A Phase 2A Multicenter, Randomized, Double Blind, Placebo-Controlled, Parallel-Group Safety and Tolerability Trial of PQ912 in Subjects with early Alzheimer's Disease

Published: 20-08-2014
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To assess the safety and tolerability of multiple doses of PQ912 compared with placebo in subjects with early stage of Alzheimers Disease.

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

Summary

ID

NL-OMON44623

Source
ToetsingOnline

Brief title
SAPHIR study

Condition

- Mental impairment disorders

Synonym
Alzheimer's disease, Dementia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Alzheimer, Dementia, Neurology, PQ912

Outcome measures

Primary outcome

The primary objective of this study is to assess the safety and tolerability of multiple doses of PQ912 compared with placebo in subjects with early stage AD.

Secondary outcome

* To explore the efficacy of PQ912 from baseline to week 12 on cognitive function, as measured by a neuropsychological test battery.

* To assess the pharmacodynamics of PQ912 and to identify therapeutic markers as measured by a panel of concept- and AD-related biomarkers in CSF.

* To investigate the effect of PQ912 on brain functional connectivity as assessed by RSfMRI.

* To provide biological support for the hypothesized PQ912 efficacy in counter-acting disruption of the functional network organization in MCI due to AD or mild dementia due to AD, using functional connectivity and network analysis in EEG.

Study description

Background summary

Alzheimers Disease is a progressive, incurable disease. It is characterized by

degeneration of large areas of the brain, resulting in slow decline of cognitive functions and behaviour with the typical symptom of memory loss in patients. Therapeutic options for Alzheimers Disease are limited and reduce only symptoms. There is a need for treatments that affect the underlying cause of the disease.

Glutaminyl cyclase (QC) is identified as the enzym responsible for forming pyroglutamated (pGlu) toxic Abeta peptids. Several studies have shown the crucial role of pGlu Abeta peptids in the pathogenesis of Alzheimers Disease. Besides pGluAbeta is a prominent part of plaques associated with Alzheimers Disease.

Study objective

To assess the safety and tolerability of multiple doses of PQ912 compared with placebo in subjects with early stage of Alzheimers Disease.

Study design

Multicenter, randomised, dubble blind, parallel group, phase IIa study

Intervention

One group will take 800mg of PQ912 daily during the first week and 1600mg daily during the 11 weeks thereafter. The patients will be treated for 12 weeks in total. Another group will take a placebo during 12 weeks.

Study burden and risks

Patients will visit the clinic six times in a total of up to 28 weeks (the screening period has a duration up to 12 weeks and the study has a duration of 16 weeks). The patients will take PQ912 or placebo for a total of 12 weeks. After the visit of 12 weeks (V5/EOT) a final follow up visit will take place.

During visits V1, V2, V3, V4, V5 and V6 blood will be withdrawn and physical examination takes place.
During visit V1 and V5 an EEG, ECG, MRI and spinal cord punction will take place.
Further several questionnaires will be taken during the study.

* Blood tests: pain when blood samples are drawn, and light-headed. Bruising, swelling and, on rare occasions, an infection.
* Electrocardiogram (ECG): some pain when the electrodes are removed from skin.
* Electroencephalogram (EEG): Placement of the electrodes on head may be slightly uncomfortable.
* Cognitive skill level tests: slightly frustrating or produce fatigue and/or

boredom.
* Lumbar puncture/spinal tap: (temporary) pain, tingling sensation, headache. Local anesthetic (lidocaine 1%) may cause an allergic reaction. The symptoms of an allergic reaction after the injection of the local anesthetic include the following: excessive pain, redness or swelling near the injection site, body rash, wheezing and difficulty breathing. On very rare occasions you can experience vomiting, infection, temporary weakness of the eye muscle causing double vision, damage to nerves in your back, bleeding into the spinal fluid space, or death.
* Magnetic resonance imaging (MRI) scan: machine attracts metal from body, people can feel *closed in* and get nervous (claustrophobia) or become uncomfortable with the loud noise when having an MRI scan in certain MRI scanners.

Contacts

Public
Probiodrug AG

Weinbergwerg 22
Halle (Salle) 06120
DE
Scientific
Probiodrug AG

Weinbergwerg 22
Halle (Salle) 06120
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed and dated written informed consent obtained from the subject in accordance with local regulations.
2. Male or surgically sterile or postmenopausal female, aged *50 to *89 years. Male subjects with childbearing potential partners are willing to and should use condoms during study medication treatment and until 28 days after the last dose of study medication.
3. Diagnosis of MCI due to AD or mild dementia due to AD with amnestic presentation, according to Alzheimer Association * National Institute on Aging (AA-NIA) criteria [Albert et al 2011; McKhann et al 2011].
4. MMSE score of 21 to 30 inclusive at screening.
5. Screening visit brain MRI scan consistent with the diagnosis of MCI due to AD or mild dementia due to AD, as judged by central rater.;6. A positive AD signature showing one of the following (either a, b, c, OR d):
a. Screening CSF sample with an A-beta 42 concentration of less than 638 ng/L AND total tau >375 ng/L, as assessed by central laboratory.
b. Screening CSF sample with an A-beta 42 concentration of less than 638 ng/L AND p-tau > 52 ng/L, as assessed by central laboratory.
c. Tau/A-beta ratio > 0.52, as assessed by central laboratory.
d. Positive amyloid PET if available prior to screening.

7. Treatment naïve, this means not having received any prior established specific treatment for MCI due to AD or mild dementia due to AD including no (prior) use of an acetylcholinesterase inhibitor, or memantine. A maximum of two months of prior cumulative treatment with an acetylcholinesterase inhibitor or memantine is allowed if the acetylcholinesterase inhibitor or memantine was
discontinued due to intolerance and if this was done at least two months prior to baseline. Use of Souvenaid will be allowed if Souvenaid was discontinued at least two months prior to baseline, or if the subject is on stable dose for at least six months prior to baseline and is willing to continue during the study on the same dose and frequency. ;8. Fluency in local language and evidence of adequate premorbid intellectual functioning in the opinion of the investigator.
9. Adequate visual and auditory abilities to perform the cognitive and functional assessments in the opinion of the investigator.
10. Outpatient with study partner (age 18 years or older) capable of accompanying the subject on all clinic visits. In accordance to Swedish regulations the availability of a study partner is not applicable for Sweden.
11. The subject and study partner are likely to be able to participate in all scheduled evaluations. In accordance to Swedish regulations the availability of a study partner is not applicable for Sweden.
12. In the opinion of the investigator, the subject and study partner can be compliant and have a high probability of completing the study. In accordance to Swedish regulations the availability of a study partner is not applicable for Sweden.

Exclusion criteria

A subject who meets ANY of the following criteria is not eligible for this study:
1. Significant neurologic disease, other than AD, that may affect cognition.
2. Atypical clinical presentations of MCI due to AD or mild dementia due to AD, such as the visual variant of AD (including posterior cortical atrophy) or the language variant (including logopenic aphasia). ;Concomitant disorders:
3. History of or screening visit brain MRI scan indicative of any other significant abnormality, including but not limited to multiple microhaemorrhages (4 or more, defined as 10 mm or less at the greatest diameter), severe white matter hyper intensities (Fazekas score 3), history or evidence of a single prior haemorrhage >1 cm3, multiple lacunar infarcts or evidence of a single prior infarct >1 cm3, evidence of a cerebral contusion, encephalomalacia, aneurysms, vascular malformations, subdural hematoma, or space-occupying lesions (e.g. brain tumours).
4. Current presence of a clinically important major psychiatric disorder (e.g. major depressive disorder) as defined by DSM-5 criteria, or symptom(s) (e.g. hallucinations) that could affect the subject*s ability to complete the study.
5. Current clinically important systemic illness that is likely to result in clinically relevant deterioration of the subject*s condition or might affect the subject*s safety during the study.
6. History of clinically evident stroke or history of clinically important and symptomatic carotid or vertebrobasilar stenosis or plaque.
7. History of seizures within the last two years prior to the screening visit.
8. Weight > 120 kg (264 lb) at screening.
9. Myocardial infarction within the last six months prior to screening.
10. History of cancer within the last two years prior to screening, with the exception of any of the following conditions: non-metastatic basal cell carcinoma, and squamous cell carcinoma of the skin
or any other cancer if evidence of no residual cancer has been clinically confirmed within the last six months before baseline.
11. History of uncontrolled hypertension (in the opinion of the investigator) within six months prior to screening.
12. Other clinically important diseases or conditions or abnormalities of vital signs, physical examination, neurologic examination, laboratory results, or ECG examination (e.g. atrial fibrillation) that could compromise the study or the safety of the subject.
13. Haemoglobin level less than 11 g/dL (6.8 mmol/L) at screening.
14. Clinically important infection within 30 days prior to screening e.g. chronic persistent or acute infection, such as bronchitis or urinary tract infection.
15. Any known hypersensitivity to any of the excipients contained in the test article formulation.
16. Severe hepatic failure (Child-Pugh C) or kidney failure (creatinine clearance (eGFR) * 30 ml/min/1.73m2) or serum creatinine above 1.5 fold of ULN or AST or ALT above 3 fold of ULN at screening. ;Concomitant Medication/Therapies:
17. The following therapies are not permitted for the given intervals prior to baseline and until V5/End-of-treatment (EOT):
* Anticoagulants (e.g. heparin and vitamin K antagonists) within 30 days prior to baseline.
;NOTE: Platelet anti-aggregants (e.g. clopidogrel bisulfate or the use of carbasalate calcium

100 mg/day, or aspirin 325 mg/day or less) are allowed if they are maintained on a stable dose regimen for at least 30 days prior tobaseline. The combination of clopidogrel and carbasalate calcium or aspirin is not allowed during the time of lumbar puncture.
* Use of experimental medications for AD or any other investigational medications or devices for treatment of indications other than AD within 60 days prior to baseline.
* Treatment with an acetylcholinesterase inhibitor or memantine or Souvenaid, except for an acetylcholinesterase inhibitor or memantine in case of clinically relevant worsening of cognitive performance during the double blind study period, and for Souvenaid if only on stable dose for at least six weeks prior to baseline.
* Treatment with immunosuppressive medications (e.g. systemic corticosteroids in a dose of more than 10 mg/day) within the last 90 days prior to baseline (topical and nasal corticosteroids and inhaled corticosteroids for asthma are permitted).
* Treatment with chemotherapeutic agents for malignancy within the last year prior to baseline.
* Concomitant treatment with strong inhibitors or moderate inducers of the metabolic enzyme CYP 2C19 or substrates with narrow therapeutic margin: fluconazole, fluvoxamin, ticlopidin, rifampicin, S-mephenytoin, repaglinide, phenytoin, phenobarbital and indometacin. A washout phase of at least two weeks before baseline is required for subjects having been treated with any of the above medicinal products.
* Concomitant treatment with St. John*s Wort (a wash out phase of at least two weeks prior to baseline is required).
* Any concomitant treatment which impairs cognitive function and cannot be washed out at least four weeks prior to baseline. ;The following requirements apply to all other medications not intended to treat AD:
* Subjects must be on stable dose for at least four weeks prior to baseline, except for medications which are administered as short courses of treatment (e.g. anti-infective) or which are to be used as needed (PRN).
* Medications which are central nervous system active and may affect cognitive function are not permitted during a period of 72 hours prior to neuropsychological testing (V1, V2 and V5/EOT).
* Hypnotics are not permitted during a period of 72 hours prior to EEG recording (V1 and V5/EOT).
* Subjects who initiate treatment or undertake dose adjustment with drugs not intended for treatment of cognitive impairment during the study may continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety.
;Other
18. Blood donation (routine blood donation) in the 90 days prior to screening.
19. History of alcohol or drug dependence or abuse as defined by DSM-5 criteria within the last two years prior to screening.
20. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, CSF shunts, claustrophobia, or metal fragments or foreign objects in the eyes, skin, or body that would contraindicate a brain MRI scan.
21. Inadequate venous access to allow multiple blood draws.

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):	05-03-2015
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PQ912
Generic name:	PQ912

Ethics review

Approved WMO Date:	20-08-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	05-02-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-07-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-08-2016

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-09-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-12-2016
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	EUCTR2014-001967-11-NL
ClinicalTrials.gov	NCT02389413
CCMO	NL49571.056.14