SYNOPSIS

Title of Study: Pilot study of the [18F]THK-5351 positron emission tomography (PET) tracer in different tauopathies **Sponsor:** Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau – IIB Sant Pau **EudraCT:** 2015-004656-22 **Sponsor's protocol code number:** IIBSP-THK-2015-77
Investigators: PI: Alberto Lleó Bisa **Research team:** Juan Fortea Ormaechea Daniel Acolea Rodríguez Mª del Valle Camacho Rafael Blesa González Ignacio Illán Gala Estrella Morenas Rodríguez Jordi Pegueroles
Study centre(s): Hospital de la Santa Creu i Sant Pau.
Publication (reference): none.
Studied period (years): 2017-2018. (date of first enrolment): 5/4/2018 (date of last completed): 29/5/2018
Phase of development: phase 1
Objectives: To study the diagnostic potential and distribution pattern of the PET tracer [18 F]THK-5351 in different clinical syndromes associated with tauopathies (Alzheimer's disease (AD), AD with Down syndrome, and Frontotemporal lobar degeneration syndromes.
Methodology: The diagnostic potential and distribution pattern of 18 F]THK-5351 the [SUVR (Standardized Uptake Value Ratio) was calculated and a Receiver Operating Characteristic (ROC) analyses was performed to analyze the discrimination capacity between cases and controls. PET scans were visually inspected by a medical expert and then analysed quantitatively. PET images were normalized to a MNI space by the use of a SPM12 (Statistical Parametric Mapping) template and SUVR was calculated in the cerebral areas of interest by dividing the mean uptake of each zone between the average uptakes in the reference area (cerebellum). For voxel-based statistical analysis, the original images were escalated in intensity dividing by the average uptake in the reference region.
Number of patients (planned and analysed): Planned: 80 Analysed: 27
Diagnosis and main criteria for inclusion: **Subjects**: A total of 80 subjects was planned: 10 cognitively normal controls, 20 patients with

AD (10 with mild cognitive impairment and 10 with mild AD dementia), 20 patients with DS (including 10 subjects without dementia and 10 subjects with AD dementia), 10 patients diagnosed of behavioral variant of frontotemporal dementia (bvFTD), 10 diagnosed of nonfluent/agrammatic (nfaPPA) and 10 4R-related syndromes (4R-S) including Progressive Supranuclear Syndrome (PSPS) and Corticobasal Syndrome (CBS).

Inclusion criteria:
Cognitively normal subjects met the following inclusion criteria: a) individuals older than 18 year giving their informed consent; b) a Mini Mental State Examination (MMSE) score between 24-30; c) absence of neither cognitive complaints nor objective memory impairment as ascertained by a normal scaled-score value (adjusted for age and educational level) at the free and cued selective reminding test (Grober, Buschke et al. 1988); c) clinical dementia rating scale (CDR) of 0 (Morris, 1993); d) core AD CSF biomarkers values should be within the normal range (according to our validated reference values).
The patients with mild cognitive impairment due to Alzheimer‟s disease (MCI-AD) met the following inclusion criteria: a) individuals older than 18 year giving their informed consent; b) Preserved activities of daily living in the IDDD Scale (Teunisse et al. 1992); c) should meet current criteria for the diagnosis of mild cognitive impairment due to Alzheimer‟s disease of high probability (Albert MS, *Alzheimer's Dement* 2011).
The patients with mild dementia due to Alzheimer‟s disease (dementia-AD) will meet the following inclusion criteria: a) individuals older than 18 year giving their informed consent; b) Mild impairment in activities of daily living in the IDDD Scale (Teunisse et al. 1992); c) should meet current criteria for the diagnosis of Alzheimer‟s disease dementia with pathophysiological evidence of Alzheimer‟s disease (McKhan GM, *Alzheimer's dement* 2011).
The patients with Down Syndrome (DS) without dementia met the following inclusion criteria: a) individuals older than 18 year giving their informed consent; b) previous diagnosis of DS; c) Intellectual Quotient > 34; d) absence of neither cognitive complaints nor objective memory impairment as ascertained by specific neuropsychological tools validated in DS.
The patients with Down syndrome with associated AD dementia (DS-AD) met the following inclusion criteria: a) individuals older than 18 year giving their informed consent; b) previous diagnosis of DS; c) objective cognitive deterioration as ascertained by specific neuropsychological tools validated in DS.
The patients with the behavioral variant of frontotemporal dementia (bvFTD) met the following inclusion criteria: a) individuals older than 18 year giving their informed consent; b) patient should meet current criteria for the diagnosis of probable o definite bvFTD (Rascovsky K, *Brain* 2011); c) core AD CSF biomarkers values should be within the normal range (according to our validated reference values).
The patients with the nonfluent/agrammatic variant of primary progressive aphasia (nfaPPA) met the following inclusion criteria: a) individuals older than 18 year giving their informed consent; b) patient should meet current criteria for the diagnosis of nfaPPA (Gorno-Tempini M, *Neurology* 2011); c) core AD CSF biomarkers values should be within the normal range (according to our validated reference values).
The patients with clinical syndromes related to 4R tauopathies (S-4RT) will verify the following inclusion criteria: a) individuals older than 18 year giving their informed consent; b) patient will meet diagnostic criteria for progressive supranuclear palsy (Litvan I, *Neurology* 1996) or corticobasal syndrome (Armstrong MJ, *Neurology* 2013); c) core AD CSF biomarkers values should be within the normal range (according to our validated reference values).

Test product product, dose and mode of administration:
The radiopharmaceutical ([18F] THK-5351) was administered intravenously in a single dose of

185Mbq.
Duration of treatment: 1 hour.
Reference therapy, dose and mode of administration: Not applicable, THK is a radiotracer. Mode of administration: IV infusion in a single dose of 185Mbq.
Criteria for evaluation: SUVR (Standardized Uptake Value Ratio) and a Receiver Operating Characteristic (ROC) analyses. Efficacy: not applicable. Safety: No adverse effects were recorded.
Statistical methods: The main variable was SUVR.
Summary - Conclusions Efficacy Results: The study enrolled 27 subjects and was terminated early due to discontinuation of the radiotracer by the manufacturer. Safety Results: The procedure was safe and no adverse effects were recorded. Conclusion: [18F] THK-5351 is a tracer that can detect tau pathology in a variety of neurodegenerative syndromes. Non-specific binding was observed in some cases. The administration of the readiotracer was not associated with adverse effects.
Date of report: July 7th, 2018