Evaluation of 18F-AV-1451 kinetic modeling in patients in Alzheimer's disease and healthy controls

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The primary objectives of this study are:* To evaluate tracer kinetic models for the purpose of quantifying specific binding of 18F-AV-1451 in cross sectional and longitudinal applications; and* To evaluate simplified methods for quantification of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Encephalopathies
Study type	Interventional

Summary

ID

NL-OMON44604

Source
ToetsingOnline

Brief title
Tau-Image

Condition

- Encephalopathies
- Dementia and amnestic conditions

Synonym
Alzheimer's Disease, dementia

Research involving
Human

Sponsors and support

Primary sponsor: Avid Radiopharmaceuticals
Source(s) of monetary or material Support: Avid Radiopharmaceuticals

Intervention

Keyword: Alzheimer, kinetic modelling, PET, Tau

Outcome measures

Primary outcome

Quantitative Specific binding of18F-AV-1451 in the brain. Simplified parametric

methods. Test-retest stability

Secondary outcome

relation with cognition

Study description

Background summary

Molecular imaging biomarkers have the potential to aid in the diagnosis of patients with cognitive impairment, who are being evaluated for Alzheimer*s disease (AD) (Dubois, 2010; McKhann, 2011). Positron emission tomography (PET) ligands such as florbetapir F 18 (Wong, 2010) may provide a minimally invasive estimate of cortical beta amyloid (A*) neuritic plaque deposition, a hallmark pathology, and a required element for the evaluation of AD neuropathologicdiagnosis (Hyman 2012).
In contrast to A* neuritic plaques, the density and distribution of phosphorylated tau, aggregated in neurofibrillary tangles, increases with AD-related cognitive impairment and correlates with neurodegeneration (Dickson et al., 1997; Duyckaerts et a., 1987). Thus, a PET imaging agent that binds to phosphorylated tau has potential application as a biomarker for disease severity/neurodegeneration and may be useful both for selecting patients for therapy and for monitoring disease progression in therapeutic trials.
18F-AV-1451(originally named [F-18]T807 by Siemens Molecular Imaging Biomarker Research group) has been developed as a positron emitting radiopharmaceutical for in vivo imaging of tau protein aggregates (Xia et al., 2013).
Autoradiography results using tissue sections from human brains showed a strong signal in the grey matter of cortical slices from tau positive brains, but weak or no binding in tau negative, A* positive, or tau and Ab negative tissue.Scatchard analysis based on this heterogeneous autoradiography assay yielded an estimated Kd of 15nM. A saturation binding experiment using purified Paired Helical Fragment Tau isolated brains of AD patientsyielded a Kd value of 0.7 nM.

AV-1451 was assessed in competitive binding assays against a panel of 72 of the most common central nervous system (CNS) targets and no clinically relevant inhibition was seen.AV-1451 was positive in the in vitro hERG assay, albeit at a concentration at least 50 fold greater than the maximum theoretical plasma concentration; in vivo cardiovascular safety pharmacology assessments in dogsshowed no evidence of QT prolongation at doses up to 50x the intended maximum human dose (MHD). Nonetheless, until sufficient human cardiovascular safety data are available, initial clinical studies will exclude subjects with a history of risk factors for Torsades de Pointes and subjects taking drugs known to prolong the QT interval.
In vivo safety pharmacology studies were also conducted in rats to determine potential effects on the CNS and respiratory systems. In these studies no clinically relevant effects were reported at doses exceeding 100x the intended MHD. Additionally, non-radioactive AV-1451 has been tested in single and repeat-dose toxicology studies in rat and dog. In each of these studies the no observable adverse effect levels (NOAELs) were the highest doses tested (150x MHD for single, 50x MHD for repeat).
Potential genotoxicity of non-radioactive AV-1451 was tested in both in vitro and in vivo assays. In the in vitro assays, AV-1451 tested positive for potential genotoxicity. However, in the in vivo rat micronucleus assay, at doses up to 750x MHD (scaled allometrically), AV-1451 showed no evidence of genotoxicity. The different results in the in vitrogenotoxicity assays and the in vivo micronucleus study are likely related to differences in the exposure conditions encountered by the target cells in the different test systems. In vivo, AV-1451 is cleared rapidly; however, the in vitro experiments employ static, prolonged exposure of cells to high concentrations of the test article. While the in vitro data show the potential for genotoxicity, the in vivo data provide assurance that genotoxicity is unlikely to occur at clinically-relevant doses for human diagnostic studies.
18F-AV-1451 has been evaluated in two human studies under the exploratory IND (Chien, et al., 2013). Adverse events reported have been mild and transient; none have been considered related to 18F-AV-1451 administration.Preliminary evaluation of the PET images suggest that 18F-AV-1451 is eliminated from normal brain yielding only a diffuse pattern of background activity (Figure 1), whereas a regionally-specific gray matter distribution is observed in subjects with high probability AD (Figure 2).

Study objective

The primary objectives of this study are:
* To evaluate tracer kinetic models for the purpose of quantifying specific binding of 18F-AV-1451 in cross sectional and longitudinal applications; and
* To evaluate simplified methods for quantification of 18F-AV-1451 uptake.

Study design

This study will evaluate18F-AV-1451 kinetic modelling in patients with Alzheimer*s disease and in cognitively normal healthy controls. Subjects will be split into 2 cohorts: cohort 1 will include approximately 5 probable AD subjects and 5 age-matched cognitively healthy volunteer subjects. Subjects in cohort 1 will receive a18F-AV-1451 PET scan at baseline and again at approximately one year later. Cohort 2 will include approximately 5 subjects with probable AD and 5 age-matched cognitively healthy volunteer subjects. Subjects enrolled in cohort 2 will receive a single 18F-AV-1451 PET scan. All AD patients will be screened according to the standardized clinical dementia screening performed at VUMCand subjects will provide informed consent before starting any study procedures. If MRI brain has been performed more than 6 months (for AD patients) or 12 months (for healthy controls) before baseline imaging, MRI brain will be repeated.
All subjects will receive a venous and arterial cannula.Approximately 240 MBq of18F-AV-1451will be injected intravenously (IV) as a bolus. Immediately following injection, a dynamic 60 minute PET scan will be performed. At approximately 80 minutes post injection, an additional dynamic PET scan will occur for 50 minutes. No more than 500cc of blood will be withdrawn. Arterial blood will be withdrawn continuously from 0-60 minutes using an online detection system which will be cross-calibrated against the PET scanner. At set times, additional manual blood samples will be taken to measure whole blood and plasma concentrations. In addition, plasma samples will be used to determine parent 18F-AV-1451fractions.
Approximately one year following the baseline scan, cohort 1 subjects will return to the clinic for a second18F-AV-1451 PET scan. Subjects will undergo the same procedures as the baseline PET visit including arterial blood draws and blood sampling to measure whole blood and plasma concentrations. Following each 18F-AV-1451 PET visit, a follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days of the imaging day,

Intervention

Name of compound: 18F-AV-1451(also known as [F-18]T807)
Dose: 240 MBq (6.5mCi)
Route of Administration: Intravenous (IV) bolus

Study burden and risks

Risks associated with participation in this study are related to 1) radiation exposure; 2) idiosyncratic reaction to the tracer; 3) placement of the arterial and intra-venous catheter; and 4) discomfort during PET scanning.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy Control Subjects:
1. Male or female * 50 years of age
2. No evidence of cognitive impairment;AD subjects:
1. Male or female * 50 years of age
2. Clinical diagnosis of probable Alzheimer's Disease (AD)
3. MMSE * 18
4. PET or CSF biomarker data supports that the subject is amyloid positive

Exclusion criteria

All subjects:

1. Current clinically significant psychiatric condition
2. Normal hemoglobin * 8 in males or * 7 in females
3. Possible pregnancy
4. MRI evidence of brain structural abnormality
5. Relevant history of drug allergy or hypersensivity
6. Current clinically significant cardiovascular disease, abnormalities on screening ECG (e.g. QTc >450msec)
7. Donated blood <6 months

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-08-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	-

Ethics review

Approved WMO Date:	28-07-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-08-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-003047-35-NL

Register	ID
CCMO	NL49986.029.14