Open-label, non-randomized, multi-centre positron emission tomography (PET) imaging study to evaluate a single dose of 250 MBq BAY858102 ([F-18]DPA-714) for its diagnostic potential in discriminating patients with probable Alzheimer's disease from healthy volunteers and to evaluate the radiation dosimetry of a single dose of 150 MBq BAY858102 ([F-18]DPA-714) in healthy volunteers

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Based on the scientific background and knowledge as detailed above this clinical proof-of-mechanism study is performed in order to determine if PET imaging with [18F]DPA-714 has the diagnostic potential to discriminate probable AD patients from...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mental impairment disorders
Study type	Observational invasive

Summary

ID

NL-OMON33492

Source
ToetsingOnline

Brief title
PET study of the tracer [18F]DPA714

Condition

- Mental impairment disorders

Synonym
Alzheimer's disease, dementia

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: sponsor

Intervention

Keyword: [18F]DPA714, Alzheimer's disease, Peripheral Benzodiazepine Receptor (PBR), PET

Outcome measures

Primary outcome

Primary variables are captured for probable AD patients and healthy volunteers

undergoing PET brain imaging:

- Standard quantification variables for each ROI/VOI derived from 3D PET

imaging and brain modeling, in particular distribution volume (DV) and binding

potential (BP), using different modeling approaches

Secondary outcome

Secondary variables are captured for probable AD patients and healthy

volunteers undergoing PET brain imaging:

- SUV values for each ROI/VOI at several time points when maximal separation

between AD patients and healthy volunteers is indicated.

- Visual analysis/description of uptake: The degree of uptake in different

brain regions will be rated on a 3-point scale.

- Classification of PET scans to cohorts (probable AD patients, healthy volunteers) by evaluation of a predefined scoring system based on visual analysis/description of brain PET scans.

The following pharmacokinetic variables are only captured for probable AD patients and healthy volunteers undergoing PET brain imaging:
- Arterial blood concentration of total 18F-radioactivity (comprising all 18F-labeled substances) and of non-metabolized [18F]DPA-714, and the pharmacokinetic parameters: Cmax (KBq/L and %ID/g); tmax (h); AUC(0-tlast) (KBq*h/L, %ID*h/L).
- Arterial plasma-concentrations of non-metabolized DPA-714 (i.e. the sum of [18F]DPA-714 and [19F]DPA-714), in pmol/L and the pharmacokinetic parameters: (Cmax (pmol/L); Cmax/D (1/L); tmax (h); AUC(0-tlast) (pmol*h/L); AUC(0-tlast)/D (h/L); AUC (pmol*h/L); AUC/D (h/L); CL (L/h), Vss (L); Vz (L); t1/2 (h); MRT (h).

Dosimetry data are only captured for healthy volunteers undergoing whole body imaging:
- Whole body biodistribution in % injected dose over time and radiation dosimetry estimates (in mGy/MBq) and effective dose (ED) (in mSv/MBq) per tissue/organ of [18F]DPA-714
- Venous blood and plasma-concentrations of total 18F-radioactivity expressed in KBq/L and %ID/g.
- Urine: Concentration of renally excreted total radioactivity (18F) during

each collection period and during the whole observation period expressed in

MBq/L and % of radioactive dose

Safety variables include:

- Adverse events

- Physical examination

- Vital signs (blood pressure, heart rate), and body temperature

- 12-lead ECG

- Laboratory evaluation of venous blood and urine samples

- Concomitant medication

- Pregnancy test (females of childbearing potential only)

Study description

Background summary

The PBR has been described as the peripheral binding site for diazepam. PBR upregulation was demonstrated in post-mortem studies on human brains of patients with Alzheimer*s disease, multiple sclerosis, Parkinson*s disease and other neurodegenerative diseases. Such consistent observations of an upregulation of the PBR in activated microglia in various brain pathologies suggest that radiolabeled PBR drug ligands may constitute suitable tools for imaging of neuroinflammation. Activated microglia have been consistently detected in close association with senile plaques
containing beta-amyloid (Abeta) protein in post-mortem studies on human brains of AD patients. It is hypothesized, that once neuroinflammation is initiated, a vicious cycle starts, which eventually enters a chronic phase, in which the disease
process cannot be resolved any more.
Clinical brain PET studies have been performed with the tracer [C-11]PK11195 which is based on targeting the PBR, in a variety of brain diseases, including AD. Significantly increased tracer uptake and increased binding potential was reported in AD patients as compared to normal controls in particular in the frontal, temporal and parietal brain areas. However, brain uptake of

[C-11]PK11195 is in general low. The ligand [F-18]DPA714 is thought to be superior to [C-11]PK11195 with regard to its binding affinity and brain uptake and therefore, should render significantly better imaging results. Moreover this tracer is labelled with 18F, which will allow for commercialization.

Study objective

Based on the scientific background and knowledge as detailed above this clinical proof-of-mechanism study is performed in order to determine if PET imaging with [18F]DPA-714 has the diagnostic potential to discriminate probable AD patients from healthy volunteers.
The purpose is further to evaluate the safety, tolerability of [18F]DPA-714. Also, dosimetery using whole-body PET scans will be determined.

Study design

Open-label, non-randomized, multicenter study. The study will be performed on an outpatient basis. Subjects will receive a PET scan of either the brain or the whole body. Subject scheduled to receive a brain PET scan will also receive a brain MRI, prior to PET scanning

Study burden and risks

Subjects are throroughly screened medically (including neuropsychological evaluation and MRI). The study itself lasts one day. A few days later a follow-up visit will take place.
The risks for the subjects are related to the placement of an arterial cannula and venapunctures. During the medical screening, clinically significant abnormalities may be found. Subjects know they will be informed if any abnormalities are found.
The study compound is administered in tracer quantities. Therefore, adverse effects are expected to be few. The radiation dose is well within limits for this type of study.

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

Inclusion criteria for AD Patients , Healthy volunteers for brain and whole body imaging
1. Participants must be able to understand the information provided on purpose and conduct of the clinical study, must be capable of giving fully informed consent in writing, and have read and signed the informed consent prior to study participation.
2. Male or females >= 50 years of age.
3. Females of child-bearing potential must provide:
- Agreement to practice adequate contraception methods (abstinence, intrauterine contraceptive device [IUCD], condoms, oral contraceptives, or other adequate barrier contraception)
- barrier contraception has to be in combination with local application of a spermicide and
- Negative urine pregnancy test results (beta-HCG)
For females >= 60 years of age postmenopausal status will be determined by medical history (last spontaneous bleeding at least 1 year prior to radiotracer administration or hysterectomy or a bilateral oophorectomy at least three months prior to radiotracer administration).;Additional inclusion criteria for healthy volunteers for brain imaging only
1. Adequate visual and auditory acuity to complete neuropsychological testing.
2. MMSE score of >= 28
3. CDR score of zero (0)
4. Confirmation by other neuropsychological test results that the volunteer does not show any signs of cognitive impairment or dementia (e.g. results lying within an interval of one standard deviation from the mean value, mean value and standard deviations adjusted for age and education);Additional inclusion criteria for probable AD patients only
1. Adequate visual and auditory acuity to complete neuropsychological testing.

2. Patient fulfills DSM-IV and NINCDS-ADRDA criteria for probable AD, which are cognitive deficits such as memory decline and impairment in at least one other cognitive domain (aphasia, apraxia, agnosia or executive dysfunction).
3. Patient has mild to moderate dementia :
- with a dementia score of >= 20 on the Mini-Mental Status Examination (MMSE)
- with a Clinical Dementia Rating score of 1 or 2 (CDR)
4. Patient has had the following further tests:
- Neurological examination
- Psychometric testing
- Brain MRI

Exclusion criteria

Exclusion criteria: healthy volunteers for brain and whole body imaging and probable AD patients
1. Any disease, condition, or concomitant medications that significantly compromises the function of the body systems and could result in excessive accumulation, impaired metabolism, altered excretion of the radiotracer, or might interfere with the conduct of the study or interpretation of the results.
2. Current unstable medical condition (e.g. unstable angina, myocardial infarction or coronary revascularization in the preceding 12 months, cardiac failure, chronic renal failure, chronic hepatic disease, severe pulmonary disease, blood disorders, poorly controlled diabetes, chronic infection)
3. Current systemic autoimmune disease or clinically relevant systemic inflammatory disease.
4. History of cancer or current cancer, including brain tumors.
5. History of or current alcohol or drug abuse/dependence or suspicion of alcohol or drug abuse/dependence.
6. History of anaphylactoid or anaphylactic reactions to any allergen including drugs and contrast media.
7. Pregnancy or lactation.
8. History of significant occupational exposure to ionizing radiation or application of radioactive substances or ionizing radiation for the purposes of diagnosis or treatment within the last year according to recommendations from current guidelines, or whose occupational exposure to radioactivity is monitored or (Netherlands only) application of radioactive substances or ionizing exposure to radiation during an investigation / study in the year preceding the PET scan
9. Haematological or biochemical parameters that are outside the normal range and are considered clinically significant by the investigator, in particular the presence of hepatitis B virus surface antigen (HBsAg), hepatitis C virus antibodies (anti-HCV) or human immune deficiency virus antibodies (anti-HIV). Minor deviations in lab parameters that are considered by the evaluating physician to be not clinically significant with respect to safety or interpretation of study results are not considered an exclusion criterion.
10. Clinically relevant findings in the 12 lead ECG as determined by evaluating physician.
11. Donation of blood within 4 weeks (12 weeks for Finland only) or plasmapheresis within 2

weeks before the radiotracer administration.
12. Criteria which in the opinion of the investigator preclude participation for scientific reasons, for reasons of compliance, or for reasons of the subject*s safety.
13. Subject is in custody by order of an authority or a court of law.
14. Exclusion periods from other studies or simultaneous participation in other clinical studies or previous assignment to radiotracer administration in this study.
15. Close affiliation with the investigational site (e.g. close relative of investigator), dependent person (e.g. employee or student of investigational site).;Additional exclusion criteria for healthy volunteers for brain imaging and probable AD patients only
1. Evidence for, history of or imaging findings indicative of any neurological disease (AD patients: other than Alzheimer*s disease, including other dementias) or psychiatric disorder, including e.g. brain surgery, intracranial hematoma, stroke/cerebrovascular disease, epilepsy, inflammatory or infectious disease, severe depression, attempted suicide or current suicidal ideation.
2. MRI brain scan findings that reveal changes indicative of stroke and/or generalized cerebrovascular disease, e.g., the ARWMC scale with a white matter lesion score of >2 and a basal ganglia score of >1.
3. Allen*s test indicative of reductions in arterial perfusion of the hand which would compromise the perfusion during arterial blood sampling
4. Receiving drug therapy with known significant action on the CNS such as NSAIDs (within 24 hours), aspirin (within 12 hours), or benzodiazepines, corticosteroids, vinpocetine, vincamine and other eburnamine derivatives, within 5 half-lives of the respective drug before radiotracer administration.
5. Subjects in whom magnetic resonance imaging (MRI) is contraindicated or receipt of any contrast material (X-ray, MRI) or radiopharmaceuticals within 48 hours or 5 half lives prior to the application of the radiotracer or if application of such a substance is planned during the observation period.;Additional exclusion criteria for healthy volunteers for brain imaging only
1. Clinical significant abnormal physical examination.
2. Family history of AD in 1st or 2nd degree relative.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-12-2009
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BAY858102 ([F-18]DPA-714)
Generic name:	BAY858102 ([F-18]DPA-714)

Ethics review

Approved WMO Date:	29-09-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-12-2009
Application type:	First submission
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	EUCTR2009-009358-26-NL
CCMO	NL28662.029.09