



Clinical trial results:

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

Summary

EudraCT number	2019-003532-23
Trial protocol	DK DE NL ES PL
Global end of trial date	12 January 2024

Results information

Result version number	v1 (current)
This version publication date	15 February 2025
First version publication date	15 February 2025

Trial information

Trial identification

Sponsor protocol code	PBD 01180
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04498650
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vivoryon Therapeutics N.V.
Sponsor organisation address	Weinbergweg 22, Halle, Germany, 06120
Public contact	CBO, Vivoryon Therapeutics N.V., +49 345 5559900, info@vivoryon.com
Scientific contact	CBO, Vivoryon Therapeutics N.V., +49 345 5559900, info@vivoryon.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2024
Global end of trial reached?	Yes
Global end of trial date	12 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess the safety and tolerability of PQ912
- To evaluate the efficacy of PQ912 on working memory and attention

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Council for Harmonisation E6 Good Clinical Practice guidelines and applicable national laws and regulatory requirements. Each patient who wanted to participate needed to have a study partner (friend or relative) who also consented to the study and could accompany the patient at each visit. A Data Safety Monitoring Board (DSMB) conducted several unblinded safety assessments of the study and was responsible for making recommendations to the Steering Committee to either continue the study unchanged, or to continue with modifications or to (temporary) stop the study, based on the observed safety profile, and provided recommendations for the dose selection of PQ912 after the first 90 subjects who reached Week 24.

Background therapy:

-

Evidence for comparator:

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Actual start date of recruitment	13 July 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 41
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 65
Country: Number of subjects enrolled	Denmark: 85
Country: Number of subjects enrolled	Germany: 64
Worldwide total number of subjects	259
EEA total number of subjects	259

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	74
From 65 to 84 years	185
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at study sites in Spain, Denmark, Poland, Germany and The Netherlands. The first ICF was signed on 13 July 2020. The last ICF was signed on 07 October 2022.

Pre-assignment

Screening details:

Documentation of medical history, physical and neurological examination, vital signs, ECG, MMSE, GDS, neuropsychological test battery, WAIS-IV, WLA, A-IADL-Q, and MRI. Blood, urine and CSF sample collection.

670 subjects were screened.

-Not meeting inclusion criteria: 397 subjects

-Consent withdrawn by subject: 10 subjects

-Other: 4 subjects

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Subject

Blinding implementation details:

To preserve blinding, PQ912 and placebo tablets were identical in appearance. Emergency unblinding for (S)AEs could be done through EDC. This option was only to be used if the subject's wellbeing required knowledge of the subject's treatment assignment and only after the investigator had made an effort to contact the Sponsor (or delegate). All calls resulting in unblinding were to be recorded and reported in the EDC.

Arms

Are arms mutually exclusive?	Yes
Arm title	PQ912

Arm description:

Subjects receiving PQ912 administered orally, 48 to 96 weeks (depending on the time of randomisation) or discontinued earlier.

Arm type	Experimental
Investigational medicinal product name	PQ912
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Week 1-2: PQ912 50 mg QD (total daily dose 50 mg)

Weeks 3-4: PQ912 50 mg BID (total daily dose 100 mg)

Weeks 5-8: PQ912 150 mg BID (total daily dose 300 mg)

Weeks 9-12: PQ912 300 mg BID (total daily dose 600 mg)

Weeks 13-48 (up to maximum Week 96): PQ912 300 mg or 600 mg BID (total daily dose 600 mg or 1200 mg)

The tablet strength of PQ912 is 50 mg and 150 mg, therefore, subjects were required to take 1 tablet per dosing (Weeks 1-8), 2 tablets per dosing (Weeks 9-12), and 2 or 4 tablets per dosing (Weeks 13-48, up to maximum Week 96).

Arm title	Placebo
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Arm description:

Subjects receiving placebo administered orally, 48 to 96 weeks (depending on the time of

randomisation) or discontinued earlier.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Week 1-2: Matching Placebo tablets, 1 tablet QD

Weeks 3-4: Matching Placebo tablets, 1 tablet BID

Weeks 5-8: Matching Placebo tablets, 1 tablet BID

Weeks 9-12: Matching Placebo tablets, 2 tablets BID

Weeks 13-48 (up to maximum Week 96): Matching Placebo tablets, 2 or 4 tablets BID

The tablet strength of PQ912 is 50 mg and 150 mg, therefore, subjects were required to take 1 tablet per dosing (Weeks 1-8), 2 tablets per dosing (Weeks 9-12), and 2 or 4 tablets per dosing (Weeks 13-48, up to maximum Week 96).

Number of subjects in period 1	PQ912	Placebo
Started	142	117
Completed	122	106
Not completed	20	11
Consent withdrawn by subject	15	7
Physician decision	-	1
Adverse event, non-fatal	4	3
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	PQ912
Reporting group description:	
Subjects receiving PQ912 administered orally, 48 to 96 weeks (depending on the time of randomisation) or discontinued earlier.	
Reporting group title	Placebo
Reporting group description:	
Subjects receiving placebo administered orally, 48 to 96 weeks (depending on the time of randomisation) or discontinued earlier.	

Reporting group values	PQ912	Placebo	Total
Number of subjects	142	117	259
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	68.6	68.3	
standard deviation	± 7.08	± 7.78	-
Gender categorical			
Units: Subjects			
Female	69	62	131
Male	73	55	128
ApoE genotype			
Apolipoprotein E (ApoE) is a class of proteins involved in the metabolism of fats in the body. ApoE is polymorphic, with three major alleles: ApoE-ε2 (cys112, cys158), ApoE-ε3 (cys112, arg158), and ApoE-ε4 (arg112, arg158). These differences alter ApoE structure and function. The E4 variant is the largest known genetic risk factor for late-onset sporadic Alzheimer's disease (AD) in a variety of ethnic groups.			
Units: Subjects			
E4 homozygous	36	30	66
E4 heterozygous	61	51	112
E4 negative	33	26	59
Not detected	4	3	7
Missing	8	7	15

End points

End points reporting groups

Reporting group title	PQ912
Reporting group description: Subjects receiving PQ912 administered orally, 48 to 96 weeks (depending on the time of randomisation) or discontinued earlier.	
Reporting group title	Placebo
Reporting group description: Subjects receiving placebo administered orally, 48 to 96 weeks (depending on the time of randomisation) or discontinued earlier.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: All subjects randomly assigned to study treatment, who received at least one treatment dose (PQ912 or placebo), and with at least one post-baseline value. Subjects who discontinued treatment before Week 48 were included in the analysis.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who had taken at least one dose of PQ912 or placebo.	

Primary: Change with time on working memory and attention as measured by the combined Z-score of the Detection test, Identification test and the 'One Back' test (attention and working memory domains) of the neuropsychological test battery (NTB)

End point title	Change with time on working memory and attention as measured by the combined Z-score of the Detection test, Identification test and the 'One Back' test (attention and working memory domains) of the neuropsychological test battery (NTB)
End point description: The CogState NTB is composed of cognitive tests indexing executive function (Detection test), attention (Identification test), and working memory (One Back test); key cognitive skills known to be compromised early in the AD process. The primary efficacy endpoint was derived as the combined Z-score calculated as the arithmetic mean of the 3 Z-scores of the Detection test, Identification test, and the One Back test (attention and working memory domains), with a higher Z-score indicating a better performance. The rate of change of the combined Z-score over time was analysed via a random coefficients model to estimate the total slope (weeks; ie change in Z-score per week) in each treatment group with the difference in total slope and its associated standard error, CI, and 2-sided p-value.	
Population: Full Analysis Set	
End point type	Primary
End point timeframe: From baseline up to Week 48 or Week 96 (depending on the time of randomisation).	

End point values	PQ912	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	117		
Units: Not applicable				
least squares mean (standard error)				
Baseline	-1.3321 ($\pm$ 0.0778)	-1.2195 ($\pm$ 0.0859)		

Week 96	-1.6175 ($\pm$ 0.1011)	-1.4768 ($\pm$ 0.1120)		
Change from baseline at Week 96	-0.2853 ($\pm$ 0.0816)	-0.2573 ($\pm$ 0.0917)		

Statistical analyses

Statistical analysis title	Primary total slope random coefficients analysis
Statistical analysis description:	
The difference in total slope (active vs placebo) was estimated using the random coefficients model. Random, subject-specific intercepts and slopes were assumed, taken from a bivariate normal distribution, centered at (0,0). The covariance structure was unrestricted. All valid observations were used. For missed baseline data at the individual test level, the most recent screening assessments were used.	
Comparison groups	PQ912 v Placebo
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8194
Method	Mixed models analysis
Parameter estimate	Slope (weeks) difference
Point estimate	-0.0003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0028
upper limit	0.0022

Secondary: Change with time in overall cognition as measured by the combined Z-score of the CogState Brief Battery (CBB)

End point title	Change with time in overall cognition as measured by the combined Z-score of the CogState Brief Battery (CBB)
End point description:	
The CBB includes the 3 tests of the primary endpoint (Detection test, Identification test and the 'One Back' test [attention and working memory domains]) plus the 'One Card Learning' test, testing the episodic visual memory. A combined Z-score was derived as the arithmetic mean of the 4 Z-scores, with a high combined Z-score indicating a better performance. The rate of change of the combined Z score over time was analysed via a random coefficients model to estimate the total slope (weeks; ie change in Z-score per week) in each treatment group, similar as done for the primary efficacy endpoint.	
Population: Full Analysis Set	
End point type	Secondary
End point timeframe:	
From baseline up to Week 48 or Week 96 (depending on the time of randomisation).	

End point values	PQ912	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	117		
Units: Not applicable				
least squares mean (standard error)				
Baseline	-1.3220 (± 0.0635)	-1.2262 (± 0.0701)		
Week 96	-1.5900 (± 0.0826)	-1.4896 (± 0.0915)		
Change from baseline at Week 96	-0.2680 (± 0.0640)	-0.2634 (± 0.0721)		

Statistical analyses

Statistical analysis title	CBB total slope random coefficients analysis
Statistical analysis description:	
The difference in total slope (active vs placebo) was estimated using the random coefficients model. Random, subject-specific intercepts and slopes were assumed, taken from a bivariate normal distribution, centered at (0,0). The covariance structure was unrestricted. All observations were used. For missed baseline data at the individual test level, the most recent screening assessments were used.	
Comparison groups	Placebo v PQ912
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9619
Method	Mixed models analysis
Parameter estimate	Slope (weeks) difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.0019

Secondary: Change with time of overall cognition as measured by the combined Z-score of the complete neuropsychological test battery (NTB)

End point title	Change with time of overall cognition as measured by the combined Z-score of the complete neuropsychological test battery (NTB)
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End point description:

The complete NTB included 8 tests (Detection test, Identification test, One Back test [attention and working memory domains], One Card Learning test, International Shopping List test [Immediate and Delayed Recall tests], Category Fluency test, and Letter Fluency test). A combined Z-score was derived as the arithmetic mean of the 8 Z-scores, with a high combined Z-score indicating a better performance. The rate of change of the combined Z score over time was analysed via a random coefficients model to estimate the total slope (weeks; ie change in Z-score per week) in each treatment group, similar as done for the primary efficacy endpoint.

Population: Full Analysis Set

End point type	Secondary
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End point timeframe:

From baseline up to Week 48 or Week 96 (depending on the time of randomisation).

End point values	PQ912	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	117		
Units: Not applicable				
least squares mean (standard error)				
Baseline	-1.5072 ($\pm$ 0.0515)	-1.4655 ($\pm$ 0.0568)		
Week 96	-1.8680 ($\pm$ 0.0681)	-1.8472 ($\pm$ 0.0753)		
Change from baseline at Week 96	-0.3608 ($\pm$ 0.0480)	-0.3818 ($\pm$ 0.0538)		

Statistical analyses

Statistical analysis title	NTB total slope random coefficients analysis
Statistical analysis description: The difference in total slope (active vs placebo) was estimated using the random coefficients model. Random, subject-specific intercepts and slopes were assumed, taken from a bivariate normal distribution, centered at (0,0). The covariance structure was unrestricted. All observations were used. For missed baseline data at the individual test level, the most recent screening assessments were used.	
Comparison groups	Placebo v PQ912
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7709
Method	Mixed models analysis
Parameter estimate	Slope (weeks) difference
Point estimate	0.0002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0013
upper limit	0.0017

Secondary: Change from baseline in daily activities as measured by Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q) total score at End of Treatment (EOT)

End point title	Change from baseline in daily activities as measured by Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q) total score at End of Treatment (EOT)
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End point description:

The A-IADL-Q long version total score is derived via a closed algorithm based on 70 items addressing

household/leisure time/work-related topics with a higher total score indicating a better performance. The subject's study partner completed the questionnaire.

Since EOT occurred at different visits for different subjects, an analysis of covariance (ANCOVA) was used to estimate and compare the change from baseline at EOT between the active and placebo groups.

Population: Full Analysis Set

End point type	Secondary
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End point timeframe:

From baseline up to EOT (depending on the time of randomisation).

End point values	PQ912	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	114		
Units: Score				
least squares mean (standard error)				
Change from baseline at EOT	-8.3975 ($\pm$ 0.7817)	-6.8452 ($\pm$ 0.8615)		

Statistical analyses

Statistical analysis title	A-IADL-Q total score at EOT - ANCOVA
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Statistical analysis description:

An ANCOVA was used to estimate and compare the change from baseline at EOT between the active and placebo groups. All observations were used.

Comparison groups	PQ912 v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1872
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1.5523
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8639
upper limit	0.7594

Secondary: Change from baseline in global relative theta (4-8 Hz) power in the electroencephalogram (EEG) at Week 48

End point title	Change from baseline in global relative theta (4-8 Hz) power in the electroencephalogram (EEG) at Week 48
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End point description:

Quantitative EEG measurements were used to evaluate brain functional network activity and connectivity. In AD, eyes closed resting state EEG shows distinct changes reflecting abnormalities of brain oscillatory activity. With disease progression, there is a gradual, diffuse slowing of brain activity. First, theta power increases and beta power decreases, followed by slowing and diminished reactivity of

the alpha peak frequency. In later stages, alpha power decreases and finally delta power increases. An increase in relative theta power is regarded as the most sensitive oscillatory activity marker in the earliest stages of AD.

The change from baseline at Week 48 was analysed using a mixed model with repeated measurements, using all observations.

Population: Full Analysis Set

End point type	Secondary
End point timeframe:	
From baseline to Week 48.	

End point values	PQ912	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	65		
Units: Hz				
least squares mean (confidence interval 95%)				
Change from baseline at Week 48	0.0168 (0.0076 to 0.0260)	0.0142 (0.0029 to 0.0255)		

Statistical analyses

Statistical analysis title	Global relative theta power - MMRM
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Statistical analysis description:

A mixed model with repeated measurements (MMRM) was used to estimate and compare the change from baseline at Week 48 between the active and placebo groups. The estimated difference between the treatment groups at Week 48 is the main result. All observations were used. Subjects without baseline values were automatically excluded.

Comparison groups	Placebo v PQ912
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7281
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.0026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0121
upper limit	0.0173

Secondary: Number of subjects with treatment-emergent adverse events (TEAEs) with severity $\geq$ grade 3 according to CTCAE

End point title	Number of subjects with treatment-emergent adverse events (TEAEs) with severity $\geq$ grade 3 according to CTCAE
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End point description:

The number of subjects with TEAEs with severity $\geq$ grade 3 (according to CTCAE v5.0) during the study.
Population: Safety Analysis Set

End point type	Secondary
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End point timeframe:

All $\geq$ grade 3 AEs that occurred or worsened after the first administration of the study treatment and up to the last visit (up to 52 to 100 weeks; 48 to 96 weeks treatment + 4 weeks of follow-up)

End point values	PQ912	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	117		
Units: Subjects				
Any TEAE of $\geq$ CTCAE Grade 3	22	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent serious adverse events (SAEs)

End point title	Number of subjects with treatment-emergent serious adverse events (SAEs)
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End point description:

The number of subjects with treatment-emergent SAEs during the study.
Population: Safety Analysis Set

End point type	Secondary
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End point timeframe:

All SAEs that occurred or worsened after the first administration of the study treatment and up to the last visit (up to 52 to 100 weeks; 48 to 96 weeks treatment + 4 weeks of follow-up)

End point values	PQ912	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	117		
Units: Subjects				
Any treatment-emergent SAE	18	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse events (TEAEs) leading to treatment discontinuation

End point title	Number of subjects with treatment-emergent adverse events (TEAEs) leading to treatment discontinuation
End point description: The number of subjects with TEAEs leading to treatment discontinuation during the study. Population: Safety Analysis Set	
End point type	Secondary
End point timeframe: All AEs leading to treatment discontinuation that occurred or worsened after the first administration of the study treatment and up to the last visit (up to 52 to 100 weeks; 48 to 96 weeks treatment + 4 weeks of follow-up).	

End point values	PQ912	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	117		
Units: Number of subjects				
Any TEAE leading to treatment discontinuation	6	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse events of special interest (AESI)

End point title	Number of subjects with treatment-emergent adverse events of special interest (AESI)
End point description: The number of subjects with treatment-emergent AESIs. An AESI is defined as an SAE, discontinuation due to TEAE or SAE, or any $\geq$ grade 3 AE (according to CTCAE) defined within either the system organ class Skin and Subcutaneous Tissue Disorders or Hepatobiliary Disorders, or a discontinuation due to an extreme liver laboratory parameter related to the liver and/or bile organ system, as defined below. - Alanine-amino transferase (ALT) or asparagine-amino transferase (AST) $>8\times$ upper limit of normal (ULN) - ALT or AST $>5\times$ULN for more than 2 weeks - ALT or AST $>3\times$ULN and (total bilirubin [T-BiL] $>2\times$ULN or international normalised ratio [INR] >1.5) - ALT or AST $>3\times$ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).	
Population: Safety Analysis Set	
End point type	Secondary
End point timeframe: All AESIs after the first administration of the study treatment and up to the last visit (up to 52 to 100 weeks; 48 to 96 weeks treatment + 4 weeks of follow-up).	

End point values	PQ912	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	117		
Units: Number of subjects				
Any treatment-emergent AESI	3	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change with time of estimated glomerular filtration rate (eGFR)

End point title	Change with time of estimated glomerular filtration rate (eGFR)
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End point description:

The eGFR is a relevant renal function parameter commonly used in clinical practice to estimate creatinine clearance, with higher scores indicating a better renal function. eGFR was estimated with the Modification of Diet in Renal Disease (MDRD) method using the equation: $32788 \times [\text{serum creatinine}]^{-1.154} \times (\text{age})^{-0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$.

The change over time in eGFR was estimated using random coefficients mixed effects modelling.

Population: Full Analysis Set; all subjects who received at least one dose, with at least one post-baseline value, a baseline eGFR value, and no missing covariate values.

End point type	Other pre-specified
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End point timeframe:

From baseline up to EOT (depending on the time of randomisation).

End point values	PQ912	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	117		
Units: mL/min/1.73m ² /year				
least squares mean (standard error)				
Change from baseline at EOT	0.83 (± 0.519)	-1.82 (± 0.606)		

Statistical analyses

Statistical analysis title	Change with time of eGFR
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Statistical analysis description:

A random coefficients analysis model was used to estimate and compare the change from baseline through EOT between the active and placebo groups. All eGFR data were used, whether scheduled or unscheduled. For missing eGFR data, no imputations were made, rather missing data were handled implicitly by use of mixed modelling.

Comparison groups	PQ912 v Placebo
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Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	random coefficients mixed effects model
Parameter estimate	Difference in annualized rate of change
Point estimate	2.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	4.22

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred or worsened after the first administration of the study treatment and up to the last visit (up to 52 to 100 weeks; 48 to 96 weeks treatment + 4 weeks of follow-up).

Adverse event reporting additional description:

The frequency threshold for reporting non-serious adverse events is 5% in any treatment group.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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Reporting groups

Reporting group title	PQ912
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Reporting group description:

Subjects receiving PQ912 administered orally, 48 to 96 weeks (depending on the time of randomisation) or discontinued earlier.

Reporting group title	Placebo
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Reporting group description:

Subjects receiving placebo administered orally, 48 to 96 weeks (depending on the time of randomisation) or discontinued earlier.

Serious adverse events	PQ912	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 142 (12.68%)	10 / 117 (8.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 142 (0.00%)	2 / 117 (1.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			

subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enterovesical fistula			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oesophageal stenosis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Exostosis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint stiffness			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 142 (0.70%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infection			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 142 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 142 (0.70%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	PQ912	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 142 (57.04%)	59 / 117 (50.43%)	
Nervous system disorders			
Dementia Alzheimer's type			
subjects affected / exposed	13 / 142 (9.15%)	8 / 117 (6.84%)	
occurrences (all)	13	8	
Headache			
subjects affected / exposed	7 / 142 (4.93%)	11 / 117 (9.40%)	
occurrences (all)	9	11	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 142 (5.63%)	4 / 117 (3.42%)	
occurrences (all)	9	4	
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	9 / 142 (6.34%) 10	11 / 117 (9.40%) 14	
Nausea subjects affected / exposed occurrences (all)	12 / 142 (8.45%) 13	4 / 117 (3.42%) 5	
Constipation subjects affected / exposed occurrences (all)	5 / 142 (3.52%) 5	6 / 117 (5.13%) 8	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	4 / 142 (2.82%) 5	10 / 117 (8.55%) 11	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	12 / 142 (8.45%) 15	3 / 117 (2.56%) 4	
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	38 / 142 (26.76%) 40	21 / 117 (17.95%) 22	
Urinary tract infection subjects affected / exposed occurrences (all)	10 / 142 (7.04%) 12	5 / 117 (4.27%) 6	
Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 142 (6.34%) 9	6 / 117 (5.13%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2020	Reason for amendment: Clarifications to blood/urine sampling, electroencephalogram (EEG) assessments, and washout periods for concomitant medication, an exploratory objective was added to evaluate serum biomarkers, correction of the WAIS IV Coding Test and widening of the range of cognitive impairment in the inclusion criteria, and updates for the use of intrauterine devices (IUDs) in association with magnetic resonance imaging (MRI).
17 June 2022	Reason for amendment: Administrative updates and clarifications on electroencephalogram (EEG) assessments, inclusion criteria, concomitant medication use, adverse event (AE) reporting, and rescreening procedures, addition of local requirements for COVID-19 testing, and addition of brain magnetic resonance imaging (MRI) in case of neuropsychiatric AEs.
07 July 2023	Reason for amendment: Administrative updates concerning the coordinating investigator, and adjustments to the endpoint ordering and analyses as specified below. - Tests were added to the exploratory efficacy objectives and endpoints: pen-and-pencil Letter and Category Fluency tests, CogState brief battery tests. - Secondary efficacy objectives and endpoints were reordered to emphasise the importance of cognition objectives. - The category 'Other Pre-specified Analyses' was added to the efficacy parameters.
06 October 2023	Reason for amendment: Administrative updates (change in biostatistician), the method of MRI reading for amyloid-related imaging abnormalities was changed to central reading, minor adjustments of exploratory endpoints, and of the proposed model for analysis of cognitive change, and a clarification was added regarding PQ912 and varoglutamstat being synonymous.
01 December 2023	Reason for amendment: Clarifications to the proposed model for analysis of cognitive change, renal safety markers were added in 'Other safety endpoints' and to blood chemistry parameters, and a reference to the investigational medicinal product handling guide was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: