Aggregated Tau Measured by Visual Interpretation of Flortaucipir Positron Emission Tomography and the Associated Risk of Clinical Progression of Mild Cognitive Impairment and Alzheimer Disease Results From 2 Phase III Clinical Trials

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IMPORTANCE Flortaucipir positron emission tomography (PET) scans, rated with a novel, US Food and Drug Administration–approved, clinically applicable visual interpretation method, provide valuable information regarding near-term clinical progression of patients with Alzheimer disease (AD) or mild cognitive impairment (MCI).

OBJECTIVE To evaluate the association between flortaucipir PET visual interpretation and patients’ near-term clinical progression.

DESIGN/SETTING/PARTICIPANTS Two prospective, open-label, longitudinal studies were conducted from December 2014 to September 2019. Study 1 screened 298 patients and enrolled 160 participants who had a flortaucipir scan at baseline visit. Study 2 selected 205 participants from the AMARANTH trial, which was terminated after futility analysis. Out of the 2218 AMARANTH participants, 424 had a flortaucipir scan around randomization, but 219 did not complete 18-month clinical dementia rating (CDR) assessments and thus were excluded. In both studies, all participants were diagnosed as clinically impaired, and they were longitudinally followed up for approximately 18 months after baseline.

MAIN OUTCOMES AND MEASURES Flortaucipir scans were rated as either advanced or nonadvanced AD pattern using a predetermined visual interpretation method. The CDR sum of box (CDR-SB) score was used as primary clinical end point measurement in both studies.

RESULTS Of the 364 study participants who had readable scans, 48% were female (n = 174 of 364), and the mean (SD) age was 71.8 (8.7) years. Two hundred forty participants were rated as having an advanced AD pattern. At 18 months follow-up, 70% of those with an advanced AD pattern (n = 147 of 210) had 1 point or more increase in CDR-SB, an event predefined as clinically meaningful deterioration. In contrast, only 46% of those with a nonadvanced AD pattern scan (n = 48 of 105) experienced the same event (risk ratio [RR], 1.40; 95% CI, 1.11-1.76; P = .005). The adjusted mean CDR-SB changes were 2.28 and 0.98 for advanced and nonadvanced AD pattern groups, respectively (P < .001). Analyses with other clinical end point assessments, as well as analyses with each individual study’s data, consistently indicated a higher risk of clinical deterioration associated with an advanced AD scan pattern.

CONCLUSIONS AND RELEVANCE These results suggest that flortaucipir PET scans, when interpreted with an US Food and Drug Administration–approved, clinically applicable visual interpretation method, may provide valuable information regarding the risk of clinical deterioration over 18 months among patients with AD and MCI.

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Alzheimer disease (AD) is characterized pathologically by tau neurofibrillary tangles (NFTs) and β amyloid plaques (Aβ). Neuropathologic criteria for the diagnosis of AD requires proof of the presence of both amyloid plaques and tangles. Previous cross-sectional studies reported that quantitative measures of flortaucipir are associated with degree of cognitive impairment and with longitudinal decline in cognitive performance. Published studies to date have focused on quantitative analyses of flortaucipir PET scans, which is suitable for research purposes but could pose a challenge in clinical practice. Visual scan interpretation may enable broader clinical application and make flortaucipir more accessible to medical practitioners and, therefore, to patients. A clinically applicable visual interpretation method was recently developed and approved by the US Food and Drug Administration (FDA). The accuracy of this method for detecting cortical tau deposition was validated in an autopsy study. To understand the prognostic value of visually interpreted flortaucipir scans, we applied this approach in 2 independent phase III clinical trials and assessed the association between flortaucipir visual interpretation patterns and participants’ clinical decline at 18 months. 

### Methods

#### Study Design

Two prospective, longitudinal clinical studies were conducted independently. Study 1 (Study 18F-AV-1451-A05; NCT02016560) was designed to evaluate the association between flortaucipir uptake at baseline and the subsequent rate of cognitive decline observed over an 18-month period. This study was conducted at 26 study sites across the United States from December 2014 to July 2017. Study 2 (Study 18F-AV-1451-PX01; NCT03901105) was designed to take advantage of data from a 24-month therapeutic trial (18D-MC-AZES/D5010C00009/AMARANTH; NCT02245737) that included flortaucipir PET scans at baseline in a subset of participants. The AMARANTH trial was designed to evaluate the treatment effect of β-secretase 1 (BACE) inhibitor AZD3293 (LY3314814; lanabecestat) but was terminated early after a futility analysis. To minimize the effect of data missing not at random owing to early termination, only participants (both lanabecestat-treated and placebo-treated) who had a flortaucipir scan at baseline and completed a clinical dementia rating (CDR) at the week 78 (18 months) were selected into Study 2. Study 2 participants were enrolled from 68 study sites worldwide from March 2017 to October 2018. Both studies tested the same hypotheses: baseline tau status, determined by flortaucipir visual interpretation patterns, would predict the risk of clinical decline over 18 months of follow-up.

### Key Points

#### Questions

What is the association between flortaucipir positron emission tomography (PET) imaging visual classification using a clinically applicable and US Food and Drug Administration–approved method and 18-month cognitive and functional decline in patients with clinically diagnosed mild cognitive impairment and dementia owing to Alzheimer disease (AD)?

#### Findings

In this analysis of 2 open-label clinical trials, visual read of an advanced flortaucipir PET AD pattern was associated with an increased risk of 18-month cognitive and functional decline compared with other scan patterns.

#### Meaning

Clinically applicable visual reads of flortaucipir PET scans may provide valuable information regarding the risk of near-term clinical deterioration among patients with clinically diagnosed mild cognitive impairment or dementia owing to AD.

Study protocols were approved by the relevant institutional review boards and all participants or authorized representatives signed informed consent prior to conduct of study procedures. Trials were conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization guideline on good clinical practice.

### Participants

Study 1 participants were cognitively impaired men and women 50 years and older with a suspected neurodegenerative cause at enrollment, and with a Mini-Mental State Examination (MMSE) score between 20 and 27, inclusive. Study 2 participants were men and women (aged 55 to 85 years) diagnosed as having mild cognitive impairment (MCI) owing to AD or probable AD dementia by National Institute on Aging-Alzheimer’s Association criteria, with Mini-Mental State Examination (MMSE) score 20 to 30 inclusive, a CDR Global score (CDR-GLOBAL) of 0.5 (MCI) or 0.5 or 1 (AD), a CDR sum of box (CDR-SB) score of at least 0.5, and a Repeatable Battery for the Assessment of Neuropsychological Status Update delayed memory score of 85 or less. All Study 2 participants were Aβ+ by amyloid PET or lumbar puncture.

#### Positron Emission Tomography Imaging Visual Interpretation

In both studies, flortaucipir scans that passed quality control were independently evaluated by 5 imaging physicians blinded to clinical information (details in eMethods in the Supplement). Readers rated each scan as either an advanced, moderate, or negative AD tau pattern (Figure 1) using a predefined visual interpretation method. For analyses purposes, imaging analysis end points were dichotomized as advanced AD tau pattern vs nonadvanced (negative or moderate) AD tau pattern. Majority reads, defined as the same interpretation from 3 or more readers for each scan, were derived mathematically based on this dichotomized end point.

#### Cognitive and Functional Assessments

In both studies, participants’ clinical progression was measured with the CDR scale, including both CDR-SB and CDR-Global, the MMSE, 11-item version of the Alzheimer Disease Assessment Scale (ADAS-Cog 11).
Assessment Scale—Cognitive subscale (ADAS-Cog11), and Functional Activities Questionnaire (FAQ). Assessments were collected at baseline and follow-up visits.

Statistical Analysis
All analyses were independently conducted for each individual study and repeated with pooled study data. For Study 1, baseline, 9-month, and 18-month visit data were used in analyses; for Study 2, baseline, 6-month, 12-month, and 18-month visits were used. Although a subset of Study 2 participants completed 24 months’ follow-up before the study was terminated, 24-month follow-up data was not used in the analyses because sample size was significantly reduced at 24 months owing to early study termination (90 of 205 participants completed 24-month assessments) and because no comparable data are available from Study 1.

Participants’ clinical progression was first assessed using predefined dichotomized outcomes, representing clinically meaningful deteriorations: 1 point or more increase in CDR-SB, any increase in CDR-Global, 4 points or more increase in ADAS-Cog11, 3 points or more decrease in MMSE, and 3 points or more increase in FAQ. The CDR-SB was prespecified as the primary endpoint for determining study success for both studies. In Study 1, Cox proportional hazard model, adjusting for baseline age, respective baseline cognitive or functional test score, and cognitive reserve (American National Adult Reading Test score [ANART]), was used to evaluate the hazard of progressing to these predefined outcomes. Hazard ratios (HR) were reported to assess the hazard difference between scan patterns. Because Study 2 included only those participants from the AMARANTH trial who had a valid baseline scan and who had completed the 18-month CDR evaluation, it was not necessary to compensate for potential information loss owing to premature discontinuation. Thus, a Poisson regression model was used to estimate the different risks of experiencing the pre-defined outcomes by scan patterns, and the risk ratios (RR) were reported accordingly. The models were adjusted for respective baseline cognitive/functional test scores, age, education, and therapeutic treatment arms from AMARANTH. For the pooled analyses, similar Poisson regression models were applied but adjusted for study identification, baseline age, and respective baseline scores.

Additionally, progression was quantified as mean change from baseline in CDR-SB, MMSE, ADAS, and FAQ, respectively. Mixed models with repeated measures (MMRM) were used to estimate the mean change by scan patterns for each cognitive/functional assessment. Covariates included baseline age, respective baseline cognitive/functional test scores, visit number, scan pattern-by-visit interaction, and baseline ANART for Study 1, or education and treatment arms for Study 2. Adjusted mean change values by scan patterns and their differences were reported along with the 2-tailed P values, with statistical significance declared at .05 level. Pooled data were analyzed with similar models, but adjusted for study identification, respective baseline score, and age. For the pooled analyses, the 6-month and 12-month visits from Study 2 were averaged to approximate the 9-month visit for comparison with the Study 1 nine-month visit.

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Participant Characteristics

In Study 1, a total of 159 participants had flortaucipir scans that passed quality control. Of these, 74 were women (47%), 154 were White (97%), and the mean (SD) age was 72.9 (9.6) years (Table 1). Study 1 participants had a mean (SD) baseline MMSE of 24.9 (2.2), CDR-SB of 3.4 (1.9), ADAS-Cog11 of 14.3 (6.1), and FAQ of 8.3 (6.8). Sixty-two (39%) were clinically diagnosed as having dementia, including 5 with a prescan working diagnosis of non-AD dementia (1 vascular, 2 frontotemporal, 1 atypical frontotemporal, and 1 Lewy body dementia; these were grouped with AD for analysis purposes). Sixty-four percent of participants (101 of 159) were Aβ+, 41% were apoipoprotein E (APOE) ε4 carriers, and 78 (49%; 76 Aβ+ and 2 Aβ−) had an advanced, 11 (7%; 9 Aβ+ and 2 Aβ−) had a moderate, and 70 (44%; 16 Aβ+ and 54 Aβ−) had a negative AD pattern. About 70% of participants finished all study visits. Of the 205 AMARANTH participants selected into Study 2, 100 were women (49%), 172 were White (84%), and mean (SD) age was 71 (7.7) years. Study 2 participants were more impaired than those in Study 1: 69% with AD; mean (SD) baseline MMSE, 23.8 (2.6); CDR-SB, 3.7 (1.5); ADAS-Cog11, 17.9 (6.0); and FAQ, 9.7 (6.5). All participants were Aβ+ per AMARANTH enrollment criteria, and 69% were APOE ε4 carriers. In Study 2, 162 participants (79%) had an advanced AD pattern, 15 (7.3%) had a moderate AD pattern, and 28 (13.7%) had a negative AD pattern.

Risk of Clinical Progression by Flortaucipir PET Scan Patterns

Pooling Study 1 and Study 2 data, 240 participants had an advanced and 124 participants had a nonadvanced AD flortaucipir scan pattern. Participants with an advanced AD scan pattern experienced more predefined clinical meaningful deterioration events than those with a nonadvanced pattern. For example, 70% of advanced vs 46% of nonadvanced pattern participants had CDR-SB 1 point or more increase (RR, 1.40; 95% CI, 1.11-1.76; P = .005). Similar statistically significant RRs were observed for the other assessments (Figure 2). At the 18-month follow-up, adjusted mean changes were CDR-SB, −2.28 vs −0.98 (P = .001); MMSE, −4.13 vs −1.27 (P = .001); FAQ, 6.15 vs 2.10 (P = .001); and ADAS-Cog11, 6.40 vs 2.30 (P = .001) for advanced vs nonadvanced AD patterns respectively (Table 2, Figure 3). All P values remained significant after Bonferroni correction for multiplicity.

Among the 3 different scan patterns, the moderate AD pattern occurred the least frequently in both studies (Table 1). Pooled data revealed an ordinal association of clinical progression by scan patterns (advanced > moderate > negative AD pattern). For example, participants deteriorated 2.3 points (P < .001), 1.7 points (P = .001), and 0.78 points (P = .005) in CDR-SB at the 18-month follow-up, respectively (eFigure 1 in
the Supplement). Similar findings were observed for MMSE, ADAS-Cog11, and FAQ. Pairwise comparisons showed that participants with an advanced AD pattern consistently had a statistically significantly larger decline than those with a negative AD pattern, while those with a moderate AD pattern were not consistently different from either advanced or negative pattern participants.

For the individual studies, analyses suggested a greater risk of clinical progression for the advanced AD pattern group, although risk differences did not always meet statistical significance. Study 1 data showed a greater risk of progression in CDR-SB for advanced AD pattern participants, and FAQ. Pairwise comparisons showed that participants with an advanced AD pattern consistently had a greater deterioration than those with a negative AD pattern, while those with a moderate AD pattern were not consistently different from either advanced or negative pattern participants.

Study 2 yielded a statistically significant RR of 1.36 for CDR-SB (95% CI, 1.03-1.79; P = .03). Other RRs for the secondary prespecified outcome measures indicated higher risk for the advanced AD pattern group, reaching statistical significance for ADAS-Cog11 (RR, 1.77; 95% CI, 1.12-2.80; P = .01) but not for CDR-Globa, MMSE (RR, 1.35; 95% CI, 0.96-1.89; P = .08), or FAQ (RR, 1.32; 95% CI, 0.98-1.78; P = .06). In both studies, MMRM analyses demonstrated greater declines for advanced AD pattern participants in all the clinical end points assessments, and comparisons with nonadvanced AD pattern participants were all statistically significant (Table 2; Figure 3).

Figure 2. Risk for Clinical Progression: Comparing Advanced Alzheimer Disease (AD) Pattern and Nonadvanced AD Pattern Groups

| Event rate, % | Lower risk for advanced AD pattern | Higher risk for advanced AD pattern | P value |
|---------------|-----------------------------------|------------------------------------|---------|
| CDR-SB        | Advanced                          | Nonadvanced                        |         |
| Study 1       | 57.10                             | 45.60                              | 1.58 (0.97-2.85) |
| Study 2       | 73.50                             | 55.80                              | 1.36 (1.03-1.79) |
| Pooled        | 70                                 | 45.70                              | 1.40 (1.11-1.76) |
| CDR-Globa     | Study 1                            | 44.40                              | 2.37 (1.32-4.26) |
| Study 2       | 43.80                             | 37.20                              | 1.28 (0.82-2.02) |
| Pooled        | 45                                 | 29.50                              | 1.60 (1.13-2.27) |
| MMSE          | Study 1                            | 47.60                              | 2.51 (1.29-4.89) |
| Study 2       | 69.60                             | 50                                 | 1.35 (0.96-1.89) |
| Pooled        | 64.40                             | 29.80                              | 1.68 (1.22-2.32) |
| ADAS-Cog11    | Study 1                            | 55.60                              | 1.36 (0.77-2.41) |
| Study 2       | 62.40                             | 33.30                              | 1.77 (1.12-2.80) |
| Pooled        | 60.50                             | 29.80                              | 1.73 (1.35-2.25) |
| FAQ           | Study 1                            | 74.60                              | 2.79 (1.67-4.64) |
| Study 2       | 70.30                             | 54.80                              | 1.32 (0.98-1.78) |
| Pooled        | 70.50                             | 40.40                              | 1.74 (1.35-2.25) |

The interreader consistency for flortaucipir scan visual interpretation was high for both Study 1 and 2 (94.5% and 91.4% agreement rate; eTable 1 in the Supplement). This high consistency level in scan interpretation also resulted in homogeneous findings similar to that observed for majority reads, eg, HR values from the analyses of CDR-SB event ranged from 1.49 to 1.70 for Study 1, and the corresponding RR values ranged from 1.25 to 1.46 for Study 2 (eTable 2 in the Supplement). The mean changes of each end point assessment by visual classification from individual reader's reads were also similar to those found using majority reads (eTable 3 in the Supplement).

The interaction of amyloid and tau on clinical progression was shown in eFigure 2 in the Supplement. Among Study 1 participants, compared with the Aβ− group, the Aβ+/advanced AD pattern group showed significantly greater CDR-SB progression (mean change, 1.99 vs 0.72; P = .02), whereas the Aβ+/nonadvanced group progressed similarly to the Aβ− group (0.86 vs 0.72; P = .84). The comparison between Aβ+/advanced and Aβ+/nonadvanced group yielded a P value at .10. Similar trends were observed for other end point assessments.

Impairment severity level at baseline was positively associated with participants’ clinical progression. For example, the entire population (regardless of tau status) had CDR-SB deteriorated from 0.51 to 3.61 points ranging from the healthiest to the most impaired MMSE baseline level (eFigure 3 in the Supplement). However, at each MMSE level, participants with an advanced AD pattern on average had a greater deterioration, eg, CDR-SB changed 0.98 to 3.97 points for advanced, whereas −0.20 to 2.02 points for nonadvanced AD group across

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The statistical analysis showed a significant difference in progression rates between the advanced and nonadvanced AD pattern groups. The risk for clinical progression associated with an advanced AD pattern was higher compared to the nonadvanced pattern, as indicated by the hazard ratios (HR) and confidence intervals (CI) for various outcomes. For example, in the CDR-SB assessment, participants with an advanced AD pattern had a higher risk of progression compared to those with a nonadvanced pattern, with an HR of 1.58 (CI: 0.97-2.85) in Study 1 and 1.60 (CI: 1.13-2.27) in Study 2. Similar trends were observed in other measures such as MMSE, ADAS-Cog11, and FAQ.

For CDR-SB progression, the interaction of amyloid and tau was also examined. Among Study 1 participants, the Aβ+/advanced AD group showed a significantly greater CDR-SB progression compared to the Aβ− group (mean change: 1.99 vs 0.72; P = .02). This indicates that the presence of both amyloid and tau is associated with a higher risk of clinical deterioration.

The interreader consistency for flortaucipir scan visual interpretation was high for both Study 1 and 2. The mean changes of each end point assessment by visual classification from individual reader’s reads were similar to those found using majority reads. The interaction of amyloid and tau on clinical progression was shown in eFigure 2 in the Supplement. In Study 1, participants with an advanced AD pattern showed greater decline compared to the nonadvanced group, with mean changes ranging from 1.99 to 3.61 points for CDR-SB.

In conclusion, the presence of both amyloid and tau is associated with an increased risk of clinical progression in AD. The advanced AD pattern is characterized by a higher risk of deterioration compared to the nonadvanced pattern, which has implications for clinical diagnosis and treatment planning.
these MMSE levels. The analysis results with other endpoint assessments were similar.

**Discussion**

The association between flortaucipir scan pattern and clinical progression over 18 months was assessed in 2 clinical studies comprising 364 cognitively impaired participants with a range of demographic characteristics, and clinical presentations similar to patients often seen in a clinical practice setting. The results indicated that an advanced AD flortaucipir pattern was associated with increased risk of clinical progression over 18 months, as demonstrated by higher event rates and larger mean deteriorations across all the clinical endpoint measurements. These were almost always statistically different from the nonadvanced AD pattern group, except for a few end points analyzed at the individual study level.

Risk ratios for pooled data ranged from approximately 1.4 to 1.8. Although this level of risk prediction may seem modest, it must be taken in context of other risk factors patients have for progression and that we studied only 18 months of change in a disease that may have a 20- to 30-year natural history. While the flortaucipir scan pattern is an important risk factor, it is likely not the sole determinant of near-term cognitive decline in AD. This is consistent with our understanding of AD, which occurs against a background of genetically and experientially determined cognitive reserve, concomitant diseases, and age-related changes, which may positively or negatively modulate the effects of underlying AD pathology and rates of progression. A diagnosis of AD itself comes with a significant increased risk of long-term cognitive and functional decline. Difficulty in predicting an exact outcome for individual patients is not unique to AD. Clinical models of cardiovascular risk assessment demonstrated similar modest levels of risk prediction. Therefore, despite rela-
tively modest effect size, flortaucipir scan patterns may provide clinically relevant prognostic information for AD patient management.

Although statistical significance was not met for all tests, data for each study similarly showed that the advanced AD pattern group was at an increased risk of clinical progression. For example, while Study 1 showed a borderline statistical significance for the primary end point assessment, Study 2 met the same prespecified criteria for the primary hypothesis (1 point or more increase in CDR-SB). The sample size difference might contribute to the different level of significance observed (111 vs 205 completers for Studies 1 and 2, respectively). Nevertheless, quantitatively assessed clinical deterioration (Figure 3; Table 2) demonstrated a statistically significantly higher risk associated with an advanced AD scan pattern in all clinical measurements, and from both studies. It is also worth noting that the magnitude of changes observed from the advanced AD pattern group were about 2-fold or larger than the other group.

Although the designs and analyses in Study 1 and Study 2 are similar, there are several important differences. Study 1 was designed to investigate a range of patients similar to those in a real-world clinical practice environment. Therefore, cognitively impaired participants were not required to meet established probable AD diagnosis criteria.\(^\text{29,30}\) In this study, only 64% of participants were Aβ+, and the dementia participants with a suspected neurodegenerative cause (n = 62) included 5 participants with dementia where AD was part of the differential diagnosis but was not the primary suspected diagnosis. In contrast, Study 2 participants were required to be Aβ+, with either MCI or probable AD. These characteristics together with the additional inclusion criterion of a score 85 or less on the Repeatable Battery for the Assessment of Neuropsychological Status Update memory index, suggest that Study 2 may have been biased toward a more-impaired/more-likely-to-progress population, despite the more liberal MMSE upper limit (30 vs 27 in Study 1). Arguably, Study 2 data, based...
on a more homogeneous and Aβ+ population, provides a more rigorous estimate of the role of tau in progression in AD-spectrum patients. Nevertheless, flortaucipir scan pattern data showed similar results across both studies in predicting clinical progression.

It is important to understand the interaction between amyloid and tau because they usually coexist in these patients. The Aβ− participants enrolled in Study 1 provided an opportunity to understand this effect. The ordinal association (Aβ−/advanced AD to Aβ+/nonadvanced AD to Aβ− in progression) as shown in eFigure 2 in the Supplement indicated that although amyloid status influences clinical progression, an advanced AD tau pattern may have a more direct association with near-term clinical progression and provides additional information beyond amyloid.

It is also important to consider that 21% of the nonadvanced AD pattern participants (n = 26 of 124) had a moderate AD pattern, and most of them (n = 24 of 26) were Aβ+. Thus, these moderate AD pattern participants likely had both hallmark pathologies of AD and would be expected to show some cognitive deterioration over 18 months. Indeed, in the pooled study data (eFigure 1 in the Supplement), at month 18, all 3 pattern groups had some clinical progression, in the order of advanced AD pattern group, moderate AD pattern group, and negative AD pattern group. Nevertheless, except for the FAQ, mean changes between moderate and negative AD pattern groups were not statistically different. These data appear to support the prespecified hypothesis for both studies, that an advanced AD pattern would be more informative when predicting participants’ near-term clinical progression than other patterns.

Limitations
The study had several limitations. To provide a potentially clinically applicable patient stratification, both the visual interpretation and the primary end points were dichotomized (eg, advanced/nonadvanced AD pattern; CDR-SB worsening 1 point or more). However, AD is a continuous, progressive pathology. Hence, the analyses here may not provide the most precise representation of the associations between baseline tau and cognitive progression. Additionally, as an observational study, only 69% of Study 1 participants (n = 111 of 160) completed the 18-month follow-up. Loss of follow-up may have affected the efficacy evaluation, possibly reflected in the borderline significant P value for the primary analysis. Study 2 participants were selected from AMARANTH trial. Although this study was terminated early and primary efficacy analyses demonstrated no therapeutic effect, there may have been an undetected effect of therapy on cognitive change that could alter the association between baseline tau levels and cognitive change. Treatment was entered as a factor in all Study 2 statistical models, and no significant interactions were found. As a result, the pooled analyses were not adjusted for treatment effect.

Lastly, at baseline, participants with an advanced AD pattern were more cognitively impaired (Table 2). Although the baseline differences are relatively small, and the studies specifically constrained the baseline MMSE range to obtain a more homogeneous sample, it would be expected that more severe patients would deteriorate faster. Thus, analyses were corrected for respective baseline cognitive or functional scores. Statistically significant differences in progression by scan patterns were observed while controlling for this possible confounding effect. In addition, baseline MMSE associated with clinical progression independent of tau pattern, as expected (eFigure 3 in the Supplement). However, at any baseline MMSE level, the advanced AD group consistently had more progression than the nonadvanced AD group. This suggests that flortaucipir scan patterns provided additional information to understand patients’ clinical progression in addition to other clinical data.

Conclusions
In summary, data from 2 independent studies consistently demonstrated that participants with a flortaucipir advanced AD tau pattern are at a higher risk of clinically meaningful deterioration. Thus, flortaucipir PET, interpreted with a clinically applicable visual method, could provide helpful information regarding anticipated clinical decline in the management of patients being assessed for causes of cognitive impairment.

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