Clinical trial results:
A Phase 2a Multicentre, Randomised, Double-blind, Placebo-controlled, Parallel-group Safety and Tolerability Study of PQ912 in Subjects with Early Alzheimer's Disease (SAPHIR)

Summary

EudraCT number	2014-001967-11
Trial protocol	NL FI DE SE BE ES
Global end of trial date	22 September 2017

Results information

Result version number	v1 (current)
This version publication date	12 April 2018
First version publication date	12 April 2018

Trial information

Trial identification

Sponsor protocol code	PBD 01071

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02389413
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Probiodrug AG
Sponsor organisation address	Weinbergweg 22, Halle, Germany, 06120
Public contact	Suzanne Bruins, Probiodrug AG, 0049 3455559900, info@probiodrug.de
Scientific contact	Suzanne Bruins, Probiodrug AG, 0049 3455559900, info@probiodrug.de

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	05 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 April 2017
Global end of trial reached?	Yes
Global end of trial date	22 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

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 needed to accompany the patient at each visit. A Safety Oversight Expert 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 observed safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 19
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Finland: 24
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 50
Worldwide total number of subjects	120
EEA total number of subjects	120

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
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)	25
From 65 to 84 years	94
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment started in March 2015 and stopped in December 2016.

Pre-assignment

Screening details:

Procedures at screening included documentation of medical history, physical and neurological examination, assessment of vital signs, electrocardiogram (ECG), Mini Mental State Exam (MMSE), Geriatric Depression Scale (GDS), neuropsychological test battery, Magnetic Resonance Imaging (MRI) and EEG. Blood, urine and CSF samples were collected.

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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

To preserve the blinding of the study, batch numbers for placebo and PQ912 were the same. Emergency unblinding for (S)AEs could be done through Electronic Data Capture (EDC). This option was to be used only 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 by EDC.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects receiving placebo administered orally, BID, 12 weeks

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: Matching Placebo tablets.
Weeks 2-12: Matching Placebo tablets.
The tablet strength of PQ912 is 200 mg, therefore subjects were required to take 2 tablets per dosing (in Week 1) or 4 tablets per dosing (in Weeks 2-12).

Arm title	PQ912

Arm description:

Subjects receiving PQ912 administered orally, BID, 12 weeks

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: PQ912 400 mg BID (total daily dose 800 mg).
Weeks 2-12: PQ912 800 mg BID (total daily dose 1600 mg).
The tablet strength of PQ912 is 200 mg, therefore subjects were required to take 2 tablets per dosing

(in Week 1) or 4 tablets per dosing (in Weeks 2-12).

Number of subjects in period 1	Placebo	PQ912
Started	60	60
Completed	60	55
Not completed	0	5
Consent withdrawn by subject	-	5

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects receiving placebo administered orally, BID, 12 weeks	
Reporting group title	PQ912
Reporting group description:	
Subjects receiving PQ912 administered orally, BID, 12 weeks	

Reporting group values	Placebo	PQ912	Total
Number of subjects	60	60	120
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	72	70.8	
standard deviation	± 6.7	± 7.6	-
Gender categorical			
Units: Subjects			
Female	28	36	64
Male	32	24	56
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 positive	43	38	81
E4 negative	16	20	36
Missing	1	2	3

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects receiving placebo administered orally, BID, 12 weeks	
Reporting group title	PQ912
Reporting group description:	
Subjects receiving PQ912 administered orally, BID, 12 weeks	

Primary: Safety primary composite endpoint	
End point title	Safety primary composite endpoint
End point description:	
The safety primary composite endpoint was based on: • Discontinuation of a subject due to SAE • Discontinuation of a subject due to AE with severity ≥ grade 3 according to CTCAE • Discontinuation of a subject due to an extreme laboratory parameter	
End point type	Primary
End point timeframe:	
From screening to last study visit. Screening to randomization: up to 12 weeks. Randomization to last study visit: 16 weeks.	

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: number of subjects				
Composite safety	0	6		
Discontinuation subject due to SAE	0	6		
Discontinuation subject due to AE ≥ CTCAE Grade 3	0	6		
Discontinuation subject due to extreme lab value	0	0		

Statistical analyses

Statistical analysis title	Composite Safety
Comparison groups	Placebo v PQ912
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.027
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.18

Notes:

[1] - RR was not possible since 1 cell was zero.

Statistical analysis title	Discontinuation subject due to SAE
Comparison groups	Placebo v PQ912
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.027
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.18

Notes:

[2] - RR was not possible since 1 cell was zero .

Statistical analysis title	Discontinuation subject due to AE ≥ CTCAE Grade 3
Comparison groups	Placebo v PQ912
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.027
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.18

Notes:

[3] - RR was not possible since 1 cell was zero.

Statistical analysis title	Discontinuation subject due to extreme lab value
Comparison groups	Placebo v PQ912

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 1
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[4] - RR was not possible since both cells were zero.

Primary: Tolerability primary composite endpoint

End point title	Tolerability primary composite endpoint

End point description:

A composite tolerability endpoint composed of:
1) The number of subjects who experienced a dose adjustment, defined as a reduction of dose from 800 BID to 400 BID, and
2) The number of subjects experiencing non-adherence to randomized treatment, defined as using less than 75% of the prescribed dose in 4 consecutive weeks including at least one week with less than 50%, or three or more consecutive days in total or seven days of interrupted use during the full 12 weeks.

End point type	Primary

End point timeframe:

From screening to last study visit. Screening to randomization: up to 12 weeks. Randomization to last study visit: 16 weeks.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: number of subjects				
Dose adjustment during treatment period	5	5		
Non-adherence to randomised treatment	2	26		

Statistical analyses

Statistical analysis title	Composite tolerability
Comparison groups	Placebo v PQ912

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	10.11

Statistical analysis title	Dose adjustment during treatment period
Comparison groups	Placebo v PQ912
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	3.28

Statistical analysis title	Non-adherence to randomised treatment
Comparison groups	Placebo v PQ912
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	13
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.23
upper limit	52.35

Secondary: Number of SAEs

End point title	Number of SAEs

End point description:

The number of SAEs occurring during the study was recorded.

End point type	Secondary

End point timeframe:

From screening to last study visit. Screening to randomization: up to 12 weeks. Randomization to last study visit: 16 weeks.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: number of events				
Number of SAEs	5	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of AEs with severity ≥ grade 3 according to CTCAE

End point title	Number of AEs with severity ≥ grade 3 according to CTCAE

End point description:

The number of AEs with severity ≥ grade 3 according to CTCAE occurring during the study was recorded.

End point type	Secondary

End point timeframe:

From screening to last study visit. Screening to randomization: up to 12 weeks. Randomization to last study visit: 16 weeks.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: number of events				
Number of AEs of ≥ CTCAE Grade 3	3	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to dose adjustment (time in days after randomisation)

End point title	Time to dose adjustment (time in days after randomisation)

End point description:

The time to dose adjustment (time in days after randomisation) was recorded during the study. Dose adjustment, i.e. reduction, was defined as a reduction of dose from 800 mg BID to 400 mg BID. If applicable, median survival time is reported. Median survival time cannot be assessed because less than 50 % of subjects showed an event before the end of study. In this case, 0 = NA.

End point type	Secondary

End point timeframe:

From screening to last study visit. Screening to randomization: up to 12 weeks. Randomization to last study visit: 16 weeks.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: days				
median (standard deviation)				
Time to dose adjustment	0 (± 0)	0 (± 0)		

Attachments (see zip file)	Time to dose adjustment/Figure 14.4.1.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Time to non-adherence (time in weeks after randomisation)

End point title	Time to non-adherence (time in weeks after randomisation)

End point description:

Time to non-adherence (time in weeks after randomisation) was recorded during the study. Non-adherence was defined as using <75% of the prescribed dose in 4 consecutive weeks including at least 1 week with <80%, or ≥3 consecutive days in total or 7 days of interrupted use during the full 12 weeks. If applicable, median survival time is reported. Median survival time cannot be assessed because less than 50 % of subjects showed an event before the end of study. In this case, 0 = NA.

End point type	Secondary

End point timeframe:

From screening to last study visit. Screening to randomization: up to 12 weeks. Randomization to last study visit: 16 weeks.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: weeks				
median (standard deviation)				
Time to non-adherence	0 (± 0)	0 (± 0)		

Attachments (see zip file)	Figure 14.4.2.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Time to non-adherence, dose adjustment, discontinuation due to SAE, AE-CTCAE3+ or extreme lab (time in weeks after randomisation).

End point title	Time to non-adherence, dose adjustment, discontinuation due to SAE, AE-CTCAE3+ or extreme lab (time in weeks after randomisation).

End point description:

Time to non-adherence, dose adjustment, discontinuation due to SAE, AE-CTCAE3+ or extreme laboratory values were recorded during the study. Dose adjustment, i.e. reduction, was defined as a reduction of dose from 800 mg BID to 400 mg BID. Non-adherence was defined as using <75% of the prescribed dose in 4 consecutive weeks including at least 1 week with <80%, or ≥3 consecutive days in total or 7 days of interrupted use during the full 12 weeks. If applicable, median survival time is reported. In this case, 0 = NA.

End point type	Secondary

End point timeframe:

From screening to last study visit. Screening to randomization: up to 12 weeks. Randomization to last study visit: 16 weeks.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: weeks				
median (standard deviation)				
Time to event	0 (± 0)	0 (± 0)		

Attachments (see zip file)	Time to event/Figure 14.4.3.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Glutaminyl cyclase (QC) activity in cerebrospinal fluid (CSF)

End point title	Glutaminyl cyclase (QC) activity in cerebrospinal fluid (CSF)

End point description:

QC activity is the primary target of the QC inhibitor PQ912.

End point type	Secondary

End point timeframe:

CSF samples for biomarker assessment were obtained at screening and V5/End-of-treatment (EoT) visits.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	26		
Units: mU/L				
median (inter-quartile range (Q1-Q3))				
Baseline	120.8 (101.3 to 140.2)	110.2 (94.8 to 134.2)		
End of treatment (EoT)	120.3 (104.1 to 137.5)	35.6 (29.7 to 63.2)		
Change over time	-0.6 (-5.5 to 4.3)	-68.9 (-87 to -56.4)		

Statistical analyses

Statistical analysis title	QC activity

Statistical analysis description:

An analysis of covariance(ANCOVA) with treatment, gender, ApoE (E4 allele present or not) and country(stratification) as factors and time between screening and baseline, baseline measure of the endpoint and age as covariates, was performed. The assumption of normally distributed residuals was not met and therefore data were log transformed.

Comparison groups	Placebo v PQ912
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	mean difference in log-transformed value
Point estimate	-0.454
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.507
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.027

Notes:

[5] - 65 subjects were included in this Per Protocol (PP) analysis.

Secondary: Target Occupancy (TO)

End point title	Target Occupancy (TO)[6]

End point description:

The target of PQ912, the QC enzyme, is present in the CSF and its activity can be measured ex vivo in CSF samples. Based on the measured QC activities pre- and post-dosing the TO can be calculated. The TO will give important information about the dose-relatedness of QC inhibition as a prerequisite for any effect on disease related pathological pathways and on cognition. TO was calculated for CSF samples

taken within 24 hours after last intake at Visit 5/EOT, where the corresponding QC activity at screening was available. Measurement of QC activity in vitro required a sample dilution and is sensitive to substrate concentration relative to Michaelis Menten constant (Km).

End point type	Secondary

End point timeframe:

CSF samples for biomarker assessment were obtained at screening and V5/End-of-treatment (EoT) visits.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: TO was not calculated for the placebo group.

End point values	PQ912			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: percent				
median (full range (min-max))				
TO	92 (82 to 96)			

Statistical analyses

No statistical analyses for this end point

Secondary: pGlu-A-beta oligomer

End point title	pGlu-A-beta oligomer

End point description:

The production of the toxic species pGlu-A-beta might be reduced by using the QC inhibitor PQ 912 and was therefore selected as biomarker in this study.

End point type	Secondary

End point timeframe:

CSF samples for biomarker assessment were obtained at screening and V5/E0T visits.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	25[7]		
Units: AU				
median (inter-quartile range (Q1-Q3))				
Baseline	0.01 (0 to 0.54)	0.51 (0.22 to 0.99)		
EoT	0.26 (0 to 0.58)	0.44 (0 to 1.42)		
Change over time	0 (-0.23 to 0.4)	0 (-0.31 to 0.85)		

Notes:

[7] - 25 subjects were analysed at baseline and for change over time, 26 subjects were analysed at EoT

Statistical analyses

Statistical analysis title	pGlu-A-beta oligomer

Statistical analysis description:

The data was dichotomized (yes/no LLOQ), reported in cross tables for baseline and EOT assessments per group and analysed using Mantel Haenszel statistics with treatment andV5/EOT as variables and V1 as confounder.

Comparison groups	Placebo v PQ912
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.369
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	6.04

Notes:

[8] - 68 subjects were included in this PP analysis

Secondary: Neurogranin

End point title	Neurogranin

End point description:

Neurogranin is a biomarker associated with synaptic dysfunction. Increases are seen in patients with AD.

End point type	Secondary

End point timeframe:

CSF samples for biomarker assessment were obtained at screening and V5/EoT visits.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[9]	26		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))				
Baseline	419 (348 to 583)	422 (314 to 530)		
EoT	411 (328 to 517)	391 (298 to 516)		
Change over time	0 (-31.5 to 16)	-22.5 (-45 to 12)		

Notes:

[9] - 41 subjects were analysed at baseline and EoT, 40 subjects were analysed for change over time

Statistical analyses

Statistical analysis title	Neurogranin

Statistical analysis description:

An analysis of covariance(ANCOVA) with treatment, gender, ApoE (E4 allele present or not) and country

(stratification) as factors and time between screening and baseline, baseline measure of the endpoint and age as covariates, was performed. The assumption of normally distributed residuals was not met and therefore data were log transformed.

Comparison groups	Placebo v PQ912
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.194
Method	ANCOVA
Parameter estimate	mean difference in log-transformed value
Point estimate	-0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.054
upper limit	0.011
Variability estimate	Standard error of the mean
Dispersion value	0.016

Notes:

[10] - 64 subjects were included in this PP analysis

Secondary: YKL40

End point title	YKL40

End point description:

YKL-40, a marker of astrocyte activation (inflammation), has been shown to be increased in subjects with AD and mild cognitive impairment due to AD, compared to matched controls and is evaluated for its potential as therapeutic marker.

End point type	Secondary

End point timeframe:

CSF samples for biomarker assessment were obtained at screening and V5/EoT visits.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[11]	26		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))				
Baseline	367 (295 to 476)	292 (232 to 412)		
EoT	353 (274 to 469)	297 (219 to 384)		
Change over time	-8 (-28.5 to 20)	-3.5 (-28 to 3)		

Notes:

[11] - 41 subjects were analysed at baseline and EoT, 40 subjects were analysed for change over time

Statistical analyses

Statistical analysis title	YKL40

Statistical analysis description:

An analysis of covariance(ANCOVA) with treatment, gender, ApoE (E4 allele present or not) and country

(stratification) as factors and time between screening and baseline, baseline measure of the endpoint and age as covariates, was performed. The assumption of normally distributed residuals was not met and therefore data were log transformed.

Comparison groups	Placebo v PQ912
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.025
Method	ANCOVA
Parameter estimate	mean difference in log-transformed value
Point estimate	-0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.059
upper limit	-0.004
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[12] - 64 subjects were included in this PP analysis

Secondary: Relative theta power

End point title	Relative theta power

End point description:

It has been widely established that in AD, eyes closed resting state EEG shows distinct changes reflecting abnormalities of brain oscillatory activity. In the earliest phase of AD, especially in late onset AD as opposed to young onset AD (< 65 years), the EEG can be normal. With progression of the disease, 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 thus regarded as the most sensitive oscillatory activity marker in the earliest stages of AD.

End point type	Secondary

End point timeframe:

EEG endpoints were assessed at screening and V5/EoT visits.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	28		
Units: not applicable				
median (inter-quartile range (Q1-Q3))				
Baseline	0.1282 (0.1028 to 0.1886)	0.1547 (0.103 to 0.23)		
EoT	0.1622 (0.1081 to 0.2018)	0.1446 (0.1078 to 0.2145)		
Change over time	0.016 (-0.0036 to 0.0338)	-0.0018 (-0.0285 to 0.0113)		

Statistical analyses

Statistical analysis title	Relative theta power

Statistical analysis description:

An analysis of covariance(ANCOVA) with treatment, gender, ApoE (E4 allele present or not) and country(stratification) as factors and time between screening and baseline, baseline measure of the endpoint and age as covariates, was performed. The assumption of normally distributed residuals was not met and therefore data were log transformed.

Comparison groups	Placebo v PQ912
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	mean difference in log-transformed value
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.114
upper limit	-0.026
Variability estimate	Standard error of the mean
Dispersion value	0.022

Notes:

[13] - 74 subjects were included in this PP analysis

Secondary: One Back Test

End point title	One Back Test

End point description:

The One Back Test is designed to assess working memory.

End point type	Secondary

End point timeframe:

Neuropsychological endpoints were assessed at screening, baseline and V5/EoT visits.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	35		
Units: log10 ms				
median (inter-quartile range (Q1-Q3))				
Baseline	2.992 (2.907 to 3.089)	3.045 (2.92 to 3.153)		
EoT	3.024 (2.916 to 3.12)	3.047 (2.92 to 3.128)		

Change over time	0.004 (-0.041 to 0.069)	-0.025 (-0.087 to 0.025)		

Statistical analyses

Statistical analysis title	One Back Test

Statistical analysis description:

An analysis of covariance(ANCOVA) with treatment, gender, ApoE (E4 allele present or not) and country(stratification) as factors and time between screening and baseline, baseline measure of the endpoint and age as covariates, was performed. The assumption of normally distributed residuals was not met and therefore data were log transformed.

Comparison groups	Placebo v PQ912
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.144
Method	ANCOVA
Parameter estimate	mean difference in log-transformed value
Point estimate	-0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.063
upper limit	0.009
Variability estimate	Standard error of the mean
Dispersion value	0.018

Notes:

[14] - 88 subjects were included in this PP analysis

Secondary: Detection Test

End point title	Detection Test

End point description:

The Detection Test is designed to assess psychomotor speed.

End point type	Secondary

End point timeframe:

Neuropsychological endpoints were assessed at screening, baseline and V5/EoT visits.

End point values	Placebo	PQ912		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	35		
Units: log10 ms				
median (inter-quartile range (Q1-Q3))				
Baseline	2.562 (2.45 to 2.675)	2.533 (2.449 to 2.603)		
EoT	2.597 (2.507 to 2.661)	2.537 (2.425 to 2.587)		

Change over time	0.008 (-0.029 to 0.081)	0.002 (-0.039 to 0.055)		

Statistical analyses

Statistical analysis title	Detection Test

Statistical analysis description:

An analysis of covariance(ANCOVA) with treatment, gender, ApoE (E4 allele present or not) and country(stratification) as factors and time between screening and baseline, baseline measure of the endpoint and age as covariates, was performed. The assumption of normally distributed residuals was not met and therefore data were log transformed.

Comparison groups	Placebo v PQ912
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.397
Method	ANCOVA
Parameter estimate	mean difference in log-transformed value
Point estimate	-0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.083
upper limit	0.033
Variability estimate	Standard error of the mean
Dispersion value	0.029

Notes:

[15] - 88 subjects were included in this PP analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening to end of study. Screening to randomization: between 4 and 12 weeks. Randomization to end of study: 16 weeks.

Adverse event reporting additional description:

Note: the frequency threshold is => 3 subjects (2.5%) reporting in total.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects receiving placebo administered orally, BID, 12 weeks. All non-serious adverse events reported here are treatment-emergent.

Reporting group title	PQ912

Reporting group description:

Subjects receiving PQ912 administered orally, BID, 12 weeks. All non-serious adverse events reported here are treatment-emergent.

Serious adverse events	Placebo	PQ912	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 60 (5.00%)	8 / 60 (13.33%)	
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	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrilation			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Optic ischaemic neuropathy			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			

subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
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			
Lumbar spinal stenosis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (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			
Gastroenteritis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	PQ912	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 60 (66.67%)	45 / 60 (75.00%)	
Investigations			

Weight decreased			
subjects affected / exposed	0 / 60 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 60 (6.67%)	4 / 60 (6.67%)	
occurrences (all)	4	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 60 (3.33%)	3 / 60 (5.00%)	
occurrences (all)	2	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 60 (6.67%)	2 / 60 (3.33%)	
occurrences (all)	4	2	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 60 (5.00%)	1 / 60 (1.67%)	
occurrences (all)	3	1	
Constipation			
subjects affected / exposed	0 / 60 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	3	
Diarrhoea			
subjects affected / exposed	1 / 60 (1.67%)	5 / 60 (8.33%)	
occurrences (all)	1	6	
Nausea			
subjects affected / exposed	4 / 60 (6.67%)	8 / 60 (13.33%)	
occurrences (all)	5	8	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 60 (3.33%)	4 / 60 (6.67%)	
occurrences (all)	2	5	
Urticaria			
subjects affected / exposed	0 / 60 (0.00%)	4 / 60 (6.67%)	
occurrences (all)	0	5	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	3 / 60 (5.00%)	1 / 60 (1.67%)	
occurrences (all)	3	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 60 (1.67%)	3 / 60 (5.00%)	
occurrences (all)	1	3	
Upper respiratory tract infection			
subjects affected / exposed	4 / 60 (6.67%)	4 / 60 (6.67%)	
occurrences (all)	4	4	
Viral upper respiratory tract infection			
subjects affected / exposed	8 / 60 (13.33%)	1 / 60 (1.67%)	
occurrences (all)	8	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 60 (1.67%)	4 / 60 (6.67%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2014	Reason for amendment: Protocol has been updated after comments from regulatory authorities Main changes: - Statistical considerations section updated to be aligned with protocol - Baseline MRI, EEG and Lumbar Puncture moved to Screening MRI, EEG and Lumbar Puncture - Added to the protocol that treatment with Standard of Care AD treatment may be started during the course of the study in case of clinical worsening - Hepatitis A and C assessments in blood added
12 February 2015	Reason for amendment: Protocol has been updated after comments from regulatory authorities. Main changes: - Definition of primary safety endpoint (composite endpoint) made more clear - Added information on the power calculations - Clarified that in Sweden no study partner would be used - Clarification on dose-adjustments during the study - GnRH and TRH measurements were added
08 December 2015	Reason for amendment: to improve recruitment/eligibility and changed on request of regulatory authorities Main changes: - The per patient screening period extended - To allow for re-screening - Tau/A-beta ratio added to inclusion criteria - Use of Souvenaid is allowed - Added: precautionary measures due to photo toxicity - Added prohibited mediation for inclusion

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported