes.

The Applicant reviewed the Lilly Safety System for the safety assessment of this application and reported eight cases of supraventricular arrhythmias (seven events of atrial fibrillation and one event of atrial flutter). The onset of atrial arrhythmia in all these cases occurred after a prolonged period of time following FTP administration ranging from 98 days to 919 days. Based on this, the Applicant concluded that there are no reports of atrial fibrillation as a TEAE in the pooled safety population used for the analyses reported in this application.

Table 21 summarizes SAEs.

Table 21. Serious Adverse Events, Safety Population, ISS

Serious Adverse Event[1]	ISS Overall N=1,921 n (%)	ISS 240 MBq N=1,192 n (%)	ISS 370 MBq N=729 n (%)
Transient ischemic attack	1 (0.1)	1 (0.1)	0 (0.0)
Acute kidney injury	1 (0.1)	0 (0.0)	1 (0.1)
Angina pectoris	1 (0.1)	0 (0.0)	1 (0.1)
Myocardial infarction	1 (0.1)	0 (0.0)	1 (0.1)
Neoplasm malignant	1 (0.1)	0 (0.0)	1 (0.1)

Source: adsl.xpt and addd.xpt; Software: Python
[1] Coded as MedDRA preferred terms
Abbreviations: ISS, integrated summary of safety; MBq, megabecquerel; N, number of subjects in group; n, number of subjects with adverse event

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

One patient in the 370 MBq group was discontinued due to an adverse event (headache).

7.6.5. Treatment-Emergent Adverse Events

Among the TEAEs, headache and injection-site pain were the most common with a frequency of 1.4% and 1.2% respectively in the overall population (1,921 subjects). The frequency of injection-site pain was 2.9% in patients who received 370 MBq versus 0.2% in patients who received 240 MBq. Frequency of headache was 2.6% in patients who received 370 MBq versus 0.6% in patients who received 240 MBq. Patients who received 370 MBq showed relatively higher frequency (1.8%) of increased blood pressure versus those who received 240 MBq (0.2%). Patients who received 370 MBq also showed a small but relatively higher frequency

(0.7%) of diarrhea versus those who received 240 MBq (0.2%). Similarly, dizziness was relatively higher in frequency in those who received 370 MBq (0.8%) versus those who received 240 MBq (0.2%).

7.6.6. Laboratory Findings

While there were changes noted in laboratory parameters between baseline and postdose time points, they were small and deemed to be not clinically significant.

The changes in the hematology parameters were minimal and within normal ranges. Analysis of chemistry parameters showed that with the exception of glucose, high-density lipoprotein cholesterol and triglycerides all the other parameters were within the normal ranges. The changes in glucose, high-density lipoprotein cholesterol and triglycerides from baseline observed in some of the subjects were deemed to possibly reflect underlying metabolism and nutritional disorders such as diabetes mellitus and differences in food intake during the imaging visits. None of the changes in the urinalysis parameters were identified as adverse events.

See also Section 16.5 for additional details.

7.7. Review Issues Relevant to the Evaluation of Risk

Overall, the data is adequate to assess the safety of Tauvid for the proposed indication of estimating the density and distribution of tau-NFTs in the brains of adult patients who are being evaluated for AD. The safety profile is well characterized and none of the identified risks preclude approval. During the review of clinical safety, we identified risk review issues related to CTE misdiagnosis, effect of MAO inhibitors on FTP binding, and QT interval prolongation. Each of these risk issues is discussed in detail below.

7.7.1. CTE Misdiagnosis

Issue

There is a potential for inappropriate use of Tauvid in patients with CTE and other non-AD tauopathies.

Background

CTE is recognized as a neurodegenerative disorder associated with repetitive head impacts sustained by contact-sport players (Gavett et al. 2011). CTE has also been described in military personnel exposed to blast injuries (Omalu et al. 2011). A definitive diagnosis of CTE can only be established through neuropathological examination. Neuropathologically, CTE is characterized by the pathognomonic tau aggregates in neurons, astrocytes and cell processes around small vessels in the depths of cortical sulci, TAR DNA binding protein 43 inclusions, B-amyloid plaques and amyloid angiopathy (McKee et al. 2016).

The increasing global health concern of CTE is fostering the development of testing for this disorder including imaging tau-tracers to identify at-risk individuals, assess disease progression over time, and monitor treatment response in clinical trials. A few studies in subjects clinically diagnosed with CTE (Mitsis et al. 2014; Dickstein et al. 2016; Stern et al. 2019), suggested that FTP may serve as a marker for tau-containing aggregates. However, these studies are limited in their design as they did not explore the correlation between FTP activity and tau lesions in postmortem brain samples (truth standard).

While the tau aggregates in CTE contain all six isoforms with the presence of both the 3R and 4R repeats of the microtubule binding domain that is similar to AD but no other tauopathies, electron cryomicroscopy studies show the tau filament conformation in CTE differs from the tau filaments in NFTs of AD (Falcon et al. 2018; Falcon et al. 2019). Marquie et al. explored the correlation between FTP binding patterns in pathologically confirmed CTE tissue using phosphor screen and high-resolution autoradiography and quantitative tau measurements obtained through immunohistochemistry, Western blotting, and tau seeding activity in the same samples (Marquie et al. 2019). Using this approach, they reported that FTP exhibits relatively low binding affinity for tau aggregates of CTE and opine that FTP has limited utility for reliable in vivo detection of tau lesions in this tauopathy.

Another study (Mantyh et al. 2020) compared in vivo FTP activity with phosphorylated tau immunohistochemical analysis of postmortem brain tissue (Mantyh et al. 2020). While the study authors detected increased FTP binding in a pattern consistent with CTE pathology, based on the relatively low signal intensity and nonsignificant correlation between the PET and autopsy findings they inferred that utility of FTP for visualization of tau pathology in CTE may be limited.

The potential value of FTP for imaging other neurodegenerative tauopathies such as frontotemporal lobar degeneration including Pick’s disease, Progressive Supranuclear Palsy, and Corticobasal degeneration is not clear. While some studies report increased FTP retention in regions of brain that contain tau lesions specific to those disorders, other studies, on the contrary, report patterns of FTP retention that are indistinguishable from patterns in normal controls (Brier et al. 2016; Cho et al. 2016a; Cho et al. 2016b). Additionally, postmortem studies using autoradiography have shown FTP to have a significantly higher affinity for the NFTs tau aggregates of AD when compared to the tau aggregates in non-AD tauopathies (Marquie et al. 2015; Lowe et al. 2016; Sander et al. 2016; Marquie et al. 2017).

Assessment

Based on the absence of evidence for utility of FTP in CTE, the team assessed that labeling needs to caution about its use for CTE in particular.

Conclusion

The team added the following in the PI:

1. Limitations of Use (in Section 1 – INDICATIONS AND USAGE) – TAUVID is not indicated for use in the evaluation of patients for chronic traumatic encephalopathy (CTE) *[see Warnings and Precautions (5.2)]*.
2. WARNINGS AND PRECAUTIONS (Section 5)
   5.2 Risk of Chronic Traumatic Encephalopathy Misdiagnosis
   The safety and effectiveness of TAUVID have not been established for patients being evaluated for CTE. Preliminary nonclinical and clinical investigation suggest differences in tau conformation and distribution may limit flortaucipir F 18 binding. Therefore, TAUVID is not indicated for detection of CTE.

7.7.2. Effect of MAO Inhibitors on FTP Binding

FTP binds to MAO-A, MAO-B and tau-NFTs with low nanomolar affinities. This high affinity binding of FTP to MAO-A and MAO-B could potentially affect the interpretation of FTP PET images. For details please refer to Section 5 of this review.

Conclusion

The team concluded to include the off-target binding potential of FTP to MAO-A and MAO-B in Section 12 of the prescribing information.

7.7.3. QT Interval Prolongation

Issue

The Applicant reports small but statistically significant increases in QTcB and QTcF intervals around 2 hours following intravenous administration of FTP when compared to baseline predose measurements. The team concluded that this observation is not clinically important. See Sections 5 of this review for a complete summary and analysis of this observation.

8. Therapeutic Individualization

8.1. Intrinsic Factors

There is no alternative dosing regimen or management strategy for subpopulations based on intrinsic factors (e.g., renal impairment, hepatic impairment, drug clearance or comorbidities). The Applicant has not conducted any studies in patients with hepatic or renal impairment.

8.2. Drug Interactions

The pharmacology of flortaucipir was assessed in in vitro experiments that determined the binding affinity for tau protein aggregates in purified human tau aggregates and postmortem human brain sections. The Kd of flortaucipir was determined on PHFs (an aggregated fibrillar form of tau pathology which is one of the defining neuropathologies of AD) that were extracted from human AD brain.

A Kd of 0.68nM was determined for tritiated flortaucipir (18F-AV-1451) by homologous competition in paired helical filament (PHF, an aggregated fibrillar form of tau pathology) extracted from human AD brain. A Kd of 0.57nM was measured by saturation binding.

Tritiated flortaucipir binds with nanomolar affinities in brain homogenates and to tau fibrils isolated from patients with Alzheimer's disease or PSP. Tritiated flortaucipir also binds with high affinities in brain homogenates containing MAO-A and MAO-B proteins.

Tritiated flortaucipir binds to recombinant human MAO-A protein with a single, high-affinity, and reversible binding site with a Kd of 1.6±0.4nM and a dissociation off rate $t_{1/2}$ of approximately 25 minutes.

Similarly, tritiated flortaucipir binds reversibly to human recombinant MAO-B at a single site with a Kd of 21±9nM and a dissociation off rate $t_{1/2}$ of <1 minute. Tritiated flortaucipir binding to human recombinant enzymes MAO-A and MAO-B was displaced by unlabeled flortaucipir with a Ki of 2.4nM and 45nM, respectively, in line with the Kd values measured with tritiated flortaucipir (Vermeiren et al. 2018). As such, flortaucipir binds with similar affinities to tau fibrils and monoamine oxidases.

MAO-A

Due to the structural similarity between flortaucipir and MAO-A ligands such as harmine and 18F-FEH, the binding of flortaucipir to MAO-A was evaluated in in vitro and in vivo experiments. The Applicant found that flortaucipir binds to recombinant human MAO-A with a Kd of 2.0nM, similar to the value reported in the literature (Vermeiren et al. 2018).

In in vivo animal studies conducted by Applicant, the biodistribution of flortaucipir was unaltered by pretreatment with the MAO-A/B inhibitor pargyline.

The Applicant has not provided clinical data to determine whether MAO-A inhibitors affect the ability of Tauvid to reliably identify tau pathology in patients with cognitive impairment evaluated for AD.

MAO-B

Clinical MAO Inhibitor Effect on Flortaucipir Binding

See Section 5 for a detailed analysis. Due to paucity of clinical data on the MAO inhibitors effect on Tauvid binding in patients with AD and MCI, further studies are warranted to conclusively determine the effect of MAO inhibitors on Tauvid binding in patients with AD and those with MCI.

8.3. Pediatric Labeling / Plans for Pediatric Drug Development

AD is a late-onset disease occurring from the 6th decade of life onward with the incidence rate doubling approximately every 5 years after age 60. Even the less common early-onset AD, resulting from rare mutations in three genes, typically begins in the 4th or 5th decade of life (Mayeux and Stern 2012). AD does not occur in the pediatric population and is listed by the FDA in adult-related conditions that may qualify a drug product for disease specific waivers for pediatric studies (September 2005). Therefore, the Applicant requested and received a full waiver from the requirement to assess the safety and effectiveness of Tauvid for the proposed indication in all pediatric age categories.

8.4. Pregnancy and Lactation

Nonclinical Data

Reproductive and developmental toxicity or carcinogenicity studies of flortaucipir to evaluate effects on female reproduction and embryo-fetal development were not conducted by the Applicant. Lactation studies have not been conducted in animals. These nonclinical studies are not necessary because Tauvid is intended as a single-use diagnostic radiopharmaceutical PET agent at microgram dose levels.

Therefore, a waiver was granted. See Section 7.1and the following FDA Guidance Documents, “Developing Medical Imaging Drugs and Biological Products Part 1: Conducting Safety Assessments” (June 2004), “Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations” (August 2018), and “M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals” (January 2010).

Clinical Data

There are no data on FTP use in pregnant women or presence of FTP in human milk, effects on breastfed infants, or milk production.

Summary and Recommendation

There are no data on the use of FTP during pregnancy and lactation to assess a drug-associated risk of birth defects, miscarriage, or potential effects on postnatal development. Tauvid is not

anticipated to be used in females of reproductive age. All radiopharmaceutical diagnostic drugs, including Tauvid, have the potential to cause fetal harm, based on the stage of fetal development and the magnitude of the radiation dose. Information has been included in Sections 8.1 through (b) (4) of the Tauvid labeling to inform on potential risks and mitigation for this drug.

9. Product Quality

The Office of Pharmaceutical Quality Review team has assessed NDA 212123 with respect to chemistry, manufacturing, and controls and recommends approval.

9.1. Device or Combination Product Considerations

See Section 6.4.1 and review of image display device expert under Section 25.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

No study conduct issues were identified. Please see Sections 22 and 25.

11. Advisory Committee Summary

The Advisory Committee meeting was cancelled, and the following Federal Registry Notification posted on April 13, 2020:

> *The Medical Imaging Drugs Advisory Committee meeting scheduled for April 23, 2020, has been cancelled. This meeting was cancelled because the issues for which the Food and Drug Administration was seeking the scientific input of the Committee have been resolved.*

III. Appendices

12. Summary of Regulatory History

Avid Radiopharmaceuticals, Inc. (Avid) submitted investigational new drug (IND) 119863; the IND was allowed to proceed on October 30, 2013, to study FTP to estimate tau pathology in adult patients being evaluated for Alzheimer's disease.

The first-in-human study was conducted under a separate IND, with 11 patients, no serious adverse events occurred. The phase 1 study was to evaluate the reproducibility of 18F AV 1451 for brain imaging to visualize Tau protein aggregates in the brain in subjects with cognitive impairment. Safety profile was adequate. The Applicant (Avid) planned additional studies: a cross-sectional comparison of Health Controls, subjects with mild cognitive impairment (MCI) and subjects with Alzheimer's disease (AD), and a longitudinal follow-up and correlation with cognitive symptoms in their previously enrolled patients.

The clinical pharmacology and dosimetry studies were completed during studies, T807000, A01, A03 and A10. Flortaucipir 18F is cleared by hepatobiliary and renal excretion. The GI tract organs and kidneys show the highest radiation absorbed doses.

Guidance Meeting January 21, 2015

Based on their earlier studies, Avid's drug developmental plan was based on the proposed indication for FTP as an imaging agent " to estimate the density (b) (4) of aggregated tau in adult patients with cognitive impairment (b) (4) Avid proposed autopsy studies (A13, A16) using the accepted TS to support the labeling statement, (b) (4)

The Agency responded that the proposed studies would not meet this claim because information (b) (4)

Guidance Meeting October 12, 2016

This meeting further discussed the analysis plans for Study A16 (phase 3 autopsy study, protocol submitted to IND June 18, 2015), including discussions of endpoints, truth standard (TS), reader

(b) (4)

Guidance Meeting August 15, 2017

The meeting was held to review the revised SAP for Study A16 (clinicopathology study between PET images and their post mortem pathology), to discuss analysis plans for confirmatory cohort Study A05 (choice of endpoints and study populations, statistical methods), and to discuss the read method to show relevance to the chosen endpoints for the studies.

Study A16, had enrolled 112 subjects of the proposed 200 subjects. The study used only FTP PET Scan, no amyloid PET scan. Three "front-runners" were unblinded and used to establish a reading method. This study is to show the sensitivity and specificity of FTP PET read in identifying tau level (neurofibrillary tangle (NFT) score).

Study A05 had enrolled 222 subjects in the exploratory cohort (phase 2) and close to 159 subjects in the confirmatory cohort (phase 3). Study A05 used both FTP and FBP PET scans at baseline for both cohorts and an FTP PET scan on the exploratory cohort group.

The Applicant proposed to (b) (4)

[redacted]

The Applicant pointed to difficulties with A16 enrollment. [redacted] FDA reaffirmed that this approach was not favored in an efficacy study.

Avid submitted the Final Agreed Initial Pediatric Study Plan on August 29, 2018. Avid requested a full waiver of pediatric studies for the indication: PET imaging agent of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles [redacted] During the new drug application (NDA) review, the Agency granted a full waiver of pediatric studies because studies are impossible or highly impracticable.

On August 30, 2018, Avid submitted the SAP for Study A16, including the neuropathology analysis plan, image review charter and blind read manual.

Pre-NDA Meeting November 2018

Avid provided details of Study A16 [redacted]. The Agency reminded Avid that their provided Study A16 results best support a labeled indication for detection of NFT B3 pathology [redacted] Given the interest in the community for use of Tauvid for other tauopathies, the Applicant's preliminary evidence of the limited utility of flortaucipir for detection of non-AD tauopathies such as chronic traumatic encephalopathy (CTE) and progressive supranuclear palsy (PSP) may need to be reflected in labeling. The Agency anticipated that this might also be an important topic for FDA advisory committee discussion.

[redacted] if Avid believed that labeling [redacted] the Agency recommended that Avid provide detailed scientific and regulatory justification in their NDA submission.

Avid submitted their NDA on September 30, 2019, with the [redacted] referenced by their clinical studies [redacted] A16, A05A04, A08, A18, LZAX; safety: A13, LZBE). NDA 212123 was an NME under the Program and was granted priority review.

13. Pharmacology Toxicology Assessments and Additional Information

13.1. Summary Review of Studies Submitted Under IND

Tauvid contains a single active pharmaceutical ingredient, FTP, a radiopharmaceutical diagnostic agent that binds to hyperphosphorylated paired helical filament (PHF)-tau enriched within neurofibrillary tangles. The proposed indication for Tauvid is for "PET imaging of the brain to estimate the density and distribution of aggregated tau-NFTs in adult patients who are being evaluated for AD [redacted] (b) (4) FTP was originally reviewed under IND 114102 as an exploratory IND and under IND 119863. All nonclinical safety studied conducted in support of Tauvid were also submitted to the NDA and are reviewed in the following sections.

13.1.1. Pharmacology (Primary and Secondary)

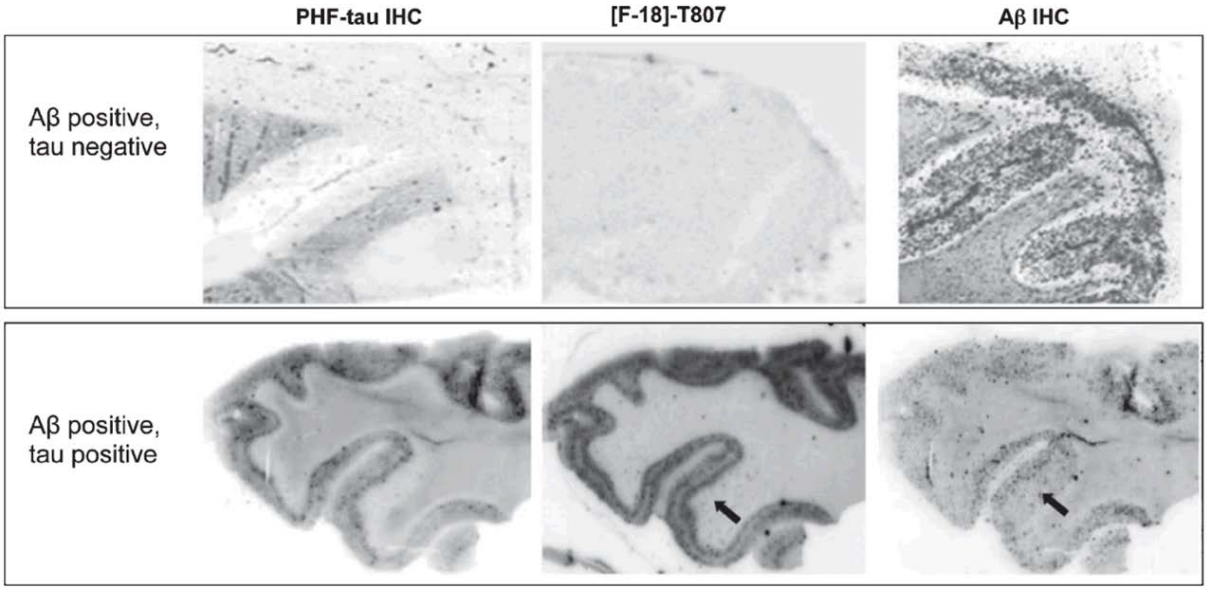
13.1.1.1. Primary Pharmacology Studies

In vitro binding and autoradiography studies were conducted on postmortem brain sections to determine binding affinity and specificity to PHF-tau. PHF-tau was immunopurified from postmortem human AD brain tissue (MC-1 anti-tau that recognizes a conformational specific epitope). FTP bound with high affinity with a dissociation constant (Kd) of 0.68nM (Study # TR-AV-1451-013). In another binding study, the Kd and B_{max} for FTP binding to isolated PHF-tau was 0.57nM and 309 pmol/mg protein respectively (Study # TR-AV-1451-156.00) demonstrating high-affinity binding.

Immunohistochemistry was conducted on adjacent sections with validated antibodies toward PHF-tau (mouse anti-Human PHF-tau antibody, AT100) and amyloid protein (rabbit anti-Human Aβ42 antibody). High-affinity binding to PHF-tau rich human brain sections from patients with AD was reported, with a Kd of 4.5nM. Weak signal was observed for brain sections rich in amyloid plaque but lacking PHF-tau (tau^- $A\beta^+$).

Specificity of FTP for PHF-tau over amyloid plaque was demonstrated by comparing autoradiography and immunohistochemistry of adjacent sections from postmortem brain of patients with AD (Chien et al. 2013) (Figure 3).

Figure 3. FTP Autoradiography and Immunohistochemistry of Brain Sections from Patients with Alzheimer's Disease

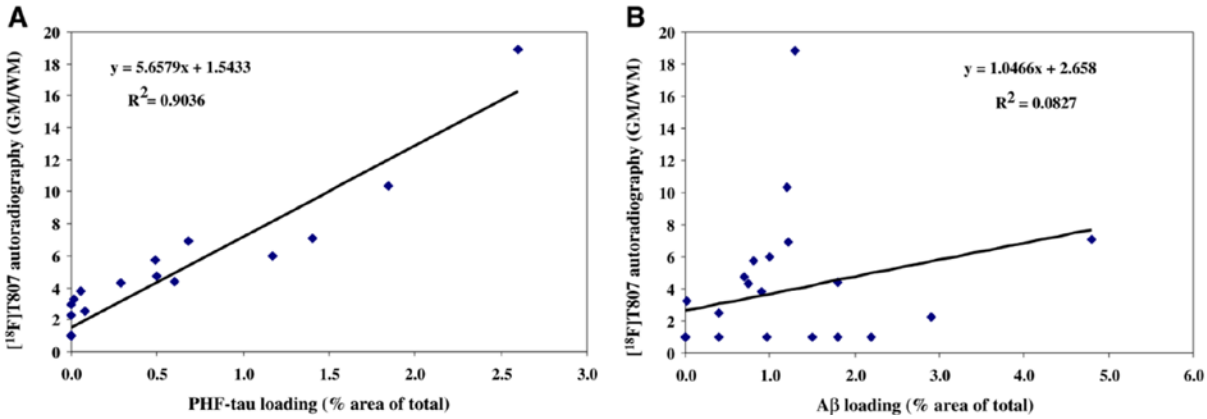


Source: Adapted from Figure 3, Chien DT et al. (2013)
Abbreviations: FTP, flortaucipir F 18; PHF, paired helical filament; IHC, immunohistochemistry

FTP uptake is colocalized with PHF-tau immunoreactivity but not with Aβ plaque immunoreactivity (compare black arrows).

Correlation between FTP autoradiography and immunohistochemistry (IHC) was evaluated by quantifying PHF-tau or Aβ42 loads across randomly imaged areas from gray matter and normalizing immunoreactive-positive area to total area in gray matter (percentage area of total) from a total of 26 human brains from patients with AD and age-matched human brains from patients without AD (Figure 4) (Xia et al. 2013).

Figure 4. Correlations of FTP (^{18}F-T807) Binding With PHF-Tau (A) and β-Amyloid Aggregate (B) IHC by Autoradiography



Source: Adapted from Figure 3, Xia CF et al. (2013)
Abbreviations: FTP, flortaucipir F 18; PHF, paired helical filament; IHC, immunohistochemistry

FTP autoradiography signal showed strong correlation with PHF-tau immunohistochemistry (r^2=0.90) on postmortem human brain sections from patients with AD and low correlation for Aβ IHC (r^2=0.08). FTP binding signal intensity in gray matter of PHF-tau demonstrated 25.7 -fold selectivity toward PHF-tau binding over Aβ (based on average signal intensity for brains with PHF-tau and Aβ loads ≥0.3% compared to brains with PHF-tau load ≥0.3% and Aβ load ≤0.3%).

13.1.1.2. Secondary Pharmacology Studies

Secondary pharmacology studies were conducted to evaluate flortaucipir uptake and binding to postmortem human tissues, comparing AD, non-AD tauopathies, and α-synuclein proteinopathies. Flortaucipir autoradiography was compared to immunoreactivity for α-synuclein, Aβ, tau, and TAR DNA-binding protein 43 (TDP-43). Flortaucipir specificity was also evaluated by in vitro and in vivo studies to determine off-target binding to monoamine oxidase (MAO)-A and MAO-B based on the structural similarity to the reversible MAO-A ligands, harmine, and 18F-fluoroethy harmol (see Table 22).

Table 22. Secondary Pharmacology Studies

Study Title (Study #)	Findings
Lack of binding of 18F-AV-1451 in α-synuclein tissue devoid of tau, Aβ amyloid, and pTDP-43 (Study # TRV-1451-074-01)	FTP autoradiography was conducted in postmortem brain tissue enriched in pathological α-synuclein but devoid of pathological tau. Postmortem human tissues included cases from PDD, PD, DLB, and MSA. Tissue blocks were analyzed by IHC for α-synuclein (LB509, mouse moAb to human synuclein), Aβ (4G8, reactive to Aβ aa 17-24 which also recognizes fibrils formed from α--synuclein and islet amyloid polypeptide and multiple systems atrophy with LB509), tau (AT8, phosphorylated PHF-tau at Ser 202 and Thr 205 and no cross-reactivity with unphosphorylated tau), and TDP43 (pTDP43). Autoradiography was compared to controls with high pathological tau and no α—synuclein as well as age-matched controls with α—synuclein or tau. No interference in PET imaging of tau in patients with AD with Tauvid would be anticipated from α -synuclein binding.
Pathological correlations of 18F-AV-1451 autoradiography and Tau AT8 immuno-fluorescence in postmortem brain sections of non-Alzheimer's disease tauopathies (PSP, PiD, CTE) (Study # TR-AV-1451-180.00)	Autoradiography (ARG) and immunohistochemistry were performed on postmortem human brain tissue with FTP and AT8 moAb to compare uptake for non-AD tauopathies PSP, PiD, and CTE. Poor overlap was observed for tau AT8 immunofluorescence signal and FTP in PiD and PSP; weak ARG signal was observed compared to extensive tau AT8 immunofluorescence. FTP signal in CTE sections was ~15-fold lower when compared to postmortem AD tissue. Weak or no binding was observed for pathological tau aggregates in non-AD tauopathies PSP, PiD, and CTE.
PET/CT Target Engagement Studies to MAO in the Rat Brain with 18F-FEH or fluoroethyl harmol and 18F-AV-1451 (Flortaucipir) (Study # TR-AV-1451-161.00)	Micro-PET imaging was conducted in vehicle control-treated and 50 mg/kg pargyline pretreated rats to evaluate the potential for FTP binding to MAO in vivo. Pargyline is an irreversible MAO inhibitor (IC_{50}=11.52nM at MAO-A and 8.2nM at MAO-B with appreciable binding to I2 imidazoline receptors). Pretreatment with pargyline did not affect uptake or washout of FTP and there was no effect on time-activity-curves over 60 min postdose. Pargyline increased washout of 18F-FEH. The absence of an effect of pargyline pretreatment on FTP uptake or washout would support limited or no binding to MAO-A in vivo.

Study Title (Study #)	Findings
Comparison of Binding of 18F-AV-1451 to Human PHF Tau and to Recombinant MAO-A (Study # TR-AV-1451-162.00)	FTP binding affinity to human recombinant MAO-A was measured in MAO-A containing microsomes and compared to MC1 moAb-purified PHF from human AD brain (PHF was analyzed by tau MC1 and AT8 ELISA). Nonspecific binding was blocked with 10µM T808 or 10µM clorgyline. FTP bound to MAO-A with a Kd of 2nM and PHF with a Kd of 0.57nM. Off-rates for FTP were 9x faster for MAO-A compared to PHF. The dissociation rate for FTP from MAO-A was also 8x faster compared to 18F-FEH. The lack of an apparent MAO-A binding may be due to greater off-rates of FTP despite nM affinity.
In vitro binding studies of AV-1451 and Recombinant Human MAO-B (Study # TR-AV-1451-163.00)	FTP binding affinity to recombinant MAO-B was evaluated with a reversible MAO-A inhibitor, safinamide, as a comparator (filtration binding studies with LC-MS for detection). Flortaucipir binding affinity to MAO-B could not be determined at high protein levels and ligand ranging from 3.5nM up to 15µM. In the study, the binding affinity (Kd) and B_{max} for safinamide to MAO-B was 57nM and 446 pmol/mg total protein, respectively. Flortaucipir only weakly inhibited safinamide binding to MAO-B in vitro, with an IC_{50} of 1.3µM. Binding to MAO-B in vivo should not be of significant concern because peak brain levels (~4nM) would be >300-fold less than the IC_{50} determined by in vitro assay.
IC_{50} determination for MAO-A and MAO-B inhibitors by 18F-AV-1451 competition binding autoradiography on normal brain tissue (Study # TR-AV-1451-179.00)	Competition binding studies were performed with postmortem normal human tissue (lacking PHF-tau) with FTP and MAO inhibitors. FTP binding to normal tissue was blocked by MAO-A inhibitors clorgyline and FES with IC_{50s} of 0.25µM and 0.78µM, respectively (The IC_{50} for cold flortaucipir was 0.27µM). In contrast FTP binding was only weakly blocked by MAO-B inhibitors deprenyl and safinamide at >10µM. These findings suggest that flortaucipir binds with low affinity to MAO-A and very weakly to MAO-B in postmortem normal human tissue and that MAO-B would not contribute much to FTP uptake in PET imaging.
In vitro binding studies of 18F-AV-1451 and recombinant MAO-B (Study # TRV-AV-1451-189)	In vitro binding assays were performed to measure FTP binding to recombinant MAO-B with tau tracer THK5251 F 18 as a comparator. THK5351 F 18 binding affinity (Kd) and B_{max} for MAO-B was 37±1.8nM and 49±6.3 pmol/mg, respectively, when control microsomes were used to define nonspecific binding; Kd and B_{max} were 39±1.1nM and 51±5.5 pmol/mg when 10µM deprenyl was used to define nonspecific binding. A Kd for FTP could not be determined with control microsomes or 10µM deprenyl to define nonspecific binding. The Applicant inferred that the study findings demonstrate artifactual binding of flortaucipir to the filter.

Abbreviations: AD, Alzheimer's disease; B_{max}, maximum number of binding sites; CT, computerized tomography; CTE, chronic traumatic encephalopathy; DLB, dementia with Lewy bodies; FTP, flortaucipir F 18; IC_{50}, concentration inhibiting 50% activity; IHC, immunohistochemistry; Kd, dissociation constant; LC-MS; liquid chromatography-mass spectrometry; MAO, monoamine oxidase; MSA, multiple systems atrophy; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; PET, positron emission tomography; PiD, Pick's disease; PSP, progressive supranuclear palsy; PHF, paired helical filament

13.1.2. Safety Pharmacology

A complete battery of in vitro and in vivo safety pharmacology studies was conducted to support safety of flortaucipir. Studies included in vitro hERG assay, central nervous system (CNS) and respiratory safety pharmacology in male Sprague Dawley rats, cardiovascular safety pharmacology in Beagle dogs, dosimetry studies in Rhesus monkeys (vital signs monitoring),

and off-target binding to CNS-enriched receptors, transporters, channels, and enzymes. Study findings are detailed below (see Table 23).

Table 23. Safety Pharmacology Studies

Study Title (Study #)	Findings
Effects on AV-1451 (LSN3182568) on cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (HEK293) (Study 130812.FMD)	hERG-transfected HEK293 cells were treated with up to 3µM flortaucipir. Flortaucipir inhibited potassium current by 84.3% at the highest concentration with an IC_{50} of 0.610µM. This was not considered to be of clinical concern because the IC_{50} would be 41-fold greater than the maximum achievable plasma concentration (15nM) following a 20 µg dose of Tauvid.
CNS Safety Pharmacology Evaluation of AV-1451 Following IV Bolus Injection Administration to Male Rats (Study 8286449)	Neurobehavioral activity (modified Irwin including home cage, hand-held, open-field, and elicited behavior) was evaluated in Crl:CD(SD) rats (eight males/group) up to 24 hours following a single IV bolus of flortaucipir (0, 50, 100, 200 µg/kg). No drug-related effects were observed up to the highest dose tested. NOEL=200 µg/kg/day (97-fold safety factor).
Respiratory Safety Pharmacology Evaluation Using Head-Out Plethysmography of AV-1451 Following IV Bolus Injection Administration to Male Rats (Study 8286450)	Respiratory parameters (respiratory rate, tidal volume, and minute volume) were evaluated in Crl:CD(SD) rats (eight males/group) up to 24 hours following a single IV bolus of flortaucipir (0, 50, 100, 200 µg/kg). No drug-related effects were observed up to the highest dose tested. NOEL=200 µg/kg/day (97-fold safety factor).
A Repeat-Dose Toxicity Study in Dogs Given AV-1451 by IV Injection for 1 Month (Study 8286448)	Heart rate, blood pressure, electrocardiography parameters, and body temperature (including toxicity assessment) were evaluated in Beagle dogs (3/sex/group) predose, on Day 1 and Day 29 of dosing (0, 5, 15, 30, 60 µg/kg/day) up to 19 hours postdose. No flortaucipir-related changes in PR interval, QRS duration, QT or QTc interval were observed on SD1 (up to 60 µg/kg/dose) or SD29 (up to 20 µg/kg/dose) Increased heart rate was identified in one of four female dogs on SD29, however findings were not considered adverse. NOEL=60 µg/kg/day in males and NOAEL=30 µg/kg/day (50-fold safety factor).
Primate Dosimetry with 18F-AV1451/18F-T807 (Study TR-AV-1451-009)	Vital signs were monitored during the dosimetry study in Rhesus macaques (two males and one female) following IV administration of 204±10 MBq FTP and no changes in heart rate, blood pressure, or respiratory rate occurred.
Assessment of Binding Potential to CNS Relevant Receptors, Channels, and Transporters (Study TR-AV-1451-007)	Off-target binding of flortaucipir was evaluated against a panel of 72 CNS targets by in vitro assays (that included receptors, channels, transporters, and enzymes (10µM drug). No significant drug-related effects, defined as >50% inhibition, were observed with exception for the norepinephrine transporter (IC_{50}=2.2µM), monoamine transporter VMAT2 (0.4µM), polyamine site of the glutamate receptor (2.7µM), µ-opiate receptor (1-10µM), and acetylcholinesterase (>1µM). IC_{50} for flortaucipir at MAO-A was 0.57µM and significantly greater at MAO-B (>1µM). The potential for adverse CNS effects due to off-target binding would be low based on a maximum flortaucipir peak brain concentration of 4nM, >100-fold less than the IC_{50} for identified targets.

Abbreviations: CNS, central nervous system; FTP, flortaucipir F 18; hERG, human Ether-a-go-go-Related Gene; IC_{50}, concentration inh biting 50% activity; IV, intravenous; MAO, monoamine oxidase; MBq, megabecquerel; NO(A)EL, no observed (adverse) effect level; SD#, Study Day #

13.1.3. Absorption, Distribution, Metabolism, Excretion / Pharmacokinetics

The in vitro and in vivo studies designed to assess the pharmacokinetics of flortaucipir (cold and F18-radiolabeled) are described below (Table 24). In vivo biodistribution and dosimetry studies were conducted in mice, rats, and nonhuman primates (*Rhesus*). In vitro analysis of metabolites indicate that rats and dogs are appropriate species for use in repeat-dose toxicity studies.

Table 24. ADME/PK Studies

Type of Study	Major Findings
Absorption	
Study not conducted	FTP is administered by intravenous (bolus) injection; therefore absorption is not applicable.
Distribution	
PET Brain Imaging in Mice and Rats of [F-18] T807 (Study # TR-AV-1451-008)	Brain uptake of FTP was evaluated by micro PET/CT imaging in mice (n=6) and rats (n=5) for 30 min following intravenous (bolus) administration (~200 µCi in mice and 400 µCi in rats). Rapid brain uptake and moderate washout was observed with peak %ID/g of 4.2 in mice and 0.5 in rats. Washout to level of skeletal muscle occurred by 26 min in mice and >30 min rats with some uptake in bone (FTP defluorination) that did not increase over time.
Biodistribution and Excretion of [F-18]T807 in Mice (Study # TR-AV-1451-008)	Biodistribution and excretion of FTP was evaluated in Foxn1nu/nu+ wild type mice (n=6) following intravenous (bolus) injection (~200 µCi). Blood samples were collected at 5, 15, and 30 min and mice were euthanized for tissue uptake (liver, kidneys, skeletal muscle, brain and femur). FTP was taken up by brain and cleared rapidly. Renal uptake and elimination were significant with moderate hepatic uptake; uptake in muscle was lower. Bone uptake (femur) was low at all time points, suggesting minimal defluorination of FTP.
Brain Uptake and Clearance Of [F-18] T807 In Nonhuman Primates (Study # TR-AV-1451-008)	Brain uptake and clearance of FTP was evaluated by PET imaging in Rhesus monkeys (n=2) with monitoring of vital signs. Moderate uptake occurred in the brain and did not fully return to baseline SUV by 90 min. Ratio of uptake in striatum, cerebellum, and cortex to white matter ranged from 1.5 to 2 at early imaging time points.
Primate Dosimetry with 18F-AV1451 / 18F-T807 (Study TR-AV-1451-009)	Whole-body PET/CT imaging over 3 hours following intravenous administration of FTP (204±10 MBq) to Rhesus monkeys (n = 2 M and 1 F), images were analyzed for biodistribution and dosimetry. Rapid tracer uptake was observed in the lungs and kidneys, followed by the liver, bladder, and small intestines. The urinary bladder wall received the highest exposure to radioactivity after FTP injection with an absorbed radiation dose of 0.16±0.04 mGy/MBq (males) and 0.22±0.06 mGy/MBq (female). The effective dose was 0.027 mSv/MBq (males) and 0.035 mSv/MBq (female). FTP was excreted mainly by the renal-urinary system, with some uptake of radioactivity in the lungs, liver and small intestine.

Type of Study	Major Findings
Metabolism	
Biostability of [F-18] T807 in Mice (Study TR-AV-1451-008)	Metabolic stability of FTP was evaluated in ICR mice (n=6 females) following intravenous injection (300 µCi). Animals were euthanized at 10 min and 30 min postinjection; blood, urine, and major organs were collected and processed to determine %ID and presence of metabolites. Half-life of FTP was <5 min and four hydrophilic metabolites were detected in plasma and tissues, F 18 was a minor metabolite. No detectible metabolites were observed in brain tissues.
Mouse and Human Liver Microsome Stability Study (Study # TR-AV-1451-008)	Stability of FTP was evaluated by in vitro assay with mouse and human microsomes (±NAPDH for 2 hours at 37°C); phenacetin and dobutamine were positive controls for mouse or human microsomes, respectively. FTP was metabolically stable in microsomes in the absence of NAPDH and rapidly metabolized in the presence of NAPDH (less stable in mouse versus human microsomes).
Human Hepatocyte Study (Study # TR-AV-1451-008)	Human hepatocytes (n=5 donors) were incubated with FTP at 37°C and samples were analyzed over 90 min by HPLC. FTP was moderately stable with formation of one major polar metabolite over time; defluorination was not observed.
In Vitro Metabolism of Compound AV-1451 (LSN3182568, T807) in Mouse, Rat, Dog, Monkey and Human Hepatocytes (Study # TR-AV-1451-008)	Hepatocytes from mouse, rat, dog, monkey, and humans were incubated with 2µM cold flortaucipir for 4 hours and analyzed by HPLC. In vitro metabolism profile of flortaucipir was similar across species by both extent of degradation and the amount and identity of metabolites formed. Findings from this study informed selection of rodent (rat) and nonrodent (dog) species for GLP toxicity studies.
^{18}F AV-1451 Metabolite Screening in Mice (Study # TR-AV-1451-188.00	Metabolite formation was evaluated in CD-1 mice (n=6) by HPLC analysis of plasma and brain samples following intravenous administration of FTP at 2, 15, and 30 minutes, postdose. FTP and three potential radio-metabolites were identified in plasma. A single peak corresponding to parent compound FTP was identified in extracted brain samples. FTP is stable in mouse brain with no brain penetrant radio-metabolites observed.
Excretion	
Biodistribution and Excretion Of [F-18] T807 In Mice (Study # TR-AV-1451-008)	Dedicated excretion studies were not conducted. The majority of FTP is distributed to excretory organs, with significant renal elimination and hepatic uptake. Similar findings were observed in PET/CT biodistribution and dosimetry in Rhesus monkeys.
TK data from general toxicology studies *Study not conducted and not needed*	N/A
TK data from reproductive toxicology studies *Study not conducted and not needed*	N/A
TK data from carcinogenicity studies *Study not conducted and not needed*	N/A

Abbreviations: CT, computerized tomography; FTP, flortaucipir F 18; GLP, good laboratory practice; HPLC, high-performance liquid chromatography; ID, injected dose; MBq, megabecquerel; µCi. Microcurie; mGy, milligray; mSv, millisievert; N/A, not applicable; NAPDH, nicotinamide adenine dinucleotide phosphate; PET, positron emission tomography; SUV, standard uptake value; TK, toxicokinetic

13.1.4. Toxicology

13.1.4.1. General Toxicology

Single-Dose Toxicology

A Single-Dose Expanded Acute Intravenous Toxicity Study in Rats/Study # 148-001

Sprague Dawley rats (10/sex/group in main and 5/sex/group in recovery treatment groups) were administered vehicle control (9% ethanol and 1% Solutol® HS 15 in 90% saline) or flortaucipir (75, 150, or 300 µg/kg) by intravenous (bolus) administration. Toxicity was evaluated by mortality, clinical observations, body weight and body weight gains, food consumption, ophthalmic examinations, clinical (hematology, coagulation, and chemistry), and gross macroscopic and histopathology evaluation. No toxicologically significant drug-related findings were observed in main (study day 3) or recovery (study day 15) animals. The no observed adverse effect level (NOAEL) for the study was 300 µg/kg; equivalent to 145-fold greater than the recommended 20 µg human dose based on body surface area scaling.

Repeat-Dose Toxicology

A Repeat-Dose Toxicity Study in Rats Given AV-1451 (LSN3182568) by Intravenous Injection for 1 Month / Study 8286447

Key study findings

- Rats received daily intravenous administration for 1 month of 0, 20, 50, or 100 µg/kg flortaucipir
- No adverse, drug-related toxicities were observed up to the highest dose tested. The NOAEL was 100 µg/kg

Conducting laboratory: [redacted] (b) (4)

GLP compliance: Yes

Table 25 and Table 26 summarize the study's design and results, respectively.

Table 25. 1-Month Rat Intravenous Toxicity Study Design

Methods	Details
Dose and frequency of dosing	0, 20, 50, 100 µg/kg; daily
Route of administration	Intravenous (bolus)
Formulation/vehicle	[redacted] (b) (4) (0.9% Sodium Chloride for Injection, USP)
Species/strain	Rat/Sprague Dawley [Crl:CD(SD)]
Number/sex/group	10
Age	10 weeks
Satellite groups/unique design	None
Deviation affecting interpretation	No

Abbreviations: USP, United States Pharmacopeia; v/v, volume/volume; w/v, weight per volume

Table 26. 1-Month Rat Intravenous Toxicity Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined at least once daily. No drug-related clinical signs noted.
Body weights	Measured twice during predose, prior to dosing on SD1, and weekly during the dosing phase. No drug-related effects on body weights or body weight gains.
Food consumption	Measured weekly. No drug-related findings
Ophthalmoscopy	Evaluated once during predose and once on SD29. No drug-related findings.
Electrocardiography	N/A
Hematology	No toxicology significant drug-related findings.
Clinical chemistry	Evaluated at necropsy (SD31). No toxicology significant drug-related findings.
Urinalysis	Evaluated at necropsy (SD31). No toxicology significant drug-related findings.
Gross pathology	Evaluated at necropsy (SD31). No drug-related macroscopic findings
Organ weights	Evaluated at necropsy (SD31). No toxicology significant drug-related findings.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy (SD31). Microscopic findings at the site of the catheter and femoral vein in the area of infusion characterized as fibrosis, intimal hyperplasia, inflammation, and/or thrombosis. Incidence and severity for animals from vehicle control and flortaucipir treated groups were similar and attributed to infusion procedure. Lung of vehicle control and flortaucipir treated groups had infusion-related perivascular eosinophil infiltrates, interstitial inflammation, granuloma, and/or thrombosis. Other findings were due to the infusion procedure or considered spontaneous and/or incidental because of low incidence and severity as expected for animal age and strain. No drug-related microscopic findings associated with flortaucipir exposure.

Abbreviations:; SD#, Study Day #

A Repeat-Dose Toxicity Study in Dogs Given AV-1451 (LSN3182568) by Intravenous Injection for 1 Month / Study 8286448

Key study findings

- Dogs received daily intravenous administration for 1 month of 0, 5, 15, or 30 µg/kg flortaucipir (60 µg/kg on Day 1 only)
- Transient increase in heart rate on dosing Day 29, ranging from 9 to 30 bpm (9 to 34%) from 1 through 2.5 hours, postdose in females only at 30 µg/kg
- Cardiovascular finding not considered adverse for a single-use agent
- No adverse, drug-related toxicities were observed up to the highest dose tested. The NOAEL was 30 µg/kg

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 27 and Table 28 summarize the study's design and results, respectively.

Table 27. 1-Month Beagle Dog Intravenous Toxicity Study Design

Methods	Details
Dose and frequency of dosing	0, 5, 15, 30 µg/kg; daily and 60 µg/kg on Day 1
Route of administration	Intravenous (bolus) to cephalic vein
Formulation/vehicle	(b) (4) (0.9% Sodium Chloride for Injection, USP)
Species/strain	Dog/Beagle
Number/sex/group	3
Age	6 to 8 months
Satellite groups/unique design	Group 5/ECG evaluation only on SD1 at 60 µg/kg AV1451
Deviation affecting interpretation	No

Abbreviations: ECG, electrocardiogram; SD1, Study Day 1; v/v, volume per volume; w/v, weight per volume

Table 28. 1-Month Beagle Dog Intravenous Toxicity Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined once daily during the dosing phase. Detailed observations twice during predose, prior to dosing on SD1, and weekly. No drug-related clinical signs noted.
Body weights	Measured twice during predose, prior to dosing on SD1, and weekly during the dosing phase. No drug-related effects on body weights or body weight gains.
Food consumption	Measured weekly. No drug-related findings.
Ophthalmoscopy	Evaluated once during predose and once on SD27. No drug-related findings.
Electrocardiography	Electrocardiography evaluation (8-lead, jacketed external telemetry) once predose, on SD1 of dosing (groups 1–5) and on SD29 (groups 1–4 only). Increased heart rate at 1, 1.5, 2, and 2.5 hours postdose on SD29 in females at 30 µg/kg dose level (34, 17, 9, 14%, qualitative but not statistically significant). No drug-related findings on SD1 at all dose levels and on SD29 up to 30 µg/kg in males and 15 µg/kg in females. No significant drug-related electrocardiography findings associated with flortaucipir exposure.
Hematology	Evaluated twice predose, at Week 2, and at necropsy (SD33). No toxicology significant drug-related findings.
Clinical chemistry	Evaluated twice predose, at Week 2, and at necropsy (SD33). No toxicology significant drug-related findings.
Urinalysis	Evaluated twice predose, at Week 2, and at necropsy (SD33). No toxicology significant drug-related findings.
Gross pathology	Evaluated at necropsy (SD33). No drug-related macroscopic findings
Organ weights	Evaluated at necropsy (SD33). No toxicology significant drug-related findings.
Histopathology Adequate battery: Yes Peer Review: Yes	Evaluated at necropsy (SD33). Macroscopic and histopathologic findings were spontaneous and/or incidental based on low incidence for vehicle control and flortaucipir treated groups, or severity as expected for animal age and strain. No drug-related microscopic findings associated with flortaucipir exposure.

Abbreviations: SD#, Study Day #

13.1.4.2. Genetic Toxicology

Table 29 summarizes the results of the genetic toxicology studies.

Table 29. Genetic Toxicology Studies

Study Title (Study #)	Key Study Findings
AV-1451 (LSN3182568) Bacterial Reverse Mutation Assay (Study # 8286444) GLP compliance: Yes Study is valid: Yes	*S. typhimurium* (TA98, TA100, TA1535) and *E. coli* (WP2uvrA) were treated for 52±4 hours with up to 5,000 µg/plate of flortaucipir in the presence and absence of S9. Cytotoxicity was observed at >500 µg/plate for some strains. Vehicle (DMSO) and positive controls (2-nitrofluorene, sodium azide, ICR-191, 4-nitroquinoline-N-oxide, benzo(a)pyrene), 2-aminoanthracene) produced appropriate responses. Flortaucipir was positive for mutagenicity in TA98, TA100, TA1537, and WP2uvrA with S9 metabolic activation (all dose levels) and in TA1535 (≥500 µg/plate) and TA1537 (≥160 µg/plate) without S9. Flortaucipir was positive for genotoxicity under the conditions of this study.
AV-1451 (LSN3182568): Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells (Study # 8286445) GLP compliance: Yes Study is valid: Yes	CHO cells were treated with up to 270 µg/mL of flortaucipir for 3 hours in the presence and absence of S9 and analyzed at 20 hours. Flortaucipir was positive for clastogenicity after 3-hours incubation with and without S9 metabolic activation, and after 20-hours incubation without S9. Flortaucipir was cytotoxic at concentrations above 22.2 µg/mL and produced a dose-dependent increase in the number of cells with aberrations at the 10.9 and 22.2 µg/mL dose level. In assays with S9 metabolic activation, cytotoxicity was observed at concentrations of 31.8 µg/mL and produced a dose-related increase in aberrations at 22.2 and 31.8 µg/mL dose levels compared to the vehicle control. Flortaucipir was cytotoxic to cells treated for 20 hours at concentrations above 7.63 µg/mL and produced a dose-related increase in the number of cells with aberrations at 3.74, 5.34, and 7.63 µg/mL dose levels. Flortaucipir was positive for genotoxicity under the conditions of this study.
AV-1451 (LSN3182568): In vivo Rat Bone Marrow Micronucleus Assay (Study # 8286446) GLP compliance: Yes Study is valid: Yes	Sprague Dawley rats (5/sex/group) were treated with flortaucipir (400, 800, 1600 µg/kg/day) or vehicle [redacted] (b) (4) on Days 1 and 2, or positive control (60 mg/kg/day) on Day 2 only, and were euthanized on Day 3. Doses were selected based on a dose range finding study. Vehicle and positive control produced appropriate responses. No drug-related increases in polychromatic erythrocytes or micronucleated cells were observed at dose levels up to 1,600 µg/kg/day. Flortaucipir was therefore considered negative for genotoxicity under the conditions of this study.

Abbreviations: DMSO, dimethyl sulfoxide; GLP, good laboratory practice; v/v, volume per volume; w/v, weight per volume

13.1.4.3. Carcinogenicity

Carcinogenicity studies were not conducted for FTP and are not needed.

13.1.4.4. Reproductive Toxicology

Reproductive and developmental toxicology studies were not conducted for FTP and are not needed.

13.1.4.5. Other Toxicology Studies

Cytotoxicity of AV-1451 (T807) in Normal and Cancer Cells

This drug screening study was performed to evaluate the cytotoxic potential of flortaucipir. Cytotoxicity was monitored by a colorimetric assay where viable cells reduce 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) to form purple formazan.

Normal (MRC5 human normal lung fibroblast, AML12 mouse normal liver cell) and tumor (LS174T human colorectal adenocarcinoma, A172 human glioblastoma cell lines) cell lines were treated with flortaucipir at up to 10µM for 24 hours. Saponin at 0.01% was used as a positive control. flortaucipir was negative for cytotoxicity at up to 10µM by MTT assay in normal and tumor cell lines.

13.1.5. Impurities/Degradants

Not applicable

13.1.6. Referenced NDAs, BLAs, DMFs

Not applicable

13.2. Individual Reviews of Studies Submitted to the NDA

Not applicable

14. Clinical Pharmacology Assessment: Additional Information

14.1. In Vitro Studies

In vitro metabolism studies were conducted to determine the individual human recombinant CYPs capable of metabolizing AV1451. Supersomes containing human recombinant cytochrome P450s (rCYPs, 0.25 mg/mL) for rCYP1A2, rCYP2B6, rCYP2C8, rCYP2C9, rCYP2C19, rCYP2D6, rCYP2J2, rCYP3A4, or rCYP3A5 were evaluated at a AV1451 concentration of 100μM. Following incubation, samples were analyzed for the disappearance of AV1451 (% remaining), using an LC/MS/MS method.

Of the rCYPs evaluated, only rCYP1A2 demonstrated substantial contribution to overall CYP-mediated hepatic clearance of AV1451. The fraction of hepatic CYP metabolism mediated by CYP1A2 was 0.976 with a minor contribution of CYP2D6 (fraction of hepatic CYP metabolism =0.024).

With respect to clearance pathways and potential victim DDI risk, CYP appears to be a relatively minor contributor to the metabolism of LSN3182568, whereas the major enzyme responsible for hepatic metabolism is AO, with some contribution by UDP-glucuronosyltransferase.

AV1451 was assessed for apparent permeability (Pe) and the potential to be a P-glycoprotein (P-gp) substrate in vitro using Madin-Darby canine kidney (MDCK) cells transfected with human MDR1 (P-glycoprotein), commonly known as MDCK-MDR1 cells. The results showed that AV1451 is not a P-gp substrate.

The ability of LSN3182568 to inhibit the metabolism of marker catalytic activities for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A was examined in vitro in human liver microsomes using concentrations of AV1451 up to 80μM. The in vitro data suggest that LSN3182568 would not be expected to cause clinically significant inhibition of the clearance of drugs metabolized by these CYP enzymes.

14.2. In Vivo Studies

This section summarizes the following three phase 1 studies: the first-in-human-study conducted under an exploratory IND; a study of in vivo brain uptake and tau protein binding; and a test-retest reproducibility study

First-in-Human Study

An, open-label, nonrandomized, multicenter, exploratory, and safety study of [F-18]T807 now known as flortaucipir F 18 was conducted by Siemens Molecular Imaging.

The primary objectives of the study were to

- Assess the safety of intravenous (IV) administration of [F-18]T807
- Evaluate the biodistribution and radiation dosimetry of [F-18]T807 in subjects with low probability of AD using PET/computed tomography (CT) whole body imaging

- Evaluate the metabolism of [F-18]T807 in subjects with low probability of AD using serial blood samples collected pre- and post-[F-18]T807 administration
- Evaluate [F-18]T807 uptake and signal/background information in brain PET/CT imaging of subjects with a high probability of currently being positive for AD and age-matched subjects with a low probability of currently being positive for AD

This exploratory, open-label, multicenter, nonrandomized study of [F-18]T807 PET/CT imaging assessed the safety of the tracer and its potential as a brain-imaging agent. The study was terminated early in anticipation of transfer of the IND from Siemens to the Applicant (Avid). Brain images were acquired in list mode during two imaging sessions: immediately following [F-18]T807 administration for 1 hour and at 80 to 100 minutes following [F-18]T807 administration. Safety measurements included vital signs, electrocardiograms (ECGs), clinical laboratory measurements, and physical exams prior to and up to 24±8 hours postadministration the [F-18]T807.

Sixteen subjects in brain imaging arm signed informed consent, seven with low probability of AD (group 1) and nine with high probability of AD (group 2).

For group 1, in the investigator's opinion, subject has a low probability of being currently positive for AD as determined by an MMSE ≥28; for group 2, in the investigator's opinion, subject has a high probability of being currently positive for AD as determined by a MMSE <17 for original protocol; MMSE ≤24 for amendment 1 of protocol.

Serial measures of standard uptake values derived for the time course PET imaging data of the brain were the primary outcome for the brain imaging subjects.

A dose of 10 mCi [F-18]T807 was used for brain imaging, the total mass dose was 13 μg or 0.3 g/kg for a 50 kg human. PET imaging extended from immediately postdose to 100 minutes postdose.

Study Results

The evaluations of the digital brain imaging data were performed off-site by a Siemens Molecular Imaging expert. The standard uptake value (SUV) time activity curves (TACs) for the 0 to 60-minute dynamic images showed a distribution of the radiotracer throughout the brains of all subjects in both the AD and HC group. The highest SUV in the cerebellum was reached between 1.6 to 9 minutes with an average of 4.6 minutes. The radiotracer cleared from the cerebellum in all the subjects with less than half of the maximum activity remaining after 30 to 50 minutes (mean = 41.5 minutes). For subjects in the HC group, radiotracer also cleared from the cortical regions at the same rate as the cerebellum. Visual inspection of static 80 to 100-minute images and review of standard uptake value ratio (SUVr) values indicated generally greater cortical radiotracer retention by subjects with high probability of AD compared to low probability subjects.

Study of In Vivo Brain Uptake and Tau Protein Binding

The Applicant conducted a phase 1 study titled, "An Exploratory Evaluation of the Tau Protein Binding Properties, Whole-Body Biodistribution and Safety of 18F-AV-1451 Injection in Healthy Volunteers and Cognitively Impaired Subjects." The objectives of the study were to

address the feasibility for further development of FTP as a tau protein targeted radiopharmaceutical by performing the following:

- Evaluate the uptake and retention of FTP in the brain
- Obtain preliminary information regarding the safety of FTP in healthy volunteers and subjects with cognitive impairment and dementia
- Obtain preliminary information regarding dosimetry of FTP in healthy volunteers
- Compare the uptake and retention of FTP to brain amyloid (Aß) status, cognitive function, and magnetic resonance imaging (MRI) scan, including retrieval of information from patients previously enrolled in tau imaging Study T807000

The subjects were assigned to one of three study cohorts as follows:

- Cohort 1: PET brain imaging cohort; approximately 16 subjects in four groups of three to four subjects each; approximately three of these subjects (any group, but not all from same group) were to be first-generation Japanese.
  - Group 1: Healthy; ≥20 to ≤40 years of age
  - Group 2: Healthy; ≥65 years of age
  - Group 3: MCI due to AD; ≥50 years of age
  - Group 4: Possible/probable AD; ≥50 years of age

An FTP PET scan was planned for all subjects in cohort 1. In addition, a florbetapir F 18 (FBP) PET scan was planned for all subjects in groups 2, 3, and 4 of cohort 1. The FTP and FBP imaging sessions had to be performed at least 48 hours apart, but could be in either order. Subjects in cohort 1 had a volume-based T1-weighted MRI of the brain.

- Cohort 2: FTP PET whole body biodistribution cohort (approximately nine healthy subjects, including three first-generation Japanese subjects); immediately following the injection of FTP, approximately 10 emission scans from the vertex of the head to the thighs were repeated over a period of about 6 hours to assess the distribution of radioactivity in the body.
- Cohort 3: MRI and amyloid extension cohort (up to 10 subjects who were successfully imaged with FTP in Study T807000). Subjects received a FBP PET scan and an MRI. Repeat scans were not performed if an electronic copy of a previous FBP PET scan or MRI scan (MRI taken within prior 12 months) was available.

Subjects who qualified for the study returned to the clinic within approximately 30 days of the screening visit for administration of FTP or FBP for injection.

Flortaucipir F 18 Brain Imaging Session

For the dynamic FTP brain imaging session, subjects received a single IV bolus injection of approximately (370 megabecquerel (MBq)) 10 mCi (±10%) of FTP followed by a saline flush. PET Imaging began immediately after the administration of FTP injection, with a 60-minute dynamic imaging plus four frames x 5 minutes at approximately 80 minutes postdose (80 to 100 minutes postdose). For subjects who could tolerate an additional 20-minute scan, an optional third scan at 110 to 130 minutes was to be taken after a 10-minute break.

For the dynamic FTP brain imaging session, subjects received a single IV bolus injection of approximately (370 megabecquerel (MBq)) 10 mCi (±10%) of FTP followed by a saline flush. PET Imaging began immediately after the administration of FTP injection, with a 60-minute

dynamic imaging plus four frames x 5 minutes at approximately 80 minutes postdose (80 to 100 minutes postdose). For subjects who could tolerate an additional 20-minute scan, an optional third scan at 110 to 130 minutes was to be taken after a 10-minute break.

Florbetapir F 18 Brain Imaging Session

For the FBP brain imaging session, subjects received a single IV bolus injection of approximately (370 MBq) 10 mCi (±10%) of FBP injection followed by a saline flush. A 10-minute brain scan (2 acquisitions of 5-minute duration) began approximately 50 minutes after injection.

Criteria for Evaluation of PET Scan Images

The quantitative evaluation for the PET brain scans used calculations to find the SUVr for cortical target areas (frontal cortex, parietal cortex, temporal cortex, hippocampus, occipital cortex, anterior cingulate, posterior cingulate, and precuneus) relative to the entire cerebellum.

For the PET (whole body) scan, volume of interest was calculated for regions of the whole body. Organ residence times were entered into the Organ Level Internal Dose Assessment/Exponential Modeling (OLINDA/EXM) radiation dosimetry code to obtain organ dose estimates and effective doses for individual subjects. The whole-body effective dose was the primary whole-body imaging outcome variable.

Study Results

The results of the quantitative assessment of global composite SUVr relative to the entire cerebellum) showed higher mean FTP SUVrs in the AD and MCI groups in comparison with cognitively normal subjects. Global composite mean (standard deviation (SD)) SUVrs relative to the entire cerebellum were as follows:

- AD: 1.780 (0.857) for FTP and 1.416 (0.386) for FBP
- MCI: 1.317 (0.161) for FTP and 1.621 (0.105) for FBP
- Young cognitively normal (YCN): 1.128 (0.047) for FTP
- Old cognitively normal (OCN): 1.107 (0.175) for FTP and 1.040 (0.160) for FBP
- Total: 1.385 (0.566) for FTP and 1.366 (0.346) for FBP

Across all subjects, there was a correlation between FBP and FTP SUVrs, both for the composite and for individual regions. Within diagnostic groups, there were no significant correlations except for frontal cortex in the AD group.

The body region that received the highest mean (SD) dose of FTP was the upper large intestine wall, which received 0.0962 (0.0134) mSv/MBq in the 73.7 kg model. Other than upper large intestine, the regions that received the highest mean doses were small intestine, liver, and kidneys.

The mean (SD) whole body effective dose of FTP using standard adult male phantom of 73.7 kg model is 0.0241 (0.0016) mSv/MBq. The mean (SD) whole body effective dose values for standard adult male model scaled to 50 kg, 60 kg and 80 kg models are 0.0311 (0.0021) mSv/MBq, 0.0275(0.0019) mSv/MBq, and 0.0229 (0.0016) mSv/MBq respectively.

Study Conclusions

The results of the quantitative assessment of global composite SUVrs relative to the entire cerebellum showed higher FTP uptake in the AD and MCI groups in comparison with cognitively normal subjects.

Test-Retest Reproducibility Study

The Applicant conducted an open-label, multicenter study (Protocol Number 18F-AV-1451-A03) evaluating the test-retest reproducibility, and safety of tau imaging with FTP.

The primary objective of this study was to evaluate test-retest reproducibility of FTP for brain imaging of aggregated tau in healthy volunteers and subjects with cognitive impairment.

Additionally, two exploratory analyses were:

- Association between results from neuropsychological testing and FTP imaging
- Assessment of test-retest reliability in the subset of subjects with cognitive signs or symptoms

Imaging Day 1 and Day 2 Procedures

Subjects who qualified for the study returned to the clinic within 30 days for the first FTP PET imaging session. Subjects were asked to return to the clinic for a second FTP PET imaging session not <48 hours and not more than 4 weeks following the initial FTP PET imaging session.

At each brain imaging session, subjects received a single IV bolus of FTP followed by a saline flush, and then at approximately 80 minutes postdose, a scan lasting 20 minutes (as four 5-minute acquisitions) was acquired. An additional scan at approximately 110 minutes postdose lasting 20 minutes (as four 5-minute acquisitions) was acquired.

A total of 24 subjects, of whom 10 had probable AD, 8 had MCI, and 6 were cognitively normal (CN) were enrolled in the study

Results: Quantitative Assessment of PET Scan Images

In order to evaluate the test-retest reproducibility of FTP for brain imaging of aggregated tau in healthy volunteers and subjects with cognitive impairment, SUVrs were calculated. For this purpose, automatic anatomical labeling volumes of interest (AAL VOIs)were obtained for cortical regions including: frontal, parietal, temporal and occipital using a subsection of cerebellum gray matter (cerebellum crus 1 AAL VOI) as a reference region. Neocortical aggregated tau binding was represented by a combination VOI SUVr derived using SUVr values from parietal, temporal and occipital areas, and weighted by the voxel counts in these regions. The intraclass correlation (ICC) was the primary metric used to evaluate the FTP SUVr reproducibility between test and retest scans across all three groups. An analysis was also conducted to evaluate the percent change (mean and SD) of SUVr values between test and retest sessions.

The AD, MCI, and CN groups had a mean (SD) age of 74.4 (7.3) years, 70.3 (5.4) years, and 62.8 (9.5) years, respectively. The mean time since diagnosis was approximately 2.4 years for the AD group and 3.5 years for the MCI group. An Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) Classifying Worst Injury score of 3 (mild TBI with loss of

consciousness) or above was recorded for 20.0% of AD subjects and 50.0% of MCI subjects. In general, baseline cognitive assessment scores reflected the greater cognitive impairment of the AD group relative to the MCI group and of both cognitively impaired groups relative to the CN group. The AD and MCI groups had an overall higher level of education than the CN group. The percentages of subjects who were ApoE positive in the AD, MCI, and CN groups were 60.0%, 62.5%, and 33.3%, respectively.

Study Results

The ICC and 95% confidence interval (CI) for the combination region for all 24 subjects in the study was 0.971 (0.935, 0.988) for 80 to 100 minutes postdose and 0.968 (0.926, 0.986) for 110 to 130 minutes postdose, indicating substantial test-retest agreement. Analysis of intrasubject test-retest variability showed a mean change (SD) in the SUVr for the combination VOI of 0.15% (4.48%) for scans 80 to 100 minutes postdose and 0.12% (5.45%) for scans 110 to 130 minutes postdose. Across regions, the SDs of percent change ranged from 3.99% to 6.15% for the 80- to 100-minute scans and from 4.65% to 7.10% for the 110- to 130-minute scans. The SD of the percent change for the combination region was significantly smaller for the 80 to 100-minute window compared to the 110 to 130-minute scan window.

15. Efficacy: Additional Information and Assessment

15.1. Subgroup Analysis by Subject Age and Sex

A subgroup analysis of reader/scan performance by subject age and by subject sex was performed in Study A16. Evaluation by age was difficult since there were only three subjects under the age of 65 and nine under the age of 75.

Evaluation by race is also difficult as the study population was dominated by one group: white, accounting for 97% of the study population.

There were 30 males and 34 females among the 64 cases in the primary analysis set of A16. With only 13 truth-standard negative cases in either subgroup, confidence limits for sensitivity and specificity are relatively broad and no strong conclusions can be drawn. However, as seen in Table 30, there is a slight trend for increased sensitivity, but no clear difference in specificity for B3 NFTs between cases from the male versus female subgroup.

Table 30. Diagnostic Performance of Individual FTP PET Scan Readers for Detection of B3 NFTs in Cases From Males and Females in Study A16

	Sensitivity		Specificity	
	Male	Female	Male	Female
Reader 1	94.4 (74.2, 99.0)	100.0 (84.5, 100.0)	66.7 (39.1, 86.2)	69.2 (42.4, 87.3)
Reader 2	83.3 (60.8, 94.2)	100.0 (84.5, 100.0)	91.7 (64.6, 98.5)	92.3 (66.7, 98.6)
Reader 3	83.3 (60.8, 94.2)	100.0 (84.5, 100.0)	91.7 (64.6, 98.5)	84.6 (57.8, 95.7)
Reader 4	83.3 (60.8, 94.2)	100.0 (84.5, 100.0)	75.0 (46.8, 91.1)	76.9 (49.7, 91.8)
Reader 5	100.0 (82.4, 100.0)	100.0 (84.5, 100.0)	50.0 (25.4, 74.6)	53.8 (29.1, 76.8)

Source: Page 112 of the Applicant's clinical efficacy summary
Abbreviations: FTP, flortaucipir F 18; NFT, neurofibrillary tangle; PET, positron emission tomography

In Study A05C, 97% were white, 83.2% were age 65 or higher, and 54% were male and 46% were female. (b) (4) [redacted]

(b) (4)

In Study FR01, the statistical reviewer (Reviewer) obtained slightly different counts for readers 3 and 5 than the Applicant reported in the primary analysis of the NFT TS by tau classification, an analysis, which included 82 patients.

For reader 3, there were five Reviewer versus six Applicant false positives and 31 Reviewer versus 30 Applicant true negatives. The Reviewer specificity was 88.6% (95% CI: 74.0, 95.5) as compared to the Applicant's 85.7% (95% CI: 70.6, 93.7). Reader 3 sensitivity was the same for Reviewer and Applicant.

For reader 5, there were seven Reviewer versus eight Applicant false positives and 28 Reviewer versus 27 Applicant true negatives. Reviewer specificity was 80.0% (95% CI: 64.1, 90.0) as compared to the Applicant's 77.1% (95% CI: 61.0, 87.9). Reader 5 sensitivity was the same for Reviewer and Applicant. These small discrepancies in FR01 results did not affect the study conclusions, e.g., both Reviewer and Applicant 95% CI lower limits for sensitivity and specificity were >50.0% for readers 3 and 5.

15.2. Clinical Study Report Synopsis: Study 18F-AV-1451-A16

Title of Study

A Clinico-Pathological Study of the Correspondence Between 18F-AV-1451 PET Imaging and Postmortem Assessment of Tau Pathology

Number of Investigators

This multicenter study included 28 principal investigators.

Study Centers

This study was conducted at 28 study centers in two countries.

Publication(s) Based on the Study

Arora A, Pontecorvo M, Mintun M, Fleisher A, Devous M, Lu M, Galante N, Stevenson P, Flitter M, Beach T, Montine T, Serrano G, Sue L, Intorcia A, Curtis C, Salloway S, Thein S, Wellman C, Perrin A, Lowe V, Grossman M, Irwin D, Ikonomovic M, Seeley W, Rabinovici G, Masdeu J. Evaluation of a visual read method for flortaucipir PET scans [abstract]. In: 13th Human Amyloid Imaging Conference Program and Abstracts; Jan 16–18, 2019; Miami, FL, p 129.

Arora AK, Pontecorvo MJ, Mintun MA, Fleisher AS, Devous MD, Lu M, Galante N, Stevenson PA, Flitter M, Truocchio SP. Evaluation of a visual read method for flortaucipir PET Scans [abstract]. J Nucl Med. 2019;60(Suppl 1):252.

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Mintun M, Devous M, Fleisher A, Ming L, Beach TG, Montine TJ, Serrano G, Curtis C, Perrin A, Salloway S, Thein S, Wellman C, Kennedy I, Navitsky M, Southekal S, Arora A, Stevenson PA, Flitter M, Pontecorvo M. Relationships between flortaucipir PET signal and tau neurofibrillary tangle pathology at autopsy [abstract]. In: 13th Human Amyloid Imaging Conference Program and Abstracts; Jan 16–18, 2019; Miami, FL, p 304.

Siderowf A, Keene CD, Beach T, Arora A, Devous Sr MD, Navitsky M, Kennedy I, Joshi A, Pontecorvo M, Lu M, Mintun M. Comparison of regional flortaucipir PET SUVr values to quantitative tau immunohistochemistry in patients with Alzheimer's disease pathology: A clinico-pathological study [abstract]. J Nucl Med. 2017;58(Suppl 1):629.

Siderowf AD, Keene CD, Beach TG, Montine TJ, Arora A, Devous MD Sr, Navitsky M, Kennedy I, Joshi AD, Pontecorvo MJ, Lu M, Serrano GE, Rose S, Wilson A, Hellstern L, Coleman N, Mintun MA. Comparison of regional flortaucipir PET to quantitative tau and amyloid immunoassay in patients with Alzheimer's disease pathology: a pilot clinico-pathological study [abstract]. Alzheimer's and Dementia. 2017;13(7):776. Abstract P2 to 383.

Length of Study

Date of first subject enrolled: October 27, 2015

Date of last subject completed: June 13, 2018

Phase of Development

This is a phase 3 study.

Objectives

Primary Objective

The primary objective of the study was to test the relationship between antemortem FTP PET imaging and tau neurofibrillary pathology associated with AD, as measured at autopsy, using the following analyses:

- The diagnostic performance (sensitivity, specificity) of five independent readers' interpretations of antemortem FTP PET images for detection of a pattern of FTP neocortical uptake that corresponded to NFTs' scores of B3 (Hyman et al. 2012; Montine et al. 2012) as measured at autopsy were evaluated; and if success criteria were met.
- The diagnostic performance (sensitivity, specificity) of five independent readers' interpretations of antemortem FTP PET images for detection of a pattern of FTP neocortical uptake that corresponds to high levels of Alzheimer's Disease Neuropathological Change (ADNC) as defined by National Institute on Aging Alzheimer's Association (NIA-AA) criteria (Hyman et al. 2012) as measured at autopsy were evaluated.

Secondary Objectives

- Assess diagnostic performance of antemortem FTP PET imaging, based on majority of interpretation of five independent readers, for detection of a pattern of FTP neocortical uptake that corresponded to NFT scores of B3 at autopsy; and for detection of a pattern of FTP neocortical uptake that corresponded to high levels of ADNC as defined by NIA-AA criteria at autopsy
- Assess agreement among readers of FTP PET scans

Study Design

This phase 3 open-label study examined the correspondence between the antemortem imaging with FTP and postmortem tau pathology in terminally ill subjects with AD or mild cognitive impairment and terminally ill subjects who were cognitively normal.

Number of Subjects

Planned: approximately 200

Enrolled: 156 (103 dementia, 3 MCI, and 50 cognitively normal)

Treated (at least one dose): 156 (103 dementia, 3 MCI, and 50 cognitively normal)

Completed: 67 (52 dementia, 1 MCI, and 14 cognitively normal)

Diagnosis and Main Criteria for Inclusion

Only subjects who met all of the following criteria were eligible to enroll in the study:

- Males or females ≥50 years of age
- Projected life expectancy of ≤6 months as determined by the principal investigator
- Could tolerate a 20-minute PET scan
- Gave informed consent or had a legally authorized representative consent for study procedures and brain donation consistent with the legal requirements of the state in which they died

Subjects were excluded from enrollment if they met the following criteria:

- Aggressively being treated with life-sustaining measures (for example, were receiving chemotherapy or currently on respirator; palliative chemotherapy was allowed)

- Known to have a structural brain lesion that would interfere either with PET imaging or pathological assessment
- Clinically significant infectious disease, such as human immunodeficiency virus infection, hepatitis, or prior disease
- Receiving any investigational medications, except with permission from the study sponsor
- Participated in an experimental study with an amyloid or tau targeting agent
- Suspected encephalopathy due to alcoholism or end-stage liver disease
- Females of childbearing potential who were pregnant or not using adequate contraception
- Risk factors for torsades de pointes or were taking drugs known to cause QT prolongation

Study Drug, Dose, and Mode of Administration

FTP (18F-AV-1451), 370 MBq [10 mCi] as an IV bolus administration

Comparator, Dose, and Mode of Administration

No comparator was administered in this study.

Duration of Treatment

All subjects received a single IV bolus administration target dose of 370 MBq (10 mCi) of FTP injection at the start of the first PET imaging visit. If death did not occur within 9 months of the FTP PET scan, a subject was given the opportunity to undergo a second FTP PET scan and continue in the protocol at the Applicant's discretion. The target dose prior to the second PET scan was the same as for the first scan.

Variables

Efficacy

The study**'s primary efficacy outcome was the performance of independent readers, blinded to clinical information, for estimating the density and distribution of aggregated tau neurofibrillary tangles in PET scans compared to the truth standard of tau pathology in the postmortem brains as scored by independent pathologists.**

Other efficacy variables included, quantitative measurement of FTP SUVr (Devous et al. 2018; Southekal et al. 2018), NFT score, NIA-AA autopsy diagnosis (Hyman et al. 2012; Montine et al. 2012), Braak stage (Braak and Braak 1991a), Consortium to Establish a Registry for Alzheimer's disease (CERAD) score, and distribution of amyloid (Thal plaque score) (Montine et al. 2012). In addition, demographic and other baseline characteristics, medical and surgical history, family neurological disease history, subjects' neurological disease history, concomitant medications and MMSE scores (Folstein et al. 1975), and IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly) scores were collected.

Visual Interpretation 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)

Safety

Safety data collected for the study included adverse events and vital signs. In addition, the results of urine or serum pregnancy test (collected from women of child-bearing potential before each PET scan), screening neurological examination, and screening physical examination were collected.

Statistical Evaluation Methods

Efficacy

The primary efficacy analysis was based on the reader's performance for detecting NFT B3 tau pathology. The hypothesis to be tested was that for at least the same three out of five independent readers, the lower bound of the two-sided 95% CI for both sensitivity and specificity of FTP PET reading interpretations would be ≥50%.

Efficacy Analysis Set 1 was used to summarize demographic and other baseline characteristics, medical/surgical history, concurrent medical conditions/diseases, family neurological disease history and subjects' neurological disease history, concomitant medications, cognition assessments at screening, exposure to FTP, and other efficacy endpoint, as well as to conduct the first primary efficacy analysis and majority of readers secondary efficacy for the NFT score TS.

Summaries were presented according to the individual reader's interpretation of the FTP PET image, majority of readers' interpretation of the FTP PET image, or by most recent neurological disease diagnosis, as appropriate. Efficacy Analysis Set 2 was used to conduct the second primary efficacy analysis and the majority-of-readers secondary efficacy analysis for the NIA-AA autopsy diagnosis. Summaries were presented according to the individual reader's or majority of readers' interpretation of the FTP PET image, as appropriate.

Safety

The Safety Analysis Set (SAF) was used to summarize demographic and other baseline characteristics, medical/surgical history, concurrent medical conditions/diseases, family neurological disease FTP assessments at screening, exposure to FTP, and all safety data. Summaries were presented overall and by most recent neurological disease diagnosis.

Summary

This phase 3, open-label study met its primary and secondary objectives to demonstrate statistically significant sensitivity and specificity of FTP for detecting tau neurofibrillary

pathology (NFT B3, corresponding to Braak stages V and VI). The main study primary efficacy analysis (n=64) met prespecified success criteria for having at least three of five PET scan readers achieve a level of sensitivity and specificity consistent with having a lower bound of the 95% CI being ≥50% in at least three of five FTP PET scan readers.

The primary analysis for detection of increased density of neocortical FTP signal that corresponds to an NFT score of B3 achieved a sensitivity range of 92.3% to 100% and specificity of 52.0% to 92.0%.

The primary efficacy results were supported by addition of the supplemental autopsy cases (SAC). The SAC was combined with the Study A16 primary analysis set and the three frontrunner cases to form the SAC full analysis population (SACFAS).

In this combined cohort, all five readers met the predefined success criteria of lower bounds of the 95% CI >50% for both sensitivity and specificity for the NFT change. Adding the academic SAC cases to the data set of Study A16 increased observed specificity without decreasing the sensitivity of FTP PET interpretation.

In regard to safety, the subjects who consented to participate in this study were a vulnerable population; all were terminally ill, most had dementia or MCI, and most were aged 65 or older. Nonetheless, few subjects experienced treatment-emergent adverse events during the 48-hour period after injection of FTP and PET scan. Two subjects died within 48 hours after administration of FTP, but their deaths were not related to study drug or procedure, according to the investigator. One subject experienced a myocardial infarction within the 48-hour period, the serious adverse events was reported as related to study drug by the investigator, but the Applicant did not consider the myocardial infarction to be reasonably possibly related to FTP or protocol procedures, given the patient's medical history of hypertension, hypercholesterolemia, and coronary artery disease.

Conclusions

Results from this phase 3 study demonstrate that FTP PET imaging can be used, with a high degree of sensitivity and specificity, to detect tau neurofibrillary pathology (NFT B3, corresponding to Braak stage V or IV).

15.3. Clinical Study Report Synopsis: Study 18F-AV-1451-FR01

Title of Study

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

Number of Investigators

This multicenter study included five principal investigators (readers)

Study Center

No new subjects were recruited and no drug was administered in this study. This report describes the results of testing an in-person reader training program using images collected in Studies 18F-

AV-1451-A16 (A16) and 18F-AV-1451-A05 (A05). This study was conducted in the United States.

Publication(s) Based on the Study

None at this time

Length of Study

Date of first read: March 27, 2019

Date of database lock: May 3, 2019

It was expected that it would take 4 to 5 days for the readers to complete the training and visual interpretation of all FTP PET images.

Phase of Development

This is a phase 3 development.

Objectives

Primary

- Test the relationship between antemortem FTP PET imaging and tau neurofibrillary pathology associated with AD, as measured at autopsy
- Assess inter-reader reliability

Secondary

- Test the relationship between antemortem FTP PET imaging of an AD pattern with uptake beyond the temporal/occipital regions (i.e., τAD++ 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++)
- Assess agreement among readers of FTP PET scans in subjects known to be from the intended population (interpretation of scans from the Applicant's Study A05)
- Assess intrareader reliability for scans read twice by each reader

Number of Subjects/Patients

No new subjects were enrolled in this study. Images from 262 scans (83 from subjects in Study A16 who had a valid scan and autopsy, 159 from subjects in Study A05 who had a valid scan, representing the intended population for clinical use, and 20 scans randomly selected for intrareader reliability from Studies A16 and A05) were used to test the reader training and inter/intrareader reliability in this study. However, one scan from Study A16 was determined to be unevaluable by the majority of readers and was therefore not included in the efficacy analyses.

Diagnosis and Main Criteria for Inclusion

FTP PET scans were selected from male and female subjects ≥50 years of age who met the inclusion criteria and were enrolled in completed Studies A16 and A05. Autopsy study subjects from Study A16 were terminally ill (≤6 months expected to end of life). The intended use cohort patients included all patients with clinically defined MCI and AD dementia from Study A05C (confirmatory cohort).

Dose and Mode of Administration

No study drug was administered in this study. Subjects in the parent studies received a single IV bolus administration target dose of 370 MBq (10 mCi) of FTP injection at the PET imaging visit. Cognitively impaired subjects in Study A16 who did not come to autopsy within 9 months after the FTP scan were either discontinued from the study or were required to undergo a repeat FTP scan for comparison to the neuropathology result.

Reference Therapy/Comparator

Not applicable

Duration of Treatment

Not applicable

Variables

Efficacy

Primary objective 1: Analysis 1

Accuracy of FTP PET scan in detecting NFT tau stage (truth standard); individual readers FTP PET scan interpretation (τAD+/τAD++ or τAD-) versus autopsy NFT score. The hypothesis to be tested is that for at least the same three out of five independent readers, the lower bound of the two-sided 95% CI for both sensitivity and specificity of FTP PET reading interpretations will be ≥50%.

Primary objective 1: Analysis 2

Accuracy of FTP PET scan interpreted as AD pattern in detecting AD neuropathological change; individual readers FTP PET scan interpretation versus NIA-AA autopsy diagnosis TS. The hypothesis to be tested is that for at least the same three out of five independent readers, the lower bound of the two-sided 95% CI for both sensitivity and specificity of FTP PET reading interpretations will be ≥50%.

Primary objective 2

Inter-reader reliability/agreement across all readers of FTP PET scan interpretation.

Secondary objective 1

Relationship between antemortem FTP PET imaging of an AD pattern with uptake beyond the temporal/occipital regions (τAD++) and tau neurofibrillary pathology associated with AD, as

measured at autopsy. Diagnostic performance was assessed relative to the autopsy NFT score TS and NIA-AA autopsy diagnosis TS.

Secondary objective 2

Inter-reader reliability of FTP PET scan interpreted as τAD++ pattern across the five readers for all cases from studies A16 and A05.

Secondary objective 3

Inter-reader agreement of FTP PET scan interpreted as AD pattern for the nonautopsy intended clinical use population (scans from Study A05).

Secondary objective 4

Intrareader agreement of FTP PET scan visual interpretation interpreted as AD pattern of 20 randomly selected cases.

Safety

Safety endpoints were not evaluated in this study.

Statistical Evaluation Methods

General Considerations

All inferential statistics performed at the two-sided, 0.05 level of significance. All statistical analyses were performed using SAS® version 9.0 or higher.

Efficacy

Primary objective 1

Accuracy of FTP PET scan interpreted as AD pattern in detecting tau-NFT stage and AD neuropathological change. The diagnostic performance (sensitivity/specificity) of five independent readers' interpretations of antemortem FTP PET imaging for detection of a pattern of FTP neocortical uptake that corresponds to NFT Score of B3 (Hyman et al. 2012; Montine et al. 2012) at autopsy, and pattern of FTP neocortical uptake that corresponds to high levels of AD neuropathologic change as defined by NIA-AA criteria (Hyman et al. 2012) were evaluated. Two-sided 95% CIs for sensitivity and specificity were calculated using the Wilson score method. The hypothesis to be tested for both primary analyses was that for at least the same three out of five independent readers, the lower bound of the two-sided 95% CI for both sensitivity and specificity of FTP PET reading interpretations would be ≥50%. The TS was constructed from NFT scores or ADNC according to NIA-AA criteria at autopsy.

Primary objective 2

Inter-reader agreement of FTP PET scan interpreted as AD pattern. The inter-reader reliability of FTP PET scan visual interpretation was assessed using Fleiss' kappa. P-values were calculated using the normal approximation method. The lower bound of the 95% CI for Fleiss' kappa was to be ≥0.6 to meet the inter-reader reliability criterion. The degree of agreement between two

readers for the interpretation of FTP PET scan was assessed in a pair-wise manner using Cohen's kappa statistics.

Secondary objective 1

Relationship between antemortem FTP PET imaging of an AD pattern with uptake beyond the temporal/occipital regions (τAD++) and tau neurofibrillary pathology associated with AD, as measured at autopsy. To further evaluate the diagnostic performance of FTP scans, the same scan interpretation from the readers was reclassified as an AD pattern with uptake beyond the temporal/occipital regions (τAD++: positive) versus otherwise (τAD+/ τAD-: negative) and compared to the TS, calculating the diagnostic performance statistics. The calculation of sensitivity, specificity, NPV, PPV, LR+, LR-, as well as the associate 95% CI were the same as the primary objective analyses.

Secondary objective 2

Inter-reader reliability of FTP PET scan interpreted as τAD++ pattern. This analysis assessed the reliability of FTP scan interpreted as τAD++ pattern across five readers using the same analysis as primary objective 2.

Secondary objective 3

Inter-reader agreement of FTP PET scan interpreted as AD pattern for intended clinical use population analysis of inter-reader reliability of FTP scan interpreted as AD pattern in intended clinical practice population were conducted similar to primary objective 2.

Secondary objective 4

Intrareader agreement of FTP PET scan visual interpretation interpreted as AD pattern intrareader reliability assessed using randomly selected 20 cases were read twice by every reader. A Cohen's kappa statistics was used to assess agreement of the two reading results and the percent of agreement between the two readings from the same reader was calculated for each reader.

Safety

Safety was not evaluated in this study.

Summary

The efficacy analysis population included all valid scan reading results from five readers on 241 cases. One subject's scan was excluded based on a majority of readers determining it to be unevaluable due to image quality (noise or low count density). The mean age of the analysis population was 75.9 years (range of 50 to 100 years). The mean age of autopsy cases was 81.6 years, compared with 72.9 years for nonautopsy cases. Study FR01 met the predetermined primary objectives, consistent with the results of the first pivotal image to autopsy trial, Study A16.

The lower confidence limits of sensitivity and specificity for a τAD FTP PET scan pattern to detect cases with tau-NFT distribution stage Braak V/VI at autopsy, and to detect cases with high AD Neuropathologic change were >50% for four of the five FTP PET scan readers for the FR01

primary analysis set (n=82). The Applicant reported overall agreement among the readers exceeded 90% with Fleiss' kappa of 0.87 (95% CI: 0.83, 0.91) for the prespecified efficacy data set (all cases, n=241), 0.82 (95% CI: 0.75, 0.88) for the n=82 autopsy cases, and 0.90 (95% CI: 0.85, 0.95) for the 159 subjects from Study A05.

Conclusions

In Study FR01, FTP demonstrated statistically significant sensitivity and specificity for identifying underlying NFT pathology and high levels of AD neuropathologic change. Study FR01 met the prespecified primary objectives. The lower confidence limits of sensitivity and specificity for a τAD FTP PET scan pattern to detect cases with tau-NFT distribution stage Braak V/VI at autopsy, and to detect cases with high AD Neuropathologic change were >0.5 for at least three of the five FTP PET scan readers for the primary analysis set (n=82). Overall agreement among the readers exceeded 90%.

In summary, these results provided a second demonstration of the sensitivity and specificity of FTP PET to estimate pattern and density of tau-NFT. Moreover, the same readers who demonstrated sensitivity and specificity on the autopsy cohort showed a high degree of inter-reader reliability in the intended target population, suggesting a good generalizability of the PET interpretation method to MCI and AD cases similar to the target population for this tracer.

Comment: *In the FR01 study, scans from A16 and A05C were pooled and reread in random order by new readers. The statistical reviewer found the Fleiss' kappa statistic (95% CI) to be 0.88 (0.86, 0.90) across all 241 patients. Exploratory analysis evaluated inter-reader agreement in the two subgroups of patients with and without autopsy. In this analysis, Fleiss' kappa (95% CI) was 0.82 (0.78, 0.86) in the patients with autopsy from Study A16 and 0.91 (0.89, 0.93) in patients without autopsy from Study A05C.*

15.4. Clinical Study Report Synopsis: Study 18F-AV-1451-A05

Title of Study

An Open-Label, Multicenter Study, Evaluating the Safety and Imaging Characteristics of 18F-AV- 1451 in Cognitively Healthy Volunteers, Subjects with Mild Cognitive Impairment, and Subjects with Alzheimer's disease

Number of Investigators

This multicenter study included 29 principal investigators.

Study Centers

This study was conducted at 29 study centers in one country.

Publication(s) Based on the Study

Pontecorvo MJ, Devous MD Sr, Kennedy I, Navitsky M, Lu M, Galante N, Salloway S, Doraiswamy PM, Southekal S, Arora AK, McGeehan A, Lim NC, Xiong H, Truocchio SP, Joshi

AD, Shcherbinin S, Teske B, Fleisher AS, Mintun MA, for the 18F-AV-1451-A05 investigators. A multicenter longitudinal study of flortaucipir (18F) in normal ageing, mild cognitive impairment and Alzheimer's disease dementia. *Brain* 2019; 142:1723 – 1735.

Pontecorvo MJ, Devous MD Sr, Navitsky M, Lu M, Salloway S, Schaerf FW, Jennings D, Arora AK, McGeehan A, Lim NC, Xiong H, Joshi AD, Siderowf A, Mintun M, for the 18F-AV-1451-A05 investigators. Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. *Brain* 2017; 140:748-763.

Schwarz AJ, Yu P, Miller BB, Shcherbinin S, Dickson J, Navitsky M, Joshi AD, Devous MD Sr, Mintun MS. Regional profiles of the candidate tau PET ligand 18F-AV-1451 recapitulate key features of Braak histopathological stages. *Brain.* 2016; 139:1539 – 1550.

Length of Study

Date of first subject enrolled (exploratory cohort): December 9, 2013

Date of first subject enrolled (confirmatory cohort): December 11, 2014

Date of last subject completed: July 28, 2017

Phase of Development

This study includes an exploratory phase and a confirmatory phase.

Objectives (Exploratory Phase)

The primary objective of the cross-sectional component was to compare FTP imaging results among subjects with AD, MCI and cognitively healthy older individuals. The primary objective of the longitudinal component was to assess the rate of change of tau deposition as measured by FTP uptake over time.

The secondary objective of the cross-sectional component was to establish a database of cognitively healthy individuals to show the spectrum of FTP imaging results in cognitively healthy individuals across a range of age strata.

Objectives (Confirmatory Cohort)

The primary objective of the confirmatory cohort, which was comprised of subjects with AD and MCI, was to provide independent validation of the relationships observed in the exploratory analyses of the first phase. In particular, the goal of the second phase is to confirm the relationship between FTP uptake in the brain as measured by PET and the subsequent rate of cognitive decline observed over longitudinal follow-up. As defined in the statistical analysis plan, this required assessing whether or not a baseline FTP PET scan is visually interpreted as τAD++, predicts a higher 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.

The secondary objective of the confirmatory (second) phase longitudinal component, as defined in the statistical analysis plan was to assess the diagnostic performance of baseline tau positivity according to a FTP scan visual interpretation, for predicting subjects' clinically meaningful cognitive and functional deterioration within 18 months of scan, as measured by the CDR-SB scales.

Study Design

Study 18F-AV-1451-A05 (A05) is a cross-sectional and longitudinal observational study that evaluated imaging characteristics of FTP in control subjects and patients with clinically defined MCI and AD dementia. This study was conducted in two phases, an exploratory/hypothesis generating phase and a confirmatory/validation phase, which had separate subjects and analyses. For both the exploratory and confirmatory phases, screening assessments included demographic information, cognitive testing, safety assessment, and MRI, including both volumetric and standard clinical sequences. Raters administering the cognitive testing were blinded to the FTP scans for subjects in the confirmatory cohort. Subjects who qualified for the study had both a FBP PET imaging session and a FTP PET imaging session at baseline. The option to participate in cerebrospinal fluid (CSF) collection by lumbar puncture (LP) was also offered to subjects >50 years of age at some centers in the exploratory phase.

In both the exploratory and confirmatory phases, subjects >50 years of age who completed the baseline FTP PET scans were asked to return for follow-up visits at 9 (±2) months and 18 (±2) months following the initial FTP scan; longitudinal follow-up visits were not conducted for the young cognitively healthy control group, as these subjects were not expected to show any change in FTP binding or cognitive performance over an 18-month time span. Cognitive assessments and updates to concomitant medications and medical history were collected at each follow-up visit. Follow-up FTP PET scans were also performed at 9 and 18 months in the exploratory cohort, but not the confirmatory cohort subjects. Subjects or their designated decision maker were contacted by phone at 5 and 14 months following the initial FTP scan to collect updated concomitant medications and medical history.

Number of Subjects

Exploratory Cohort

Planned: 230

Enrolled: 223

Treated (at least one dose): 222

Completed: 167

Confirmatory Cohort

Planned: 150

Enrolled: 160

Treated (at least one dose): 160

Completed: 111

Diagnosis and Main Criteria for Inclusion

The study was designed to evaluate the brain tau protein imaging properties and safety of FTP in male or female subjects ≥50 years of age.

Exploratory Cohort

This cohort included subjects with cognitive impairment (MCI (MMSE ≥24) and possible or probable AD (MMSE >10)) and cognitively normal (MMSE ≥29) young (≥20 to <40 years) and older (≥50 years) healthy volunteers.

Confirmatory Cohort

This cohort included subjects with MCI or dementia with a suspected neurodegenerative cause (all but five of whom had working diagnoses of possible or probable AD) with MMSE between 20 and 27 inclusive.

Study Drugs, Dose, and Mode of Administration

FTP (18F-AV-1451), 370 MBq [10 mCi] as an IV bolus administration. Florbetapir F 18 370 MBq [10 mCi] as an IV bolus administration.

Comparator, Dose, and Mode of Administration

No comparator was administered in this study.

Duration of Treatment

Exploratory Cohort

All subjects except for YCN subjects, received a single IV bolus administration target dose of 370 MBq (10 mCi) of FTP injection at each of the baseline, 9-month, and 18-month visits. The YCN subjects only received a single IV bolus administration of FTP injection with a target dose of 370 MBq (10 mCi) at the baseline visit. All subjects also received a single IV bolus administration of FBP with target dose of 370 MBq (10 mCi) at the baseline visit. The FTP and FBP imaging sessions occurred ≥48 hours apart.

Confirmatory Cohort

All subjects received a single IV bolus administration target dose of 370 MBq (10 mCi) of FTP injection and a single IV bolus administration or FBP with a target dose of 379 MBq (10 mCi) at the baseline visit. The FTP and FBP imaging sessions occurred ≥48 hours apart.

Variables

Image Interpretation and Analysis

Five nuclear medicine or radiology physicians independently interpreted the FTP PET scans as either not consistent with an AD pattern (τAD-); or consistent with an AD pattern (τAD+, τAD++) according to the criteria described below.

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 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)

A single external expert nuclear medicine physician interpreted the FBP PET scans as either positive (Aβ+) or negative (Aβ-) in accordance with the current approved interpretation methods. Both FBP and FTP scans were also evaluated quantitatively according to published methods (Joshi et al. 2015; Pontecorvo et al. 2017; Devous et al. 2018; Southekal et al. 2018; Pontecorvo et al. 2019).

Efficacy

The analysis in the exploratory phase of this study were all exploratory so there was no a priori designated primary efficacy variable. The primary efficacy variable for the confirmatory cohort was the CDR-SB score change from baseline, to be compared between cases with scans determined to have a τAD++ pattern versus cases that do not have a τAD++ pattern. For these analyses, the majority read of the five independent readers was used. Other key efficacy variables included FTP SUVr, FTP visual interpretation, FBP SUVr, FBP visual interpretation, Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), Clinical Dementia Rating (CDR) Scale, MMSE, and FAQ.

Safety

Treatment-emergent adverse events (TEAEs) were observed continuous during the FTP and FBP imaging sessions and at a follow-up phone call 48 hours post imaging. Blood and urine were collected for laboratory analysis prior to FTP administration and prior to discharge. Vital signs were collected and ECG were performed prior to FTP administration, immediately post dose and prior to discharge.

Statistical Evaluation Methods

General Considerations

Frequency distributions, including counts and percentages were included for all categorical outcomes. Summary statistics, including mean, SD, median, minimum and maximum values, are presented for all continuous outcomes. Unless otherwise specified, hypothesis testing was two-sided with a type I error rate of 0.05. All statistical analyses were performed using SAS® version 9.3 or higher.

Efficacy

Exploratory cohort

- Quantitative assessment of images. A 1-way analysis of variance (ANOVA) was used to compare the mean FTP SUVr values between diagnostic groups (AD, MCI, and OCN). The F test was used to test for the difference in SUVr values among all diagnostic groups while contrasts within the ANOVA model were used to perform comparisons between diagnostic

groups. Due to the obvious age difference, the YCN group was not included in the analysis as described above. Instead, a 2-sample t-test between OCN and YCN was performed to evaluate the differences between OCN and YCN subjects. Additionally, an analysis of covariance was used to compare the mean SUVr values between diagnostic groups (AD, MCI, and OCN) within amyloid beta status (Aβ+, Aβ-), as well as compare mean SUVr values between Aβ status within diagnosis groups while adjusting for age as a continuous covariate. The least square (LS) mean estimates were provided, as well as LS mean differences through proper contrast set up within the analysis of covariance models. This analysis was performed on the multiblock-barycentric-discriminant-analysis (MUBADA) SUVr as well as the SUVr for each brain region.

- Qualitative assessment of images. FTP scan visual interpretation results were summarized by clinical diagnosis and by amyloid status as decided by visual interpretation of FBP scans. Except for YCN, the overall association of frequency by diagnosis groups and by amyloid status was tested with a Mantel-Haenszel test. Pearson's Chi-squared test, or Fisher's exact test when appropriate, was used to test for the general association of tau scan interpretation results by amyloid status, and tau scan interpretation results by clinical diagnosis respectively.

Confirmatory cohort

The primary hypothesis to be evaluated was that the hazard of progressing to the clinically meaningful event as determined by CDR-SB value change (1 point or more increase) within 18 months would be significantly greater for subjects with FTP scans rated (by the majority of the five readers) as a τAD++ pattern, as compared to those with scans rated as non-τAD++ (τAD- and τAD+ but not τAD++). The hypothesis was tested using a Cox proportional hazard model, adjusting for baseline CDR-SB score, age, and ANART score. The secondary analysis used dichotomized CDR-SB change (1 point or more increase versus otherwise) as a TS to assess the diagnostic performance (sensitivity and specificity) of baseline τAD++ status (as determined by both the majority and individual readers) for detecting subjects who would experience 1 point or more increase in CDR-SB at Month 18.

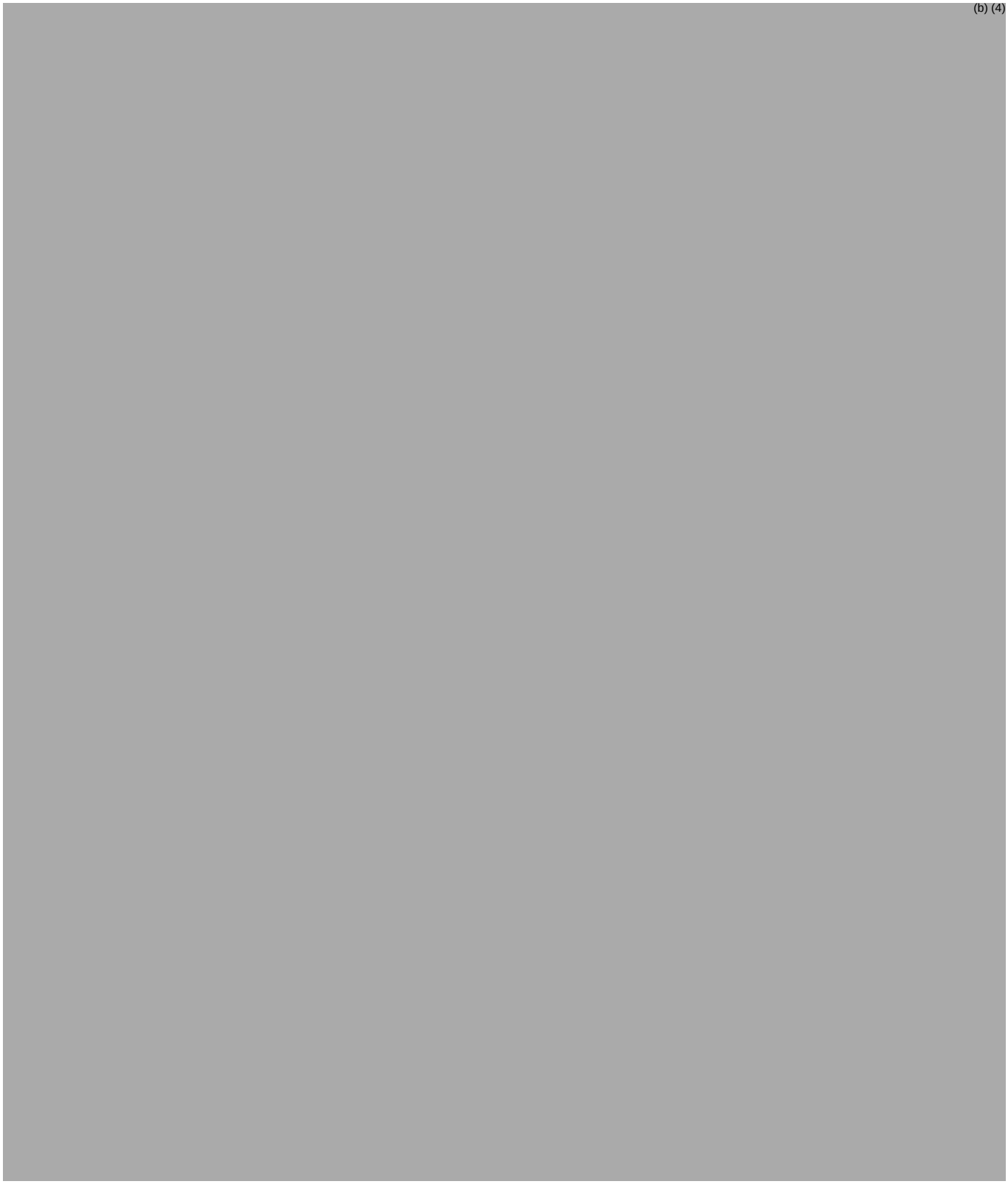
Additional exploratory analyses evaluated the hazard ratios (HRs) and diagnostic performance for FTP PET relative to clinically meaningful change in CDR global (change >0), MMSE (3 or more points decrease), FAQ (3 or more points increase) and ADAS (4 or more points increase), and also looked at an alternative threshold for CDR-SB (2.5 points or greater increase). Mixed model with repeated measures (MMRM) analyses also modeled mean change in each cognitive/functional variable as related to majority FTP visual interpretation. Finally, the inter-reader and intrareader reliability of the PET interpretation was assessed with kappa statistics. Safety: all safety analyses were conducted separately for FTP and FBP injections. Only observed data were used for safety analyses, and missing data were not imputed. Safety data are presented overall and by diagnosis group. Frequency distributions, including counts and percentages were summarized for TEAEs.

Summary

This study was conducted in two phases: a phase 2 exploratory phase and a phase 3 confirmatory phase. The overarching goal of the exploratory phase was to further investigate the pattern of FTP PET imaging across the range of disease, in cognitively healthy subjects through patients

with cognitive decline. Additionally, the exploratory phase investigated relationships between FTP PET and cognitive decline over the 18-month study period, and served to generate hypotheses tested in the confirmatory phase.

(b) (4)



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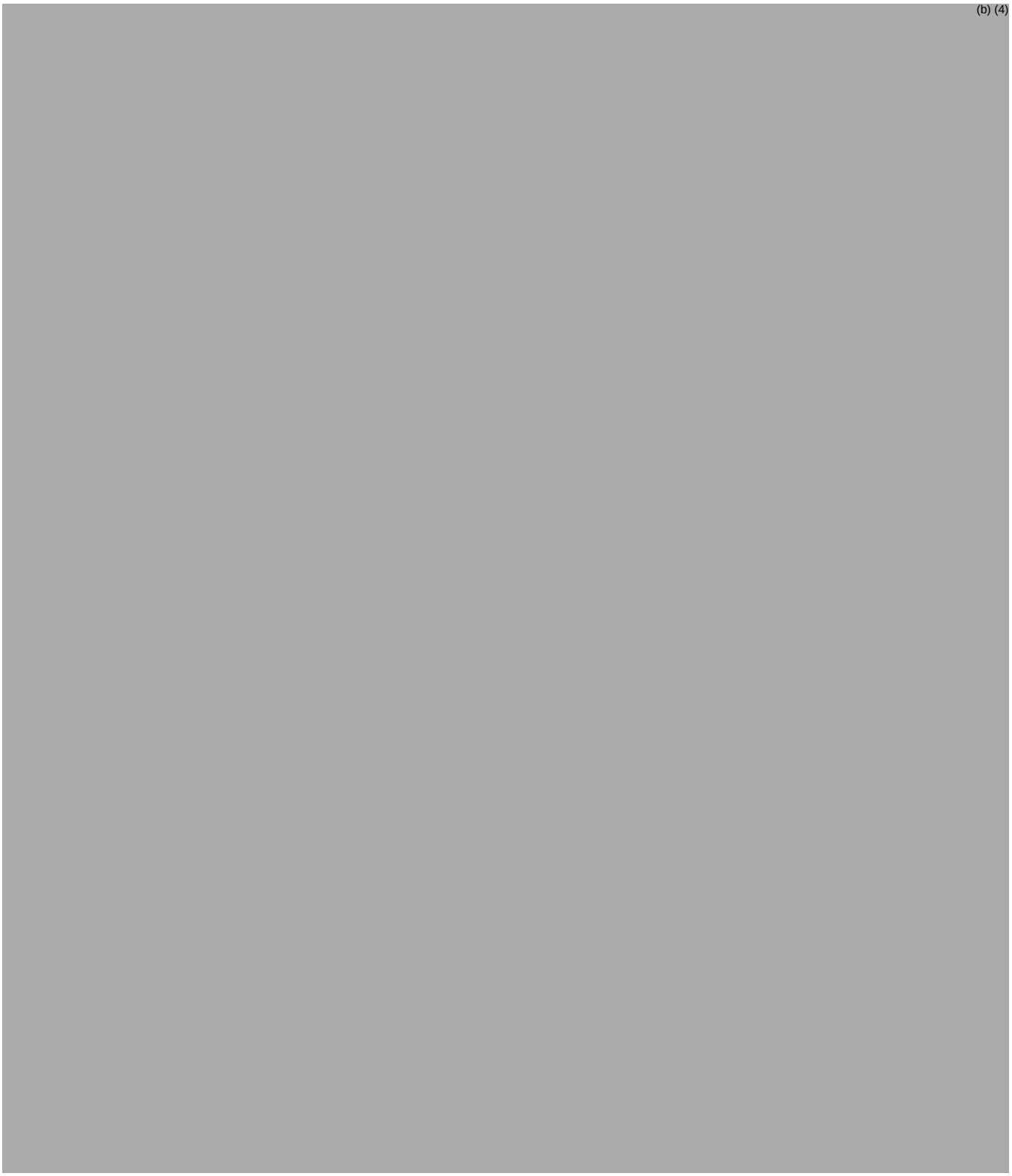

Safety

There were no deaths or discontinuations due to TEAEs. The serious adverse events (SAEs) that were reported in both phases were determined to be not related to FTP by the respective

investigators. The majority of the TEAEs were related to injection site pain or headache. In the exploratory phase, 4.95% of TEAEs were due to a cluster of terms associated with increased blood pressure (blood pressure increased, blood pressure systolic increased, and hypertension). No TEAEs associated with increased blood pressure were reported in the confirmatory phase. While there were statistically significant changes to QTcB, QTcF, and heart rate primarily at the discharge time point, there were no PCS changes in any ECG parameters at any point during the study. The statistically significant change from baseline increase seen in heart rate, RR interval, and QTc is more likely due to imaging day procedures and less likely to be associated with FTP injection, given its short half-life.

Applicant's Conclusions

(b) (4)

Comments: (b) (4)

15.5. Clinical Study Report Synopsis: Study 18F-AV-1451-PX01

Title of Study

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)

Number of Investigators

This study included five nuclear imaging physicians who served as investigator/readers.

Study Center

No new subjects were recruited, and no drug was administered in this study. This report describes the results of testing an in-person reader training program using images collected in a substudy of parent study I8DMC-AZES (AZES). This study was conducted in the United States.

Publication(s) Based on the Study

None at this time.

Length of Study

Date of first read: March 28, 2019

Date of database lock: May 6, 2019

Phase of Development

This is a phase 3 clinical trial.

Objectives

Primary

- Assess whether a visual interpretation (τAD++ versus non-τAD++ pattern) of the baseline FTP PET scan can predict the risk of subjects' clinically meaningful cognitive and functional deterioration within 18 months of scan, as measured by the CDR-SB change from baseline (CFB).

Secondary

- Assess whether a visual interpretation (τAD++ versus non-τAD++ pattern) of the baseline FTP PET scan can predict the risk of subjects' clinically meaningful cognitive and functional deterioration within 18 months of scan, as measured by MMSE, 11-item version of the ADAS-Cog11, FAQ, and Clinical Dementia Rating Scale (CDR) Global CFB.
- Assess the relationship between visual interpretation (τAD++ versus non-τAD++ pattern) of the baseline FTP PET scan and magnitude of cognitive and functional deterioration within 18

months of scan, as measured by the mean CFB of CDR-SB, MMSE, ADAS-Cog11, and FAQ.

- Assess inter-reader reliability of the FTP PET scan visual interpretation by five independent, blinded readers.

Study Design

This study evaluated an in-person training program intended to be used to educate physicians in the interpretation of FTP PET images. Five imaging physicians (readers) independently interpreted the FTP PET scans collected from the AZES PET substudy. No new subjects were enrolled or treated in this study. The imaging physician readers were trained on the FTP PET scan read methodology using the previously established visual read method, which is identical to that used for Study A05C.

Training consisted of teaching the readers the steps of interpretation, followed by a practice session using a set of demonstration and practice cases. Physician readers were blinded to subject diagnosis and all demographic and clinical data from Study AZES. After the training phase, each blinded reader independently read 205 FTP PET baseline scans from Study 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" in a random sequence.

The readers visually interpreted each baseline FTP PET scan to identify patterns of tracer uptake that predict risk of clinically meaningful deterioration as determined by CDR-SB value change (1 point or more increase) within 18 months.

Number of Subjects

No new subjects were enrolled in this study. Images from 205 subjects who had a valid baseline FTP scan, and a CFB value of CDR-SB at 18 months were interpreted.

Diagnosis and Main Criteria for Inclusion

The study population for Study AZES consisted of subjects aged 55 to 85 years with MCI due to AD or probable AD by National Institute of Aging (NIA)-Alzheimer's Association criteria, 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 FBP PET or lumbar puncture. Subjects whose scans were read in Study PX01 had a baseline FTP scan, an 18-month CDR assessment, and met Study AZES inclusion criteria.

Dose and Mode of Administration

No study drug was administered in this study. At each FTP imaging visit in parent Study AZES, all subjects received a single IV bolus administration of approximately 240 MBq (6.5 mCi) of FTP injection followed by a saline flush.

Reference Therapy/Comparator

Not applicable

Duration of Treatment

Not applicable

Variables

Efficacy

Primary objective

- Baseline tau status and risk of clinically meaningful cognitive and functional deterioration (≥1 point increase in CDR-SB) within 18 months. Whether baseline tau status as determined by FTP 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 was defined as CDR-SB CFB with an increase of 1 point or more within 18 months.

Secondary objectives

- Clinically meaningful deterioration at 18 months by tau status on other cognitive/functional measures. Prognostic value of visual interpretation (τAD++ versus non-τAD++ pattern) of the baseline FTP PET scan and risk of subjects' clinically meaningful cognitive and functional deterioration within 18 months of scan, as measured by:
  - MMSE decreased by 3 points or more
  - ADAS-Cog11 increased by 4 points or more
  - FAQ increased by 3 points or more
  - CDR global with any increase
- Mean change of cognitive/functional assessments at 18 months by FTP PET visual interpretation (τAD++ versus non-τAD++). The relationship between visual interpretation (τAD++ versus non-τAD++ pattern) of the baseline FTP PET scan and magnitude of cognitive and functional deterioration within 18 months of scan, as measured by the mean CFB of CDR-SB, MMSE, ADAS-Cog11, and FAQ.
- Inter-reader reliability. Inter-reader reliability of the FTP PET scan visual interpretation (τAD++ versus non-τAD++) by five independent, blinded readers.

Safety

Safety endpoints were not evaluated in this study.

Statistical Evaluation Methods

General Considerations

All inferential statistics performed at the two-sided, 0.05 level of significance. All statistical analyses were performed using SAS® version 9.2 or higher.

Primary Objective

The primary objective was to determine baseline tau status and the risk of a clinically meaningful cognitive and functional deterioration (≥1 point increase in CDR-SB) within 18 months. The

primary efficacy variable was the dichotomized CDR-SB score CFB (1 point or more increase versus otherwise).

A Poisson regression model was used to calculate the ratio of risk for τAD++ subjects over non-τAD++ (τAD+/ τAD-) subjects. The risk ratio of τAD++ rated subjects progressing to the event over non-τAD++ rated subjects, along with a 95% CI and the associated p-value were provided. Clinically meaningful deterioration (CMD) defined as ≥1 point increase within 18 months was used as the dependent variable, and the model was adjusted for baseline age, years of education (categorical), CDR-SB score, and therapeutic treatment assignment from the AZES study (lanabecestat – 20 mg or 50 mg, or placebo). The hypothesis to be tested was that the risk of progressing to a clinically meaningful event as determined by CDR-SB value change at 18 months would be significantly greater for the subjects in the τAD++ group compared to those in the non-τAD++ (τAD+/ τAD-).

Secondary Objectives

- Clinically meaningful deterioration at 18 months by tau status on other cognitive/functional measures. To fully assess the prognostic value of tau scan, these CMDs were assessed for the secondary objective analysis:
  - MMSE decreased by 3 points or more
  - ADAS-Cog11 increased by 4 points or more
  - FAQ increased by 3 points or more
  - CDR global with any increase

  The analyses were identical to the primary objective analysis, with four dependent variables for CMDs as described above, and the adjustment of corresponding baseline scores.
- Mean change of cognitive/functional assessments at 18 months by FTP PET visual interpretation (τAD++ versus non-τAD++). To assess the mean change of MMSE, ADAS-Cog11, FAQ, and CDR-SB at 18 months by tau status, an MMRM was used. For each analysis, the change from baseline value from relative measurement was the dependent variable, and the model included the fixed effects of tau status (τAD++ or non-τAD++), visit (categorical covariate), tau status-by-visit interaction, therapeutic treatment assignment from the AZES study (lanabecestat – 20 mg or 50 mg, or placebo), and years of education (categorical), as well as corresponding baseline measurement score and age as continuous covariates. The objective of this analysis was to test the hypothesis that τAD++ subjects would demonstrate an increased rate of cognitive deterioration compared with non-τAD++ subjects at 18 months, as measured by the MMSE, ADAS-Cog11, FAQ, and CDR-SB.
- Inter-reader reliability. The inter-reader reliability of FTP scan interpretation (τAD++ versus non-τAD++) across the five independent readers was assessed using Fleiss' kappa statistics. The overall percent of agreement, Fleiss' kappa, and 95% CI around kappa value were provided. Pairwise comparisons between readers were presented with simple kappa statistics evaluating agreement.

Safety

Safety was not evaluated in this study.

Summary

(b) (4)

Applicant's Conclusions

(b) (4)

(b) (4)

Comments:

(b) (4)

16. Clinical Safety Assessment Additional Information and Assessment

16.1. Adverse Events by System Organ Class

AEs categorized by system organ class are listed in Table 38.

Table 38. Adverse Events by System Organ Class, Safety Population, ISS

System Organ Class	ISS Overall N=1,921 n (%)	ISS 240 MBq N=1,192 n (%)	ISS 370 MBq N=729 n (%)
Nervous system disorders	46 (2.4)	16 (1.3)	30 (4.1)
General disorders and administration site conditions	39 (2.0)	6 (0.5)	33 (4.5)
Gastrointestinal disorders	20 (1.0)	9 (0.8)	11 (1.5)
Investigations	16 (0.8)	6 (0.5)	10 (1.4)
Skin and subcutaneous tissue disorders	15 (0.8)	11 (0.9)	4 (0.5)
Musculoskeletal and connective tissue disorders	13 (0.7)	7 (0.6)	6 (0.8)
Vascular disorders	13 (0.7)	6 (0.5)	7 (1.0)
Psychiatric disorders	12 (0.6)	7 (0.6)	5 (0.7)
Infections and infestations	11 (0.6)	11 (0.9)	0 (0.0)
Eye disorders	10 (0.5)	7 (0.6)	3 (0.4)
Injury, poisoning and procedural complications	10 (0.5)	6 (0.5)	4 (0.5)
Cardiac disorders	8 (0.4)	3 (0.3)	5 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (0.3)	4 (0.3)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	3 (0.2)	1 (0.1)	2 (0.3)
Metabolism and nutrition disorders	2 (0.1)	0 (0.0)	2 (0.3)
Renal and urinary disorders	2 (0.1)	0 (0.0)	2 (0.3)
Hepatobiliary disorders	1 (0.1)	1 (0.1)	0 (0.0)
Surgical and medical procedures	1 (0.1)	1 (0.1)	0 (0.0)
Ear and labyrinth disorders	1 (0.1)	0 (0.0)	1 (0.1)

Source: adae.xpt; Software: Python
Abbreviations: ISS, integrated summary of safety; N, number of subjects in group; n, number of subjects with at least one event; MBq, megabecquerel

16.2. Adverse Events by System Organ Class and Preferred Term

AEs categorized by system organ class and preferred term are listed in Table 39.

Table 39. Adverse Events by System Organ Class and Preferred Term, Safety Population, ISS

System Organ Class Preferred Term	ISS Overall N=1,921 n (%)	ISS 240 MBq N=1,192 n (%)	ISS 370 MBq N=729 n (%)
Nervous system disorders	46 (2.4)	16 (1.3)	30 (4.1)
Headache	24 (1.2)	7 (0.6)	17 (2.3)
Dizziness	6 (0.3)	2 (0.2)	4 (0.5)
Gait disturbance	1 (0.1)	1 (0.1)	0 (0.0)
Superficial siderosis of central nervous system	2 (0.1)	2 (0.2)	0 (0.0)
Paraesthesia	2 (0.1)	0 (0.0)	2 (0.3)
Altered state of consciousness	1 (0.1)	1 (0.1)	0 (0.0)
Cerebral infarction	1 (0.1)	1 (0.1)	0 (0.0)
Cognitive disorder	1 (0.1)	1 (0.1)	0 (0.0)
Dysarthria	1 (0.1)	1 (0.1)	0 (0.0)
Facial paresis	1 (0.1)	1 (0.1)	0 (0.0)
Hyperreflexia	1 (0.1)	1 (0.1)	0 (0.0)
Sedation	1 (0.1)	1 (0.1)	0 (0.0)
Transient ischaemic attack	1 (0.1)	1 (0.1)	0 (0.0)
Amnesia	1 (0.1)	0 (0.0)	1 (0.1)
Disturbance in attention	1 (0.1)	0 (0.0)	1 (0.1)
Dizziness postural	1 (0.1)	0 (0.0)	1 (0.1)
Dysgeusia	1 (0.1)	0 (0.0)	1 (0.1)
Head discomfort	1 (0.1)	0 (0.0)	1 (0.1)
Hypoaesthesia	1 (0.1)	0 (0.0)	1 (0.1)
Hypoxic-ischaemic encephalopathy	1 (0.1)	0 (0.0)	1 (0.1)
Memory impairment	1 (0.1)	0 (0.0)	1 (0.1)
Somnolence	1 (0.1)	0 (0.0)	1 (0.1)
Tremor	1 (0.1)	0 (0.0)	1 (0.1)
General disorders and administration site conditions	39 (2.0)	6 (0.5)	33 (4.5)
Injection site pain	23 (1.2)	2 (0.2)	21 (2.9)
Fatigue	4 (0.2)	1 (0.1)	3 (0.4)
Injection site extravasation	4 (0.2)	0 (0.0)	4 (0.5)
Injection site bruising	2 (0.1)	1 (0.1)	1 (0.1)
Gait disturbance	1 (0.1)	1 (0.1)	0 (0.0)
Pyrexia	1 (0.1)	1 (0.1)	0 (0.0)
Night sweats	1 (0.1)	1 (0.1)	0 (0.0)
Application site irritation	1 (0.1)	0 (0.0)	1 (0.1)
Application site laceration	1 (0.1)	0 (0.0)	1 (0.1)
Asthenia	1 (0.1)	0 (0.0)	1 (0.1)
Feeling abnormal	1 (0.1)	0 (0.0)	1 (0.1)
Therapeutic response unexpected	1 (0.1)	0 (0.0)	1 (0.1)

System Organ Class Preferred Term	ISS Overall N=1,921 n (%)	ISS 240 MBq N=1,192 n (%)	ISS 370 MBq N=729 n (%)
Gastrointestinal disorders	20 (1.0)	9 (0.8)	11 (1.5)
Diarrhoea	7 (0.4)	2 (0.2)	5 (0.7)
Nausea	4 (0.2)	2 (0.2)	2 (0.3)
Vomiting	2 (0.1)	1 (0.1)	1 (0.1)
Abdominal discomfort	1 (0.1)	1 (0.1)	0 (0.0)
Change of bowel habit	1 (0.1)	1 (0.1)	0 (0.0)
Eructation	1 (0.1)	1 (0.1)	0 (0.0)
Faeces soft	1 (0.1)	1 (0.1)	0 (0.0)
Oral disorder	1 (0.1)	1 (0.1)	0 (0.0)
Abdominal pain	1 (0.1)	0 (0.0)	1 (0.1)
Flatulence	1 (0.1)	0 (0.0)	1 (0.1)
Frequent bowel movements	1 (0.1)	0 (0.0)	1 (0.1)
Oral pain	1 (0.1)	0 (0.0)	1 (0.1)
Investigations	16 (0.8)	6 (0.5)	10 (1.4)
Blood pressure increased	7 (0.4)	2 (0.2)	5 (0.7)
Blood pressure systolic increased	3 (0.2)	0 (0.0)	3 (0.4)
Weight increased	2 (0.1)	2 (0.2)	0 (0.0)
Platelet count decreased	2 (0.1)	0 (0.0)	2 (0.3)
Electrocardiogram t wave abnormal	1 (0.1)	1 (0.1)	0 (0.0)
Nuclear magnetic resonance imaging abnormal	1 (0.1)	1 (0.1)	0 (0.0)
Heart rate increased	1 (0.1)	0 (0.0)	1 (0.1)
Skin and subcutaneous tissue disorders	15 (0.8)	11 (0.9)	4 (0.5)
Dermatitis contact	3 (0.2)	2 (0.2)	1 (0.1)
Rash	2 (0.1)	1 (0.1)	1 (0.1)
Alopecia	1 (0.1)	1 (0.1)	0 (0.0)
Dry skin	1 (0.1)	1 (0.1)	0 (0.0)
Hyperhidrosis	1 (0.1)	1 (0.1)	0 (0.0)
Livedo reticularis	1 (0.1)	1 (0.1)	0 (0.0)
Night sweats	1 (0.1)	1 (0.1)	0 (0.0)
Pruritus	1 (0.1)	1 (0.1)	0 (0.0)
Skin exfoliation	1 (0.1)	1 (0.1)	0 (0.0)
Skin hypopigmentation	1 (0.1)	1 (0.1)	0 (0.0)
Erythema	1 (0.1)	0 (0.0)	1 (0.1)
Rash papular	1 (0.1)	0 (0.0)	1 (0.1)
Musculoskeletal and connective tissue disorders	13 (0.7)	7 (0.6)	6 (0.8)
Muscle spasms	4 (0.2)	1 (0.1)	3 (0.4)
Back pain	3 (0.2)	3 (0.3)	0 (0.0)
Arthralgia	2 (0.1)	2 (0.2)	0 (0.0)
Pain in extremity	2 (0.1)	1 (0.1)	1 (0.1)
Muscular weakness	1 (0.1)	1 (0.1)	0 (0.0)
Myalgia	1 (0.1)	1 (0.1)	0 (0.0)
Musculoskeletal discomfort	1 (0.1)	0 (0.0)	1 (0.1)
Myopathy	1 (0.1)	0 (0.0)	1 (0.1)
Vascular disorders	13 (0.7)	6 (0.5)	7 (1.0)
Hypertension	5 (0.3)	0 (0.0)	5 (0.7)
Orthostatic hypotension	3 (0.2)	3 (0.3)	0 (0.0)
Flushing	2 (0.1)	1 (0.1)	1 (0.1)
Haemorrhage	1 (0.1)	1 (0.1)	0 (0.0)
Hypotension	1 (0.1)	1 (0.1)	0 (0.0)
Hot flush	1 (0.1)	0 (0.0)	1 (0.1)

System Organ Class Preferred Term	ISS Overall N=1,921 n (%)	ISS 240 MBq N=1,192 n (%)	ISS 370 MBq N=729 n (%)
Psychiatric disorders	12 (0.6)	7 (0.6)	5 (0.7)
Agitation	4 (0.2)	1 (0.1)	3 (0.4)
Restlessness	2 (0.1)	1 (0.1)	1 (0.1)
Affective disorder	1 (0.1)	1 (0.1)	0 (0.0)
Delusion of replacement	1 (0.1)	1 (0.1)	0 (0.0)
Depression	1 (0.1)	1 (0.1)	0 (0.0)
Hallucination, auditory	1 (0.1)	1 (0.1)	0 (0.0)
Hallucination, visual	1 (0.1)	1 (0.1)	0 (0.0)
Insomnia	1 (0.1)	1 (0.1)	0 (0.0)
Mental disorder	1 (0.1)	0 (0.0)	1 (0.1)
Panic attack	1 (0.1)	0 (0.0)	1 (0.1)
Infections and infestations	11 (0.6)	11 (0.9)	0 (0.0)
Nasopharyngitis	2 (0.1)	2 (0.2)	0 (0.0)
Upper respiratory tract infection	2 (0.1)	2 (0.2)	0 (0.0)
Bronchitis	1 (0.1)	1 (0.1)	0 (0.0)
Chronic sinusitis	1 (0.1)	1 (0.1)	0 (0.0)
Localised infection	1 (0.1)	1 (0.1)	0 (0.0)
Oral herpes	1 (0.1)	1 (0.1)	0 (0.0)
Pharyngitis	1 (0.1)	1 (0.1)	0 (0.0)
Urinary tract infection	1 (0.1)	1 (0.1)	0 (0.0)
Viral infection	1 (0.1)	1 (0.1)	0 (0.0)
Eye disorders	10 (0.5)	7 (0.6)	3 (0.4)
Cataract	3 (0.2)	3 (0.3)	0 (0.0)
Maculopathy	2 (0.1)	2 (0.2)	0 (0.0)
Corneal disorder	1 (0.1)	1 (0.1)	0 (0.0)
Eye pruritus	1 (0.1)	1 (0.1)	0 (0.0)
Lens disorder	1 (0.1)	1 (0.1)	0 (0.0)
Meibomian gland dysfunction	1 (0.1)	1 (0.1)	0 (0.0)
Vitreous disorder	1 (0.1)	1 (0.1)	0 (0.0)
Cyanopsia	1 (0.1)	0 (0.0)	1 (0.1)
Eye irritation	1 (0.1)	0 (0.0)	1 (0.1)
Ocular hyperaemia	1 (0.1)	0 (0.0)	1 (0.1)
Injury, poisoning and procedural complications	10 (0.5)	6 (0.5)	4 (0.5)
Fall	4 (0.2)	3 (0.3)	1 (0.1)
Laceration	2 (0.1)	2 (0.2)	0 (0.0)
Procedural headache	2 (0.1)	0 (0.0)	2 (0.3)
Eye contusion	1 (0.1)	1 (0.1)	0 (0.0)
Skin abrasion	1 (0.1)	1 (0.1)	0 (0.0)
Procedural vomiting	1 (0.1)	0 (0.0)	1 (0.1)
Cardiac disorders	8 (0.4)	3 (0.3)	5 (0.7)
Bradycardia	3 (0.2)	2 (0.2)	1 (0.1)
Angina pectoris	2 (0.1)	0 (0.0)	2 (0.3)
Bundle branch block right	1 (0.1)	1 (0.1)	0 (0.0)
Cardiac failure congestive	1 (0.1)	0 (0.0)	1 (0.1)
Myocardial infarction	1 (0.1)	0 (0.0)	1 (0.1)
Supraventricular extrasystoles	1 (0.1)	0 (0.0)	1 (0.1)

System Organ Class Preferred Term	ISS Overall N=1,921 n (%)	ISS 240 MBq N=1,192 n (%)	ISS 370 MBq N=729 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (0.3)	4 (0.3)	1 (0.1)
Basal cell carcinoma	2 (0.1)	2 (0.2)	0 (0.0)
Meningioma	1 (0.1)	1 (0.1)	0 (0.0)
Seborrhoeic keratosis	1 (0.1)	1 (0.1)	0 (0.0)
Skin cancer	1 (0.1)	1 (0.1)	0 (0.0)
Neoplasm malignant	1 (0.1)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	3 (0.2)	1 (0.1)	2 (0.3)
Dyspnoea	1 (0.1)	1 (0.1)	0 (0.0)
Bronchial secretion retention	1 (0.1)	0 (0.0)	1 (0.1)
Epistaxis	1 (0.1)	0 (0.0)	1 (0.1)
Metabolism and nutrition disorders	2 (0.1)	0 (0.0)	2 (0.3)
Decreased appetite	1 (0.1)	0 (0.0)	1 (0.1)
Hypomagnesaemia	1 (0.1)	0 (0.0)	1 (0.1)
Renal and urinary disorders	2 (0.1)	0 (0.0)	2 (0.3)
Acute kidney injury	1 (0.1)	0 (0.0)	1 (0.1)
Urinary incontinence	1 (0.1)	0 (0.0)	1 (0.1)
Hepatobiliary disorders	1 (0.1)	1 (0.1)	0 (0.0)
Cholelithiasis	1 (0.1)	1 (0.1)	0 (0.0)
Surgical and medical procedures	1 (0.1)	1 (0.1)	0 (0.0)
Cataract operation	1 (0.1)	1 (0.1)	0 (0.0)
Ear and labyrinth disorders	1 (0.1)	0 (0.0)	1 (0.1)
Vertigo	1 (0.1)	0 (0.0)	1 (0.1)

Source: adae.xpt; Software: Python
Abbreviations: ISS, integrated summary of safety; N, number of subjects in group; n, number of subjects with at least one event; MBq, megabecquerel

16.3. Adverse Events by FDA Medical Query and Preferred Term

AEs categorized by FDA broad and narrow medical query and preferred terms are listed in Table 40 and Table 41.

Table 40. Adverse Events by FDA Medical Query (Broad) and Preferred Term, Safety Population, ISS

FDA Medical Query	ISS Overall N=1921 n (%)	ISS 240 MBq N=1192 n (%)	ISS 370 MBq N=729 n (%)
Local administration reactions (broad FMQ)	29 (1.5)	3 (0.3)	26 (3.6)
Injection site pain	23 (1.2)	2 (0.2)	21 (2.9)
Injection site extravasation	4 (0.2)	0 (0.0)	4 (0.5)
Injection site bruising	2 (0.1)	1 (0.1)	1 (0.1)
Headache (broad FMQ)	27 (1.4)	7 (0.6)	20 (2.7)
Headache	24 (1.2)	7 (0.6)	17 (2.3)
Procedural headache	2 (0.1)	0 (0.0)	2 (0.3)
Head discomfort	1 (0.1)	0 (0.0)	1 (0.1)

FDA Medical Query	ISS Overall N=1921 n (%)	ISS 240 MBq N=1192 n (%)	ISS 370 MBq N=729 n (%)
Systemic hypertension (broad FMQ)	15 (0.8)	2 (0.2)	13 (1.8)
Blood pressure increased	7 (0.4)	2 (0.2)	5 (0.7)
Hypertension	5 (0.3)	0 (0.0)	5 (0.7)
Blood pressure systolic increased	3 (0.2)	0 (0.0)	3 (0.4)
Arrhythmia (broad FMQ)	11 (0.6)	4 (0.3)	7 (1.0)
Dizziness	6 (0.3)	2 (0.2)	4 (0.5)
Bradycardia	3 (0.2)	2 (0.2)	1 (0.1)
Supraventricular extrasystoles	1 (0.1)	0 (0.0)	1 (0.1)
Heart rate increased	1 (0.1)	0 (0.0)	1 (0.1)
Syncope (broad FMQ)	10 (0.5)	6 (0.5)	4 (0.5)
Dizziness	6 (0.3)	2 (0.2)	4 (0.5)
Orthostatic hypotension	3 (0.2)	3 (0.3)	0 (0.0)
Hypotension	1 (0.1)	1 (0.1)	0 (0.0)
Diarrhoea (broad FMQ)	8 (0.4)	2 (0.2)	6 (0.8)
Diarrhoea	7 (0.4)	2 (0.2)	5 (0.7)
Frequent bowel movements	1 (0.1)	0 (0.0)	1 (0.1)
Dizziness (broad FMQ)	8 (0.4)	2 (0.2)	6 (0.8)
Dizziness	6 (0.3)	2 (0.2)	4 (0.5)
Dizziness postural	1 (0.1)	0 (0.0)	1 (0.1)
Vertigo	1 (0.1)	0 (0.0)	1 (0.1)
Nausea (broad FMQ)	7 (0.4)	3 (0.3)	4 (0.5)
Nausea	4 (0.2)	2 (0.2)	2 (0.3)
Procedural vomiting	1 (0.1)	0 (0.0)	1 (0.1)
Vomiting	2 (0.1)	1 (0.1)	1 (0.1)
Somnolence (broad FMQ)	7 (0.4)	3 (0.3)	4 (0.5)
Fatigue	4 (0.2)	1 (0.1)	3 (0.4)
Somnolence	1 (0.1)	0 (0.0)	1 (0.1)
Sedation	1 (0.1)	1 (0.1)	0 (0.0)
Altered state of consciousness	1 (0.1)	1 (0.1)	0 (0.0)
Vomiting (broad FMQ)	7 (0.4)	3 (0.3)	4 (0.5)
Nausea	4 (0.2)	2 (0.2)	2 (0.3)
Procedural vomiting	1 (0.1)	0 (0.0)	1 (0.1)
Vomiting	2 (0.1)	1 (0.1)	1 (0.1)
Anxiety (broad FMQ)	7 (0.4)	2 (0.2)	5 (0.7)
Agitation	4 (0.2)	1 (0.1)	3 (0.4)
Tremor	1 (0.1)	0 (0.0)	1 (0.1)
Restlessness	2 (0.1)	1 (0.1)	1 (0.1)
Panic attack	1 (0.1)	0 (0.0)	1 (0.1)
Vertigo (broad FMQ)	7 (0.4)	2 (0.2)	5 (0.7)
Dizziness	6 (0.3)	2 (0.2)	4 (0.5)
Vertigo	1 (0.1)	0 (0.0)	1 (0.1)
Myalgia (broad FMQ)	6 (0.3)	2 (0.2)	4 (0.5)
Muscle spasms	4 (0.2)	1 (0.1)	3 (0.4)
Myalgia	1 (0.1)	1 (0.1)	0 (0.0)
Musculoskeletal discomfort	1 (0.1)	0 (0.0)	1 (0.1)
Fatigue (broad FMQ)	6 (0.3)	1 (0.1)	5 (0.7)
Fatigue	4 (0.2)	1 (0.1)	3 (0.4)
Somnolence	1 (0.1)	0 (0.0)	1 (0.1)
Asthenia	1 (0.1)	0 (0.0)	1 (0.1)

FDA Medical Query	ISS Overall N=1921 n (%)	ISS 240 MBq N=1192 n (%)	ISS 370 MBq N=729 n (%)
Haemorrhage (broad FMQ)	5 (0.3)	3 (0.3)	2 (0.3)
Injection site bruising	2 (0.1)	1 (0.1)	1 (0.1)
Haemorrhage	1 (0.1)	1 (0.1)	0 (0.0)
Eye contusion	1 (0.1)	1 (0.1)	0 (0.0)
Epistaxis	1 (0.1)	0 (0.0)	1 (0.1)
Psychosis (broad FMQ)	5 (0.3)	3 (0.3)	2 (0.3)
Delusion of replacement	1 (0.1)	1 (0.1)	0 (0.0)
Hallucination, auditory	1 (0.1)	1 (0.1)	0 (0.0)
Hallucination, visual	1 (0.1)	1 (0.1)	0 (0.0)
Paraesthesia	2 (0.1)	0 (0.0)	2 (0.3)
Mania (broad FMQ)	5 (0.3)	2 (0.2)	3 (0.4)
Agitation	4 (0.2)	1 (0.1)	3 (0.4)
Restlessness	2 (0.1)	1 (0.1)	1 (0.1)
Rash (broad FMQ)	5 (0.3)	2 (0.2)	3 (0.4)
Rash papular	1 (0.1)	0 (0.0)	1 (0.1)
Skin exfoliation	1 (0.1)	1 (0.1)	0 (0.0)
Rash	2 (0.1)	1 (0.1)	1 (0.1)
Erythema	1 (0.1)	0 (0.0)	1 (0.1)
Malignancy (broad FMQ)	4 (0.2)	3 (0.3)	1 (0.1)
Basal cell carcinoma	2 (0.1)	2 (0.2)	0 (0.0)
Skin cancer	1 (0.1)	1 (0.1)	0 (0.0)
Neoplasm malignant	1 (0.1)	0 (0.0)	1 (0.1)
Hypotension (broad FMQ)	4 (0.2)	4 (0.3)	0 (0.0)
Orthostatic hypotension	3 (0.2)	3 (0.3)	0 (0.0)
Hypotension	1 (0.1)	1 (0.1)	0 (0.0)
Nasopharyngitis (broad FMQ)	4 (0.2)	4 (0.3)	0 (0.0)
Pharyngitis	1 (0.1)	1 (0.1)	0 (0.0)
Nasopharyngitis	2 (0.1)	2 (0.2)	0 (0.0)
Chronic sinusitis	1 (0.1)	1 (0.1)	0 (0.0)
Irritability (broad FMQ)	4 (0.2)	1 (0.1)	3 (0.4)
Agitation	4 (0.2)	1 (0.1)	3 (0.4)
Back pain (broad FMQ)	3 (0.2)	3 (0.3)	0 (0.0)
Back pain	3 (0.2)	3 (0.3)	0 (0.0)
Confusional state (broad FMQ)	3 (0.2)	1 (0.1)	2 (0.3)
Somnolence	1 (0.1)	0 (0.0)	1 (0.1)
Disturbance in attention	1 (0.1)	0 (0.0)	1 (0.1)
Altered state of consciousness	1 (0.1)	1 (0.1)	0 (0.0)
Erythema (broad FMQ)	3 (0.2)	1 (0.1)	2 (0.3)
Flushing	2 (0.1)	1 (0.1)	1 (0.1)
Erythema	1 (0.1)	0 (0.0)	1 (0.1)
Urticaria (broad FMQ)	3 (0.2)	1 (0.1)	2 (0.3)
Rash papular	1 (0.1)	0 (0.0)	1 (0.1)
Rash	2 (0.1)	1 (0.1)	1 (0.1)
Acute coronary syndrome (broad FMQ)	3 (0.2)	0 (0.0)	3 (0.4)
Myocardial infarction	1 (0.1)	0 (0.0)	1 (0.1)
Angina pectoris	2 (0.1)	0 (0.0)	2 (0.3)
Myocardial infarction (broad FMQ)	3 (0.2)	0 (0.0)	3 (0.4)
Myocardial infarction	1 (0.1)	0 (0.0)	1 (0.1)
Angina pectoris	2 (0.1)	0 (0.0)	2 (0.3)
Myocardial ischaemia (broad FMQ)	3 (0.2)	0 (0.0)	3 (0.4)
Angina pectoris	2 (0.1)	0 (0.0)	2 (0.3)
Myocardial infarction	1 (0.1)	0 (0.0)	1 (0.1)

FDA Medical Query	ISS Overall N=1921 n (%)	ISS 240 MBq N=1192 n (%)	ISS 370 MBq N=729 n (%)
Arthralgia (broad FMQ)	2 (0.1)	2 (0.2)	0 (0.0)
Arthralgia	2 (0.1)	2 (0.2)	0 (0.0)
Arthritis (broad FMQ)	2 (0.1)	2 (0.2)	0 (0.0)
Arthralgia	2 (0.1)	2 (0.2)	0 (0.0)
Dyspepsia (broad FMQ)	2 (0.1)	2 (0.2)	0 (0.0)
Abdominal discomfort	1 (0.1)	1 (0.1)	0 (0.0)
Eructation	1 (0.1)	1 (0.1)	0 (0.0)
Pruritus (broad FMQ)	2 (0.1)	2 (0.2)	0 (0.0)
Pruritus	1 (0.1)	1 (0.1)	0 (0.0)
Eye pruritus	1 (0.1)	1 (0.1)	0 (0.0)
Abdominal pain (broad FMQ)	2 (0.1)	1 (0.1)	1 (0.1)
Abdominal discomfort	1 (0.1)	1 (0.1)	0 (0.0)
Abdominal pain	1 (0.1)	0 (0.0)	1 (0.1)
Paraesthesia (broad FMQ)	2 (0.1)	0 (0.0)	2 (0.3)
Paraesthesia	2 (0.1)	0 (0.0)	2 (0.3)
Hypoaesthesia	1 (0.1)	0 (0.0)	1 (0.1)
Thrombocytopenia (broad FMQ)	2 (0.1)	0 (0.0)	2 (0.3)
Platelet count decreased	2 (0.1)	0 (0.0)	2 (0.3)
Alopecia (broad FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Alopecia	1 (0.1)	1 (0.1)	0 (0.0)
Bronchospasm (broad FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Dyspnoea	1 (0.1)	1 (0.1)	0 (0.0)
Cholecystitis (broad FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Cholelithiasis	1 (0.1)	1 (0.1)	0 (0.0)
Depression (broad FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Depression	1 (0.1)	1 (0.1)	0 (0.0)
Dyspnoea (broad FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Dyspnoea	1 (0.1)	1 (0.1)	0 (0.0)
Insomnia (broad FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Insomnia	1 (0.1)	1 (0.1)	0 (0.0)
Pyrexia (broad FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Pyrexia	1 (0.1)	1 (0.1)	0 (0.0)
Acute kidney injury (broad FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Acute kidney injury	1 (0.1)	0 (0.0)	1 (0.1)
Decreased appetite (broad FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Decreased appetite	1 (0.1)	0 (0.0)	1 (0.1)
Dysgeusia (broad FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Dysgeusia	1 (0.1)	0 (0.0)	1 (0.1)
Tachycardia (broad FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Heart rate increased	1 (0.1)	0 (0.0)	1 (0.1)
Tremor (broad FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Tremor	1 (0.1)	0 (0.0)	1 (0.1)
Urinary retention (broad FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Urinary incontinence	1 (0.1)	0 (0.0)	1 (0.1)

Source: adae.xpt; Software: Python
Abbreviations: ISS, integrated summary of safety; MBq, megabecquerel; CI, confidence interval; N, number of subjects; n, number of subjects with at least one event; FMQ, FDA Medical Query

Table 41. Adverse Events by FDA Medical Query (Narrow) and Preferred Term, Safety Population, ISS

FDA Medical Query	ISS Overall N=1921 n (%)	ISS 240 MBq N=1192 n (%)	ISS 370 MBq N=729 n (%)
Local administration reactions (narrow FMQ)	29 (1.5)	3 (0.3)	26 (3.6)
Injection site pain	23 (1.2)	2 (0.2)	21 (2.9)
Injection site extravasation	4 (0.2)	0 (0.0)	4 (0.5)
Injection site bruising	2 (0.1)	1 (0.1)	1 (0.1)
Headache (narrow FMQ)	26 (1.4)	7 (0.6)	19 (2.6)
Headache	24 (1.2)	7 (0.6)	17 (2.3)
Procedural headache	2 (0.1)	0 (0.0)	2 (0.3)
Systemic hypertension (narrow FMQ)	15 (0.8)	2 (0.2)	13 (1.8)
Blood pressure increased	7 (0.4)	2 (0.2)	5 (0.7)
Hypertension	5 (0.3)	0 (0.0)	5 (0.7)
Blood pressure systolic increased	3 (0.2)	0 (0.0)	3 (0.4)
Dizziness (narrow FMQ)	8 (0.4)	2 (0.2)	6 (0.8)
Dizziness	6 (0.3)	2 (0.2)	4 (0.5)
Dizziness postural	1 (0.1)	0 (0.0)	1 (0.1)
Vertigo	1 (0.1)	0 (0.0)	1 (0.1)
Diarrhoea (narrow FMQ)	7 (0.4)	2 (0.2)	5 (0.7)
Diarrhea	7 (0.4)	2 (0.2)	5 (0.7)
Haemorrhage (narrow FMQ)	5 (0.3)	3 (0.3)	2 (0.3)
Epistaxis	1 (0.1)	0 (0.0)	1 (0.1)
Eye contusion	1 (0.1)	1 (0.1)	0 (0.0)
Haemorrhage	1 (0.1)	1 (0.1)	0 (0.0)
Injection site bruising	2 (0.1)	1 (0.1)	1 (0.1)
Fatigue (narrow FMQ)	5 (0.3)	1 (0.1)	4 (0.5)
Fatigue	4 (0.2)	1 (0.1)	3 (0.4)
Asthenia	1 (0.1)	0 (0.0)	1 (0.1)
Malignancy (narrow FMQ)	4 (0.2)	3 (0.3)	1 (0.1)
Skin cancer	1 (0.1)	1 (0.1)	0 (0.0)
Basal cell carcinoma	2 (0.1)	2 (0.2)	0 (0.0)
Neoplasm malignant	1 (0.1)	0 (0.0)	1 (0.1)
Hypotension (narrow FMQ)	4 (0.2)	4 (0.3)	0 (0.0)
Orthostatic hypotension	3 (0.2)	3 (0.3)	0 (0.0)
Hypotension	1 (0.1)	1 (0.1)	0 (0.0)
Nasopharyngitis (narrow FMQ)	4 (0.2)	4 (0.3)	0 (0.0)
Pharyngitis	1 (0.1)	1 (0.1)	0 (0.0)
Nasopharyngitis	2 (0.1)	2 (0.2)	0 (0.0)
Chronic sinusitis	1 (0.1)	1 (0.1)	0 (0.0)
Arrhythmia (narrow FMQ)	4 (0.2)	2 (0.2)	2 (0.3)
Bradycardia	3 (0.2)	2 (0.2)	1 (0.1)
Supraventricular extrasystoles	1 (0.1)	0 (0.0)	1 (0.1)
Nausea (narrow FMQ)	4 (0.2)	2 (0.2)	2 (0.3)
Nausea	4 (0.2)	2 (0.2)	2 (0.3)
Rash (narrow FMQ)	4 (0.2)	2 (0.2)	2 (0.3)
Rash	2 (0.1)	1 (0.1)	1 (0.1)
Rash papular	1 (0.1)	0 (0.0)	1 (0.1)
Skin exfoliation	1 (0.1)	1 (0.1)	0 (0.0)
Irritability (narrow FMQ)	4 (0.2)	1 (0.1)	3 (0.4)
Agitation	4 (0.2)	1 (0.1)	3 (0.4)
Back pain (narrow FMQ)	3 (0.2)	3 (0.3)	0 (0.0)
Back pain	3 (0.2)	3 (0.3)	0 (0.0)

FDA Medical Query	ISS Overall N=1921 n (%)	ISS 240 MBq N=1192 n (%)	ISS 370 MBq N=729 n (%)
Psychosis (narrow FMQ)	3 (0.2)	3 (0.3)	0 (0.0)
Delusion of replacement	1 (0.1)	1 (0.1)	0 (0.0)
Hallucination, auditory	1 (0.1)	1 (0.1)	0 (0.0)
Hallucination, visual	1 (0.1)	1 (0.1)	0 (0.0)
Erythema (narrow FMQ)	3 (0.2)	1 (0.1)	2 (0.3)
Erythema	1 (0.1)	0 (0.0)	1 (0.1)
Flushing	2 (0.1)	1 (0.1)	1 (0.1)
Vomiting (narrow FMQ)	3 (0.2)	1 (0.1)	2 (0.3)
Procedural vomiting	1 (0.1)	0 (0.0)	1 (0.1)
Vomiting	2 (0.1)	1 (0.1)	1 (0.1)
Myocardial ischemia (narrow FMQ)	3 (0.2)	0 (0.0)	3 (0.4)
Myocardial infarction	1 (0.1)	0 (0.0)	1 (0.1)
Angina pectoris	2 (0.1)	0 (0.0)	2 (0.3)
Arthralgia (narrow FMQ)	2 (0.1)	2 (0.2)	0 (0.0)
Arthralgia	2 (0.1)	2 (0.2)	0 (0.0)
Pruritus (narrow FMQ)	2 (0.1)	2 (0.2)	0 (0.0)
Pruritus	1 (0.1)	1 (0.1)	0 (0.0)
Eye pruritus	1 (0.1)	1 (0.1)	0 (0.0)
Abdominal pain (narrow FMQ)	2 (0.1)	1 (0.1)	1 (0.1)
Abdominal discomfort	1 (0.1)	1 (0.1)	0 (0.0)
Abdominal pain	1 (0.1)	0 (0.0)	1 (0.1)
Myalgia (narrow FMQ)	2 (0.1)	1 (0.1)	1 (0.1)
Myalgia	1 (0.1)	1 (0.1)	0 (0.0)
Musculoskeletal discomfort	1 (0.1)	0 (0.0)	1 (0.1)
Somnolence (narrow FMQ)	2 (0.1)	1 (0.1)	1 (0.1)
Sedation	1 (0.1)	1 (0.1)	0 (0.0)
Somnolence	1 (0.1)	0 (0.0)	1 (0.1)
Paraesthesia (narrow FMQ)	2 (0.1)	0 (0.0)	2 (0.3)
Hypoesthesia	1 (0.1)	0 (0.0)	1 (0.1)
Paresthesia	2 (0.1)	0 (0.0)	2 (0.3)
Thrombocytopenia (narrow FMQ)	2 (0.1)	0 (0.0)	2 (0.3)
Platelet count decreased	2 (0.1)	0 (0.0)	2 (0.3)
Alopecia (narrow FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Alopecia	1 (0.1)	1 (0.1)	0 (0.0)
Depression (narrow FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Depression	1 (0.1)	1 (0.1)	0 (0.0)
Dyspepsia (narrow FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Eructation	1 (0.1)	1 (0.1)	0 (0.0)
Dyspnea (narrow FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Dyspnea	1 (0.1)	1 (0.1)	0 (0.0)
Insomnia (narrow FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Insomnia	1 (0.1)	1 (0.1)	0 (0.0)
Pyrexia (narrow FMQ)	1 (0.1)	1 (0.1)	0 (0.0)
Pyrexia	1 (0.1)	1 (0.1)	0 (0.0)
Acute coronary syndrome (narrow FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Myocardial infarction	1 (0.1)	0 (0.0)	1 (0.1)
Acute kidney injury (narrow FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Acute kidney injury	1 (0.1)	0 (0.0)	1 (0.1)
Anxiety (narrow FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Panic attack	1 (0.1)	0 (0.0)	1 (0.1)
Decreased appetite (narrow FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Decreased appetite	1 (0.1)	0 (0.0)	1 (0.1)

FDA Medical Query	ISS Overall N=1921 n (%)	ISS 240 MBq N=1192 n (%)	ISS 370 MBq N=729 n (%)
Dysgeusia (narrow FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Dysgeusia	1 (0.1)	0 (0.0)	1 (0.1)
Myocardial infarction (narrow FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Myocardial infarction	1 (0.1)	0 (0.0)	1 (0.1)
Tachycardia (narrow FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Heart rate increased	1 (0.1)	0 (0.0)	1 (0.1)
Tremor (narrow FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Tremor	1 (0.1)	0 (0.0)	1 (0.1)
Vertigo (narrow FMQ)	1 (0.1)	0 (0.0)	1 (0.1)
Vertigo	1 (0.1)	0 (0.0)	1 (0.1)

Abbreviations: ISS, integrated summary of safety; FMQ, FDA Medical Query; MBq, megabecquerel; N, number of subjects in group; n, number of subjects with adverse event

16.4. Adverse Drug Reactions

AEs considered adverse drug reactions are listed in order of frequency in Table 42.

Table 42. Adverse Drug Reactions,[1] Safety Population, ISS

Adverse Event[2]	ISS Overall N=1,921 n (%)	ISS 240 MBq N=1,192 n (%)	ISS 370 MBq N=729 n (%)
Headache	24 (1.2)	7 (0.6)	17 (2.3)
Injection site pain	23 (1.2)	2 (0.2)	21 (2.9)
Blood pressure increased	7 (0.4)	2 (0.2)	5 (0.7)
Diarrhoea	7 (0.4)	2 (0.2)	5 (0.7)
Dizziness	6 (0.3)	2 (0.2)	4 (0.5)
Hypertension	5 (0.3)	0 (0.0)	5 (0.7)
Fall	4 (0.2)	3 (0.3)	1 (0.1)
Nausea	4 (0.2)	2 (0.2)	2 (0.3)
Agitation	4 (0.2)	1 (0.1)	3 (0.4)
Fatigue	4 (0.2)	1 (0.1)	3 (0.4)
Muscle spasms	4 (0.2)	1 (0.1)	3 (0.4)
Injection site extravasation	4 (0.2)	0 (0.0)	4 (0.5)
Back pain	3 (0.2)	3 (0.3)	0 (0.0)
Cataract	3 (0.2)	3 (0.3)	0 (0.0)
Orthostatic hypotension	3 (0.2)	3 (0.3)	0 (0.0)
Bradycardia	3 (0.2)	2 (0.2)	1 (0.1)
Dermatitis contact	3 (0.2)	2 (0.2)	1 (0.1)
Blood pressure systolic increased	3 (0.2)	0 (0.0)	3 (0.4)
Arthralgia	2 (0.1)	2 (0.2)	0 (0.0)
Basal cell carcinoma	2 (0.1)	2 (0.2)	0 (0.0)
Laceration	2 (0.1)	2 (0.2)	0 (0.0)
Maculopathy	2 (0.1)	2 (0.2)	0 (0.0)
Nasopharyngitis	2 (0.1)	2 (0.2)	0 (0.0)
Superficial siderosis of central nervous system	2 (0.1)	2 (0.2)	0 (0.0)
Upper respiratory tract infection	2 (0.1)	2 (0.2)	0 (0.0)
Weight increased	2 (0.1)	2 (0.2)	0 (0.0)
Flushing	2 (0.1)	1 (0.1)	1 (0.1)
Injection site bruising	2 (0.1)	1 (0.1)	1 (0.1)
Pain in extremity	2 (0.1)	1 (0.1)	1 (0.1)
Rash	2 (0.1)	1 (0.1)	1 (0.1)

Adverse Event[2]	ISS Overall N=1,921 n (%)	ISS 240 MBq N=1,192 n (%)	ISS 370 MBq N=729 n (%)
Restlessness	2 (0.1)	1 (0.1)	1 (0.1)
Vomiting	2 (0.1)	1 (0.1)	1 (0.1)
Angina pectoris	2 (0.1)	0 (0.0)	2 (0.3)
Paraesthesia	2 (0.1)	0 (0.0)	2 (0.3)
Platelet count decreased	2 (0.1)	0 (0.0)	2 (0.3)
Procedural headache	2 (0.1)	0 (0.0)	2 (0.3)
Abdominal discomfort	1 (0.1)	1 (0.1)	0 (0.0)
Affective disorder	1 (0.1)	1 (0.1)	0 (0.0)
Alopecia	1 (0.1)	1 (0.1)	0 (0.0)
Altered state of consciousness	1 (0.1)	1 (0.1)	0 (0.0)
Bronchitis	1 (0.1)	1 (0.1)	0 (0.0)
Bundle branch block right	1 (0.1)	1 (0.1)	0 (0.0)
Cataract operation	1 (0.1)	1 (0.1)	0 (0.0)
Cerebral infarction	1 (0.1)	1 (0.1)	0 (0.0)
Change of bowel habit	1 (0.1)	1 (0.1)	0 (0.0)
Cholelithiasis	1 (0.1)	1 (0.1)	0 (0.0)
Chronic sinusitis	1 (0.1)	1 (0.1)	0 (0.0)
Cognitive disorder	1 (0.1)	1 (0.1)	0 (0.0)
Corneal disorder	1 (0.1)	1 (0.1)	0 (0.0)
Delusion of replacement	1 (0.1)	1 (0.1)	0 (0.0)
Depression	1 (0.1)	1 (0.1)	0 (0.0)
Dry skin	1 (0.1)	1 (0.1)	0 (0.0)
Dysarthria	1 (0.1)	1 (0.1)	0 (0.0)
Dyspnoea	1 (0.1)	1 (0.1)	0 (0.0)
Electrocardiogram t wave abnormal	1 (0.1)	1 (0.1)	0 (0.0)
Eructation	1 (0.1)	1 (0.1)	0 (0.0)
Eye contusion	1 (0.1)	1 (0.1)	0 (0.0)
Eye pruritus	1 (0.1)	1 (0.1)	0 (0.0)
Facial paresis	1 (0.1)	1 (0.1)	0 (0.0)
Faeces soft	1 (0.1)	1 (0.1)	0 (0.0)
Gait disturbance	1 (0.1)	1 (0.1)	0 (0.0)
Haemorrhage	1 (0.1)	1 (0.1)	0 (0.0)
Hallucination, auditory	1 (0.1)	1 (0.1)	0 (0.0)
Hallucination, visual	1 (0.1)	1 (0.1)	0 (0.0)
Hyperhidrosis	1 (0.1)	1 (0.1)	0 (0.0)
Hyperreflexia	1 (0.1)	1 (0.1)	0 (0.0)
Hypotension	1 (0.1)	1 (0.1)	0 (0.0)
Insomnia	1 (0.1)	1 (0.1)	0 (0.0)
Lens disorder	1 (0.1)	1 (0.1)	0 (0.0)
Livedo reticularis	1 (0.1)	1 (0.1)	0 (0.0)
Localised infection	1 (0.1)	1 (0.1)	0 (0.0)
Meibomian gland dysfunction	1 (0.1)	1 (0.1)	0 (0.0)
Meningioma	1 (0.1)	1 (0.1)	0 (0.0)
Muscular weakness	1 (0.1)	1 (0.1)	0 (0.0)
Myalgia	1 (0.1)	1 (0.1)	0 (0.0)
Night sweats	1 (0.1)	1 (0.1)	0 (0.0)
Nuclear magnetic resonance imaging abnormal	1 (0.1)	1 (0.1)	0 (0.0)
Oral disorder	1 (0.1)	1 (0.1)	0 (0.0)
Oral herpes	1 (0.1)	1 (0.1)	0 (0.0)
Pharyngitis	1 (0.1)	1 (0.1)	0 (0.0)
Pruritus	1 (0.1)	1 (0.1)	0 (0.0)
Pyrexia	1 (0.1)	1 (0.1)	0 (0.0)
Seborrheic keratosis	1 (0.1)	1 (0.1)	0 (0.0)

Adverse Event[2]	ISS Overall N=1,921 n (%)	ISS 240 MBq N=1,192 n (%)	ISS 370 MBq N=729 n (%)
Sedation	1 (0.1)	1 (0.1)	0 (0.0)
Skin abrasion	1 (0.1)	1 (0.1)	0 (0.0)
Skin cancer	1 (0.1)	1 (0.1)	0 (0.0)
Skin exfoliation	1 (0.1)	1 (0.1)	0 (0.0)
Skin hypopigmentation	1 (0.1)	1 (0.1)	0 (0.0)
Transient ischemic attack	1 (0.1)	1 (0.1)	0 (0.0)
Urinary tract infection	1 (0.1)	1 (0.1)	0 (0.0)
Viral infection	1 (0.1)	1 (0.1)	0 (0.0)
Vitreous disorder	1 (0.1)	1 (0.1)	0 (0.0)
Abdominal pain	1 (0.1)	0 (0.0)	1 (0.1)
Acute kidney injury	1 (0.1)	0 (0.0)	1 (0.1)
Amnesia	1 (0.1)	0 (0.0)	1 (0.1)
Application site irritation	1 (0.1)	0 (0.0)	1 (0.1)
Application site laceration	1 (0.1)	0 (0.0)	1 (0.1)
Asthenia	1 (0.1)	0 (0.0)	1 (0.1)
Bronchial secretion retention	1 (0.1)	0 (0.0)	1 (0.1)
Cardiac failure congestive	1 (0.1)	0 (0.0)	1 (0.1)
Cyanopsia	1 (0.1)	0 (0.0)	1 (0.1)
Decreased appetite	1 (0.1)	0 (0.0)	1 (0.1)
Disturbance in attention	1 (0.1)	0 (0.0)	1 (0.1)
Dizziness postural	1 (0.1)	0 (0.0)	1 (0.1)
Dysgeusia	1 (0.1)	0 (0.0)	1 (0.1)
Epistaxis	1 (0.1)	0 (0.0)	1 (0.1)
Erythema	1 (0.1)	0 (0.0)	1 (0.1)
Eye irritation	1 (0.1)	0 (0.0)	1 (0.1)
Feeling abnormal	1 (0.1)	0 (0.0)	1 (0.1)
Flatulence	1 (0.1)	0 (0.0)	1 (0.1)
Frequent bowel movements	1 (0.1)	0 (0.0)	1 (0.1)
Head discomfort	1 (0.1)	0 (0.0)	1 (0.1)
Heart rate increased	1 (0.1)	0 (0.0)	1 (0.1)
Hot flush	1 (0.1)	0 (0.0)	1 (0.1)
Hypoesthesia	1 (0.1)	0 (0.0)	1 (0.1)
Hypomagnesaemia	1 (0.1)	0 (0.0)	1 (0.1)
Hypoxic-ischemic encephalopathy	1 (0.1)	0 (0.0)	1 (0.1)
Memory impairment	1 (0.1)	0 (0.0)	1 (0.1)
Mental disorder	1 (0.1)	0 (0.0)	1 (0.1)
Musculoskeletal discomfort	1 (0.1)	0 (0.0)	1 (0.1)
Myocardial infarction	1 (0.1)	0 (0.0)	1 (0.1)
Myopathy	1 (0.1)	0 (0.0)	1 (0.1)
Neoplasm malignant	1 (0.1)	0 (0.0)	1 (0.1)
Ocular hyperemia	1 (0.1)	0 (0.0)	1 (0.1)
Oral pain	1 (0.1)	0 (0.0)	1 (0.1)
Panic attack	1 (0.1)	0 (0.0)	1 (0.1)
Procedural vomiting	1 (0.1)	0 (0.0)	1 (0.1)
Rash papular	1 (0.1)	0 (0.0)	1 (0.1)
Somnolence	1 (0.1)	0 (0.0)	1 (0.1)
Supraventricular extrasystoles	1 (0.1)	0 (0.0)	1 (0.1)

Adverse Event[2]	ISS Overall N=1,921 n (%)	ISS 240 MBq N=1,192 n (%)	ISS 370 MBq N=729 n (%)
Therapeutic response unexpected	1 (0.1)	0 (0.0)	1 (0.1)
Tremor	1 (0.1)	0 (0.0)	1 (0.1)
Urinary incontinence	1 (0.1)	0 (0.0)	1 (0.1)
Vertigo	1 (0.1)	0 (0.0)	1 (0.1)

Source: adae.xpt; Software: Python
[1] Treatment-emergent adverse event defined as undesirable experiences, signs or symptoms that begin or worsen in intensity or frequency ≤48 hours after the FTP dose injection (or ≤2 days for studies designed for biomarker purposes).
[2] Coded as MedDRA preferred terms
Abbreviations: ISS, integrated summary of safety; MBq, megabecquerel; N, number of subjects in group; n, number of subjects with adverse event

16.5. Laboratory Parameters

Changes from baseline in laboratory parameters are listed in Table 43.

Table 43. Laboratory Parameters, Overall Mean Change From Baseline to Postdose, Safety Population for Diagnosis Studies, ISS

Laboratory Test	Mean Change (SD)	Median Change (Min, Max)
Alanine aminotransferase (µkat/L)	-0.007 (0.043)	0 (-0.5177 - 0.2839)
Albumin (g/L)	-0.558 (2.451)	-1 (-19 - 9)
Alkaline phosphatase (µkat/L)	-0.012 (0.076)	-0.0167 (-0.4175 - 0.2839)
Aspartate aminotransferase (µkat/L)	-0.006 (0.062)	0 (-1.1189 - 0.3006)
Basophils (10^9/L)	0.003 (0.033)	0 (-0.39 - 0.23)
Basophils/leukocytes (%)	0.046 (0.446)	0 (-2 - 3)
Bicarbonate (mmol/L)	0.242 (2.084)	0.3000 (-6.9 - 9)
Bilirubin (µmol/L)	-0.661 (1.774)	0 (-11.9725 - 5.1312)
Calcium (mmol/L)	-0.006 (0.092)	0 (-0.775 - 0.525)
Carbon dioxide (mmol/L)	-0.8 (1.814)	-1 (-3 - 2)
Chloride (mmol/L)	0.528 (1.903)	0 (-7 - 15)
Cholesterol (mmol/L)	0.032 (0.297)	0.0259 (-0.8276 - 1.1895)
Creatinine (µmol/L)	-2.274 (6.964)	0 (-26.52 - 17.6804)
Eosinophils (10^9/L)	0.008 (0.063)	0.01 (-0.37 - 0.43)
Eosinophils/leukocytes (%)	0.065 (0.912)	0.10000 (-6 - 6)
Ery. mean corpuscular hemoglobin (pg)	-0.008 (0.796)	0 (-2 - 3)
Ery. mean corpuscular HGB concentration (mmol/L)	-0.212 (0.784)	0 (-3.7236 - 2.4824)
Ery. mean corpuscular volume (fL)	0.961 (2.746)	0 (-6 - 11)
Erythrocytes (/HPF)	-0.86 (2.814)	0 (-23 - 8)
Erythrocytes (10^12/L)	-0.001 (0.23)	0 (-1.4 - 1.2)
Gamma glutamyl transferase (µkat/L)	-0.006 (0.04)	0 (-0.3006 - 0.2171)
Globulin (g/L)	-0.292 (2.13)	0 (-10 - 9)
Glucose	-0.019 (0.411)	0 (-4 - 4)
Glucose (mmol/L)	-0.455 (1.552)	-0.222 (-9.3795 - 9.324)
HDL cholesterol (mmol/L)	-0.007 (0.308)	-0.0259 (-2.2533 - 1.5022)
Hematocrit (Proportion of 1.0)	0.004 (0.025)	0 (-0.13 - 0.1)
Hemoglobin (mmol/L)	-0.006 (0.433)	0 (-2.6087 - 2.1118)
Hyaline casts (/LPF)	-21.5 (16.263)	-21.5 (-33 - -10)
Ketones	0.011 (0.181)	0 (-2 - 2)
Leukocyte esterase	-0.06 (0.598)	0 (-3 - 3)
Leukocytes (/HPF)	-2.238 (13.339)	0 (-70 - 90)
Leukocytes (10^9/L)	0.165 (0.929)	0.14 (-6.36 - 4.97)
Lymphocytes (10^9/L)	0.164 (0.364)	0.17 (-1.96 - 2.69)

Laboratory Test	Mean Change (SD)	Median Change (Min, Max)
Lymphocytes atypical (10^9/L)	-0.24 (0.424)	-0.24 (-0.54 - 0.06)
Lymphocytes atypical/leukocytes (%)	-1 (1.414)	-1 (-2 - 0)
Lymphocytes/leukocytes (%)	1.799 (3.977)	2 (-20.5 - 18)
Magnesium (mmol/L)	0.017 (0.043)	0 (-0.2469 - 0.1646)
Monocytes (10^9/L)	0.015 (0.132)	0.01 (-0.57 - 0.77)
Monocytes/leukocytes (%)	0.05 (1.8)	0 (-7.4 - 9.4)
Neutrophils (10^9/L)	-0.024 (0.725)	-0.0600 (-4.07 - 4.19)
Neutrophils/leukocytes (%)	-1.954 (4.415)	-2.1 (-20.6 - 19.2)
Nitrite	0.003 (0.216)	0 (-2 - 2)
Occult blood	-0.007 (0.133)	0 (-1 - 1)
pH	0.1 (0.515)	0 (-1.5 - 2)
Phosphate (mmol/L)	0.011 (0.13)	0 (-0.5168 - 0.7429)
Platelets (10^9/L)	-9.356 (28.864)	-8 (-226 - 144)
Potassium (mmol/L)	0.025 (0.383)	0 (-1.5 - 1.6)
Protein	-0.4 (0.548)	0 (-1 - 0)
Protein (g/L)	-0.865 (3.777)	-1 (-27 - 15)
Sodium (mmol/L)	0.486 (1.847)	0 (-7 - 9)
Specific gravity	-0.004 (0.006)	-0.0030 (-0.024 - 0.0150)
Squamous epithelial cells (/HPF)	-9 (NA)	-9 (-9 - -9)
Transitional epithelial cells (/HPF)	-1 (NA)	-1 (-1 - -1)
Triglycerides (mmol/L)	-0.059 (0.551)	-0.0678 (-2.7346 - 3.9098)
Urate (µmol/L)	-5.757 (15.075)	-5.9485 (-59.4849 - 41.6395)
Urea nitrogen (mmol/L)	-0.135 (0.504)	-0.3570 (-3.57 - 2.142)
Uric acid crystals (µmol/L)	-6.767 (15.41)	-5.9485 (-148.7123 - 47.5879)
Urobilinogen	0.001 (0.037)	0 (0 - 1)

Source: adae.xpt; Software: Python
Studies include AV1451-A01, AV1451-A03, AV1451-A04, AV1451-A05, AV1451-A07, AV1451-A08, AV1451-A09, AV1451-A10, AV1451-A11, AV1451-A16, AV1451-A18, and T807000 with 833 unique subjects.
Abbreviations: HDL, high-density lipoprotein; HGB, hemoglobin; HPF, high power field; ISS, integrated summary of safety; LPF, low power field; µkat, microkatal; NA, not applicable; SD, standard deviation

Blood Pressure Increased

The Applicant also reports statistically significant but small changes in several vital signs compared to the baseline measurement. Seventeen of the subjects were observed to have potentially clinically significant blood pressure elevations on 19 occasions. Significantly elevated systolic blood pressure readings in 15 of the measurements ranged from 181 to 224 mm Hg and represented increases of 20 to 78 mm Hg above predose values. Six of the significantly elevated diastolic blood pressure measurements ranged from 105 to 198 mm Hg, representing increases of 15 to 68 mm Hg above predose values. These elevations were reported to have generally occurred at the time of discharge about 2 to 3 hours after injection.) and not immediately during postdose time period (5 to 10 minutes after injection) when blood concentrations of FTP would be highest.

The majority of these subjects also had a history of hypertension/high blood pressure or showed elevated predose blood pressure readings. Further, as there was no clinically meaningful relationship to the mass dose of study drug, the Applicant opined that these events are likely related to the time of blood pressure measurements and the PET imaging procedure and not related to the study drug.

16.6. Subgroup Analyses

Subgroup analysis age (≥65 years and <65 years), gender, and race (white and nonwhite) did not reveal any clinically significant difference in pattern or frequency of TEAEs, vital sign measurements, or clinical laboratory results in the subgroups analyzed (see Table 44 through Table 49).

Table 44. Adverse Events by Age (≥65), Study Type, Cognitive Status, and Dosage, Safety Population, ISS

	Overall N=1921 n (%)				240 MBq N=1192 n (%)				370 MBq N=729 n (%)		
	Diagnosis Studies			Biomarker Studies	Diagnosis Studies			Biomarker Studies	Diagnosis Studies		
	CI	CN	Total	CI	CI	CN	Total	CI	CI	CN	Total
Age ≥65, N	438	180	618	926	21	77	98	926	417	103	520
Patients with at least 1 AE	52 (11.9)	21 (11.7)	73 (11.8)	76 (8.2)	0 (0.0)	3 (3.9)	3 (3.1)	76 (8.2)	52 (12.5)	18 (17.5)	70 (13.5)
Injection site pain	13 (3.0)	2 (1.1)	15 (2.4)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	13 (3.1)	2 (1.9)	15 (2.9)
Headache	8 (1.8)	3 (1.7)	11 (1.8)	1 (0.1)	0 (0.0)	2 (2.6)	2 (2.0)	1 (0.1)	8 (1.9)	1 (1.0)	9 (1.7)
Blood pressure increased	3 (0.7)	1 (0.6)	4 (0.6)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.7)	1 (1.0)	4 (0.8)
Dizziness	3 (0.7)	0 (0.0)	3 (0.5)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	3 (0.7)	0 (0.0)	3 (0.6)
Hypertension	3 (0.7)	1 (0.6)	4 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	1 (1.0)	4 (0.8)
Injection site extravasation	3 (0.7)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	3 (0.6)
Diarrhoea	2 (0.5)	1 (0.6)	3 (0.5)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.5)	1 (1.0)	3 (0.6)
Muscle spasms	2 (0.5)	1 (0.6)	3 (0.5)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.5)	1 (1.0)	3 (0.6)
Platelet count decreased	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.4)
Acute kidney injury	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Agitation	1 (0.2)	1 (0.6)	2 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	1 (1.0)	2 (0.4)
Amnesia	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Angina pectoris	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Application site laceration	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Asthenia	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Blood pressure systolic increased	1 (0.2)	1 (0.6)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (1.0)	2 (0.4)
Bronchial secretion retention	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Cyanopsia	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Dermatitis contact	1 (0.2)	1 (0.6)	2 (0.3)	1 (0.1)	0 (0.0)	1 (1.3)	1 (1.0)	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.2)
Dizziness postural	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Procedural headache	0 (0.0)	1 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)

Source: adsl.xpt, adae.xpt
For the subject who participated >1 study, the greater age value is used to perform analysis by age subgroup
Abbreviations: AE, adverse event; CI, cognitively impaired; CN, cognitively normal; ISS, integrated summary of safety; MBq, megabecquerel; N, number of subjects in group; n, number of subjects with adverse event

Table 45. Adverse Events by Age (<65), Study Type, Cognitive Status, and Dosage, Safety Population, ISS

	Overall N=1921 n (%)				240 MBq N=1192 n (%)				370 MBq N=729 n (%)		
	Diagnosis Studies			Biomarker Studies	Diagnosis Studies			Biomarker Studies	Diagnosis Studies		
	CI	CN	Total	CI	CI	CN	Total	CI	CI	CN	Total
Age <65, N	123	95	218	159	6	3	9	159	117	92	209
Patients with at least 1 AE	17 (13.8)	15 (15.8)	32 (14.7)	9 (5.7)	1 (16.7)	1 (33.3)	2 (22.2)	9 (5.7)	16 (13.7)	14 (15.2)	30 (14.4)
Headache	5 (4.1)	4 (4.2)	9 (4.1)	3 (1.9)	0 (0.0)	1 (33.3)	1 (11.1)	3 (1.9)	5 (4.3)	3 (3.3)	8 (3.8)
Injection site pain	3 (2.4)	3 (3.2)	6 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.6)	3 (3.3)	6 (2.9)
Agitation	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Angina pectoris	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Decreased appetite	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Diarrhoea	1 (0.8)	1 (1.1)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.1)	2 (1.0)
Epistaxis	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Erythema	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Feeling abnormal	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Hypertension	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Injection site extravasation	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Myalgia	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	1 (16.7)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (0.8)	0 (0.0)	1 (0.5)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.9)	0 (0.0)	1 (0.5)
Oral pain	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Pain in extremity	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Rash	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Supraventricular extrasystoles	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Abdominal pain	0 (0.0)	1 (1.1)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.5)
Application site irritation	0 (0.0)	1 (1.1)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.5)
Blood pressure increased	0 (0.0)	1 (1.1)	1 (0.5)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (1.1)	1 (0.5)
Blood pressure systolic increased	0 (0.0)	1 (1.1)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.5)
Procedural headache	0 (0.0)	1 (1.1)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.5)

Source: adsl.xpt, adae.xpt
For the subject who participated >1 study, the greater age value is used to perform analysis by age subgroup
Abbreviations: AE, adverse event; CI, cognitively impaired; CN, cognitively normal; ISS, integrated summary of safety; MBq, megabecquerel; N, number of subjects in group; n, number of subjects with adverse event

Table 46. Adverse Events by Sex (Male), Study Type, Cognitive Status, and Dosage, Safety Population, ISS

	Overall N=1921 n (%)				240 MBq N=1192 n (%)				370 MBq N=729 n (%)		
	Diagnosis Studies			Biomarker Studies	Diagnosis Studies			Biomarker Studies	Diagnosis Studies		
	CI	CN	Total	CI	CI	CN	Total	CI	CI	CN	Total
Male, N	313	158	471	493	17	37	54	493	296	121	417
Patients with at least 1 AE	28 (8.9)	25 (15.8)	53 (11.3)	44 (8.9)	1 (5.9)	2 (5.4)	3 (5.6)	44 (8.9)	27 (9.1)	23 (19.0)	50 (12.0)
Headache	5 (1.6)	5 (3.2)	10 (2.1)	3 (0.6)	0 (0.0)	2 (5.4)	2 (3.7)	3 (0.6)	5 (1.7)	3 (2.5)	8 (1.9)
Injection site pain	4 (1.3)	5 (3.2)	9 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	5 (4.1)	9 (2.2)
Diarrhoea	2 (0.6)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.7)	0 (0.0)	2 (0.5)
Hypertension	2 (0.6)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.5)
Application site laceration	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Asthenia	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Blood pressure increased	1 (0.3)	1 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.8)	2 (0.5)
Blood pressure systolic increased	1 (0.3)	2 (1.3)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (1.7)	3 (0.7)
Cyanopsia	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Dizziness	1 (0.3)	1 (0.6)	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.3)	1 (0.8)	2 (0.5)
Epistaxis	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Fall	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.3)	0 (0.0)	1 (0.2)
Feeling abnormal	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Flushing	1 (0.3)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.3)	0 (0.0)	1 (0.2)
Hypoaesthesia	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Injection site extravasation	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Memory impairment	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Muscle spasms	1 (0.3)	1 (0.6)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.3)	1 (0.8)	2 (0.5)
Myalgia	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	1 (5.9)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Procedural headache	0 (0.0)	2 (1.3)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	2 (0.5)

Source: adsl.xpt, adae.xpt
Abbreviations: AE, adverse event; CI, cognitively impaired; CN, cognitively normal; ISS, integrated summary of safety; MBq, megabecquerel; N, number of subjects in group; n, number of subjects with adverse event

Table 47. Adverse Events by Sex (Female), Study Type, Cognitive Status, and Dosage, Safety Population, ISS

	Overall N=1921 n (%)				240 MBq N=1192 n (%)				370 MBq N=729 n (%)		
	Diagnosis Studies			Biomarker Studies	Diagnosis Studies			Biomarker Studies	Diagnosis Studies		
	CI	CN	Total	CI	CI	CN	Total	CI	CI	CN	Total
Female, N	248	117	365	592	10	43	53	592	238	74	312
Patients with at least 1 AE	41 (16.5)	11 (9.4)	52 (14.2)	41 (6.9)	0 (0.0)	2 (4.7)	2 (3.8)	41 (6.9)	41 (17.2)	9 (12.2)	50 (16.0)
Injection site pain	12 (4.8)	0 (0.0)	12 (3.3)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	12 (5.0)	0 (0.0)	12 (3.8)
Headache	8 (3.2)	2 (1.7)	10 (2.7)	1 (0.2)	0 (0.0)	1 (2.3)	1 (1.9)	1 (0.2)	8 (3.4)	1 (1.4)	9 (2.9)
Injection site extravasation	3 (1.2)	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.3)	0 (0.0)	3 (1.0)
Agitation	2 (0.8)	0 (0.0)	2 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.8)	0 (0.0)	2 (0.6)
Angina pectoris	2 (0.8)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.6)
Blood pressure increased	2 (0.8)	1 (0.9)	3 (0.8)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	2 (0.8)	1 (1.4)	3 (1.0)
Dizziness	2 (0.8)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.6)
Hypertension	2 (0.8)	1 (0.9)	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	1 (1.4)	3 (1.0)
Platelet count decreased	2 (0.8)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.6)
Acute kidney injury	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Amnesia	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Bronchial secretion retention	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Decreased appetite	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Dermatitis contact	1 (0.4)	1 (0.9)	2 (0.5)	0 (0.0)	0 (0.0)	1 (2.3)	1 (1.9)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Diarrhoea	1 (0.4)	2 (1.7)	3 (0.8)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	2 (2.7)	3 (1.0)
Dizziness postural	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Erythema	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Eye irritation	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Fatigue	1 (0.4)	1 (0.9)	2 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	1 (1.4)	2 (0.6)
Hot flush	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)

Source: adsl.xpt, adae.xpt
Abbreviations: AE, adverse event; CI, cognitively impaired; CN, cognitively normal; ISS, integrated summary of safety; MBq, megabecquerel; N, number of subjects in group; n, number of subjects with adverse event

Table 48. Adverse Events by Race (White), Study Type, Cognitive Status, and Dosage, Safety Population, ISS

	Overall N=1921 n (%)				240 MBq N=1192 n (%)				370 MBq N=729 n (%)		
	Diagnosis Studies			Biomarker Studies	Diagnosis Studies			Biomarker Studies	Diagnosis Studies		
	CI	CN	Total	CI	CI	CN	Total	CI	CI	CN	Total
White, N	512	230	742	912	26	78	104	912	486	152	638
Patients with at least 1 AE	64 (12.5)	27 (11.7)	91 (12.3)	79 (8.7)	1 (3.8)	3 (3.8)	4 (3.8)	79 (8.7)	63 (13.0)	24 (15.8)	87 (13.6)
Injection site pain	14 (2.7)	2 (0.9)	16 (2.2)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	14 (2.9)	2 (1.3)	16 (2.5)
Headache	11 (2.1)	6 (2.6)	17 (2.3)	3 (0.3)	0 (0.0)	2 (2.6)	2 (1.9)	3 (0.3)	11 (2.3)	4 (2.6)	15 (2.4)
Hypertension	4 (0.8)	1 (0.4)	5 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	1 (0.7)	5 (0.8)
Blood pressure increased	3 (0.6)	1 (0.4)	4 (0.5)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.6)	1 (0.7)	4 (0.6)
Dizziness	3 (0.6)	1 (0.4)	4 (0.5)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	3 (0.6)	1 (0.7)	4 (0.6)
Injection site extravasation	3 (0.6)	0 (0.0)	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	3 (0.5)
Agitation	2 (0.4)	1 (0.4)	3 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.4)	1 (0.7)	3 (0.5)
Diarrhoea	2 (0.4)	1 (0.4)	3 (0.4)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.4)	1 (0.7)	3 (0.5)
Muscle spasms	2 (0.4)	1 (0.4)	3 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.4)	1 (0.7)	3 (0.5)
Platelet count decreased	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Acute kidney injury	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Amnesia	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Angina pectoris	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Application site laceration	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Asthenia	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Blood pressure systolic increased	1 (0.2)	1 (0.4)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.7)	2 (0.3)
Bronchial secretion retention	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Cyanopsia	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Decreased appetite	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Dermatitis contact	1 (0.2)	1 (0.4)	2 (0.3)	1 (0.1)	0 (0.0)	1 (1.3)	1 (1.0)	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.2)
Procedural headache	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)

Source: adsl.xpt, adae.xpt
Abbreviations: AE, adverse event; CI, cognitively impaired; CN, cognitively normal; ISS, integrated summary of safety; MBq, megabecquerel; N, number of subjects in group; n, number of subjects with adverse event

Table 49. Adverse Events by Race (Non-White), Study Type, Cognitive Status, and Dosage, Safety Population, ISS

	Overall N=1921 n (%)				240 MBq N=1192 n (%)				370 MBq N=729 n (%)		
	Diagnosis Studies			Biomarker Studies	Diagnosis Studies			Biomarker Studies	Diagnosis Studies		
	CI	CN	Total	CI	CI	CN	Total	CI	CI	CN	Total
Non-White, N	49	45	94	145	1	2	3	145	48	43	91
Patients with at least 1 AE	5 (10.2)	9 (20.0)	14 (14.9)	5 (3.4)	0 (0.0)	1 (50.0)	1 (33.3)	5 (3.4)	5 (10.4)	8 (18.6)	13 (14.3)
Headache	2 (4.1)	1 (2.2)	3 (3.2)	1 (0.7)	0 (0.0)	1 (50.0)	1 (33.3)	1 (0.7)	2 (4.2)	0 (0.0)	2 (2.2)
Injection site pain	2 (4.1)	3 (6.7)	5 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.2)	3 (7.0)	5 (5.5)
Angina pectoris	1 (2.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.1)
Diarrhoea	1 (2.0)	1 (2.2)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	1 (2.3)	2 (2.2)
Injection site extravasation	1 (2.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.1)
Blood pressure increased	0 (0.0)	1 (2.2)	1 (1.1)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (2.3)	1 (1.1)
Blood pressure systolic increased	0 (0.0)	1 (2.2)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (1.1)
Fatigue	0 (0.0)	1 (2.2)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (1.1)
Insomnia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal discomfort	0 (0.0)	1 (2.2)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (1.1)
Nausea	0 (0.0)	1 (2.2)	1 (1.1)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (2.3)	1 (1.1)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Procedural headache	0 (0.0)	1 (2.2)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (1.1)
Skin exfoliation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo	0 (0.0)	1 (2.2)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (1.1)
Procedural headache	0 (0.0)	1 (2.2)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (1.1)

Source: adsl.xpt, adae.xpt
Abbreviations: AE, adverse event; CI, cognitively impaired; CN, cognitively normal; ISS, integrated summary of safety; MBq, megabecquerel; N, number of subjects in group; n, number of subjects with adverse event

17. Mechanism of Action / Drug Resistance Additional Information and Assessment

None.

18. Other Drug Development Considerations Additional Information

None.

19. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

See Section 25 (OSI Good Clinical Practice Expert).

20. Labeling Summary of Considerations and Key Additional Information

At the time of the review cycle wrap-up, over the course of three rounds of back-and-forth negotiation, the review division and the Applicant had agreed to multiple revisions of the PI submitted September 29, 2019. Discussion of major PI revisions are integrated in appropriate sections throughout this review document. For prominent examples, see cross-references listed below:

- 1 INDICATIONS AND USAGE: Sections 6.4.2, 6.4.3, 7.7.1, and 25 (Neurology Expert).
- 2 DOSAGE AND ADMINISTRATION: Sections 6.4.1 and 25 (Image Display Device Expert).
- 5 WARNINGS AND PRECUATIONS: Sections 6.3 and 6.4.2.
- 8 USE IN SPECIFIC POPULATIONS: Section 25 (Radiopharmaceutical Dosimetry Expert).
- 12 CLINICAL PHARMACOLOGY: Section 5.
- 14 CLINICAL STUDIES: Sections 6.3, 6.4.2, and 15.

21. Postmarketing Requirements and Commitments

None.

22. Financial Disclosure

Table 50. Covered Clinical Studies

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3309 independent investigators (291 principal investigators and 3018 subinvestigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): Five		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

23. References

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Guidances for Industry

Guidance for Industry *Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations* (August 2018)

Guidance for Industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010)

Guidance for Industry *Developing Medical Imaging Drug and Biological Products, Part 3: Design, Analysis, and Interpretation of Clinical Studies* (June 2004)

Draft Guidance for Industry *How to Comply with the Pediatric Research Equity Act* (September 2005)

24. Review Team

Table 51. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Lisa Skarupa
Nonclinical Reviewer	Jonathan Cohen, Ph.D.
Nonclinical Team Leader	Adebayo Laniyonu, Ph.D.
Office of Clinical Pharmacology Reviewer(s)	Christy John, PhD
Office of Clinical Pharmacology Team Leader(s)	Christy John, PhD
Clinical Reviewer	Venkata S. Mattay, MD
Clinical Team Leader	Anthony Fotenos, MD, PhD
Statistical Reviewer, Primary	Tristan Massie, PhD
Statistical Reviewer, Secondary	Jyoti Zalkikar, PhD
Statistical Team Leader	Sue-Jane Wang, PhD
Cross-Disciplinary Team Leader	Anthony Fotenos, MD, PhD
Division Director (OCP)	Nam Atiqur Rahman, PhD
Division Director (OB)	Sue-Jane Wang, PhD
Division Director (DMIP)	Libero Marzella, MD, PhD
Office Director (designated signatory authority)	Charles Ganley, MD

Table 52. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Drug Substance: Shomo Mitra, PhD / Martin Haber, PhD
	Drug Product: Elise Luong, PhD / Danae Christodoulou, PhD
	Facilities: Laurie Nelson, PhD / Krishna Ghosh, PhD
	Microbiology: Avital Shimanovich, PhD / Erika Pfeiler, PhD
	Technical Lead: Eldon Leutzinger, PhD
	Sr. Regulatory Business Process Manager: Anika Lalmansingh, PhD
OPDP	LCDR David Foss, PharmD, LCDR Jim Dvorsky, PharmD
OSI	John Lee, MD / Phillip Kronstein, MD / Kassa Ayalew, MD, MPH Division of Clinical Compliance Evaluation, Good Clinical Practice Assessment Branch
OSE RPM	Tri Bui Nguyen, PhD
OSE/DMEPA	Sarah Vee, PharmD / Devin Kane / Hina Mehta, PharmD
DPMH	Christos Mastroyannis, MD / Tamara Johnson, MD, MS / Lynne P. Yao, MD
DN1	Ranjit Mani, MD / Eric Bastings, MD
DCRP	Christine Garnett, PharmD, Nan Zheng, PhD
CDRH	User Guide: Lora Deuitch, PhD / Julie Sullivan, PhD / Michael O'Hara
DCP	Eric Brodsky, MD, Associate Director of Labeling Policy Team

OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
CDRH = Center for Devices and Radiological Health
DCP = Division of Clinical Policy
DCRP = Division of Cardiology and Renal Products
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatric and Maternal Health
DN1 = Division of Neurology 1

25. Expert Reviews

Cardiac Safety Expert Review

APPEARS THIS WAY ON ORIGINAL

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 18, 2019

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products / CDER

To: Lisa Skarupa, RPM
DMIP

Subject: QT-IRT Consult to NDA 212123 (SDN 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 10/30/2019 regarding the Division's QT related findings. The QT-IRT reviewed the following materials:

- Sponsor's clinical overview, safety summary, and summary of clinical pharmacology (Submission 0001);
- Proposed label (Submission 0001); and
- Highlights of clinical pharmacology and cardiac safety (Submission 0010).

1 QT-IRT Responses

Question from the Division: F18-Flortaucipir was designed to image aggregated tau neurofibrillary tangles of Alzheimer's disease. Sponsor reports small but statistically significant increases in QTcB and QTcF intervals around two hours following intravenous administration of F18-Flortaucipir when compared to baseline pre-dose measurements. We request your advice from the perspective of safety, drug-drug interactions and exclusionary criteria to be included in the label.

Response: We do not propose QT-related labeling language for the small increases in QTcF observed in the safety database. Our recommendation is based on totality of evidence in the submission:

1) The in vitro hERG study provided a large exposure margin considering the low amount dosed for a single use regimen.
2) The safety ECG data were not designed to quantify drug effect on the QT/QTc interval. Without a proper placebo control, it is not known if the small increases in QTcF from baseline at the end of scanning is related to drug treatment or other physiological factors (e.g., autonomic responses to the imaging process, subject handling before ECG measurement, etc.).
3) There are no subjects with marked QT increases (i.e., QTcF interval > 500 msec or an increase of 60 msec or greater above predose values).
4) There are no reports of cardiac safety events as specified in Section IV of E14 guidance in the pooled safety dataset.

2 BACKGROUND

2.1 Product Information

Flortaucipir F18 (18F-AV-1451, [F-18]T807, [18F]T807, LY3191748; MW: 262.27 g/mol; proposed proprietary name: Tauvid) is an 18F-labeled diagnostic positron emission tomography (PET) radiopharmaceutical that was designed to image aggregated tau neurofibrillary tangles (NFTs) (b) (4) in the brains of patients with cognitive impairment being evaluated for AD (b) (4) The maximum mass dose is a single dose of 20 µg.

2.2 Sponsor's position related to the question

Not applicable.

2.3 Nonclinical Cardiac Safety

AV-1451 was positive in the hERG assay, with an IC50 of 0.610 µM. However, cardiovascular safety testing in dogs did not reveal any AV-1451-induced adverse effects up to 100x and 50x MHD (allometrically scaled) on Days 1 and 29 of testing, respectively. No compound-related changes in QTc occurred in either gender at any timepoint.

Reviewer's Comment: *Assuming a full 20 µg dose is administered, the maximum theoretical flortaucipir peak plasma concentration is 3.8 ng/mL based on an assumed distribution restricted to blood volume (about 5.2 L in an adult human). Assuming a fraction unbound of 5.3%, the ratio between hERG IC50 and free Cmax (0.724 nM) is approximately 794-fold.*

2.4 Clinical Cardiac Safety

19 clinical trials (13 diagnostic studies, 6 biomarker studies) – 4 studies had ECG monitoring pre- and post-dose.

2085 enrolled subjects; 2013 with a least 1 dose of flortaucipir (921 from diagnostic studies; 1092 from biomarker studies); 774 had ECGs taken immediately post-dose and 785 had ECGs taken at end of scan.

No cardiac safety events as specified in Section IV of E14 guidance were observed in the pooled safety database. No QTcF changes from baseline greater than 60 msec or QTcF > 500 ms were observed in any patients for whom QT interval data were available.

2.5 Summary results of prior QTc assessments

The sponsor has not conducted any formal QT assessment.

In the diagnostic studies, singlet electrocardiogram measurements were conducted prior to flortaucipir dose, immediately post-dose (0 to 5 minutes post-infusion), and at the end of scan (approximately 90 to 120 minutes post-infusion). In the pooled safety analysis, there were small, statistically significant increases in QTcB and QTcF at the end of scan time point at each imaging visit that were not considered to be clinically significant. The mean change from predose in QT interval duration (Fredericia correction method; QTcF) of 5.14 msec (± 12.09 msec; SD) at approximately 90 to 120 minutes post-infusion was observed for 785 measurements. While the absence of placebo- or active compound comparator groups limits interpretation of these findings, it is noted that the mean 5.14 msec increase in QTcF approximates the regulatory threshold of concern (5 msec); however, the upper limit of the 90% confidence interval [equivalent to a one-sided 95% confidence interval] was 5.85 msec, which is well below the 10 msec threshold of concern. No study subjects demonstrated a QTcF interval > 500 msec or an increase of 60 msec or greater above predose values. Scatterplots of QTcF change from pre-dose values vs. flortaucipir mass dose failed to demonstrate statistically significant correlations at either the immediate post-dose or end of scan timepoints.

Some patients with a history of cardiac rhythm disturbances and/or concomitant QT-influencing medications appeared in the safety analysis population. No clinically significant differences in mean change from predose for QTcF were identified for subjects with a history of cardiac rhythm disturbance when compared to subjects without such a history, nor were any significant differences observed when subjects receiving concomitant medications known to influence QT interval duration were compared with subjects not receiving such medications. The small numbers of scans for these comparisons (n=30 for history of rhythm disturbance and n=20 for subjects with concomitant QT-influencing medications) limits the statistical power of any comparisons.

Refer to safety summary (Section 2.7.4.4.2) for tabulated summary of ECG findings.

Reviewer's comments: *These safety ECG data do not appear to have adequate quality to support an evaluation of the QT prolongation risks with the flortaucipir F18 treatment. While the sampling schedule included Tmax of the parent drug (i.e., end of IV administration), it is not known whether the Tmax of the major metabolites were covered. In addition, it is not known how these ECG intervals were measured and analyzed (i.e. methods of reading, blinding of the ECG reader to treatment).*

2.6 Relevant details of planned Phase 3 study

Not applicable.

Reviewer's comments:

- *The Tmax of Flortaucipir F18 is immediately at the end of the infusion. According to the summary of clinical pharmacology, flortaucipir was gradually metabolized, with parent flortaucipir accounting for ~86% of plasma radioactivity at 5 min post-dose, ~34% at 80 min post-dose, and ~22% at 130 minutes post-dose. 2 metabolites were detected in*

HPLC/methanol soluble fraction accounted for 30% to 35% of plasma radioactivity ≥80 min post-dose. Mass-based concentration data were not available.

- *Radioactivity in plasma was 0.0024 (0.00078) at 5 min post-dose, 0.0013 (0.00076) at 15 min post-dose, and remained a similar level until ~130 min post-dose (the last sampling time point).*
- *Available data appear to suggest the formation of major metabolites. We defer the need for further characterization of the metabolites to the review division.*

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

3 Appendix. IRT's Highlights of Clinical Pharmacology and Cardiac Safety (with edits)

Therapeutic dose and exposure	Recommended radioactive dose: 370 MBq (10 mCi). Injection volume and regimen: up to 10 mL by single intravenous bolus injection. Maximum mass dose: 20 µg Mean Cmax and AUC for a single maximum dose have not been calculated as the product is administered as a microdose. Blood/plasma bioanalytical assays to detect flortaucipir concentrations have not been developed. Mean Cmax and AUC at the steady state are not applicable. Product is intended as a single intravenous dose. Assuming a full 20 µg dose is administered, the maximum theoretical flortaucipir peak plasma concentration is 3.8 ng/mL based on an assumed distribution restricted to blood volume (about 5.2 L in an adult human) and assuming that 100% of the drug is unbound.	
Maximum tolerated dose	Not studied in humans. The NOAEL in rat is > 100 µg/kg (50x MHD, allometrically scaled); the NOAEL in dog is 30 µg/kg (50x MHD, allometrically scaled)	
Principal AE	The most common reported adverse reactions were headache (1.3%), injection site pain (1.2%), and blood pressure increased (0.7%). There are no dose-limiting adverse events.	
Maximum dose tested and exposures achieved	Single Dose	The maximum mass dose recorded in the clinical database was calculated to be 13.7 µg. The maximum theoretical peak plasma concentration is 2.6 ng/mL based on an assumed distribution restricted to blood volume (about 5.2 L in an adult human) and assuming that 100% of the drug is unbound.
	Multiple Dose	Not applicable.
Range of linear PK: Unknown		
Accumulation at steady state: Not applicable.		
Metabolites	A human mass balance study including quantitation and identification of metabolites was not conducted. However, based on radio-profiling via HPLC, in addition to the parent, 2 metabolite peaks were detected in the HPLC/methanol soluble fraction. The activity of these in vitro and in vivo metabolites is unknown.	
Absorption	Bioavailability	Intravenous injection is 100% bioavailable.
	Tmax	Maximum plasma concentration is at end of the single IV bolus infusion.
Distribution	Vd/F or Vd	Unknown. Assumed to be whole blood volume.
	% bound	In vitro, plasma protein binding is 94.7% (0.2% SD)
Elimination	Route	A human mass balance study was not conducted for flortaucipir. Primary route: hepatobiliary from radiotracer biodistribution studies. Other route: urinary
	Terminal t½	Incalculable due to very low blood radioactivity. Plasma total radioactivity (including parent and all its metabolites) fell below 10% of the theoretical maximum concentration by 5 mins post-dose. t½ of the metabolites is unknown
	CL/F or CL	Unknown. Parent flortaucipir accounted for approximately 86% of plasma radioactivity at 5 minutes postdose, approximately 34% at 80 minutes post-dose, and approximately 22% at 130 minutes postdose.
Intrinsic Factors: The effect of age, sex, race, and organ impairment on drug exposure has not been studied.		
Extrinsic Factors	Drug interactions	No clinical DDI studies were conducted. In vitro, flortaucipir F19 (the non-radioactive form of flortaucipir F18) did not cause clinically relevant inhibition of the activity of several cytochrome P450 enzymes (CYPs 3A, 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6) or the transporter P-glycoprotein (Pgp). In vitro, flortaucipir F19 is a substrate of CYP1A2 (primarily) and CYP2D6 (minor contribution). However, in vitro studies suggest CYPs play a minor role in the overall clearance of flortaucipir compared to other clearance routes such as aldehyde oxidase. Therefore, inhibitors of CYP1A2 and 2D6 are unlikely to cause clinically meaningful changes in the PK of flortaucipir F18.
	Food Effect	Not studied.

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Expert Reviews (cont'd)

Drug Promotion Expert Review

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 12, 2020

To: Venkata Mattay, M.D.
Division of Medical Imaging and Radiation Medicine (DMIRM)

Lisa Skarupa, Regulatory Project Manager, DMIRM

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TAUVID™ (Flortaucipir F 18 injection), for intravenous use

NDA: 212123

In response to DMIRM consult request dated December 3, 2019, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for Tauvid.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMIRM on March 10, 2020, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 30, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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Expert Reviews (cont'd)

Good Clinical Practice Expert Review

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Clinical Inspection Summary

Date	April 15, 2020
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Lisa Skarupa, Regulatory Project Manager Anand Mattay, M.D., Medical Officer Anthony Fotenos, M.D., Clinical Team Leader Division of Medical Imaging Products (DMIP)
Application	NDA 212123
Applicant	Avid Radiopharmaceuticals, Inc.
Drug	Flortaucipir F 18 Injection
NME / Original NDA	Yes
Review Status	Priority
Proposed Indication	For use with brain PET to evaluate Alzheimer's disease
Consultation Date	December 31, 2019
CIS Goal Date	March 30, 2020 (original); April 20, 2020 (extended)
Action Goal Date	May 29, 2020
PDUFA Due Date	May 29, 2020

I. OVERALL ASSESSMENT OF INSPECTIONAL FINDINGS AND RECOMMENDATIONS

Studies 18F-AV-1451-A05 and 18F-AV-1451-A16 were audited at good clinical practice (**GCP**) inspections of two contract research organization (**CRO**) sites (one site per study). The two studies supported the utility of Flortaucipir (18F-AV-1451, Flortaucipir F 18, Tauvid®) as a new molecular entity (**NME**) injectable imaging agent for use with positron emission tomography (**PET**) in evaluating Alzheimer's disease (**AD**).

No significant GCP deficiencies were observed for either study. For both CRO sites, study conduct appeared GCP-compliant. All audited data were adequately verifiable against source records and case report forms (**CRFs**). The study data audited at inspection appear reliable as reported in the NDA.

II. BACKGROUND

AD is the most common cause of dementia in the elderly, affecting > 4 million seniors in the United States. Mild cognitive impairment (**MCI**) is an intermediate stage between dementia and normal cognitive decline of aging, which appears to increase AD risk. Most cases of AD are sporadic but rare mutations are inherited (autosomal dominant). The diagnosis of AD during life often proves incorrect at autopsy.

The aggregated tau neurofibrillary tangles (**at-NFTs**) appear to be important for the pathogenesis of AD, and potentially also for its diagnosis using Flortaucipir, a biomarker for at-NFTs. (b) (4) (b) (4)

This NDA is supported by four major studies, of which the following two were identified for on-site data audit. No clinical investigator (**CI**) sites were identified for inspection.

Study 18F-AV-1451-A05: *An Open-Label, Multicenter Study, Evaluating the Safety and Imaging Characteristics of 18F-AV-1451 in Cognitively Healthy Volunteers, Subjects with Mild Cognitive Impairment, and Subjects with Alzheimer's Disease*

This Phase 2/3, open-label, single-arm observational study was conducted between 2013 and 2017 in 382 adult subjects (safety analysis set) at 29 CI sites in the United States (**US**). The study was conducted as two separate sequential sub-studies (different subjects), exploratory (Phase 2, 222 subjects) and confirmatory (Phase 3, 160 subjects).

- The major exploratory objectives were to compare the flortaucipir imaging results across AD, MCI, or normal subjects, and to measure the rate of tau deposition (flortaucipir uptake) in these subjects over 18 months.

- The primary confirmatory objective was to establish a relationship between flortaucipir uptake on PET and subsequent cognitive decline over 18 months. Image interpretation in (confirmatory sub-study) was blinded to all subject data, including cognitive data.

The exploratory sub-study enrolled subjects of age ≥ 50 years determined to have either MCI (based on scores ≥ 24-28 in the questionnaire instrument *Mini-Mental State Examination*, **MMSE**) or dementia (MMSE score >10-23, possible/probable AD), as well as healthy normal volunteers of age ≥ 20-39 years or ≥ 50 years (MMSE score ≥ 29). The confirmatory sub-study enrolled only those subjects with MCI or dementia with a suspected neurodegenerative cause (MMSE ≥ score 20-27).

Florbetapir is an approved agent similar to flortaucipir but with different performance characteristics for diagnosing AD by PET. Both sub-studies included PET also using florbetapir to explore the relationship between the imaging results obtained with florbetapir and (versus) flortaucipir. The two agents were each administered (370 MBq, 10 mCi) at baseline to all subjects as a single intravenous (**IV**) bolus injection (paired PET, ≥ 48 hours apart). In the exploratory sub-study, flortaucipir (alone) was administered also at 9 and 18 months only for subjects of age ≥ 50 years.

Flortaucipir PET scans were interpreted by five independent nuclear medicine or radiology physicians as either inconsistent with AD (**τAD-**) or consistent with AD (**τAD+** / **τAD++**) according to established diagnostic criteria as specified in *PET Imaging Manual*. A single external nuclear medicine physician interpreted the florbetapir PET scans as either positive (**Aβ+**) or negative (**Aβ-**) in accordance with the current diagnostic criteria. The primary analysis variable for the overall study was the correlation between florbetapir PET results (majority read of 5 readers, τAD++ versus τAD+ or τAD-) and the change in score from baseline in *Clinical Dementia Rating Scale, Sum of Boxes* (**CDR-SB**).

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

This Phase 3, open-label, single-arm observational study was conducted between 2015 and 2018 in 156 adult subjects (safety analysis set) at 28 CI sites in US and Australia. The primary study objective was to examine the correlation between ante-mortem flortaucipir PET and post-mortem at-NFTs (autopsy). All subjects were terminally ill and consented to brain donation: 103 dementia, 3 MCI, and 50 cognitively normal.

All subjects received a single IV bolus of flortaucipir (370 MBq, 10 mCi) at the start of the PET imaging visit. If death did not occur within 9 months, a second flortaucipir-PET could be performed. Image and pathology interpretations were (partially) blinded to each other and to subject identity (including cognitive status). The primary analysis variable was the overall diagnostic performance (sensitivity and specificity) of the consensus PET interpretation (≥ 3 of 5 readers), using at-NFT histopathology as the truth standard (**TS**).

III. INSPECTION RESULTS

1 (b) (4)

Inspection Dates: (b) (4)

Study 18F-AV-1451-A05: This CRO performed many key functions for Study A05, including study coordination and oversight, database management, data compilation and analysis, and internal audit. The CRO inspection consisted of general records review (contract with sponsor, study protocol, and center SOP manuals). No source records or eCRFs were available at this CRO site for NDA data verification.

No significant deficiencies were observed. The database interface and system controls appeared robust, including special controls to prevent errors in image receipt/retrieval, data entry/modification, and internal audit trail. Software validation, adherence to SOP, and recordkeeping appeared rigorous. Study conduct at this CRO site appeared GCP-compliant overall, including sponsor oversight.

Note: The Establishment Inspection Report (**EIR**) for this inspection has not been received from the field office and the results reported in this Clinical Inspection Summary (**CIS**) are based on preliminary communication with the field investigator. Upon receipt and review of the EIR at OSI, an addendum to this CIS will be forwarded to the review division if new significant findings are discovered; otherwise, OSI's written post-inspection correspondence letter to the inspected entity (to be copied to review division) indicates completion of EIR review with confirmation of the findings as reported in this CIS.

2. Banner Sun Health Research Institute

Thomas G. Beach, M.D.
10515 West Santa Fe Drive
Sun City, AZ 85351

Inspection Dates: March 16-19, 2020

Study 18F-AV-1451-A16: This CRO site generated the histopathology data which served as the reference against which the interpreted PET imaging data were evaluated to determine the performance characteristics (sensitivity and specificity) of flortaucipir-PET in diagnosing/tracking AD. Brains of 69 subjects (of 156 enrolled in study) were received at this laboratory site, of which 67 were examined for pathology (gross and microscopic).

The CRO inspection consisted of general records review (contract with sponsor, study protocol, and center SOP manuals) and NDA data verification. Case records were reviewed in detail for 40 subjects, selected to include 1-2 subjects from each contributing

CI site (otherwise random). The following NDA (pathology) data were verified against on-site source records and CRFs:

- Listing 16.2-8.3.1, *Consensus Panel B Scores*
- Listing 16.2-8.3.2, *Consensus Panel Summary Scores*
- Listing 16.2-8.3.3, *Consensus Panel Autopsy NFT Score*

No significant deficiencies were observed. Study conduct appeared GCP-compliant overall, including sponsor oversight. All audited NDA data were adequately verifiable against source records and CRFs.

Note for this CIS

The original OSI Consult (*Request for GCP Inspections*) had identified four CRO inspections, the two reported above and additionally:

- (b) (4) which performed the major study tasks for Study 18F-AV-1451-A05 related to image interpretation, including reader training, image randomization, reader oversight, database access management, and internal audit. All source records for image interpretation were available at this site.
- (b) (4) which performed the major study tasks related to image interpretation in Study A16, including reader training, image randomization, reader oversight, database access management, and internal audit. All source records for image interpretation in Study 18F-AV-1451-A16 were available at this CRO site.

The COVID-19 global pandemic has significantly limited OSI's ability to conduct on-site GCP inspections. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for the two above CRO inspections (b) (4) were reevaluated. Following discussions between OSI and OND, a decision was made that assessment of the application could proceed without the two CRO GCP inspections.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Phillip D. Kronstein, M.D.
Team Leader
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Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

CC:

Central Document Room / NDA 212123

DMIP / Clinical Team Leader / Anthony Fotenos
DMIP / Medical Officer / Anand Mattay
DMIP / Regulatory Project Manager / Lisa Skarupa

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OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters

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Expert Reviews (cont'd)

Image Display Device Expert Review

APPEARS THIS WAY ON ORIGINAL

Consulting Review Memo

To: Anthony Fotenos, M.D.
Lead Medical Officer, CDER/OND/ORO/OSM/DMIRM

From: Lora Deuitch, Ph.D.
Scientific Reviewer, CDRH/OPEQ/OHT7/DRH/NMRT

Through: Julie Sullivan, Ph.D.
Acting Assistant Director, CDRH/OPEQ/OHT7/DRH/NMRT

and Michael O'Hara, Ph.D.
Deputy Division Director, CDRH/OPEQ/OHT7/DRH

Date: May 1st, 2020

Subject: NDA 212123 – [^{18}F]Flortaucipir (TAUVID) – Avid Pharmaceuticals Inc.

Summary:
Avid Pharmaceuticals seeks to introduce the PET radiotracer [^{18}F]Flortaucipir (Tauvid) into interstate commerce. [^{18}F]Flortaucipir is a radioactive diagnostic agent for neurofibrillary tangles in Alzheimer's disease. The post-image analysis of [^{18}F]Flortaucipir is detailed, and the instructions included in the prescription label were unclear. Specifically, it was unclear if the instructions were applicable to only one type of PACS system, thus limiting the accessibility of the radiotracer to clinics with different PACS systems. Therefore, CDER sought input from CDRH/DRH on the applicability of the instructions across different nuclear medicine PACS systems. DRH found the instructions to be unclear and expressed doubts as to whether the instructions could be executed by users. Therefore, CDER and DRH requested the sponsor to develop user guides for the most widely-used nuclear medicine PACS systems, for the purpose of guiding image readers through the image set-up process. The sponsor provided user guides for (b) (4) software, and stated that they would continue to release new user guides depending on demand. DRH finds the information in the user guides adequate for image preparation.

Proposed Indications and Usage:
TAUVID™ is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles (b) (4) in adult patients who are being evaluated for AD (b) (4)

Drug Description/Application:
The ability to image and estimate the density and distribution of neurofibrillary tangles (NFTs), one of the two pathological hallmarks of AD, has significant implications in the diagnosis and management of patients afflicted with or

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Lora Deuitch, DRH/NMRT
May 1, 2020

Expert Reviews (cont'd)

Maternal Health Expert Review

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health PLLR Memorandum

Date: February19, 2020 **Date Consulted:** December 3, 2019

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne Yao, MD, Director, DPMH

To: Division of Medical Imaging Products (DMIP)

Drug: Tauvid (Flortaucipir [F18] Injection for Intravenous Use)

NDA: 212123

Applicant: Avid Radiopharmaceuticals Inc (a wholly owned subsidiary of Eli Lilly and Company)

Subject: Pregnancy and Lactation Labeling

Proposed Indication: For Positron Emission Tomography (PET) imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles (b) (4) in adult patients who are being evaluated for AD (b) (4)

Materials Reviewed:

- Original application, NDA 212123, submitted September 30, 2019
- Applicant's proposed labeling for Tauvid, submitted September 30, 2019
- DMIP's consult request to DPMH for Tauvid Flortaucipir [F18] Injection for Intravenous Use, in DARRTS December 3, 2019, Reference ID: 4528140

Consult Question: "Please evaluate the proposed labeling for compliance with the Pregnancy and Lactation Labeling Rule (PLLR) requirements and any additional labeling recommendations from the Maternal Health Team to ensure the safe use of Flortaucipir [F18] Injection for Intravenous Use in patients of childbearing potential."

INTRODUCTION AND BACKGROUND

On September 30, 2019, the applicant submitted the original NDA 212123 for Tauvid (Flortaucipir [F18] Injection), a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles (b) (4) in adult patients who are being evaluated for AD (b) (4) With this submission, the applicant provided labeling to comply with PLLR. The Division of Medical Imaging Products (DMIP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide recommendations on the content and format for the *Pregnancy* and *Lactation* subsections of Tauvid as per PLLR.

Tauvid Drug Characteristics[1]

- Established Pharmaceutical Class: Radioactive Diagnostic Agent for Positron Emission Tomography
- Mechanism of Action: Flortaucipir F 18 binds to aggregated tau protein. In brains of patients with AD, tau (b) (4)
- Molecular weight of 262.27 Daltons
- The solution is supplied ready to use and each milliliter contains up to 2.0 micrograms of Flortaucipir and 300-1900 MBq (8.1-51 mCi)
- Half-life of 109.77 minutes.
- Flortaucipir [F18] is not genotoxic. It increases the percent of cells with structural aberrations

Diagnostic Imaging During Pregnancy and Lactation[2]

In a recent DPMH PLLR review for another radiopharmaceutical, Jeanine Best, RN, PNP, reviewed and evaluated the published literature for use of radiopharmaceuticals during pregnancy and lactation. She states that:

- The International Radiation Protection Association (IRPA considers that pregnancy is not a reason to withhold necessary imaging procedures in pregnant women as most of the commonly used radiopharmaceuticals (I 131 is an exception) result in low fetal radiation doses and pose little risk to the fetus or later in childhood. The benefits of nuclear imaging procedures in a pregnant woman usually outweigh the minimal risks associated with small amounts of radiation exposure to the fetus. Radiation risk is most significant during organogenesis and early fetal period, less in the 2nd trimester, and least in the 3rd trimester. Malformations have a threshold at 100-200 mGy and are typically CNS-related.
- The American College of Obstetricians and Gynecologists (ACOG) states that: Imaging procedures should be used prudently and only when use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient. If these techniques are necessary for a diagnosis in question, they should not be withheld from a pregnant woman.

[1] Refer to proposed labeling for Tauvid (Flortaucipir [F18] Injection)

[2] Jeanine Best RN, PNP Labeling Review of Fluoroestradiol F 18 injection, in DARRTS, dated December 16, 2019, Reference ID: 4534583

- Most radiopharmaceuticals are present in breastmilk; therefore, unless there are data that demonstrate otherwise, some radioactive compound will be measured in breastmilk after administration of a radiopharmaceutical. Breastfeeding should be interrupted until the radiopharmaceutical is no longer found in breastmilk in an amount estimated to limit an effective dose of 1 mSv to the breastfed infant/child. It is reasonable to delay resumption of breastfeeding for 10 half-lives of the radionuclide, a period of time that is usually sufficient to reduce the infant dose through breastmilk to acceptable levels.

Alzheimer's Disease

Alzheimer disease (AD) is the most common cause of dementia and one of the leading sources of morbidity and mortality in the aging population. The main neuropathologic changes of AD are diffuse and neuritic plaques, marked by extracellular amyloid beta deposition, and neurofibrillary tangles, comprised of the intracellular accumulation of hyperphosphorylated tau (p-tau) protein.[3] The neuropathologic assessment of AD includes both evaluation of neuropathologic changes and correlation with clinical, neuropsychologic, neuroimaging, and other laboratory data.[4,5] Essential neuropathologic changes of AD include the following:

- Neuritic plaques, associated with neuronal injury and characterized by amyloid formed from amyloid beta plus dystrophic neurites that frequently have phospho-tau immunoreactivity[6,7,8]
- Extracellular deposits of amyloid beta peptides
- Neurofibrillary degeneration, best exemplified by neurofibrillary tangles.

AD is increasingly prevalent with advancing age.[9] In the United States in 2011, there were an estimated 4.5 million individuals over the age of 65 years living with clinical AD; this included 0.7 million people age 65 to 74 years, 2.3 million age 75 to 84, and 1.8 million 85 years and older.[10]

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[4] Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Trojanowski JQ, Vinters HV, Hyman BT, National Institute on Aging, Alzheimer's Association: National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol. 2012 Jan;123(1):1-11.

[5] 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

[6] Masliah E, Terry RD, Mallory M, Alford M, Hansen LA: Diffuse plaques do not accentuate synapse loss in Alzheimer's disease. Am J Pathol. 1990;137(6):1293

[7] Masliah E, Mallory M, Deerinck T, DeTeresa R, Lamont S, Miller A, Terry RD, Carragher B, Ellisman M: Re-evaluation of the structural organization of neuritic plaques in Alzheimer's disease. J Neuropathol Exp Neurol. 1993 Nov;52(6):619-32.

[8] Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R: Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991 Oct;30(4):572-80.

[9] Rocca WA, Petersen RC, Knopman DS, Hebert LE, Evans DA, Hall KS, Gao S, Unverzagt FW, Langa KM, Larson EB, White LR: Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. Alzheimers Dement. 2011;7(1):80.

[10] Hebert LE, Weuve J, Scherr PA, Evans DA: Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology. 2013 May;80(19):1778-83.

Families displaying autosomal dominant inheritance of the disorder, develop symptoms of AD between the ages of 30 and 60 years. Most, but not all, families with early-onset AD show an autosomal dominant pattern of inheritance.[4]

The Alzheimer's Association reports from the International Conference 2018 in Chicago[11], on sex differences associated with dementia and Alzheimer's disease across the life course, including a large-scale study of reproductive history and dementia risk in women. New results reported at AAIC 2018 suggest:

- No associations between dementia risk and number of children, number of miscarriages, age at first menstrual period, and reproductive period (years between first menstrual period and menopause).
- In a separate study, no correlation between cumulative months of pregnancy and Alzheimer's risk.
- The long held thought that hormone therapy negatively affects cognition is challenged.
- A need for sex-based standards for cognitive assessments, to improve early detection in women.

"More women than men have Alzheimer's disease or other dementias; almost two-thirds of Americans with Alzheimer's are women," said Maria Carrillo, PhD, Alzheimer's Association Chief Science Officer. According to Alzheimer's Association 2018 Alzheimer's Disease Facts and Figures, of the 5.5 million people age 65 or older with Alzheimer's in the United States, 3.4 million are women and 2.0 million are men.

In the literature, there are no pregnancies reported in women with AD.

REVIEW

PREGNANCY

Applicant's Review

Nonclinical Data

No reproductive and developmental toxicity or carcinogenicity evaluations were conducted. The Applicant received a waiver from the FDA for conducting these studies because women of reproductive age are generally not in the age range for clinical expression of AD. In general animal toxicity studies, daily intravenous injection of flortaucipir [F18] for at least 1 month was well-tolerated in rats at dose levels up to 100 μg/kg and in dogs at dose levels up to 30 μg/kg. In female dogs at 30 μg/kg, increased heart rate was observed. Clinical significance for humans at the proposed maximum recommended human dose (MRHD) is undetermined. Thus, the NOAEL in rat is considered to be greater than 100 μg/kg (50x MHD); the NOAEL in dogs is considered to be 30 μg/kg (50x MRHD).

Human Data

No human data exist. The drug has not been used in pregnant women and no pregnancies have been reported during the drug development program.

Pharmacovigilance Review

The Applicant does not report any pregnancies during the drug development program in clinical trials.

Drug Utilization

This is a new drug product that has not been approved yet. Therefore, there is no drug utilization to be reported.

[11] Alzheimer's Association AAIC Press Office, July 23, 2018

DPMH Review
DPMH searched PubMed, EMBASE, Micromedex. No relative information was identified. GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk does not have an entry.

Summary
There are no data of use of Tauvid in pregnant women. Therefore, the data are insufficient to determine a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes.

LACTATION
Non clinical Data
The Applicant did not conduct any lactation studies in animals

Human Data
Neither the applicant nor this reviewer identified any published literature regarding use of flortaucipir [F18] during lactation. From the Applicant's pharmacovigilance, there are no cases of women who were exposed to the drug during lactation. No clinical lactation studies were conducted.

GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk and Thomas Hale in Medications &Mothers' Milk do not have an entry for flortaucipir [F18].

Summary
No information exists regarding the presence of flortaucipir [F18] in human milk, the effects of flortaucipir [F18] on the breastfed infant, or the effects of flortaucipir [F18] on milk production. As stated above, most radiopharmaceuticals are present in breastmilk. It is reasonable to delay resumption of breastfeeding for 10 half-lives of the radionuclide, a period of time that is usually sufficient to reduce the infant dose through breastmilk to acceptable levels; therefore, women should not breastfeed for 24 hours (>10 half-lives of radioactive decay for the F18 isotope) following administration of Tauvid.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
No information exists on the effects of flortaucipir [F18] in females and males of reproductive potential (fertility) in the published literature, GG Briggs and RK Freeman or Reprotox. In addition, there is no data to support recommendations for pregnancy testing or contraception use. (b) (4)

LABELING RECOMMENDATIONS
DPMH revised subsections 8.1, 8.2. (b) (4) and section 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

Tauvid (flortaucipir [F18] Injection for Intravenous Use) labeling was structured to be consistent with the PLLR as follows:

- Pregnancy, Subsection 8.1

Formatted to include: *"Risk Summary"*, heading.

- Lactation, Subsection 8.2

Formatted to include: *"Risk Summary"* heading.

(b) (4)

- Patient Counseling Information, Section 17

Updated to correspond with changes made to section 8.1 and 8.2 of the labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

DOSAGE AND ADMINISTRATION

- It is recommended to assess pregnancy status before administering Tauvid to a female of reproductive potential

----------USE IN SPECIFIC POPULATIONS----------

• **Lactation**: Interrupt breastfeeding. A lactating woman should pump and discard breast milk for 24 hours after TAUVID administration. (8.2).

FULL PRESCRIBING INFORMATION: CONTENTS

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

2.2 Recommended Dosing and Administration Instructions

Administration

- It is recommended to assess pregnancy status before administering Tauvid to a female of reproductive potential

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TAUVID is not likely to be used in females of reproductive age. There are no available data on Tauvid use in pregnant women. No animal reproduction studies have been conducted with flortaucipir [F18]. All radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of radiation dose. Advise a pregnant woman of the potential risks of fetal exposure to radiation doses with administration of Tauvid.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

There is no information on the presence of flortaucipir [F18] in human milk, the effects on the breastfed infant, or the effects on milk production. Advise a lactating woman that like with all radiopharmaceuticals used for imaging purposes, when she uses TAUVID during breastfeeding, she should interrupt breastfeeding and pump and discard breastmilk for 24 hours (>10 half-lives of radioactive decay after TAUVID (flortaucipir [F18]) administration in order to minimize radiation exposure to a breastfed infant.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise a pregnant woman of the potential risks of fetal exposure to radiation doses with TAUVID *[see Use in Specific Populations (8.1)]*.

Lactation

Advise a lactating woman to interrupt breastfeeding and pump and discard breastmilk for 24 hours after TAUVID administration in order to minimize radiation exposure to a breastfed infant. *[see Use in Specific Populations (8.2)]*.

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/s/

CHRISTOS MASTROYANNIS
02/20/2020 08:30:27 PM

TAMARA N JOHNSON
02/21/2020 10:29:43 AM

LYNNE P YAO
02/21/2020 02:56:28 PM

Expert Reviews (cont'd)

Medication Error Expert Reviews

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 6, 2020
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	NDA 212123
Product Name and Strength:	Tauvid (flortaucipir F-18) injection, 300 MBq/mL – 1,900 MBq/mL (8.1 mCi/mL – 51 mCi/mL)
Applicant/Sponsor Name:	Avid Radiopharmaceuticals, Inc.
OSE RCM #:	2019-2103-2
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Avid submitted revised container labels and carton labeling received on April 29, 2020 for Tauvid NDA 212123. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] We reviewed the revised container and shield carton labeling for Tauvid (Appendix A) to determine if it is acceptable from a medication error perspective.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Kane D. Label and Labeling Review for Tauvid (NDA 212123). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 15. RCM No.: 2019-2103-1.

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/s/

DEVIN R KANE
05/06/2020 01:22:37 PM

HINA S MEHTA
05/11/2020 10:22:05 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 15, 2020
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	NDA 212123
Product Name and Strength:	Tauvid (flortaucipir F-18) Injection, 300 MBq/mL – 1,900 MBq/mL (8.1 mCi/mL – 51 mCi/mL)
Applicant/Sponsor Name:	Avid Radiopharmaceuticals, Inc.
OSE RCM #:	2019-2103-1
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 27, 2020 for Tauvid. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] We reviewed the revised container and shield carton labeling for Tauvid (Appendix A) to determine if it is acceptable from a medication error perspective.

2 CONCLUSION

The revised vial container label and shield carton labeling is unacceptable from a medication error perspective. We note the lack of a strength statement, use of symbols, the lack of the use of a comma for numbers greater than 1,000, and lack of units after every number. We provide recommendations for Avid below.

2.1 RECOMMENDATIONS FOR AVID RADIOPHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

[a] Kane, D. Label and Labeling Review for Tauvid (NDA 212123). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 24. RCM No.: 2019-2103.

A. General Comments for Vial Container Label and Shield Carton Labeling
    1. As currently presented, the total strength for Tauvid is not provided on the vial container label or the shield carton labeling. We recommend including the statement “300 MBq to 1,900 MBq (8.1 mCi to 51 mCi) at End of Synthesis” on the label and labeling.

B. Vial Container Label
    1. Consider stating numbers greater than 1,000 with a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100”. Include a comma in the value 1,900 MBq to prevent misinterpretation.
    2. We recommend avoiding the use of symbols and abbreviations to prevent confusion. Replace the use of “-“ with the intended meaning “to” when presenting ranges.
    3. As currently presented, the appropriate units are not provided next to each number on the label. We recommend including units after every number for clarity. For example, revise the contents statement to read “300 MBq to 1,900 MBq (8.1 mCi to 51 mCi)”.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 24, 2020
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	NDA 212123
Product Name and Strength:	Tauvid (flortaucipir F-18) Injection, 300 MBq/mL – 1,900 MBq/mL (8.1 mCi/mL to 51 mCi/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Avid Radiopharmaceuticals, Inc.
FDA Received Date:	September 30, 2019
OSE RCM #:	2019-2103
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Avid Radiopharmaceuticals, INC. submitted NDA 212123 Tauvid (flortaucipir F-18) injection on September 30, 2019. Tauvid is radioactive diagnostic agent being proposed for positron emission tomography (PET) imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles (b) (4) in adult patients who are being evaluated for AD (b) (4) We evaluated the proposed container labels, shield labeling, and Prescribing Information (PI) for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Medical Imaging and Radiation Medicine (DMIRM)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	No statement referring healthcare professionals to the full PI for instructions on preparation and image display.	Lack of instructions may lead to improper preparation, image display, or interpretation.	We recommend adding a bullet to read "See Full Prescribing Information for preparation, administration, imaging and dosimetry information. (2.2, 2.3, 2.4, 2.5)

Table 2. Identified Issues and Recommendations for Division of Medical Imaging and Radiation Medicine (DMIRM)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	As currently presented the second bullet with the dose and administration is unclear.	Lack of clarity for dosage and administration may lead to medication errors.	Revise second bullet to clarify the statement regarding (b) (4) and move this to be the first bullet in this section.
3.	As currently presented the first bullet of Dosage and Administration lacks information on all safety measures that need to be followed.	Lack of important safety measures can lead to unintended exposure of radioactive material.	Revise first bullet to read (b) (4)
4.	The dosage form is not provided in the Dosage Forms and Strengths Section.	Lack of information may lead to confusion.	Revise to read "Injection: (b) (4) 300 MBq/mL to 1,900 MBq/mL (8.1 mCi/mL to 51 mCi/mL) of flortaucipir F18 Injection (b) (4)".
Full Prescribing Information – Section 2 Dosage and Administration			
1.	There are no subheadings under Section 2.2 for dosage and administration.	Lack of subheadings may cause confusion.	Revise Section 2.2 to include separate subheadings for "Recommended Dose" and for "Administration".
2.	Instructions for proper technique are not provided.	Given this is a sterile radioactive product it is critical that proper precautions are taken while drawing the dose from the multi-dose vial.	We recommend the addition of the statement, "Use aseptic technique and radiation shielding during all operations involved in the manipulations and administration of Tauvid", to Section 2.2 under the subheading Administration.
3.	Lack of statement on calculation of recommended dose.	Lack of this statement may lead to confusion.	Add a bullet with the statement "Calculate necessary volume to administer based on calibration time and dose."
4.	Lack of statement on disposal of any unused product.	Lack of this statement may lead to confusion.	Add a bullet with the statement "Dispose of unused drug in compliance with applicable regulations."

Table 2. Identified Issues and Recommendations for Division of Medical Imaging and Radiation Medicine (DMIRM)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
5.	The Dosage Forms and Strengths Section is unclear.	Lack of information may lead to confusion.	Revise to read "Injection: clear, colorless solution free of visible particulate matter in a 30 mL or 50 mL multiple-dose vial containing 300 MBq/mL to 1,900 MBq/mL (8.1 mCi/mL to 51 mCi/mL) of flortaucipir F18 Injection, at calibration time. (3)".
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	No instructions provided on how to properly dispose of Tauvid.	Proper disposal of radioactive materials is required.	We recommend adding proper disposal instructions. Include the statement "This radiopharmaceutical is for distribution and use by persons licensed authorized by the U.S. Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State. Store and dispose of Flortaucipir F18 in compliance with the appropriate regulations of the government agency authorized to license the use of this radionuclide."
2.	No information provided on how long after end of synthesis Tauvid expires.	Lack of information may lead to confusion.	We recommend adding a statement to clearly define when Tauvid expires.

Table 3. Identified Issues and Recommendations for Avid Radiopharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	Proposed proprietary name and established names lack	Proprietary name and established name should be the most prominent	Ensure the proprietary name, established name, and dosage form are among the most

Table 3. Identified Issues and Recommendations for Avid Radiopharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	prominence on vial and shield labels.	information on the label in order to be in accordance with 21 CFR 201.10(g)(2).	prominent information on the label. This can be established by increasing the font size of the proprietary name and utilizing bold font. Ensure that the established name is at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).
2.	Route of administration lacks prominence.	Route of Administration should be prominent in order to avoid confusion.	Revise the route statement to "For Intravenous Use Only" and increase its prominence to ensure this information is not overlooked.
3.	Use of trailing zero for dosing statement on the vial and shield labels.	The use of trailing zeros has led to ten-fold overdoses.	Remove trailing zero from the dosing statements on the shield and vial labels (e.g. change 2.0 mg of flortaucipir to 2 mg).
4.	Dose statement is not available on the vial or shield labels.	The dosage statement should meet 21 CFR 201.55 and maintain consistency with Prescribing Information.	We recommend you add the usual dose statement, "Dosage: See prescribing information".
5.	Expiration Date information lacks prominence.	Lack of prominence for important information may lead to confusion.	Move expiration date information to above batch number so it is not overlooked. Add statement to clearly define when Tauvid expires after end of synthesis.
6.	The Prescribing Information states that (b) (4) However, this information is not provided on the label.	End user may store (b) (4)	We recommend adding the storage requirements, "Store vial upright in a lead shielding container at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)", to the shield container label.

4 CONCLUSION

Our evaluation of the proposed Tauvid prescribing information (PI), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Error! Reference source not found. for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Avid Radiopharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for TAUVID that Avid Radiopharmaceuticals, Inc. submitted on 9/30/2019.

Table 4. Relevant Product Information for Tauvid	
Initial Approval Date	N/A
Active Ingredient	Flortaucipir F-18
Indication	flortaucipir F18 Injection is a radioactive diagnostic agent for PET imaging of the brain to estimate the density and pattern of aggregated tau in adult patients who are being evaluated for Alzheimer's Disease (AD) (b) (4) (b) (4)
Route of Administration	Intravenous
Dosage Form	Injection
Strength	300 MBq/mL – 1,900 MBq/mL (51 mCi/mL)
Dose and Frequency	370 MBq (10 mCi) once
How Supplied	Supplied in multi-dose vials. (b) (4)
Storage	Stored at room temperature in (b) (4) shielding.
Container Closure	(b) (4) shield container to minimize radiation exposure.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Tauvid labels and labeling submitted by Avid Radiopharmaceuticals, Inc. on September 30, 2019. The materials reviewed include:

- Vial Labels
- Shield Labels
- Prescribing Information (image not shown), available from \\cdsesub1\evsprod\nda212123\0001\m1\us\annotated.pdf

F.2 Label and Labeling Images

- Vial Container label(s) – 30 mL

- Vial Container Label(s) – 50 mL

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004

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/s/

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Expert Reviews (cont'd)

Neurology Expert Review

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Date: January 21, 2020

From: Eric Bastings, M.D.
Acting Division Director

Subject: NDA 212123 (TAUVID™; flortaucipir)
Consultative Review

To: Director, Division of Medical Imaging

Enclosed is the Division's response to your request

Review and Evaluation of Clinical Data

NDA (Serial Number)	**212123 (0001)**
Sponsor:	**Avid Radiopharmaceuticals**
Product:	**Flortaucipir F18 Injection (TAUVID)**
Proposed Indication:	(b) (4)
Material Submitted:	**Original New Drug Application**
Correspondence Date:	**9/30/19**
Date Received By Reviewer:	**10/12/19**
Date Review Completed:	**1/21/20**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This consultative request from the Division of Medical Imaging Products pertains to an original New Drug Application (NDA) for flortaucipir F18 injection (TAUVID™).

Flortaucipir F18 injection (flortaucipir) is an intravenously-administered radioactive compound. This compound is intended for use in the positron emission tomographic imaging of the neurofibrillary tangles (comprised of aggregated tau protein) (b) (4)

It is proposed by the sponsor that in adult patients who are being evaluated for Alzheimer's Disease (b) (4), a positron emission tomographic scan using flortaucipir can (b) (4)

While this Division and reviewer were informed of the submission of the current NDA soon after it was first received by the Agency, a request to address specific questions pertaining to this application was received by this reviewer on December 23, 2019.

In this review, the following names are used interchangeably: "flortaucipir F18;" "flortaucipir;" and "TAUVID™(TAUVID, Tauvid)."

The name "^{18}F-AV-1451" has also been used for flortaucipir.

2. Text Of Consult Request

The following (in blue font) is the full text of the consultation request that was received from Venkata S Anand Mattay, MD, clinical reviewer in the Division of

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(b) (4)

Ranjit B. Mani, M.D.
Medical Reviewer

Eric P. Bastings, M.D.
Acting Division Director

rbm
cc:
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Expert Reviews (cont'd)

Proprietary Name Safety Expert Review

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 17, 2019
Application Type and Number:	NDA 212123
Product Name and Strength:	Tauvid (flortaucipir F 18) injection, 300 MBq/mL to 1,900 MBq/mL (8.1 mCi/mL to 51 mCi/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Avid Radiopharmaceuticals (Avid)
Panorama #:	2019-34783340
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Tauvid, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A respectively. Avid submitted an external name study, conducted by (b) (4) for this proposed proprietary name, which we reviewed in our previous evaluation of the proposed proprietary name.[a]

1.1 REGULATORY HISTORY

Avid previously submitted the proposed proprietary name, Tauvid on August 8, 2018. We found the name, Tauvid conditionally acceptable under IND 119863 on January 31, 2019.[a]

Thus, Avid submitted the name, Tauvid, for review on September 30, 2019 under NDA 212123.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on September 30, 2019.

- Intended Pronunciation: TAAOW-vihd
- Active Ingredient: flortaucipir F 18
- Indication of Use: Positron Emission Tomography (PET) imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles (b) (4) in adult patients who are being evaluated for AD (b) (4) (b) (4)
- Route of Administration: intravenous injection
- Dosage Form: injection
- Strength: 300 MBq/mL to 1,900 MBq/mL (8.1 mCi/mL to 51 mCi/mL))
- Dose and Frequency: 370 MBq (10 mCi), administered as a single intravenous bolus
- How Supplied: supplied in 30 mL or 50 mL vials containing a clear, colorless solution
- Storage: Store TAUVID at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. The product does not contain a preservative. Store TAUVID within the original container with appropriate radiation shielding.

[a] Ogbonna, C. Proprietary Name Review for Tauvid (IND 119863). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 31. Panorama No. 2018-25117266.

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Tauvid.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Tauvid would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Medical Imaging Products (DMIP) concurred with the findings of OPDP's assessment for Tauvid.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Tauvid.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary name[b].

2.2.2 Components of the Proposed Proprietary Name

Avid indicated in their submission that the proposed proprietary name, Tauvid, is derived from the proposed mechanism of action of Flortaucipir F18 binding to aggregated tau protein in the brain (TAU). This proprietary name is comprised of a single word. In our previous review, we evaluated the incorporation of the letters 'vid', which are shared with that of the Applicant's name (Avid) and the letter string 'au', which is an abbreviation for the direction "each ear or both ears".[c] We agree with our previous assessment.

2.2.3 Comments from Other Review Disciplines at Initial Review

In response to the OSE, October 20, 2019 e-mail, the Division of Medical Imaging Products (DMIP) did not forward any comments or concerns relating to Tauvid at the initial phase of the review.

2.2.4 FDA Name Simulation Studies

Seventy-three practitioners participated in DMEPA's prescription studies for Tauvid. The responses did not directly overlap with any currently marketed products or any products in the pipeline. Four respondents in the voice study interpreted the proposed proprietary name as Tovid, which is a close variation to the marketed product, Tovet. We evaluated the name pair, Tauvid and Tovet, further and find that there are sufficient orthographic and phonetic differences (See Appendix E):

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[b] USAN stem search conducted on November 1, 2019.

[c] Ogbonna, C. Proprietary Name Review for Tauvid (IND 119863). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 31. Panorama No. 2018-25117266.

Orthographically, the additional letter 'u' in Tauvid and the last letters (d vs. t) provide some differences. Phonetically the second syllables (vihd vs. vet) of this name pair sound different when spoken. The usual dose for Tauvid is 370 MBq (10 mCi) administered once as a single intravenous bolus. The dose/directions for Tovet is to apply to affected area twice daily for up to 2 weeks (or use as directed). Therefore, there is no overlap in dose or frequency between the products. Furthermore, Tauvid will be prepared by a nuclear pharmacy as the product is a diagnostic radiopharmaceutical product indicated for Positron Emission Tomography (PET) imaging of the brain and is limited to specialized handling, preparation, and dispensing. The setting of use of these two products in the medication use process differ and therefore, it is unlikely that Tovet would be confused for Tauvid and used in this setting. Therefore, due to the above considerations, we do not think that the name pair is vulnerable to name confusion.

Appendix B contains the results from the verbal and written prescription studies.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Our POCA search[d] identified 86 names with the combined score of ≥55% or individual orthographic or phonetic score of ≥70%. We had identified and evaluated some of the names in our previous proprietary name review. We re-evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the name. We note that none of the product characteristics have changed and we agree with the findings from our previous review for the names evaluated previously. Therefore, we identified eight names not previously analyzed. These names are included in Table 1 below.

2.2.6 Names Retrieved for Review Organized by Name Pair Similarity

Table 1 lists the number of names retrieved from our POCA search. These name pairs are organized as highly similar, moderately similar or low similarity for further evaluation.

Table 1. Names Retrieved for Review Organized by Name Pair Similarity

Similarity Category	Number of Names
Highly similar name pair: combined match percentage score ≥70%	1
Moderately similar name pair: combined match percentage score ≥55% to ≤ 69%	6
Low similarity name pair: combined match percentage score ≤54%	1

[d] POCA search conducted on November 1, 2019 in version 4.3.

2.2.7 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the eight names contained in Table 1 determined none of the names will pose a risk for confusion with Tauvid as described in Appendices C through H.

2.2.8 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Medical Imaging Products (DMIP) via e-mail on December 9, 2019. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Medical Imaging Products (DMIP) on December 17, 2019, they stated no additional concerns with the proposed proprietary name, Tauvid.

3 CONCLUSION

The proposed proprietary name, Tauvid, is acceptable.

If you have any questions or need clarifications, please contact Tri Bui-Nguyen, OSE project manager, at 240-402-3726.

3.1 COMMENTS TO AVID RADIOPHARMACEUTICALS

We have completed our review of the proposed proprietary name, Tauvid, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your submission, received on September 30, 2019, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. *USAN Stems (https://www.ama-assn.org/about/united-states-adopted-names-approved-stems)*

   USAN Stems List contains all the recognized USAN stems.

2. *Phonetic and Orthographic Computer Analysis (POCA)*

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. Misbranding Assessment: For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. Safety Assessment: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [e]

[e] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

*Table 2- Prescreening Checklist for Proposed Proprietary Name

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	Is the proposed name obviously similar in spelling and pronunciation to other names?
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	Are there inert or inactive ingredients referenced in the proprietary name?
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	Does the proprietary name include combinations of active ingredients?
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	Is there a United States Adopted Name (USAN) stem in the proprietary name?
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	Is this proprietary name used for another product that does not share at least one common active ingredient?
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	Is this a proprietary name of a discontinued product?
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.

- Moderately similar pair: combined match percentage score ≥55% to ≤ 69%.
- Low similarity: combined match percentage score ≤54%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names[f]. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
    - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).

- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might

[f] Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

   Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

   In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

   When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	Y/N	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	Y/N	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is **≥55%** to **≤69%).**

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names <u>with</u> overlapping or similar strengths or doses.

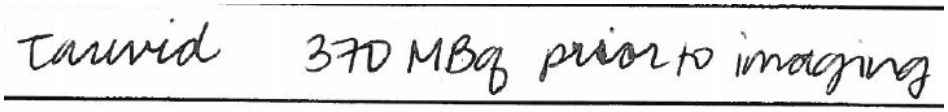
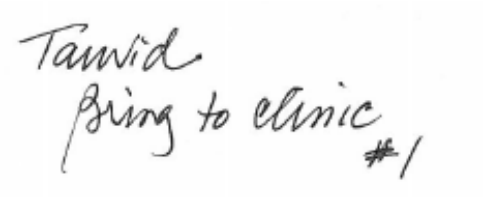
	Orthographic Checklist (Y/N to each question)	Phonetic Checklist (Y/N to each question)
	• Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	• Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is **≤54%).**

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Tauvid Study (Conducted on November 7, 2019)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order:  	Tauvid Bring to clinic #1
Outpatient Prescription:  	

FDA Prescription Simulation Responses (Aggregate Report)

Study Name: Tauvid

212 People Received Study

73 People Responded

Total	39	13	21	73
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
HAVID	0	1	0	1
TABID	0	1	0	1
TAMID	1	0	0	1
TAMLID	1	0	0	1
TAMNID	2	0	0	2
TAMVID	3	0	0	3
TANVID	17	0	1	18
TARIVID	0	0	12	12
TARVID	1	0	0	1
TARVIQUE	0	1	0	1
TARWID	1	0	0	1
TAUVID	8	4	8	20
TAUWID	2	0	0	2
TAVID	0	1	0	1
TAVVID	1	0	0	1
TAWBID	0	1	0	1
TAWID	2	0	0	2
TOVID	0	4	0	4

Appendix C: Highly Similar Names (e.g., combined POCA score is ≥70%)

No.	Proposed name: Tauvid Established name: flortaucipir F 18 Dosage form: injection Strength(s): 300 MBq/mL to 1,900 MBq/mL (8.1 mCi/mL to 51 mCi/mL) Usual Dose: 370 MBq (10 mCi) as a single intravenous bolus	POCA Score (%)	Orthographic and/or phonetic differences in the names sufficient to prevent confusion Other prevention of failure mode expected to minimize the risk of confusion between these two names.
1.	Tauvid	100	Subject of this review.

Appendix D: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose

No.	Name	POCA Score (%)
2.	(b) (4) ***	59
3.	***	58

Appendix E: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	Proposed name: Tauvid Established name: flortaucipir F 18 Dosage form: injection Strength(s): 300 MBq/mL to 1,900 MBq/mL (8.1 mCi/mL to 51 mCi/mL) Usual Dose: 370 MBq (10 mCi) as a single intravenous bolus	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
4.	(b) (4) *** Proposed proprietary name found unacceptable in OSE Review# 2019-32435296 for ANDA 210524/S-002. Product currently approved under established name Ammonia N 13.	62	The prefixes/infixes (Tau vs. (b) (4)) of the names provide sufficient orthographic differences. (b) (4) syllables sound different.
5.	(b) (4) ***	60	This name pair has sufficient orthographic and phonetic differences.
6.	Tovet	57	Orthographic: The suffix 'et' vs 'id' provide some differences.

No.	Proposed name: Tauvid Established name: flortaucipir F 18 Dosage form: injection Strength(s): 300 MBq/mL to 1,900 MBq/mL (8.1 mCi/mL to 51 mCi/mL) Usual Dose: 370 MBq (10 mCi) as a single intravenous bolus	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
			Phonetic: The second syllables (vet vs. vihd) of this name pair sound different when spoken. Dose and frequency: The dose for Tovet is to apply to affected area twice daily for up to 2 weeks (or use as directed) whereas the usual dose for Tauvid is 370 MBq (10 mCi) once as a single intravenous bolus. Setting of Use: Tauvid will be prepared by a nuclear pharmacy as the product is a diagnostic radiopharmaceutical product and is limited to specialized handling, preparation, and dispensing. The setting of use of these two products in the medication use process differ and therefore, it is unlikely that Tovet would be confused for Tauvid and used in this setting.

Appendix F: Low Similarity Names (e.g., combined POCA score is ≤54%)

No.	Name	POCA Score (%)
7.	Tvia	50 (O 70)

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described. – N/A

Appendix H: Names not likely to be confused due to absence of attributes that are known to cause name confusion[g].

No.	Name	POCA Score (%)
8.	Dayvigo***	57

[g] Shah, M, Merchant, L, Chan, I, and Taylor, K. Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

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Expert Reviews (cont'd)

Radiopharmaceutical Dosimetry Expert Review

Response to Avid Regarding Newborn Effective Dose Associated with Lactating Women Administered *Tauvid* (Flortaucipir ^{18}F, FTP)

April 30, 2020

1. To address radioisotope-activity excretions in breast milk for ^{18}F-radiolabeled pharmaceuticals *other* than FDG, i.e., *where there are no measured milk-activity data*, we approximate the maximum **fraction** of administered radiopharmaceutical activity that could be cumulatively ingested from breast milk as the **ratio** of the *energy absorbed in the breasts* of an adult (mathematical phantom) to the *total energy absorbed* in all of the organs/tissue of the adult (phantom). Albeit an overestimation, this approximation is expedient. Organ absorbed-energy is the product of organ mass [1, 2] and organ absorbed-dose [1].

   Starting with the following values for FDG parameters as "controls" to bridge to corresponding parameters for other ^{18}F-radiolabeled pharmaceuticals, we approximate $\mathbf{f_{breast\ milk}}$ (FDG)$|_{\mathbf{max}}$ ≈ **absorbed-energy ratio** (FDG) = **0.0028**. The effective dose per unit activity ingested by a newborn can be extrapolated from the FDG dosimetry tabulation [1] for one-year-olds: **E** (FDG) per unit *newborn-ingested* activity = $\mathbf{0.21\ mSv/MBq_{newborn}}$. Hence **E**$|_{\mathbf{max}}$ (FDG, newborn) per unit activity *administered to the breast-feeding mother* = 0.21 $mSv_{newborn}/MBq_{newborn}$ × 0.0028 [$MBq_{newborn}/MBq_{mother}$] = $\mathbf{5.8 \times 10^{-4}\ mSv_{newborn}/MBq_{mother}}$.

   In sum, the values derived via this absorbed-energy approximation for FDG are nearly consistent as upper bounds to respective estimates of the cumulatively-ingested fraction of administered FDG activity and effective dose (per maternal-administered activity) to a breast-feeding infant. The latter estimates are based on independent measurements of activity in expressed breast milk and differing models of breast-feeding schedules, namely, {$\mathbf{f_{breast\ milk}}$ ≈ **0.0010**; **E** ≈ $\mathbf{2.4\times 10^{-4}\ mSv_{infant}/MBq_{mother}}$} [3], and {$\mathbf{f_{breast\ milk}}$ ≈ **0.00070**; **E** ≈ $\mathbf{6.7 \times 10^{-4}\ mSv_{infant}/MBq_{mother}}$} [4]. Moreover, when the breast-feeding schedule applied in study [4] is normalized to that of study [3], study-[4] values are calculated as {$\mathbf{f_{breast\ milk}}$ ≈ **0.00098**; **E** ≈ $\mathbf{4.8 \times 10^{-4}\ mSv_{infant}/MBq_{mother}}$}, each value less than the respective upper bound estimated according to the absorbed-energy approximation: {$\mathbf{f_{breast\ milk}}$ (FDG)$|_{\mathbf{max}}$ = **0.0028**, **E**$|_{\mathbf{max}}$ (FDG) = $\mathbf{5.8 \times 10^{-4}\ mSv_{newborn}/MBq_{mother}}$}.

2. Applying the breast-absorbed-energy approximation (described in the preceding paragraph) for newborn ingestion of breast milk following administration of Tauvid (FTP) to a breast-feeding woman, and modeling the infant-feeding schedule as described in refs. [3 and 5], we calculate $\mathbf{f_{breast\ milk}}$ (FTP)$|_{\mathbf{max}}$ = **0.0023** and **E**$|_{\mathbf{max}}$ (FTP) = $\mathbf{0.27\ mSv_{newborn}/MBq_{newborn}}$ [6], which imply that **E**$|_{\mathbf{max}}$ (FTP) = $\mathbf{6.2 \times 10^{-4}\ mSv_{newborn}/MBq_{mother}}$. Hence, for the recommended amount of FTP activity (370 MBq [6]) that could be administered via injection into a breast-feeding woman, through multiple subsequent feedings, a newborn could cumulatively incur an effective dose of **E**$|_{\mathbf{max}}$ (FTP) = $\mathbf{0.23\ mSv_{newborn}}$ from the internal biodosimetric distribution of ^{18}F-FTP.

3. To estimate the contributions to the newborn's effective dose from external sources of irradiation (namely, from the breast and the rest of the body of the breast-feeding woman),

we apply the external-radiation modeling developed in a report [7][1] by a subcommittee of the NRC Advisory Committee on the Medical Use of Isotopes (ACMUI). Since the radiant energy is primarily that of the 511-keV gamma rays arising from positron-electron annihilation, it is reasonable to approximate that energy as homogeneously penetrant and uniformly absorbed throughout the habitus of a newborn. In this circumstance, the numerical value of the newborn whole-body absorbed dose per unit administered activity estimated with the external irradiation model [7][1] would numerically equal that of the newborn effective dose (or effective dose equivalent) per unit administered activity. Furthermore, the presumed uniformity of the absorbed dose (per unit administered activity) throughout the newborn means that the effective dose (per unit administered activity) depends only on the external source of radiant gamma-ray energy emanating from the radioisotope (^{18}F) distribution within the woman; the newborn dose from an external source would **not** depend on the biodosimetric distribution of the pharmacophore within the newborn. In other words, this modeling approach [7][1] to estimate the contribution to newborn effective dose from maternally sourced external irradiation of the newborn would likely be valid for any ^{18}F-radiolabeled pharmaceutical administered to the breast-feeding woman.

Hence, for the recommended amount of FTP activity (370 MBq [6]) that could be administered via injection into a breast-feeding woman, we calculate that through multiple subsequent feedings, a newborn could cumulatively incur an effective dose of $\mathbf{E_{ext}}$ (FTP) = $\mathbf{0.46\ mSv_{newborn}}$ from the external radiant energy emitted by the breast-feeding woman.

4. For the recommended amount of FTP activity (370 MBq [6]) that could be administered via injection into a breast-feeding woman, we calculate that through multiple subsequent feedings, a newborn could cumulatively incur a **total effective dose** of $\mathbf{E_{tot}}$ **(FTP)** = $\mathbf{0.69\ mSv_{newborn}}$ from the internal biodosimetric distribution of ^{18}F-FTP which the newborn infant ingests from breast feeding plus from the external radiant energy emitted by the breast-feeding woman. Although this estimated value is less than the 1-mSv threshold [8 – 10] that would necessitate instructions [8,11] for interruption of the infant's breast-feeding schedule, there is significantly large modeling uncertainty, at least a factor ~ 1.5 and likely more. As a conservative safety precaution, we therefore suggest that following radiopharmaceutical administration, breast feeding be interrupted for an interval of four hours, which in models of breast-feeding schedules is the upper range characterizing the interval between feeding sessions for newborn infants.

References and notes

[1] ICRP Publication 128, *Radiation Dose from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances*, approved by the International Commission on Radiological Protection in July 2014, *Annals of the ICRP*, Vol. 44, No. 2S, Sage Journals, 2015.

Note: See Annex section A.1 (Organ and tissue masses for different ages) p. 39, and Table A.1 (Masses of models of selected organs and tissues at different ages) pp. 40-41: The masses of the phantom used for calculation of S values are those presented by M.G. Stabin and J.A. Siegel, "Physical Models and Dose Factors for Use in Internal Dose Assessment," *Health Physics*, Vol. 85, No. 3, pp. 294-310, Sep 2003.

[1] In our calculations to evaluate absorbed dose (mGy) from estimated external exposure (in roentgens, R), we multiply the radionuclide specific gamma ray constant Γ by a factor 8.76 mGy/R, a factor that was not explicitly included in the external-irradiation model of ref. [7].

For our calculations, age-dependent organ masses were adopted mostly from ICRP Publication 128 [1] and some from ICRP Publication 110 [2]. **See section C.15. (FDG), pp. 107-109 of ICRP Publication 128, for ^{18}F-FDG radiation dosimetry biokinetic modeling, references, and organ absorbed-dose and effective-dose estimates.**

[2] ICRP Publication 110, *Adult Reference Computational Phantoms*, *Annals of the ICRP*, Vol. 39, No. 2, pp. 48-51, April 2009.

Note: Male and female body masses for the computational phantoms are listed in Table 5.1 (Main characteristics of the adult male and female reference computational phantoms), p. 39; adult endosteal masses: Table 4.2, p. 36. For our calculations, age-dependent organ masses were adopted mostly from ICRP Publication 128 [1] and some from ICRP Publication 110 [2].

[3] Rodney J. Hicks, David Binns, and Michael G. Stabin, "Pattern of Uptake and Excretion of ^{18}F-FDG in the Lactating Breast," *The Journal of Nuclear Medicine*, Vol. 42, No. 8, pp. 1238-1242, Aug 2001.

Note:

The feeding schedule in ref. [3] is based on that of ref. [5]: this model assumes a first feeding 3 h post-administration, then every 4 h thereafter, 142 mL of breast milk per feeding. At the nominal "3 h" (actually reported [3] as 195 min = 3.25 h) after ^{18}F-FDG administration (at t = 0), the authors measured an activity concentration in milk of 5.6 Bq/mL per MBq administered activity [3]. When one accounts for radioisotope physical decay from t = 0, the value measured at 3.25 h post-administration represents the peak concentration of breast-milk activity, 19 Bq/mL per MBq administered activity. Starting at t = 3.25 h after administration and for successive 4-hour intervals, we summed the contributions of multiple feedings and obtained a total fraction $\mathbf{f_{breast\ milk} = 0.00102}$ of administered activity that would be cumulatively ingested by the breast-feeding infant.

Using a "dose factor" of "0.23 mGy/MBq" activity ingested, which we construe as implicitly assuming uniform internal irradiation throughout the infant corresponding to an effective dose of 0.23 mSv/MBq activity ingested, the paper [3] estimates a cumulative effective dose to the infant of approximately "0.085 mSv" from ingested activity. We checked the consistency of this reported value (0.085 mSv) as follows: 0.085 mSv/(0.23 mSv per MBq infant-ingested) = 0.37 MBq infant-ingested activity. The value we estimated, $f_{breast\ milk}$ = 0.00102, implies that 0.37 MBq/0.00102 = 363 MBq of ^{18}F-FDG activity was administered to the woman. However, 363 MBq is discrepant from the range of administered ^{18}F-FDG activity, 50 – 160 MBq reported for the sodium-iodide-detector PET scanner actually used in the study [3] rather than the more conventional bismuth-germanate-detector PET scanners requiring administered doses in the range 300 – 500 MBq [3]. One can resolve the discrepancy with an assumption that the authors [3] erroneously applied the t = 0 milk-activity concentration (19 Bq/mL per MBq administered activity) instead of the value (5.6 Bq/mL per MBq administered activity) actually measured at 3.25 h after administration. Applying (erroneously) the value 19 Bq/mL per MBq administered activity at 3.25 h, one would obtain a fraction 0.0035 of administered activity that could be cumulatively ingested and implying that 0.37 MBq/0.0035 = 106 MBq of ^{18}F-FDG activity would have been administered to the woman, a value within the reported range of activity *actually administered*. In other words, identifying this presumed error yields an expected amount of administered activity actually administered in study [3]. The upshot of this analysis is that the estimated value 0.085 mSv [3] is erroneously too high. If we apply the fraction $\mathbf{f_{breast\ milk} = 0.00102}$, appropriately calculated from the reported milk-activity concentration, to the estimated 106 MBq of administered activity, we estimate that 0.108 MBq would be ingested by an infant and, with the study's assumption of an effective dose dose of 0.23 mSv/MBq infant-ingested, we estimate that the effective dose to the infant would be approximately **0.025 mSv**, and the infant effective dose per administered activity to the breast-feeding woman would be 0.025 mSv/106 MBq = $\mathbf{2.4 \times 10^{-4}\ mSv/MBq_{administered}}$.

[4] Sigrid Leide-Svegborn et al., "Excretion of radionuclides in human breast milk after nuclear medicine examinations. Biokinetics and dosimetric data and recommendations on

breastfeeding interruption," *European Journal of Nuclear Medicine and Molecular Imaging*, Vol. 43, No. 5, pp. 808-821, May 2016.

Note [bolded italics added]: Page 810 of this paper includes the following statement: "The proposed recommendations on breastfeeding interruption were based on an ***effective dose limit of 1 mSv*** to the infant, which is the general limit recommended by the ICRP for protection of members of the general public" (where the statement cites the ref. [9]).

[5] Michael G. Stabin and Hazel B. Breitz, "Breast Milk Excretion of Radiopharmaceuticals: Mechanisms, Findings, and Radiation Dosimetry," *The Journal of Nuclear Medicine*, Vol. 41, No. 5, pp. 863-873, May 2000.

[6] Tauvid (Flortaucipir ^{18}F, ^{18}F-FTP) draft label, March 27, 2020.

Note: The basis of our calculations was the radiation dosimetry table of the Tauvid draft label. The values of that table are similar to those in a brief article by Jae Yong Choi et al., "Human Radiation Dosimetry of [^{18}F]AV-1451(T807) to Detect Tau Pathology," *Molecular Imaging and Biology*, Vol. 18, pp. 479-482, published online January 4, 2016.

[7] Vasken Dilsizian et al., *Advisory Committee on Medical Uses of Isotopes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials*, Final Report, dated February 1, 2018; revised June 19, 2018; submitted June 26, 2018; endorsed in a unanimous vote by ACMUI September 20 – 21, 2018.

[8] Code of Federal Regulations, Title 10, Part 35, Section 75, *Release of individuals containing unsealed byproduct material implants containing byproduct material* (10 CFR 35.75). Also see 10 CFR 20.1301, *Dose limits for individual members of the public*.

[9] ICRP Publication 103, *The 2007 Recommendations of the International Commission on Radiological Protection*, approved by the Commission in March 2007, *Annals of the ICRP*, Vol. 37, Nos. 2 – 4, Apr – Jun 2007.

Note [bolded italics added]: Section 6.5 ("Comparison of radiological protection criteria"), p. 116, Table 8 of this publication presents the following individual dose limits applicable for planned public exposure: an ***effective dose of 1 mSv in a year***; an ***equivalent dose of 15 mSv/year*** to the lens of the eye; and an ***equivalent dose of 50 mSv/year*** to the skin. There is no equivalent-dose limit for any other organ or tissue.

[10] NCRP Report No. 180, *Management of Exposure to Ionizing Radiation: Radiation Protection Guidance for the United States (2018). Recommendations of the National Council on Radiation Protection and Measurements*, Dec 31, 2018.

Note 1 [bolded italics added]: Section 5.3 ("Public Exposure"), sub-section 5.3.1 ("Protection Against Stochastic Effects"), p. 57 of this NCRP report states "NCRP recommends that the ***annual effective dose*** to a member of the public from the continuous or reasonably anticipated presence of a source should not exceed ***1 mSv***. This recommendation is suitable for use as a regulatory dose limit when the source is stable, characterized, and subject to an advance control program."

Note 2: The National Council on Radiation Protection and Measurements (NCRP) is a non-profit corporation chartered by Congress in 1964.

[11] U.S. Nuclear Regulatory Commission, Regulatory Guide 8.39, *Release of Patients Administered Radioactive Materials*, Apr 1997, accessed via

https://www.nrc.gov/docs/ML0037/ML003739575.pdf, Mar 13, 2020; Errata to RG 8.39, May 1997, accessed via https://www.nrc.gov/docs/ML0037/ML003739562.pdf, Mar 17, 2020.

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