*A Phase 2b Multicentre, Randomised, Double-blind, Placebo-controlled, Parallel Group Dose Finding, Safety, Tolerability and Efficacy Study of PQ912 in Subjects with Mild Cognitive Impairment and Mild Dementia due to Alzheimer*s Disease.*

Published: 23-04-2020
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Primary objectives:Safety for Dose Selection• To assess the safety and tolerability of PQ912Efficacy • To evaluate the efficacy of PQ912 on working memory and attentionSecondary Objectives:Safety• To assess the safety and tolerability of long-term...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Dementia and amnestic conditions
Study type	Interventional

Summary

ID

NL-OMON52535

Source
ToetsingOnline

Brief title
VIVIAD

Condition

- Dementia and amnestic conditions

Synonym
Alzheimer's disease, dementia

Research involving

Human

Sponsors and support

Primary sponsor: Vivoryon Therapeutics N.V.
Source(s) of monetary or material Support: Vivoryon Therapeutics N.V.

Intervention

Keyword: Alzheimer's Disease, Glutaminyl Cyclase inhibitor, Mild Cognitive Impairment, Mild Dementia

Outcome measures

Primary outcome

The primary objectives of this study are to assess the safety and tolerability

of PQ912 and to evaluate the efficacy of PQ912; i.e. the primary efficacy

endpoint is the linear change in time on working memory and attention as

measured by the detection test, identification test and the one back test of

the Neuropsychological Test Battery (NTB).

Secondary outcome

The Secondary Objectives:

- To assess the safety and tolerability of long-term PQ912

- To evaluate the efficacy of PQ912 on brain activity (electroencephalography

(EEG))

- To evaluate the efficacy of PQ912 on cognition

- To evaluate the efficacy of PQ912 on activities of daily living

The Exploratory Objectives:

- To evaluate the efficacy of PQ912 on cognition by the WAIS-IV Coding Test

- To evaluate the efficacy of PQ912 on language derived cognition by

Winterlight speech assessment (WLA)

- To evaluate the efficacy of PQ912 on functional neuronal network activity and

connectivity (EEG)

- To evaluate the efficacy of PQ912 on biomarkers measured in CSF, plasma, and

serum

- To evaluate the level of PQ912 and its metabolites in plasma and CSF

- To evaluate the performance of serum biomarkers as alternatives to CSF

biomarkers

Study description

Background summary

Dementia, including Alzheimer*s Disease (AD), is one of the biggest global public health challenges facing our generation. Today, over 45 million people worldwide live with the condition and this number is expected to more than triple by 2050 to 152 million. AD is a progressive, incurable disease. It is characterised 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. At present, approved pharmacological therapy for AD consists of symptomatic treatments. These drugs provide a modest positive effect on cognitive function and activities of daily living in some patients, but also cause side effects in a substantial number of treated patients. Being symptomatic treatments, these drugs do not slow down the underlying neuropathological disease process. There is a need for treatments that can prevent the progression of AD by intervening in specific parts of the neuropathological processIn

PQ912 is aan investigational drug that works by inhibiting an enzyme

(glutaminyl cyclase), which is associated with the formation of specific protein fragments that cause brain cells to degenerate or die. By inhibiting this enzyme, the degeneration of the brain cells can be prevented. PQ912 is the first orally available small molecule QC inhibitor to be developed for the treatment of AD.

Study objective

Primary objectives:

Safety for Dose Selection
• To assess the safety and tolerability of PQ912
Efficacy
• To evaluate the efficacy of PQ912 on working memory and attention

Secondary Objectives:

Safety
• To assess the safety and tolerability of long-term PQ912
Efficacy
• To evaluate the efficacy of PQ912 on brain activity (electroencephalography (EEG))
• To evaluate the efficacy of PQ912 on cognition
• To evaluate the efficacy of PQ912 on activities of daily living

Exploratory Objectives:

Efficacy
• To evaluate the efficacy of PQ912 on cognition by the WAIS-IV Coding Test
• To evaluate the efficacy of PQ912 on language derived cognition by Winterlight speech assessment (WLA)
• To evaluate the efficacy of PQ912 on functional neuronal network activity and connectivity (EEG)
• To evaluate the efficacy of PQ912 on biomarkers measured in CSF, plasma, and serum
• To evaluate the level of PQ912 and its metabolites in plasma and CSF
• To evaluate the performance of serum biomarkers as alternatives to CSF biomarkers

Study design

The VIVIAD study is a Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Dose Finding, Safety and Tolerability Phase 2b study comparing PQ912: 300 mg or 600 mg BID, as recommended by the DSMB) to

placebo for 48 weeks (maximally 96 weeks) in 250 subjects with mild cognitive impairment (MCI) due to AD or mild dementia due to AD.

Intervention

The patients will be orally administrated with PQ912 or placebo tablets once daily in weeks 1 and 2 and twice daily orally from week 3 onwards (BID). The total treatment duration is between 48-96 weeks. Patients will be randomized 1:1:1 (placebo, 300mg, 600 mg all BID) for the first 90 included, and 1:1 (placebo and dose decided by DSMB) from patient 91 onwards. All tablets will be taken after a meal.
- Dose in weeks 1 and 2: 50 mg once daily (evening) or placebo
- Dose in weeks 3 and 4: 50 mg BID or placebo
- Dose in weeks 5-8: 150 mg BID or placebo
- Dose in weeks 9-12: 300 mg BID or placebo
- Dose in weeks 13-24 (until DSMB dose decision): First 90 subjects: 300 mg BID or 600 mg BID or placebo 1:1:1.
Subjects randomized between the 90th subject has reached the 24 week visit and the DSMB will have taken a decision on the PQ912 dose: 300 mg BID or placebo 1:1. After the DSMB decision, all subjects randomised to PQ912 will receive the chosen dose (300 mg or 600 mg BID).
Subjects randomized to placebo will stay on placebo. Subjects who still are to be randomized after the DSMB decision: the selected PQ912 dose (300 mg or 600 mg BID) or placebo 1:1.
- Dose in weeks 25-48 (up to week 96): the selected PQ912 dose (300 mg or 600 mg BID) as recommended by the DSMB or placebo

Furthermore, the following study procedures/assessments will be performed: physical and neurological examination, ECG and vital signs, questionnaires, blood sampling, urine collection, MRI, encephalography and lumbar puncture (for cerebrospinal fluid collection).

Study burden and risks

The schedule of activities, which summarizes the frequency and timing of the various measurements, can be found in the protocol (pages 25-27).

Discomforts and risks associated with participation:

Study treatment:
Some participants may experience side effects to the study treatment. In previous human studies with PQ912, the most commonly reported events were headache and gastrointestinal disorders, such as nausea, flatulence, constipation, abdominal pain, diarrhoea and vomiting, as well as reactions related to the skin, liver and bile organ-system. The most frequently reported skin reactions in previous trials were rash and urticaria, which in rare cases

have been severe.

Pregnancy and breastfeeding:
Women of childbearing potential must agree to use a highly effective method of contraception throughout the trial (after informed consent signature) and for at least 3 months after the last study treatment application.
Man must agree to use a condom if they are sexually active with women of childbearing potential and to refrain from donating sperm throughout the trial (after informed consent signature) and for at least 3 months after the last study treatment application. Furthermore, a heterosexual man must ensure that their female partner uses an effective method of contraception.

Blood sampling:
Blood sampling will occur at every visit to the study center. Collection of blood may cause discomfort, bruising and very rarely infection at the site where the skin is punctured by the needle. The patient may also experience dizziness, nausea or fainting during blood taking.

Electrocardiogram (ECG):
ECGs will be performed at 3 occasions during the study. ECGs are painless, but sometimes a rash or irritation can happen at the site where the electrodes are placed.

Electroencephalogram (EEG):
An assessment of the electrical activity of the brain (EEG) will be performed at up to 3 occasions during this study. The procedure is painless and consists of nineteen electrodes being placed in different locations on the head of the patient.

Cerebrospinal Fluid samples:
In order to acquire a sample of the cerebrospinal fluid, a lumbar puncture is performed in the lumbar region. Lumbar punctures will be performed at 2 occasions during the study. During the lumbar puncture, a needle will be inserted between two lumbar bones to remove a sample of cerebrospinal fluid (maximum 10 mL per sample over approximately 15 minutes). Though lumbar punctures are generally recognized as safe, they do carry some risks, including headache, dizziness, nausea and vomiting, back pain or discomfort, and bleeding.

Magnetic Resonance Imaging (MRI):
MRIs will be performed at 2 occasions during the study. A brain MRI scan will take between 20 and 40 minutes to perform. The scan itself is painless, but the patient may find it uncomfortable to lie still for this time or might have problems being in an enclosed space. In general, the potential side effects of magnetic and electric fields on humans are unclear. In particular, the possible effects on an unborn baby are not well known. However, no serious biological

effects have been reported from the magnetic fields used in clinical MRI.

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. Signed and dated written informed consent obtained from the subject in accordance with local regulations
2. Male or female, aged >= 50 to <= 80 years
3. A biomarker profile reflecting Alzheimer's Disease (AD), according to the Alzheimer Association - National Institute on Aging (AA-NIA) Research Framework [Jack et al 2018] defined as follows:
a) Screening CSF sample with an Aβ42 concentration of <1000 pg/ml AND p-tau >19 pg/ml, or a ratio of p-tau/Aβ42 of >=0.024 as assessed by central laboratory, (Elecsys assay), OR, in case of subjects in whom CSF sampling is not feasible

due to medical or technical reasons:
b) Existing Positive amyloid Positron-Emission Tomography (PET) evidence within six months of the screening visit
4. Clinical syndrome of mild cognitive impairment (MCI) or mild dementia according to the AA-NIA Research Framework [Jack et al 2018]
5. A cognitive impairment in the WAIS-IV Coding Test of at least 0.5 standard deviations below the normative data
6. Meeting the completion and performance criteria for the Cogstate Neuropsychological Test Battery (NTB)
7. Be in a stable therapeutic condition with respect to the current AD condition: either without specific current approved treatment (minimum wash-out period from a prior treatment is 10 weeks and currently no plan to initiate currently approved treatment or being on an approved treatment for AD on a stable dose for at least 10 weeks
8. Fluency in local language and evidence of adequate 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 capable of accompanying the subject on all applicable clinic visits.
11. The subject and study partner are likely to be able to participate in all scheduled evaluations according to country and site practices.

Exclusion criteria

1. Significant neurological or psychiatric disorders, 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), frontal variant or the language variant (including logopenic aphasia)
3. Moderate and severe dementia with a Mini Mental State Examination (MMSE) score below 20
4. History of (maximally six months from screening) or screening visit brain MRI scan indicative of any other significant abnormality, including but not limited to severe white matter hyperintensities (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)
5. 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
6. 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

7. History of clinically evident stroke
8. History of seizures within the last two years prior to the screening visit
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. Note: subjects can be included in the study with a prior history of cancer if evidence of no residual disease 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, neurological examination, laboratory results, or electrocardiogram (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. Known, untreated or insufficiently treated hypothyroidism, vitamin B12 or folate deficiency
16. Any known hypersensitivity to the investigational product PQ912 or any of the excipients (section 6.2. of the study protocol)
17. Severe hepatic failure (Child-Pugh C) or kidney failure (creatinine clearance (eGFR) <= 30 ml/min/1.73m2) as estimated using the MDRD method, or serum creatinine above 1.5-fold of Upper Limit of Normal (ULN) or Asparagine-Amino Transferase (AST) or Alanine-Amino Transferase (ALT) above 3 fold of ULN at screening.
18. 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. Claustrophobia or presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, CSF shunts, 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
22. Personnel involved in the conduct of the study: Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Vivoryon employees directly involved in the conduct of the trial
23. Previous participation in any investigational trial within the last 60 days of the screening visit
24. of prohibited medications or of measures/ interventions
o Immunosuppressive medications (e.g. systemic corticosteroids in a dose equivalent to more than 10 mg of prednisolone/day) within the last 90 days prior to baseline
o Chemotherapeutic agents for malignancy within the last year prior to baseline
o Concomitant treatment which may impair cognitive function requires a wash out

phase of at least 5 half-lives of the treatment prior to screening (short acting hypnotics are not permitted 72 hours before EEG or cognitive testing)
o Anticoagulants (e.g. heparin, vitamin K antagonists or direct thrombin inhibitors) within 30 days prior to screening and V8 (week 48)/ EOT. The combination of clopidogrel and carbasalate calcium or aspirin is not allowed during the time of lumbar puncture. Clopidogrel or aspirin alone is allowed.
o Strong inhibitors or inducers of CYP2C19: fluconazole, fluvoxamin, ticlopidin and rifampin (washout phase of at least two weeks before baseline)
o Substrates of CYP2C19 with a narrow therapeutic margin: S mephenytoin, phenytoin, phenobarbital and indomethacin (washout phase of at least two weeks before baseline)
o St. John*s Wort (a wash out phase of at least 2 weeks prior to baseline is required)
25. For women of childbearing potential:
(a) Pregnancy (i.e. positive pregnancy test at Screening) or breastfeeding
(b) Failure to agree to practice a highly effective method of contraception, from enrolment up to at least 3 months after the study end
26. For sexually active men with a female partner of childbearing potential: failure to agree to use condom from enrolment up to at least 3 months after the study end

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):	21-10-2020
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	/
Generic name:	substance: (5S)l-(lH-benzimidazol-6-yl)-5-(4-propoxyphenyl)-2-Imidazolidinone, hydrochloride

Ethics review

Approved WMO Date:	23-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-09-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-05-2021
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	21-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-12-2023
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	EUCTR2019-003532-23-NL
CCMO	NL72803.056.20