In vivo characterization of the PET pharmacokinetic properties of T807 in humans

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USA

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Alzheimer's disease & other dementias

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Research Abstract

? DESCRIPTION (provided by applicant): The public health burden of AD is increasing with devastating projections on an international basis. Although much knowledge has been gained recently about the AD disease process, as a result of PET Aß imaging in combination with MRI Hippocampal volume, FDG PET, Aß and tau cerebrospinal fluid (CSF) concentrations and cognitive performance – there is still much to be understood, particularly as the field moves further from end-stage disease to preclinical AD. Jack and Holtzmann (2013) concluded that 5 AD biomarkers were sufficiently validated for inclusion into clinical diagnostic criteria and therapeutic trial use that fall into 2 broad measures: (1) Aß deposition (Aß PET, CSF Aß) and (2) neurodegeneration (FDG PET, MRI HV, CSF tau). The development of promising tau-specific PET agents, such as [18F]T807 (also named [18F]AV-1451), could lead to a new 6th AD biomarker for regional brain aggregated tau levels in vivo. The first human T807 PET studies show promise for the in vivo detection of aggregated tau load but tissue ratio data (i.e., SUVR) suggest that the relative T807 uptake kinetics may vary across observed levels of in vivo binding, with early and stable onset of the SUVR plateau across regions for controls and mild binders, more variability in the approach to plateau for moderate binders and nearly steady accumulation for high binders. This raises concern that regional T807 tissue ratios determined at a fixed time interval within the 100 min post-injection PET scan interval (commonly used) may not serve as robust binding measures, across subject groups and regions. The proposed research is an essential step toward “”sufficient validation”” of such a biomarker in its aim to characterize the in vivo PET kinetics of T807 and verify feasible methods for valid and consistent cross-sectional and longitudinal data collection and interpretation. This research will primarily focus on the AD disease spectrum and study 30 subjects screened with [11C]PiB (PiB): 15 PiB(-) controls [5 young, 10 elderly] and 15 PiB(+) subjects [5 elderly controls, 5 mild cognitive impairment, 5 AD]. We will augment this characterization by also exploring: (1) T807 kinetics in a small group of subjects with Progressive Supranuclear Palsy and (2) relationships between in vivo T807 PET and neuropathology measures of tau load and other neuropathology measures. It is very likely that [18F]T807 will be the most widely used PET tau imaging agent, at least initially. Studies are ongoing or being initiated at several sites (e.g., Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4) study). There is a need for a careful systematic evaluation of T807 kinetics in an AD research population, during the early use of this new technology.

Lay Summary

PUBLIC HEALTH RELEVANCE: The development of promising tau-specific PET agents, such as [18F]T807 (or [18F]AV-1451), could lead to a new AD biomarker for regional brain aggregated tau levels in vivo. The first human [18F]T807 PET studies show promise but tissue ratio data suggest that the stability of the [18F]T807 relative uptake kinetics can vary across levels of in vivo binding, such that regional T807 tissue ratios determined at a fixed time window within a 100 min post-injection PET scan interval may not serve as robust binding measures, across subject groups and regions. The proposed research will characterize the in vivo PET kinetics of [18F]T807 in control, mild cognitive impairment and AD subjects and verify feasible methods to enable consistent routine data collection and interpretation over time, across the AD-disease spectrum. This is an essential early step toward “”sufficient validation”” of a new AD biomarker to complement Aß PET, FDG PET, MRI hippocampal volume and CSF Aß/tau measures.

Further information available at:

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