A PHASE 2, RANDOMIZED, DOUBLE BLIND PLACEBO CONTROLLED TRIALTO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND EFFICACY OF PF-04360365 (PONEZUMAB) IN ADULT SUBJECTS WITH PROBABLE CEREBRAL AMYLOID ANGIOPATHY

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Primary Objective:- To evaluate the efficacy of PF-04360365 (ponezumab) in subjects with probableCAA as compared to placebo on a BOLD fMRI measure of cerebrovascularreactivity.Secondary Objectives:- To evaluate the efficacy of PF-04360365 (ponezumab...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON40546

Source
ToetsingOnline

Brief title
Ponezumab - Cerebral Amyloid Angiopathy

Condition

- Central nervous system vascular disorders
- Vascular haemorrhagic disorders

Synonym
CAA, cerebral amyloid angiopathy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cerebral amyloid angiopathy (CAA), Phase 2, ponezumab

Outcome measures

Primary outcome

Primary Endpoints:

• The change from baseline to Day 2 or Day 90 in cerebrovascular reactivity as measured by the slope (amplitude over time to peak) from visual task-evoked fMRI.

Secondary outcome

Secondary Endpoints:

• The change from baseline to Day 2 or Day 90 in cerebrovascular reactivity as measured by the time to peak, magnitude, and time to baseline from visual task-evoked fMRI.

• The change from baseline of total plasma Aβ species at specified endpoints after the initial dose of study medication on the concentration.

Exploratory Endpoint:

• The change from baseline to Day 2 or Day 90 on cerebral blood flow as

measured by

arterial spin labeling (ASL).

Safety Endpoints:

• The change from baseline at specified time points on brain structural MRI

following

each dose of ponezumab: CMBs, VE, infarcts.

• The change from baseline at specified time points on the Montreal Cognitive

Assessment (MoCA).

• Other safety endpoints include changes from baseline on C-SSRS, physical and

neurological assessments, laboratory assessments, 12-lead ECG, vital signs,

immunogenicity, AE monitoring.

Study description

Background summary

CAA is a pathological condition caused by the progressive deposition of amyloid, predominantly Aβ40, within the walls of cerebral blood vessels with a predisposition for the vessels of the occipital lobe. Using the Boston criteria, probable CAA may be defined as two or more lobar brain hemorrhages (micro or macro) in an individual >=55 years old, with possible CAA defined as having one brain hemorrhage. CAA may exist as an isolated diagnosis, either in sporadic or familial forms or be part of a more encompassing pathology.

The progressive deposition of amyloid affects the structural integrity of the blood vessel wall with the loss of vascular smooth muscle cells and elastic elements, being replaced by the amyloid protein. This weakening of the blood vessel wall may result in microaneurysm formation with microhemorrhages (cerebral microbleeds (CMB), <=10 mm in diameter) or macro hemorrhages with devastating consequences. CMB frequency has been associated with both macro intracranial hemorrhage (ICH) and with cognitive decline. Micro and macro infarcts also occur with blood vessel occlusion due to vascular injury and

amyloid protein accumulation. All these pathologies can ultimately affect neuronal viability and also lead to clinical consequences such as cognitive impairment and progressive dementia, in addition to the structural abnormalities of hemorrhage, infarct, white matter changes, cerebral microbleeds and vasogenic edema.

Cognitive difficulties can be demonstrated in multiple domains, including perceptual speed, episodic memory, visual spatial abilities and global cognition. The visual-spatial deficit is of particular interest given the predominance of the CAA burden in the occipital cerebrovasculature. Although not entirely clear, some of the reasons for amyloid deposition within this particular vascular bed include the tortuosity of the blood vessels, the particularly low neprilysin levels in the occipital cerebrovasculature and the high amount of Aβ40 produced in the smooth muscle cells of the occipital blood vessels resulting in impaired elimination of amyloid.

More recently, effects of CAA on the function of the cerebrovasculature have begun to be characterized, with reduced blood flow velocities in response to a task as well as impaired vascular reactivity noted by task (visual)-evoked fMRI. Findings of altered cerebrovascular reactivity have also been consistently demonstrated in mouse transgenic models of amyloid over expression.

PF-04360365 (ponezumab) is a humanized immunoglobulin G2 (IgG2) monoclonal antibody directed against an epitope encompassing the C-terminal amino acids 30-40 of the Aβ1-40 peptide derived from the Amyloid Precursor Protein (APP). In mouse models of brain amyloid over-expression (Tg2576), the murine version of PF-04360365 (ponezumab) was associated with a significant reduction in brain microhemorrhages and inflammation. Moreover, there was histopathologic evidence of amyloid plaque clearing and improvement in learning and memory. More recently, two hundred 16-19-month old female Tg2576 mice were injected intraperitoneally with a murine surrogate of the humanized anti-Aβ mAb ponezumab once weekly for up to 26 weeks at doses of 10, 30, or 100 mg/kg. Brains were examined microscopically for microhemorrhages. No compound-related anatomic macroscopic or microscopic findings were present. There was no increase in severity of pathology (eg, micro- or macro hemorrhage in mice given the murine version of ponezumab, at any dose. PF-04360365 at doses of 10 mg/kg and 30 mg/kg demonstrated a reduction in cerebral blood vessels positive for Aβ40, suggesting that PF-04360365 may have a beneficial impact on the CAA component of their disease.

To date, PF-04360365 has been studied in 7 clinical trials (3 single dose, 4 multiple dose), almost exclusively in mild-moderate Alzheimer*s patients. PF-04360365 has a very predictable, dose proportional pharmacokinetic profile with a terminal elimination half-life of ~6 weeks. A total of 326 subjects have been dosed with active PF-04360365 therapy (N=322 AD subjects, N= 4 healthy volunteers). PF-04360365 was very well tolerated throughout the AD clinical

program, being studied over a 100-fold dose range (0.1 mg/kg to 10 mg/kg, i.v.) with dosing frequency ranging from every month to every 3 months. A maximum tolerated dose has not been achieved.

The preclinical and clinical safety profile (including lack of antibody formation) and efficacy (CMB reduction) including subjects who had a diagnosis of CAA, predictable pharmacokinetics and Aβ1-40 specificity of PF-04360365 provide a strong rationale for the study of PF-04360365 in a sporadic CAA population. Perhaps most importantly, the high prevalence of CAA in Alzheimer's disease provides preliminary information regarding the safety profile of PF-04360365 in subjects with CAA, suggesting that the administration of PF-04360365 to subjects with co-morbid CAA associated with Alzheimer*s disease is safe and well tolerated. Development of ponezumab was terminated for mild-moderate AD based on a futility analysis for efficacy, although the mAb was noted to be safe and well tolerated in the AD population.

Study objective

Primary Objective:
- To evaluate the efficacy of PF-04360365 (ponezumab) in subjects with probable CAA as compared to placebo on a BOLD fMRI measure of cerebrovascular reactivity.

Secondary Objectives:
- To evaluate the efficacy of PF-04360365 (ponezumab) in subjects with probable CAA as compared to placebo on additional BOLD fMRI measures of cerebrovascular reactivity.
- To evaluate the effect of PF-04360365 (ponezumab) in subjects with probable CAA
as compared to placebo on changes in the concentration of total plasma Aβ.

Exploratory Objective:
• To evaluate the effect of PF-04360365 (ponezumab) in subjects with probable CAA
as compared to placebo on cerebral blood flow.

Safety Objective:
• To evaluate the safety, tolerability and pharmacokinetics of PF-04360365 (ponezumab) to subjects with probable CAA.

Additional Pharmacogenomic Research (Optional)
- Investigations of the disease under study in the clinical trial, and related conditions.
- Samples may be used as controls. This includes use in case -control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies.

related to pharmacogenomics.

Study design

A9951024 is a randomized double-blind, parallel group, placebo-controlled trial examining intravenous loading dose of 10 mg/kg at Day 1 and 7.5 mg/kg maintenance doses at Days 30 and 60 of PF-04360365 (ponezumab) in adult subjects with probable CAA using the Boston criteria.

Intervention

Intravenous loading dose of 10 mg/kg at Day 1 and 7.5 mg/kg maintenance doses at Days 30 and 60 of PF-04360365 (ponezumab) .

Study burden and risks

Ponezumab is designed to only stick to amyloid, that may be responsible for some of the problems and difficulties seen in patients with CAA, such as the ability to think, reason, remember and perform daily tasks as well as the bleeding and impaired function seen in brain blood vessels. It is hoped that ponezumab will help in the treatment of cerebral amyloid angiopathy however, this cannot be guaranteed. The information obtained from this study may also help to treat future patients with cerebral amyloid angiopathy. To date, PF-04360365 (ponezumab) has been studied in 7 clinical trials (3 single dose, 4 multiple dose), almost exclusively in mild-moderate Alzheimer*s patients. PF-04360365 (ponezumab) has a very predictable, dose proportional pharmacokinetic profile with a terminal elimination half-life of ~6 weeks. A total of 326 subjects have been dosed with active PF-04360365 (ponezumab) therapy (N=322 AD subjects, N= 4 healthy volunteers).

PF-04360365 (ponezumab) was very well tolerated throughout the AD clinical program, being studied over a 100-fold dose range (0.1 mg/kg to 10 mg/kg, i.v.) with dosing frequency ranging from every month to every 3 months. A maximum tolerated dose has not been achieved. In a Phase 2 study (A9951002), 138 mild-to-moderate AD subjects were dosed with intravenous PF-04360365 (ponezumab) therapy q2 months for a total of 18 months and followed for an additional 6 months. A total of 14.4% of subjects had one or two lobar CMBs at baseline, consistent with the Boston criteria for possible or probable CAA, respectively. Thus, a significant number of these subjects at baseline carried the diagnosis of co-morbid CAA in addition to AD, a value that increased throughout the duration of the two year trial. Ponezumab was noted to be safe and well tolerated. There were no reports of brain macrohemorrhage with active therapy and one report of asymptomatic vasogenic edema that was detected by routine scheduled brain MRI six months following their last infusion of 18 months active PF-04360365 (ponezumab: 0.5 mg/kg dose cohort) therapy (ie, 24 months following the initiation of drug therapy).

Moreover, a trend for a reduction in the incidence of AD subjects with new (post baseline) supratentorial lobar cerebral microbleeds was noted in the pooled ponezumab group vs. placebo (12.9% vs. 20.4%) after 24 months, complementing the reduction in cerebrovascular Aβ1-40 seen in Tg2576 mice. In summary, the preclinical and clinical safety profile (including lack of antibody formation) and efficacy (CMB reduction) including subjects who had a diagnosis of CAA, predictable pharmacokinetics and Aβ1-40 specificity of PF-04360365 (ponezumab) provide a strong rationale for the study of PF-04360365 (ponezumab) in a sporadic CAA population. Perhaps most importantly, the high prevalence of CAA in Alzheimer's disease provides preliminary information regarding the safety profile of PF-04360365 (ponezumab) in subjects with CAA, suggesting that the administration of PF-04360365 (ponezumab) to subjects with co-morbid CAA associated with Alzheimer*s disease is safe and well tolerated.

The additional visits to the hospital, measuring your blood pressure, heart rate, temperature and weight more frequently, urine drug test, urine samples, additional blood draws, MRI scans, physical and neurological exams and ECG*s are not part of the patients normal treatment. These additional study procedures will ask for extra time investment from the patient. With at least one overnight stay in the hospital. As in all studies with an investigational drug there are possible risks and side effects that might not be known yet, but in 7 previous clinical trials, ponezumab was shown to be generally safe and well tolerated.
There is no therapeutic available to treat CAA, and very few, if any, clinical trials to progress drug development in this indication. This relatively small proof of mechanism study will provide the required information to support the sponsor*s decision to advance ponezumab in the next, larger, longer, phase 2/3 study (multiple hundreds of subjects, exposed to ponezumab for several years).

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

1. Men, and women of non-childbearing potential between the ages of 55 and 80 years old who have the diagnosis of probable CAA using the Boston criteria and have an acceptable sMRI in the previous 12 months for review. Female subjects who are not of childbearing potential (ie, meet at least one of the following criteria):
- Have undergone hysterectomy or bilateral oophorectomy;
- Have medically confirmed ovarian failure;
- Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; with laboratory confirmation.;2. CAA disease has not resulted in any meaningful clinical cognitive or functional deficit as documented by the PI in consultation with the sponsor.
3. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the trial.
4. Subjects are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.
5. In general good health, in the opinion of the Principal Investigator (PI), based on medical history, physical examination, vital signs, 12-lead ECG, and laboratory values, including hematology and chemistry values.
6. Subjects must have corrected vision at or better than 20/50 as assessed with a Snellen chart. If glasses are required to meet these criteria, they must be MRI-compliant glasses provided by the site.
7. An acceptable screening fMRI that passes QC requirements.

Exclusion criteria

1. Co-morbid diagnosis of clinically documented Alzheimer's disease or significant cognitive impairment;;- A score of < 26 on the MMSE;;2. History of cancer within the last 5 years (except for cutaneous basal cell, squamous cell cancer resolved by excision, colon polyp

resolved by excision, or non-progressive prostate cancer per investigator*s judgment).
3. History of clinically significant (as determined by the PI) cardiac arrhythmia or heart block (eg sick sinus syndrome, ventricular tachycardia or fibrillation, sustained supraventricular tachycardia, symptomatic bradycardia, congenital long QT interval syndrome, atrial fibrillation).
4. History or diagnosis of clinically significant (as determined by the PI) ischemic heart disease (eg, angina, clinically significant coronary artery disease, myocardial infarction in the past 2 years), congestive heart failure, cardiomyopathy, myocarditis, left ventricular hypertrophy, valvular heart disease.
5. History of clinically significant (as determined by the PI) renal disease, such as glomerulonephritis, nephrotic syndrome, single kidney or polycystic kidney.
6. Subjects with uncontrolled hypertension (>=170/100).
7. History of clinically significant (as determined by the PI) syncope, epilepsy, head trauma, or clinically significant unexplained loss of consciousness within the last 5 years.
8. A diagnosis of major depressive disorder or other psychiatric illness as the primary diagnosis per the DSM-IV TR criteria per the investigator*s judgment.
9. History of schizophrenia, bipolar disorder, or other severe mental illness.
10. Known history of alcohol or drug abuse (as defined by the DSM-IV-TR) within 5 years prior to dosing or a positive result as a result of illicit drugs on the drug screening test.
11. Known positive HIV status.
12. Subjects who reside in a nursing home or that are inpatients in a hospital.
13. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation orinvestigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
14. Pregnant females; breastfeeding females; females of childbearing potential; males of childbearing potential not using highly effective contraception or not agreeing to use highly effective contraception for at least 28 days after last dose of investigational product; males of childbearing potential not using two (2) methods of highly effective contraception or not agreeing to use two (2) methods of highly effective contraception for at least 28 days after last dose of investigational product.
15. Subject*s body weight cannot exceed 100 kg.;Exclusions Related to Medications or Procedures
1. Previous exposure to investigational or non-investigational immune- or biologic therapies for Alzheimer*s disease such as anti-Aβ antibodies, or β- or γ-secretase inhibitors.
2. Any contraindications to MRI such as, but not limited to cardiac pacemaker; implanted cardiac defibrillator; aneurysm clips; carotid artery vascular clamp; neurostimulator; insulin or infusion pumps; implanted drug infusion device; bone growth/fusion stimulator; cochlear, otologic, ear implant; severe claustrophobia or requiring sedation; passive implants that may be weakly ferromagnetic in the vicinity of the RF coil that may cause image artifacts in the head scans; obesity or body habitus that exceeds MRI table weight limits or prevents subject from fitting into the scanner.
3. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody or IgG-fusion protein.
4. Medications that may negatively affect cognitive function, such as anticholinergics (including agents with pronounced anticholinergic properties such as amitriptyline) and anticonvulsants (eg, gabapentin and valproic acid) are not allowed with the following

caveats:;- Sedatives and tranquilizers (eg, benzodiazepine and non-benzodiazepine hypnotics) used as a sleeping aid and taken routinely are allowable provided that subjects have been on a stable dose for at least 60 days prior to dosing;
- Anti-epileptic drugs for reasons other than seizures are permitted provided that subjects have been on a stable dose for at least 60 days prior to dosing. Topiramate and barbiturates are excluded.;5. The following medications are excluded if used from 1 month prior to the Screening visit through the end of the study:
- Anti-coagulants;
- Approved cognitive enhancers (cholinesterase inhibitors, memantine).
6. The use of anti-inflammatory (NSAIDS and steroids) drugs prescribed specifically/solely for treatment of CAA (other stable use permitted).;For exclusion criteria 7 and 8 Related to Medications or Procedures please refer to the protocol.

Study design

Design

Study phase:	2
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):	08-10-2014
Enrollment:	5
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	03-01-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-09-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2013-001557-27-NL
ClinicalTrials.gov	NCT01821118
CCMO	NL46075.041.13