A multi-center, parallel-group, double-blind, placebo-controlled single and multiple dose escalation study to assess the safety and tolerability and the pharmacokinetic properties of SAR228810 given as IV infusion or as SC injection in patients with mild to moderate Alzheimer*s Disease.

Published: 28-03-2013
Last updated: 24-04-2024

- To assess the safety and tolerability of escalating single and multiple IV doses of SAR228810 in AD patients- To evaluate the pharmacokinetic properties of SAR228810 in plasma and CSF after escalating single and multiple IVdoses of SAR228810 in AD…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cognitive and attention disorders and disturbances
Study type	Interventional

Summary

ID

NL-OMON38433

Source
ToetsingOnline

Brief title
A dose escalation study in Alzheimer's disease

Condition

- Cognitive and attention disorders and disturbances

Synonym
Alzheimer's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: Sanofi-Aventis

Intervention

Keyword: Alzheimer's disease, amyloid beta, dose escalation, monoclonal antibody

Outcome measures

Primary outcome

Primary and main secondary endpoints

Safety:

- CSF safety laboratory evaluation

- Brain MRI scans

- optional: PET-scanning with 18F-flutametamol

- Clinical examination including neurological assessment

- Local tolerability

- Clinical assessment scales

- Vital signs

- 12-lead ECGs

- Clinical laboratory evaluations

- Suicidality assessment

- Anti-drug antibody (ADA) assessment

Pharmacokinetics:

- various pharmacokinetic endpoints in plasma and CSF

- Immunogenicity testing for anti-SAR228810 antibodies

Pharmacodynamics:

- various protein markers for Alzheimer's disease

Secondary outcome

NA

Study description

Background summary

Alzheimer*s disease is a progressive dementing disease, neuropathologically characterized by deposits of extracellular amyloid-β (Aβ) plaques, neuronal fibrillary tangles and cerebral neuronal loss. Several findings suggest that Aβ, particularly the 42-amino acid form (Aβ1-42), is a major factor in the pathogenesis of AD. Aβ self-aggregates into multiple conformers, including Aβ oligomers, protofibrillar and fibrillar aggregates which are toxic to neurons. Immunotherapy against Aβ peptides, either by administration of antibodies or by vaccination against different forms of Aβ, is one of the few current therapeutic strategies with the potential to prevent formation and to trigger the degradation of amyloid plaques. SAR228810 is a humanized monoclonal antibody (mAb) specific to human amyloid-β (Aβ) and is being developed to stop or decrease the disease progression of Alzheimer's disease.

Study objective

- To assess the safety and tolerability of escalating single and multiple IV doses of SAR228810 in AD patients
- To evaluate the pharmacokinetic properties of SAR228810 in plasma and CSF after escalating single and multiple IV doses of SAR228810 in AD patients
- To assess the safety and tolerability of single and multiple SC doses of

SAR228810 in AD patients
- To evaluate the pharmacokinetic properties of SAR228810 in plasma and CSF after single and multiple SC doses of
SAR228810 in AD patients
- To evaluate relative bioavailability of SAR228810 after SC administration in comparison to IV administration.

Study design

Phase 1, multi-center study, double-blind, randomized, placebo-controlled, sequential ascending single and multiple dose
study with parallel groups;

Intervention

Part 1

4 cohorts in single dose IV:
- cohort 1 = 100mg or placebo
- cohort 2 = 300mg or placebo
- cohort 3 = 600mg or placebo
- cohort 4 = 1000mg or placebo
2 cohorts in single dose SC:
- cohort 1 = 100mg or placebo
- cohort 2 = 450mg or placebo

Part 2
3 cohorts in multiple doses IV, doses are dependent of part 1 findings
- cohort 1 = 100mg or placebo
- cohort 2 = 200mg or placebo
- cohort 3 = 400mg or placebo
1 cohort in multiple doses SC
- no more than 450mg

Study burden and risks

Burden
20 visits (voor MAD 450mg SC cohort 22x), of which two times an overnight stay in the hospital.
Subjects in the MAD 450mg SC cohort will be dosed 9 times during the MAD part, whereas the subjects in the other cohorts will be dosed 7 times during the MAD part. The reason herefore is that the MAD 450mg SC cohort will be dosed once every 3 weeks instead of once every 4 weeks for the others MAD cohorts.
23 times blood sampling (MAD 450mg SC cohort 25x) via IV canula or venal

puncture

Possible side effects
- bruises, pain, infection from the venal puncture
- lumbar puncture: irritation of nerves, post-puncture headache (both self-limiting), meningitis (highly unlikely)
- study drug (rare): cerebral microhemorrhages, brain edema, allergic reaction

The finding of a treatment for Alzheimer's disease and the potential advantage for the study patients sufficiently outweigh the burden and possible side effects

Contacts

Public
Sanofi-aventis

Avenue Pierre Brossolette 1
Chilly Mazarin 91385
FR
Scientific
Sanofi-aventis

Avenue Pierre Brossolette 1
Chilly Mazarin 91385
FR

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Demography
I 01. Male or female patients with mild to moderate Alzheimer*s disease, aged between 50 and
85 years inclusive.
I 02. Body weight between 50.0 and 110.0 kg inclusive.
Health Status
I 03. Meets NINCDS-ADRDA criteria for probable Alzheimer*s disease [National Institute of Neurologic and Communicative Disorders and Stroke - AD and Related Disorders Association]
I 04. mini-mental state examination (MMSE) score of 16*28 (inclusive)
I 05. in reasonable and stable health state for Alzheimer*s patients of this age and stage of disease as assessed by a comprehensive clinical assessment (detailed medical history and complete physical examination).
I 06. Normal vital signs after 10 minutes resting in supine position:
- 95 mmHg < systolic blood pressure < 180 mmHg
- 45 mmHg < diastolic blood pressure < 95 mmHg
- 50 bpm < heart rate < 100 bpm
I 07. Normal standard 12-lead ECG after 10 minutes resting in supine position;
120 ms < PR < 220 ms, QRS < 120 ms, QTc <= 475 ms.
I 08. Laboratory parameters within the normal range, unless the Investigator considers an abnormality to be clinically irrelevant for Alzheimer*s patients of this age and stage of disease.
I 09. If female, patient must use a double contraception method, except if she is sterilized for more than 3 months or postmenopausal. The accepted double contraception methods include use of a highly effective method of birth control (intra-uterine device or hormonal contraception) in addition to one of the following contraceptive options: 1) condom, in addition to spermicide; 2) diaphragm or cervical/vault cap, in addition to spermicide. Menopause is defined as over the age of 60 years, or between 45 and 60 years being amenorrheic for at least 2 years with plasma FSH level > 30 UI/L.
For sexually active male subjects with partners of childbearing potential: accepting to use a double effective method of contraception during the study and for 16 weeks after the last dosing. Accepted double contraception algorithms: (condom associated with spermicide) plus (occlusive cap or intrauterine device or hormonal contraceptive).
For sexually active male subjects whose partners are pregnant or not of childbearing potential: accepting to use condoms from the first study drug administration up to 16 weeks after last dosing.
Regulations
I 10. Having given written informed consent prior to any procedure related to the study. Depending on national law the informed consent of a patient*s caregiver has also to be obtained where applicable.
For a patient who is unable to understand the patients* study information or is unable to give informed consent due to his/her cognitive status, either written informed consent could be obtained from the patient*s legal representative if this is in accordance with all legislation for clinical trials in the respective country, or the patient must not be included.
I 11. Covered by a Health Insurance System where applicable, and/or in compliance with the

recommendations of the national laws in force relating to biomedical research.
I 12. Not under any administrative or legal supervision (eg detainees or mentally ill).
For special cases of AD refer to I 10.
Specific to the study
I 13. MRI consistent with Alzheimer*s disease, not indicating any other cause for dementia symptoms than Alzheimer*s disease.
I 14. The Alzheimer's type of the dementia must have been confirmed before randomization of a
patient by specific CSF biomarkers (Aβ1-42 and/or p-Tau) or by brain amyloid PET scanning.
I 15. Rosen Modified Hachinski Ischemic score <= 4
I 16. If on symptomatic treatment for Alzheimer*s disease (AChEI or/and memantine), must be
stable in the last 30 days before screening

Exclusion criteria

Medical history and clinical status
E 01. clinically significant neurological disease other than Alzheimer*s disease;
E 02. had a major psychiatric disorder;
E 03. had a history of stroke, seizures, brain neoplasms, brain surgery, or any cerebrovascular disorder (including TIA);
E 04. Any presence of severe, uncontrolled and/or unstable cardiovascular, cerebrovascular, pulmonary, gastrointestinal, hepatic, renal, metabolic, hematological, neurological, endocrine, autoimmune, osteo-muscular, articular, systemic, ocular, gynecologic (if female), malignant neoplastic, or infectious disease, or signs of acute illness that would increase significantly the risks for the patient in participating in this study.
E 05. History or presence of severe, uncontrolled and/or unstable angiopathy or vasculitis.
E 06. History of deep vein thrombosis or pulmonal embolism or familial predisposition for deep vein thrombosis or pulmonal embolism.
E 07. Frequent headaches and/or migraine, recurrent nausea and/or vomiting (more than twice a
month).
E 08. Blood donation, any volume, within 2 months before inclusion.
E 09. Symptomatic postural hypotension, whatever the decrease in blood pressure, or asymptomatic postural hypotension defined by a decrease in systolic blood pressure >=20 mmHg within 3 minutes when changing from the supine to the standing position.
E 10. Presence or history of drug hypersensitivity, auto-immune or allergic disease diagnosed and treated by a physician.
E 11. History or presence of drug or alcohol abuse (alcohol consumption >40 grams per day).
E 12. Excessive consumption of beverages with xanthine bases (>4 cups or glasses per day).
E 13. If female, pregnancy (defined as positive β-HCG blood test), breast-feeding.
Interfering substance
E 14. Currently taking anticonvulsants, antiparkinsonians, antipsychotics, anticoagulants (e.g. cumarines and related drugs, direct thrombin inhibitors, Factor Xa inhibitors), P2Y12 receptor inhibitors (e.g. clopidogrel) or narcotic drugs, recent immunosuppressive or

cancer chemotherapy drugs, or cognitive enhancers.
Concomitant therapies that are allowed if given at a stable dose for at least 30 days before screening are: acetylcholinesterase inhibitors and/or memantine; SSRI antidepressants (no tricyclics); acetyl salycilic acid (ASA) at a dose <= 160 mg/day; Vitamin B12; lipid lowering drugs;
antihypertensives; zaleplon, zolpidem and zopiclone; low-dose benzodiazepine treatment.
Other stable concomitant medications may be allowed on an individual basis if the investigator has no safety concerns.
E 15. Having had a vaccination within less than 2 weeks prior to or after a dosing during the scheduled treatment periods
E 16. Having taken part in a clinical trial with a non-approved vaccination as investigational product in the past
General conditions
E 17. Any patient who, in the judgment of the Investigator, is likely to be non-compliant during
the study, or unable to cooperate because of a language problem or poor mental development.
E 18. Any patient in the exclusion period of a previous study according to applicable regulations.
In case of previous participation in a trial with monoclonal antibodies, the exclusion period should be not shorter than 6 months between the last visit of the previous study and screening visit of the present study.
E 19. Any patient that has been administered other anti-Aβ monoclonal antibodies or Aβ vaccines in other clinical trials
E 20. Any patient who cannot be contacted in case of emergency.
E 21. Any patient who is the Investigator or any sub-investigator, research assistant, pharmacist,
study coordinator, or other staff thereof, directly involved in the conduct of the protocol.
Biological status
E 22. Positive reaction to any of the following tests: hepatitis B surface (HBs Ag) antigen, antihepatitis C virus (anti-HCV2) antibodies, anti-human immunodeficiency virus 1 and 2 antibodies (anti-HIV1 and anti HIV2 Ab).
E 23. Positive results on urine drug screen (amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates).
E 24. Positive alcohol test.
Specific to the study
E 25. Cerebrospinal fluid (CSF): CSF/Serum albumin ratio, CSF IgG and IgM indices and/or CSF cell counts indicating CNS diseases or injuries other than Alzheimer*s disease, e.g. stroke, neuroborreliosis, Guillain-Barré syndrome, multiple sclerosis, vascular dementia, or other infectious or inflammatory CNS diseases.
E 26. Brain MRI at screening/baseline revealing
- more than 4 cerebral microhemorrhages (regardless of their anatomical location or diagnostic characterization as *possible* or *definite*), or
- a single area of superficial siderosis, or
- evidence of a prior macrohemorrhage
E 27. Presence of any contraindication for CSF sampling by lumbar puncture, including coagulopathy and thrombocytopenia,

E 28. Presence of any contraindication to have MRI scans performed (e.g. pacemaker, vascular
clips etc.)
E 29. History or presence of clinically relevant cardiac disease. If considered to be indicated by
the investigator, a consultation of a cardiologist has to be performed prior to inclusion/start of dosing.;Additional exclusion criteria to take part in the brain amyloid PET scanning:
E 30. Any contraindication to have a PET scan performed
E 31. Known intolerance to the PET tracer 18F-flutemetamol and/or its excipients
E 32. Any past exposure to ionizing radiation that exceeds the applicable national and international recommendations.
E 33. Any past or planned exposure to ionizing radiation that would - together with the radiation resulting from the administrations of the PET tracer used in this study - exceed the applicable national and international recommendations.
E 34. Not having given a separate written informed consent for the PET scanning with 18Fflutemetamol.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-05-2013
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO

Date:	28-03-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-06-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-07-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-10-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2011-002910-35-NL
CCMO	NL44045.056.13