Clinical trial results:
A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy And Safety Study of Crenezumab in Patients With Prodromal to Mild Alzheimer's Disease

Summary

EudraCT number	2016-003288-20
Trial protocol	GB ES EE PT BE DE GR FR SE DK IT
Global end of trial date	11 June 2019

Results information

Result version number	v2 (current)
This version publication date	05 August 2020
First version publication date	11 June 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BN29553

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03114657
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
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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	11 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 June 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of Crenezumab

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	13 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Argentina: 11
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Brazil: 56
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	China: 9
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Spain: 72
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Italy: 90
Country: Number of subjects enrolled	Japan: 42
Country: Number of subjects enrolled	Korea, Republic of: 27
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Peru: 19
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Portugal: 13

Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Serbia: 11
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United States: 194
Country: Number of subjects enrolled	South Africa: 7
Worldwide total number of subjects	806
EEA total number of subjects	321

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)	164
From 65 to 84 years	634
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 209 centers in 27 countries.

Pre-assignment

Screening details:

A total of 806 participants were enrolled at 209 centers. 4 participants did not receive any study treatment meaning that the modified intent-to-treat and safety populations consisted of 802 participants.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received intravenous (IV) infusion of Placebo every 4 weeks (Q4W) for 100 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was administered by intravenous (IV) infusion every 4 weeks (Q4W) at a matching dosage to Crenezumab of 60mg/kg.

Arm title	Crenezumab

Arm description:

Subjects received intravenous (IV) infusion of Crenezumab every 4 weeks (Q4W) for 100 weeks.

Arm type	Experimental
Investigational medicinal product name	Crenezumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Crenezumab was administered by intravenous (IV) infusion every 4 weeks (Q4W) at a dose of 60mg/kg.

Number of subjects in period 1	Placebo	Crenezumab
Started	399	407
Completed	0	0
Not completed	399	407
Adverse event, serious fatal	4	-
Physician decision	2	2
Consent withdrawn by subject	28	22
Adverse event, non-fatal	9	6
Study Terminated By Sponsor	355	374
Multiple Reasons	1	2
Symptomatic Deterioration	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received intravenous (IV) infusion of Placebo every 4 weeks (Q4W) for 100 weeks.	
Reporting group title	Crenezumab
Reporting group description:	
Subjects received intravenous (IV) infusion of Crenezumab every 4 weeks (Q4W) for 100 weeks.	

Reporting group values	Placebo	Crenezumab	Total
Number of subjects	399	407	806
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	86	78	164
From 65-84 years	310	324	634
85 years and over	3	5	8
Age Continuous Units: Years			
arithmetic mean	70.7	71.1	
standard deviation	± 7.9	± 7.5	-
Sex: Female, Male Units:			
Female	225	231	456
Male	174	176	350
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	42	35	77
Not Hispanic or Latino	334	348	682
Not Stated	15	19	34
Unknown	8	5	13
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	8	5	13
Asian	45	47	92
Black or African American	4	3	7
Multiple	4	3	7
Unknown	5	7	12
White	333	342	675

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received intravenous (IV) infusion of Placebo every 4 weeks (Q4W) for 100 weeks.	
Reporting group title	Crenezumab
Reporting group description:	
Subjects received intravenous (IV) infusion of Crenezumab every 4 weeks (Q4W) for 100 weeks.	
Subject analysis set title	Placebo (Modified ITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Subjects received intravenous (IV) infusion of Placebo every 4 weeks (Q4W) for 100 weeks. The Modified Intent-To-Treat population (Placebo (n = 398); Cren (n = 404)) was defined as all randomized subjects who received at least 1 dose of study drug, with subjects grouped according to the treatment assigned at randomization.	
Subject analysis set title	Crenezumab (Modified ITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Subjects received intravenous (IV) infusion of Crenezumab every 4 weeks (Q4W) for 100 weeks. The Modified Intent-To-Treat population (Placebo (n = 398); Cren (n = 404)) was defined as all randomized subjects who received at least 1 dose of study drug, with subjects grouped according to the treatment assigned at randomization.	
Subject analysis set title	Placebo (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received intravenous (IV) infusion of Placebo every 4 weeks (Q4W) for 100 weeks. The Safety analysis population included all randomized subjects who received at least 1 dose of study drug with subjects grouped according to actual treatment received. If a subject received at least 2 vials of crenezumab, then they were placed in the crenezumab arm.	
Subject analysis set title	Crenezumab (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received intravenous (IV) infusion of Crenezumab every 4 weeks (Q4W) for 100 weeks. The Safety analysis population included all randomized subjects who received at least 1 dose of study drug with subjects grouped according to actual treatment received. If a subject received at least 2 vials of crenezumab, then they were placed in the crenezumab arm.	

Primary: Change from Baseline to Week 77 in Clinical Dementia Rating-Sum of Boxes (CDR-SB) Scale Score

End point title	Change from Baseline to Week 77 in Clinical Dementia Rating-Sum of Boxes (CDR-SB) Scale Score
End point description:	
The CDR-SB rates impairment in 6 categories (memory, orientation, judgement and problem solving, community affairs, home and hobbies and personal care) on a 5-point scale in which no impairment = 0, questionable impairment = 0.5 and mild, moderate and severe impairment = 1, 2 and 3 respectively. The score range is from 0 to 18 with a high score indicating a high disease severity. The difference in mean change from Baseline to Week 77 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline for this primary endpoint. Data after 29 January 2019 are censored for the primary and secondary efficacy analyses to avoid potential biases due to investigators, participants, raters, etc. being potentially influenced by early closure of the study due to lack of efficacy.	
End point type	Primary
End point timeframe:	
Baseline, Week 77	

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15[1]	12[2]		
Units: Units on a Scale				
least squares mean (standard error)				
Week 77	3.19 (± 0.434)	1.89 (± 0.471)		

Notes:

[1] - Data presented is only for subjects that were included in the actual analysis.

[2] - Data presented is only for subjects that were included in the actual analysis.

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Crenezumab (Modified ITT) v Placebo (Modified ITT)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2.6
Variability estimate	Standard error of the mean
Dispersion value	0.633

Secondary: Change from Baseline to Week 77 in Alzheimer's Disease Assessment Scale-Cognition 13 (ADAS-Cog-13) Subscale Score

End point title	Change from Baseline to Week 77 in Alzheimer's Disease Assessment Scale-Cognition 13 (ADAS-Cog-13) Subscale Score

End point description:

The ADAS-Cog-13 assesses multiple cognitive domains including memory, comprehension, praxis, orientation, and spontaneous speech. Most of these are assessed by tests although some are rated by the clinician on a 5-point scale. The ADAS-Cog-13 is the ADAS-Cog-11 with 2 further items: delayed word recall and total digit cancellation. The score range for ADAS-Cog-13 is from 0 to 85 with high scores representing severe dysfunction. The difference in mean change from Baseline to Week 77 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 77

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	12		
Units: Units on a Scale				
least squares mean (standard error)				
Week 77	8.90 (± 1.382)	7.16 (± 1.526)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	5.89
Variability estimate	Standard error of the mean
Dispersion value	2.028

Secondary: Change from Baseline to Week 77 in Alzheimer's Disease Assessment Scale-Cognition 11 (ADAS-Cog-11) Subscale Score

End point title	Change from Baseline to Week 77 in Alzheimer's Disease Assessment Scale-Cognition 11 (ADAS-Cog-11) Subscale Score

End point description:

The ADAS-Cog-11 assesses multiple cognitive domains including memory, comprehension, praxis, orientation, and spontaneous speech. Most of these are assessed by tests although some are rated by the clinician on a 5-point scale. The score range for ADAS-Cog-11 is from 0 to 70 with high scores representing severe dysfunction. The difference in mean change from Baseline to Week 77 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 77

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	12		
Units: Units on a Scale				
least squares mean (standard error)				
Week 77	7.16 (± 1.452)	6.84 (± 1.592)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.03
upper limit	4.68
Variability estimate	Standard error of the mean
Dispersion value	2.124

Secondary: Change from Baseline to Week 77 on Severity of Dementia, Assessed Using the CDR-Global Score (CDR-GS)

End point title	Change from Baseline to Week 77 on Severity of Dementia, Assessed Using the CDR-Global Score (CDR-GS)

End point description:

The CDR-GS represents a semi-structured interview which rates impairment in 6 categories (memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care) on a 5-point scale in which CDR 0 = no dementia and CDR 0.5, 1, 2 or 3 = questionable, mild, moderate or severe dementia respectively. The range in scores for the CDR-GS is from 0 to 3 and a high score on the CDR-GS would indicate a high disease severity. The difference in mean change from Baseline to Week 77 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 77

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	12		
Units: Units on a Scale				
least squares mean (standard error)				
Week 77	0.39 (± 0.096)	0.29 (± 0.102)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.39
Variability estimate	Standard error of the mean
Dispersion value	0.141

Secondary: Change from Baseline to Week 77 on Severity of Dementia, Assessed Using the Mini Mental State Evaluation (MMSE)

End point title	Change from Baseline to Week 77 on Severity of Dementia, Assessed Using the Mini Mental State Evaluation (MMSE)

End point description:

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment. The questions target 6 areas: orientation, registration, attention, short-term recall, language and constructional praxis/visuospatial abilities. The scores on the MMSE range from 0 to 30, with higher scores indicating better function. The difference in mean change from Baseline to Week 77 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 77

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	12		
Units: Units on a Scale				
least squares mean (standard error)				
Week 77	-3.63 (± 0.672)	-3.21 (± 0.740)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.42
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.985

Secondary: Change from Baseline to Week 77 on Function as assessed by (ADCS-ADL) Total Score

End point title	Change from Baseline to Week 77 on Function as assessed by (ADCS-ADL) Total Score

End point description:

The ADCS-ADL (Alzheimer's Disease Cooperative Study-Activities of Daily Living) is the scale most widely used to assess functional outcomes in subjects with AD. The ADCS-ADL covers both basic ADL (e.g., eating and toileting) and more complex 'instrumental' ADL or iADL (e.g., using the telephone, managing finances and preparing a meal). The ADCS-ADL consists of 23 questions with a score range of 0 to 78 where a higher score represents better function. The difference in mean change from Baseline to Week 77 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 77

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	12		
Units: Units on a Scale				
least squares mean (standard error)				
Week 77	-8.83 (± 2.064)	-6.31 (± 2.278)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.74
upper limit	3.7
Variability estimate	Standard error of the mean
Dispersion value	3.052

Secondary: Change from Baseline to Week 77 on Function as assessed by (ADCS-iADL) Instrumental Score

End point title	Change from Baseline to Week 77 on Function as assessed by (ADCS-iADL) Instrumental Score

End point description:

The ADCS-iADL (Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living) measures activities such as using the telephone, managing finances and preparing a meal. The ADCS-iADL consists of 16 questions with a score range of 0 to 56 where a higher score represents better function. The difference in mean change from Baseline to Week 77 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 77

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	12		
Units: Units on a Scale				
least squares mean (standard error)				
Week 77	-6.69 (± 1.692)	-5.51 (± 1.872)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.29
upper limit	3.92
Variability estimate	Standard error of the mean
Dispersion value	2.501

Secondary: Change from Baseline to Week 77 on Function as assessed by the Functional Activities Questionnaire (FAQ) total score

End point title	Change from Baseline to Week 77 on Function as assessed by the Functional Activities Questionnaire (FAQ) total score

End point description:

The Functional Activities Questionnaire (FAQ) is an instrument consisting of 10 items and assesses instrumental, social and cognitive functioning. The score range is from 0 to 30 with higher scores representing higher impairment. The difference in mean change from Baseline to Week 77 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 77

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	12		
Units: Units on a Scale				
least squares mean (standard error)				
Week 77	5.00 (± 0.991)	4.37 (± 1.059)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.25
upper limit	3.51
Variability estimate	Standard error of the mean
Dispersion value	1.42

Secondary: Change from Baseline to Week 77 on a Measure of Dependence Level Assessed from the ADCS-ADL Score

End point title	Change from Baseline to Week 77 on a Measure of Dependence Level Assessed from the ADCS-ADL Score

End point description:

Please note that for this Outcome Measure, no subjects were evaluated at all as the derivation of this endpoint was not pre-specified before the Sponsor terminated the study and therefore it was not reported.

End point type	Secondary

End point timeframe:

Baseline, Week 77

End point values	Placebo	Crenezumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: Units on a Scale				
least squares mean (standard error)	()	()		

Notes:

[3] - No Subjects were evaluated at all as described above.

[4] - No Subjects were evaluated at all as described above.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 53 on Behavior in Neuropsychiatric Inventory Questionnaire (NPI-Q) Total Score

End point title	Change from Baseline to Week 53 on Behavior in Neuropsychiatric Inventory Questionnaire (NPI-Q) Total Score

End point description:

The NPI-Q evaluates 12 neuropsychiatric disturbances common in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavioral disturbances and appetite/eating abnormalities. The severity of each neuropsychiatric symptom is rated on a 3-point scale (mild, moderate and marked). The total severity score range is from 0 to 36 with higher scores representing higher severity. Difference in mean change from Baseline to Week 53 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures adjusting for disease severity, APOEe4 status, geographic region and the use/non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 53

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	102	110		
Units: Units on a Scale				
least squares mean (standard error)				
Week 53	-0.00 (± 0.852)	0.76 (± 0.886)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.75
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.502

Secondary: Quality of Life-Alzheimer's Disease (QoL-AD) Scale Score

End point title	Quality of Life-Alzheimer's Disease (QoL-AD) Scale Score

End point description:

The QoL-AD (Quality of Life - Alzheimer's Disease) scale assesses QoL in subjects who have dementia. The QoL-AD consists of 13 items covering aspects of subjects' relationships with friends and family, physical condition, mood, concerns about finances and overall assessment of QoL. Items are rated on 4-point Likert-type scales ranging from 1 [poor] to 4 [excellent]. The score range is from 13 to 52, with higher scores indicating a better QoL. The difference in mean change from Baseline to Week 77 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 77

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	11		
Units: Units on a Scale				
least squares mean (standard error)				
Week 77	-1.61 (± 1.310)	-1.16 (± 1.432)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	2.39

Variability estimate	Standard error of the mean
Dispersion value	1.383

Secondary: Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) Scale Score

End point title	Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) Scale Score

End point description:

The ZCI-AD is a modified version of the Zarit Burden Interview, which was originally designed to reflect the stresses experienced by caregivers of people with dementia. This modified version includes slight modifications in item and title wording (e.g., removal of "your relative" to refer directly to the patient, removal of "burden" from title) and the use of 11-point numerical rating scales. The ZCI-AD scale consists of a total of 30 items. Total scores will be calculated with a total score range from 0 to 300 (higher scores indicate a higher burden on the caregiver). The difference in mean change from Baseline to Week 53 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 53

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101	108		
Units: Units on a Scale				
least squares mean (standard error)				
Week 53	9.20 (± 9.292)	2.65 (± 9.643)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	6.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.35
upper limit	17.44
Variability estimate	Standard error of the mean
Dispersion value	5.527

Secondary: European Quality of Life-5 Dimensions (EQ-5D) Questionnaire Domain Scores for Subjects

End point title	European Quality of Life-5 Dimensions (EQ-5D) Questionnaire Domain Scores for Subjects

End point description:

The EQ-5D is a standardized measure of health status designed to provide a simple generic measure of health for clinical and economic appraisal. It is broadly applicable across a wide range of health conditions and treatment. The EQ-5D assesses five domains to provide a health state index. These are anxiety/depression, pain/discomfort, usual activities, mobility, and self-care. The scores on the EQ-5D ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). The difference in mean change from Baseline to Week 77 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 77

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	12		
Units: Units on a Scale				
least squares mean (standard error)				
Week 77	-3.69 (± 3.961)	-3.39 (± 4.392)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.31
upper limit	11.71
Variability estimate	Standard error of the mean
Dispersion value	5.831

Secondary: European Quality of Life-5 Dimensions (EQ-5D) Questionnaire Domain Scores for Caregivers

End point title	European Quality of Life-5 Dimensions (EQ-5D) Questionnaire Domain Scores for Caregivers

End point description:

The EQ-5D is a standardized measure of health status designed to provide a simple generic measure of health for clinical and economic appraisal. It is broadly applicable across a wide range of health conditions and treatment. The EQ-5D assesses five domains to provide a health state index. These are anxiety/depression, pain/discomfort, usual activities, mobility, and self-care. The scores on the EQ-5D ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). The difference in mean change from Baseline to Week 77 between Crenezumab and Placebo treated subjects was estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 77

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	12		
Units: Units on a Scale				
least squares mean (standard error)				
Week 77	-4.07 (± 2.724)	-0.68 (± 3.031)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	4.73
Variability estimate	Standard error of the mean
Dispersion value	3.94

Secondary: Percentage of Subjects with Adverse Event (AEs) and Serious Adverse Event (SAEs)

End point title	Percentage of Subjects with Adverse Event (AEs) and Serious

	Adverse Event (SAEs)

End point description:

An Adverse Event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events.

End point type	Secondary

End point timeframe:

Baseline up until 16 weeks after the last dose of study drug (up to 117 weeks).

End point values	Placebo (Safety)	Crenezumab (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	398	404		
Units: Percentage				
number (not applicable)				
AEs	73.1	73.5		
SAEs	10.6	8.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Anti-Crenezumab Antibodies

End point title	Percentage of Subjects with Anti-Crenezumab Antibodies

End point description:

Please note that for this Outcome Measure, no Subjects were evaluated at all as the existing immunogenicity data from an identical study (Study BN29552) showed a low potential of Crenezumab to induce Anti-Drug Antibodies (ADAs).

End point type	Secondary

End point timeframe:

Baseline up to Week 105

End point values	Placebo (Safety)	Crenezumab (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[5]	0[6]		
Units: Percentage				
number (not applicable)				

Notes:

[5] - ADAs were not collected in this study due to low induction potential of Crenezumab.

[6] - ADAs were not collected in this study due to low induction potential of Crenezumab.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Crenezumab

End point title	Serum Concentration of Crenezumab[7]

End point description:

Serum concentration data for Crenezumab will be tabulated and summarized. Descriptive summary statistics will include the arithmetic mean and SD. Since a sparse PK sampling design is being used, population (non-linear mixed-effects) modeling will be used to analyze the dose concentration-time data of crenezumab. Information from other clinical studies may be incorporated to establish the PK model. The PK Analysis population was defined as all subjects who have received at least one dose of crenezumab and with at least one evaluable post-dose PK sample. Please note that Post-dose samples were not collected at Weeks 5, 13, 37, 53 and 77. Data presented below is only for subjects that were included in the actual analysis. 999 = Not Estimable. (n=X) refers to Number of Subjects analysed at each timepoint.

End point type	Secondary

End point timeframe:

Pre-infusion (0 hour), 60-90 minutes post-infusion on Day 1 Week 1 and on Week 25; Weeks 13 (Pre-dose), 37 (Pre-dose), 53 (Pre-dose) and 77 (Pre-dose) (infusion length = as per the Pharmacy Manual)

Notes:

[7] - 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: PK Analysis was only conducted on the Crenezumab treatment group and so data for Placebo was not reported.

End point values	Crenezumab			
Subject group type	Reporting group			
Number of subjects analysed	404			
Units: ug/mL				
arithmetic mean (standard deviation)				
Week 1 Day 1 Predose (n=138)	999 (± 999)			
Week 1 Day 1 Postdose (n=110)	1260 (± 437)			
Week 5 Predose (n=138)	246 (± 128)			
Week 13 Predose (n=128)	360 (± 162)			
Week 25 Predose (n=125)	401 (± 196)			
Week 25 Postdose (n=106)	1650 (± 443)			
Week 37 Predose (n=97)	456 (± 351)			
Week 53 Predose (n=32)	401 (± 130)			
Week 77 Predose (n=3)	357 (± 94.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Amyloid Beta (Abeta) 40 Concentrations

End point title	Plasma Amyloid Beta (Abeta) 40 Concentrations[8]

End point description:

Plasma Abeta 40 concentrations will be measured over time and descriptive summary statistics will include the arithmetic mean and SD. The PD Analysis population was defined as all subjects who have received at least one dose of crenezumab and with at least one evaluable post-dose PK sample. Data presented below is only for subjects that were included in the actual analysis. Please note that Pre-dose samples were only collected at Weeks 1 and 53. (n=X) refers to Number of Subjects analysed at each timepoint.

End point type	Secondary

End point timeframe:

Week 1 Day 1; Weeks 53

Notes:

[8] - 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: PD Analysis was only conducted on the Crenezumab treatment group and so data for Placebo was not reported.

End point values	Crenezumab			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1 Day 1 Predose (n=36)	0.415 (± 0.0687)			
Week 53 Predose (n=13)	46.6 (± 6.91)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Amyloid Beta (Abeta) 42 Concentrations

End point title	Plasma Amyloid Beta (Abeta) 42 Concentrations[9]

End point description:

Plasma Abeta 42 concentrations will be measured over time and descriptive summary statistics will include the arithmetic mean and SD. The PD Analysis population was defined as all subjects who have received at least one dose of crenezumab and with at least one evaluable post-dose PK sample. Data presented below is only for subjects that were included in the actual analysis. Please note that Pre-dose samples were only collected at Weeks 1 and 53. (n=X) refers to Number of Subjects analysed at each timepoint.

End point type	Secondary

End point timeframe:

Week 1 Day 1; Weeks 53

Notes:

[9] - 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: PD Analysis was only conducted on the Crenezumab treatment group and so data for Placebo was not reported.

End point values	Crenezumab			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1 Day 1 Predose (n=36)	0.0331 (± 0.00463)			
Week 53 Predose (n=13)	2.94 (± 0.473)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline to Week 105 in Whole Brain Volume as Determined by Magnetic Resonance Imaging (MRI)

End point title	Percentage Change from Baseline to Week 105 in Whole Brain Volume as Determined by Magnetic Resonance Imaging (MRI)

End point description:

Percentage Change in Whole Brain Volume will be measured over time and descriptive summary statistics will include the arithmetic mean, median, range, SD, and coefficient of variation, as appropriate. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline. Data presented below is only for subjects that were included in the actual analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 105

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	4		
Units: Percentage				
least squares mean (standard error)				
Week 105	-2.71 (± 0.444)	-2.15 (± 0.345)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.01
upper limit	0.89
Variability estimate	Standard error of the mean
Dispersion value	0.622

Secondary: Percentage Change from Baseline to Week 105 in Ventricle Volume as Determined by Magnetic Resonance Imaging (MRI)

End point title	Percentage Change from Baseline to Week 105 in Ventricle

	Volume as Determined by Magnetic Resonance Imaging (MRI)

End point description:

Percentage Change in Ventricle Volume will be measured over time and descriptive summary statistics will include the arithmetic mean, median, range, SD, and coefficient of variation, as appropriate. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to estimate the mean change from baseline. Data presented below is only for subjects that were included in the actual analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 105

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	4		
Units: Percentage				
least squares mean (standard error)				
Week 105	18.78 (± 1.343)	17.18 (± 1.145)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	4.9
Variability estimate	Standard error of the mean
Dispersion value	1.668

Secondary: Percentage Change from Baseline to Week 105 in Hippocampal Volume as Determined by Magnetic Resonance Imaging (MRI)

End point title	Percentage Change from Baseline to Week 105 in Hippocampal Volume as Determined by Magnetic Resonance Imaging (MRI)

End point description:

Percentage Change in Hippocampal Volume will be measured over time and descriptive summary statistics will include the arithmetic mean, median, range, SD, and coefficient of variation, as appropriate. Mixed model repeated measures (MMRMs) adjusting for disease severity, APOEe4 status, geographic region, and the use or non-use of anti-dementia medications at baseline were used to

estimate the mean change from baseline. Data presented below is only for subjects that were included in the actual analysis.

End point type	Secondary
End point timeframe:	
Baseline, Week 105	

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	2		
Units: Percentage				
least squares mean (standard error)				
Week 105	-6.34 (± 0.338)	-5.98 (± 0.290)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	4
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	0.41
Variability estimate	Standard error of the mean
Dispersion value	0.373

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up until 16 weeks after the last dose of study drug (up to 117 weeks).	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	Placebo
Reporting group description: Subjects received intravenous (IV) infusion of Placebo every 4 weeks (Q4W) for 100 weeks.	
Reporting group title	Crenezumab
Reporting group description: Subjects received intravenous (IV) infusion of Crenezumab every 4 weeks (Q4W) for 100 weeks.	

Serious adverse events	Placebo	Crenezumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 398 (10.55%)	33 / 404 (8.17%)	
number of deaths (all causes)	6	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BONE GIANT CELL TUMOUR MALIGNANT			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLEAR CELL ENDOMETRIAL CARCINOMA			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
LUNG ADENOCARCINOMA			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG NEOPLASM MALIGNANT			

subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROSTATE CANCER			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
ARTERIOVENOUS FISTULA			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSIVE CRISIS			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	1 / 398 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL VASCULAR DISORDER			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SHOCK HAEMORRHAGIC			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			
CARDIAC ABLATION			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
KNEE ARTHROPLASTY			

subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST DISCOMFORT			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST PAIN			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
subjects affected / exposed	2 / 398 (0.50%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COUGH			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	2 / 398 (0.50%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 398 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
AGGRESSION			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DELUSION			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSIVE SYMPTOM			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

SUICIDE THREAT			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ARTHROSCOPY			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
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 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLAVICLE FRACTURE			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CRANIOCEREBRAL INJURY			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
FALL			
subjects affected / exposed	6 / 398 (1.51%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
HIP FRACTURE			
subjects affected / exposed	3 / 398 (0.75%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

LOWER LIMB FRACTURE			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENISCUS INJURY			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PUBIS FRACTURE			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIB FRACTURE			
subjects affected / exposed	1 / 398 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL HAEMATOMA			
subjects affected / exposed	0 / 398 (0.00%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	2 / 398 (0.50%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (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	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			

subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRIFASCICULAR BLOCK			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
AMYOTROPHIC LATERAL SCLEROSIS			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL ARTERIOSCLEROSIS			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC CEREBRAL INFARCTION			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPEECH DISORDER			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPERIOR SAGITTAL SINUS THROMBOSIS			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			

subjects affected / exposed	2 / 398 (0.50%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 398 (0.25%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
TINNITUS			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VERTIGO			
subjects affected / exposed	2 / 398 (0.50%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
COLITIS ISCHAEMIC			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin and subcutaneous tissue disorders			
SKIN ULCER			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
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			
ARTHRITIS			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (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			
BACTERAEMIA			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
BRONCHITIS			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS STAPHYLOCOCCAL			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE INFECTION			

subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROBACTER PNEUMONIA			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOCARDITIS			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	2 / 398 (0.50%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER ABSCESS			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROSYPHILIS			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHARYNGITIS STREPTOCOCCAL			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	2 / 398 (0.50%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
PNEUMONIA INFLUENZAL			

subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL BACTERAEMIA			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Crenezumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 398 (19.35%)	85 / 404 (21.04%)	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	20 / 398 (5.03%)	19 / 404 (4.70%)	
occurrences (all)	34	26	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	15 / 398 (3.77%)	27 / 404 (6.68%)	
occurrences (all)	18	29	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	22 / 398 (5.53%)	25 / 404 (6.19%)	
occurrences (all)	28	30	
Infections and infestations			

NASOPHARYNGITIS subjects affected / exposed occurrences (all)	25 / 398 (6.28%) 32	24 / 404 (5.94%) 28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2018	Following updates were made: [1] Restructuring of Secondary Efficacy objectives; [2] Restructuring and updating of PK and Biomarker objectives; [3] Revision of the Statistical Considerations and Analysis plan section and [4] Minor updates made to other sections including Background on Alzheimer's disease, alignment with latest Investigator's Brochure, Biomarkers, Overall Benefit-Risk Summary, Overview of Study Design, use of medical food supplements, requirements for the removal of no planned changes of Alzheimer's medications for 6 months post-randomization, screening window duration, exclusion criteria, Permitted Therapies, Amyloid-related imaging abnormalities (ARIA) text and the Schedule of Activities.

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.

This study was discontinued due to an interim analysis in the BN29552 study, which indicated that Crenezumab was unlikely to meet its primary endpoint. No subjects reached Week 105 for primary and secondary efficacy endpoints.

Notes: