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Brain Tau Imaging - FDA Approval of Flortaucipir F18 Injection

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Alzheimer's disease (AD) is the most common among neurodegenerative dementias. Currently, there are more than 5.8 million Americans with AD. Worldwide, there are at least 50 million people with AD or other dementias and these numbers are projected to triple by the year 2050[1].

Timely and accurate diagnosis of AD can guide patients and their families through an anxious and uncertain experience by helping them anticipate future needs including monitoring for progression, safety and functional assessment. The accuracy of a clinical diagnosis of AD by dementia experts is modest[2] and a definitive diagnosis of AD can only be established by demonstrating the presence of beta-amyloid (Aβ) plaques and tau-neurofibrillary tangles (NFTs) in the brain[3].

The Food and Drug Administration (FDA) previously approved radioactive PET tracers (florbetapir F-18, florbetaben F-18, and flutemetamol F-18) to assess the presence of Aβ plaques in the brain. However, by itself, the presence of Aβ in a brain PET scan is not sufficient for a diagnosis of AD. Confirmation of the presence of NFTs, the second pathological hallmark of AD, is necessary for making a diagnosis of Definite AD. The NFTs in AD typically exist as paired helical filaments and accumulate in a distinct spatiotemporal pattern[3]. Accumulation starts in the transentorhinal cortex before spreading to the medial and inferior temporal lobe, the parietal-occipital regions and the rest of the neocortex[3]. This distribution of NFTs in AD is classified into four stages: B0 - no NFTs; B1 (Braak stages I/II) - NFTs predominantly in the entorhinal cortex and closely related areas; B2 (Braak stages III/IV) – abundant NFTs in the hippocampus and amygdala with some extension into association cortex; B3 (Braak stages V/VI) – NFTs widely distributed throughout the neocortex[3]. Evidence shows that the severity of

cognitive impairment in AD parallels the level of neocortical NFT pathology[4], and at least a B2 level of tau pathology with co-existing Aβ and neuritic plaques is necessary to confer a diagnosis of AD[3].

Recently, the FDA approved flortaucipir F-18 (FTP), a new PET molecular entity designed to estimate the density and distribution of the aggregated intracellular NFTs[5] in patients with cognitive impairment who are evaluated for Alzheimer's disease. For this approval, the FDA relied on the results of two clinical studies (NCT02516046 and NCT03901092) with FTP scans interpreted by multiple independent readers blinded to all clinical information.

The first efficacy study assessed the accuracy of FTP in estimating the density and distribution of aggregated NFTs in the brains of patients with terminal illness who participated in a postmortem brain donation program. The patients, who had a range of cognitive function, underwent FTP scans and were followed until they died. The results of the premortem FTP scans were compared with the brain tau neuropathology autopsy findings as the truth standard. Diagnostic performance statistics were calculated by defining a positive scan as a B3 level of NFT pathology and a negative scan as B0, B1, or B2 NFT level.

For the interpretation of the scans, a reader assessed the uptake of FTP in the neocortical grey matter regions only. A negative scan (e.g. Panel A in Figure) typically shows no increased neocortical activity or shows increased neocortical activity isolated to the mesial temporal, anterolateral temporal, and/or frontal regions. A positive scan (e.g. Panel B in Figure) typically shows widespread neocortical activity in the posterolateral temporal, occipital, parietal/precuneus, medial prefrontal/cingulate and lateral prefrontal regions. The readers showed a high probability for correctly identifying patients with B3 tau pathology [sensitivity (95% CI) across the readers ranged from 92% (80, 97) to 100% (91, 100)] and an average to high probability for correctly identifying patients without B3 level tau pathology [specificity across the readers ranged from 52% (34, 70) to 92% (75, 98)].

The second efficacy study assessed inter-reader agreement. The study included the same patients with terminal illness as in the first study, and patients with cognitive impairment being evaluated for AD; the latter represent the indicated population. Agreement across readers for distinguishing positive from negative FTP scans was high (Fleiss' kappa statistic (95% CI) = 0.87 (0.83, 0.91).

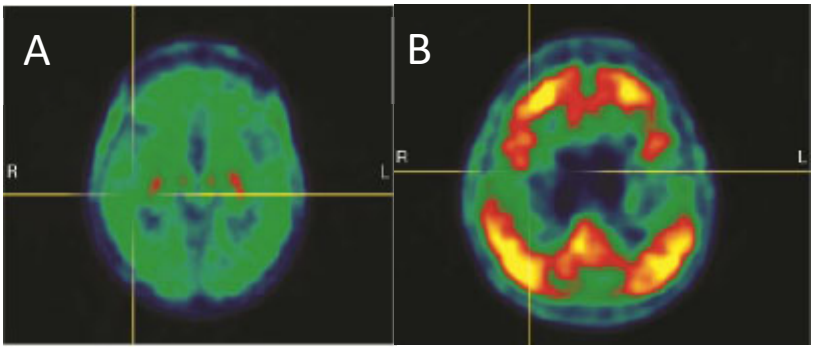
Exploratory analyses of FTP scan for distinguishing B2-B3 from B0-B1 tau pathology showed numerically lower sensitivity when compared to sensitivity for distinguishing B3 from B0-B1-B2 tau pathology. Therefore, patients with clinically meaningful tau pathology (B2) may be missed. These concerns are described in the Warnings and Precautions section of the prescribing information (PI)[5] to caution for the risk of misdiagnosis in patients evaluated for Alzheimer's disease. As risk mitigation, additional evaluation to confirm absence of AD pathology is recommended in patients with a negative FTP reading. As AD is a progressive disease, subsequent testing in patients with worsening cognitive function is likely to demonstrate progression to B3 level of tau pathology.

In preclinical studies, FTP was shown to reliably bind to the AD-specific intracellular, phosphorylated, paired helical filamental tau[6]. Differences in tau conformation may limit FTP binding in chronic traumatic encephalopathy[7]. Therefore, the following "Limitations of Use" text is included in the PI[5] - "TAUVID is not indicated for use in the evaluation of patients for chronic traumatic encephalopathy (CTE)"

The indication for FTP can be classified as pathology assessment. This indication is established by demonstrating in a defined clinical setting that a diagnostic radiopharmaceutical has sufficient accuracy in identifying or characterizing the pathology. Further development of tau imaging for the diagnosis and management of patients with cognitive impairment is anticipated. For example, the prognostic usefulness of tau imaging for progression of cognitive and functional impairment due to AD

has not been established and will need to be addressed by further study. The utility of tau imaging for selecting patients and predicting responses to investigational disease-modifying therapies also warrants exploration.

On the background of the approved amyloid PET tracers, FDA approval of FTP sets the stage for the development of clinical experience with tau pathology assessment vis a vis other approaches in the evaluation of patients with cognitive decline.



Examples of Negative and Positive FTP Scans

Uptake of FTP in the neocortical grey matter regions only was assessed for scan interpretation.

Panel A: example of a "negative" scan in a patient with absence of neocortical activity; off target binding is noted in the choroid plexus and brainstem nuclei

Panel B: example of a "positive" scan in a patient showing increased neocortical activity in medial prefrontal/cingulate, lateral prefrontal, parietal, occipital and precuneus regions.

Flortaucipir F18 Scan Usage: Information Summary

A positive flortaucipir scan:
- indicates the presence of widely distributed tau neuropathology in the neocortical areas (B3 tau pathology)

A negative flortaucipir scan:
- does not rule out the presence of B2 or lower tau pathology or amyloid pathology; additional evaluation to confirm the absence of AD pathology may be necessary
- subsequent testing in patients with worsening cognitive function may be necessary to detect progression to B3 level of tau pathology

Important flortaucipir scan limitations:

- a positive scan by itself does not establish a diagnosis of Alzheimer's disease or other cognitive disorder
- a scan cannot be used in the evaluation of patients for chronic traumatic encephalopathy or other non-AD tauopathies

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