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New Studies Suggest Relationship between Tau Pathology and Progression of Alzheimer's Disease

Results Presented at the Alzheimer's Association International Conference® 2016 (AAIC® 2016)

INDIANAPOLIS, July 27, 2016 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced results from two distinct analyses of a phase 2 study using the tau imaging agent flortaucipir ([18F] AV-1451) that evaluated the relationship between tau tangles and the progression of Alzheimer's disease. The first analysis, "Evolution of [18F] AV-1451 PET Tau Signal: Interim Analysis of an 18 Month Phase 2 Study," suggested the presence of tau tangles increased significantly over an 18-month period, consistent with ongoing cognitive decline in beta-amyloid positive patients. Further, patients with more tau at baseline accumulated tau at a faster rate, indicating the development of Alzheimer's disease accelerates as it progresses.[1] The second analysis, "The Relationship of [18F] AV-1451 PET Tau Images to Changes in Cognition over Time," suggested a correlation between the location of tau in the brain and progression of cognitive decline in beta-amyloid positive patients.[2] These findings were presented today at the Alzheimer's Association International Conference® 2016 (AAIC® 2016) in Toronto, Canada.

"These data are exciting because they suggest new insights into the relationships between tau deposits and the progression of Alzheimer's disease," said Mark Mintun, M.D., chief medical officer, Avid Radiopharmaceuticals, a wholly owned subsidiary of Lilly. "We hope these results can help guide future studies to further our understanding of the mechanisms of Alzheimer's disease and speed the development of treatments."

The primary objective of the first analysis was to characterize the rate of change in the tau signal in Alzheimer's disease to follow disease progression.[1] The primary objective of the second analysis was to understand how the uptake patterns of flortaucipir relate to cognitive performance.[2] Flortaucipir is Lilly's phase 3 tau positron emission tomography (PET) imaging agent, an investigational chemical entity being studied for the imaging of tau pathology. Tau imaging agents may enable researchers to noninvasively examine the degree and extent of tau pathology in the brain, quantify changes in tau deposition over time, evaluate its relation to cognition and assess the efficacy of Alzheimer's disease therapeutics.[3] As a marker of neurodegeneration, tau imaging may serve as an adjunct tool to aid in diagnosis, as well as in disease staging. A tau-PET tracer could potentially also allow for a selection of pathology-positive individuals and monitor the effectiveness of therapy.[3]

"This is the first time an analysis has shown a correlation between tau tangles and cognitive decline in patients living with Alzheimer's disease," said Michael Devous, Ph.D., vice president, Avid Radiopharmaceuticals, a wholly owned subsidiary of Lilly. "As tau pathology is considered a biomarker of cognitive decline, understanding the patterns in the tau signal specific to Alzheimer's disease might be useful in predicting disease progression."

Alzheimer's disease, the most common form of dementia, causes progressive decline in memory and other aspects of cognition.[4] Beta-amyloid plaques and tau tangles are two known hallmark pathologies of Alzheimer's disease and each works in different ways.[4] Tau protein forms into neurofibrillary tangles, which are abnormal collections of twisted protein threads found inside nerve cells. These tangles start in the areas of the brain important for memory, then proceed throughout the rest of the brain as symptoms progress.[5]

Evolution of [18F] AV-1451 PET Tau Signal: Interim Analysis of an 18 Month Phase 2 Study[1]

Study Methods

Two hundred and seventeen subjects clinically diagnosed as young healthy controls, old healthy controls, with mild cognitive impairment or with AD were enrolled for flortaucipir PET imaging at baseline, nine months, and 18 months. Repeat flortaucipir scans were collected at a nine-month visit and an 18-month visit. Images were co-registered and resampled into Montreal Neurological Institute (MNI) atlas space. Activity in atlas-based and large average regions of interest (ROI) was normalized by cerebellar gray matter to create standard uptake value ratio (SUVr). Amyloid imaging was done at baseline

and reviewed using standard methods to determine amyloid positivity.

Key Results Highlights

- Flortaucipir PET tau signal in beta-amyloid positive subjects increased significantly over 18 months across multiple brain regions, consistent with ongoing neurodegeneration.
- Although preliminary, the correlation of change in SUVr to both age and baseline SUVr could indicate differences in aggressiveness and underlying stage of the disease.
- Interim analysis of the 18-month data showed the amyloid-beta positive group had a significant cortical flortaucipir increase based on a large cortical ROI.
- No significant change was seen in the cortex of amyloid-beta negative subjects.

The Relationship of [18F] AV-1451 PET Tau Images to Changes in Cognition over Time[2]

Study Methods

PET scan results were studied in 86 amyloid-positive healthy (n=5), mild cognitive impartment (MCI) (n=47) or AD (n=34) subjects. Voxel-wise SUVr was calculated relative to a data-driven reference region. Cognitive assessments included Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog) and an extensive neuropsychological battery. Spearman correlations comparing voxel-wise SUVr images to cognitive scores at baseline defined domain-specific VOIs (CogVOIs). In addition, relationships between CogVOI SUVrs and changes in cognition after 18 months were also explored by correlation analyses.

Key Results Highlights

- Current data suggest increased baseline tau correlates with cognitive impairment in a domain-specific pattern. Further, VOIs in the regions defined by that pattern reveal that greater baseline tau is associated with greater cognitive decline after 18 months.
  - Correlations between regional distribution of tau as assessed by Flortaucipir PET imaging and cognition were seen at baseline for several but not all cognitive tests (greater tau associated with worse performance).
  - Voxel-wise SUVr values correlated with cognitive scores in a domain-dependent spatial distribution.
  - CogVOI SUVRs were related to changes in cognition after 18 months for many of the domains for which there were baseline relationships. However, in most cases these correlations were similar to those found for a large cortical ROI that also discriminated between diagnostic groups at baseline.
  - For a few cognitive tests (ADAS, Word recognition), the best predictor of 18 month cognitive change was the ROI defined by the baseline tau/cognition correlation.

About Flortaucipir
Flortaucipir is Lilly's phase 3 tau PET imaging agent, an investigational chemical entity being studied for the imaging of tau pathology.

About Alzheimer's Disease
Alzheimer's disease is a fatal illness that causes progressive decline in memory and other aspects of cognition. It is the most common form of dementia, accounting for 60 to 80 percent of dementia cases.[6,7] It is estimated that there are nearly 47 million people living with dementia worldwide.[6] The number of people affected by dementia is expected to reach nearly 75 million in 2030 and 132 million in 2050.[6] Estimates vary, but experts suggest that as many as 5.4 million Americans may have Alzheimer's disease.[8]

About Eli Lilly and Company
Lilly is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at www.lilly.com and newsroom.lilly.com/social-channels.

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This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about tau imaging agent flortaucipir to evaluate the relationship between tau tangles and the progression of Alzheimer's disease, and reflects Lilly's current beliefs. However, as with any pharmaceutical product or diagnostic tool,

there are substantial risks and uncertainties in the process of development and commercialization. Among other things, there can be no guarantee that future study results will be consistent with study findings to-date, or that tau imaging agent will receive regulatory approvals or prove to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's most recent 10-K and 10-Q filings with the United States Securities and Exchange Commission. Except as may be required by law, Lilly undertakes no duty to update forward-looking statements for events occurring after the date of this release

[1] Mintun M, Devous M, Joshi A, Kennedy I, et al. Evolution of [18F] AV-1451 PET tau signal: Interim analysis of an 18 month Phase 2 study. Presented at Alzheimer's Association International Conference (AAIC) 2016, July 24 - 28, 2016; Toronto, Canada.

[2] Devous M, Navitsky M, Siderowf A, et al. The Relationship of [18F] AV-1451 PET Tau Images to Changes in Cognition over Time. Presented at Alzheimer's Association International Conference (AAIC) 2016, July 24 - 28, 2016; Toronto, Canada.

[3] James O, et. al. PET Imaging of Tau Pathology in Alzheimer's Disease and Tauopathies. Neurology. March 2015. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4353301/. Accessed July 2016.

[4] Alzheimer's Association. What Is Alzheimer's Disease? http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp. Published January 2016. Accessed July 2016.

[5] Alzheimer's Society. How does tau, a hallmark of Alzheimer's disease, affect the connections between brain cells? https://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=2507. Accessed July 2016.

[6] Alzheimer's Disease International. Dementia statistics. http://www.alz.co.uk/research/statistics. Accessed July 2016.

[7] Alzheimer's Association. What Is Dementia? http://www.alz.org/what-is-dementia.asp. Published January 2016. Accessed July 2016.

[8] Alzheimer's Association. 2016 Alzheimer's Disease Facts and Figures. *Alzheimer's & Dementia*. Available at http://www.alz.org/documents_custom/2016-facts-and-figures.pdf. Accessed July 2016.

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