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	2015-003034-27
Trial protocol	ES SE GB LT HU PT CZ FI BE DK AT SI PL DE BG HR FR IT
Global end of trial date	31 May 2019

Results information

Result version number	v1
This version publication date	08 June 2020
First version publication date	08 June 2020

Trial information

Trial identification

Sponsor protocol code	BN29552

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02670083
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
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 May 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	22 March 2016
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: 16
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Canada: 45
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Costa Rica: 7
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Spain: 108
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	Hong Kong: 7
Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 50
Country: Number of subjects enrolled	Japan: 20
Country: Number of subjects enrolled	Korea, Republic of: 24

Country: Number of subjects enrolled	Lithuania: 10
Country: Number of subjects enrolled	Mexico: 32
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Russian Federation: 38
Country: Number of subjects enrolled	Slovenia: 1
Country: Number of subjects enrolled	Sweden: 16
Country: Number of subjects enrolled	Turkey: 16
Country: Number of subjects enrolled	Ukraine: 8
Country: Number of subjects enrolled	United States: 254
Worldwide total number of subjects	813
EEA total number of subjects	344

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)	182
From 65 to 84 years	625
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 249 centers in 30 countries.

Pre-assignment

Screening details:

A total of 813 subjects were enrolled at 249 centers. 4 subjects did not receive any study treatment meaning that the modified intent-to-treat and safety populations consisted of 809 subjects.

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	Subject, Investigator

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	409	404
Completed	88	85
Not completed	321	319
Adverse event, serious fatal	4	6
Consent withdrawn by subject	32	31
Physician decision	-	2
Adverse event, non-fatal	16	13
Study Terminated By Sponsor	257	254
Multiple Reasons	9	9
Non-Compliance With Study Drug	1	-
Symptomatic Deterioration	-	2
Lost to follow-up	2	2

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	409	404	813
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)	99	83	182
From 65-84 years	306	319	625
85 years and over	4	2	6
Age Continuous Units: Years			
arithmetic mean	70.3	71.0	
standard deviation	± 8.4	± 7.9	-
Sex: Female, Male Units:			
Female	247	236	483
Male	162	168	330
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	39	32	71
Not Hispanic or Latino	361	369	730
Not Stated	7	2	9
Unknown	2	1	3
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	5	10	15
Asian	28	28	56
Black or African American	3	5	8
Multiple	0	1	1
Unknown	13	8	21
White	360	352	712

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 = 407); Cren (n = 402)) 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 = 407); Cren (n = 402)) 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 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.	

Primary: Change from Baseline to Week 105 in Clinical Dementia Rating-Sum of Boxes (CDR-SB) Score

End point title	Change from Baseline to Week 105 in Clinical Dementia Rating-Sum of Boxes (CDR-SB) 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 105 between Crenezumab and Placebo treated participants 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, subjects, 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 105	

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	88[1]	86[2]		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	3.42 (± 0.263)	3.59 (± 0.264)		

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	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.86
upper limit	0.53
Variability estimate	Standard error of the mean
Dispersion value	0.354

Secondary: Change from Baseline to Week 105 on Cognition, as assessed by Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) (subscale) 13 (ADAS-Cog-13)

End point title	Change from Baseline to Week 105 on Cognition, as assessed by Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) (subscale) 13 (ADAS-Cog-13)

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 105 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. 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	86	80		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	9.55 (± 0.824)	9.82 (± 0.841)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.39
upper limit	1.87
Variability estimate	Standard error of the mean
Dispersion value	1.083

Secondary: Change from Baseline to Week 105 on Cognition, as assessed by Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) (subscale) 11 (ADAS-Cog-11)

End point title	Change from Baseline to Week 105 on Cognition, as assessed by Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) (subscale) 11 (ADAS-Cog-11)

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 105 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. 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	86	80		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	8.43 (± 0.758)	8.53 (± 0.773)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.08
upper limit	1.88
Variability estimate	Standard error of the mean
Dispersion value	1.006

Secondary: Change from Baseline to Week 105 on Severity of Dementia, Assessed Using the CDR-Global Score (CDR-GS)

End point title	Change from Baseline to Week 105 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 105 between Crenezumab and Placebo treated participants 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. 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	88	86		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	0.55 (± 0.056)	0.50 (± 0.056)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.076

Secondary: Change from Baseline to Week 105 on Severity of Dementia, Assessed Using the Mini Mental State Evaluation (MMSE)

End point title	Change from Baseline to Week 105 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 105 between Crenezumab and Placebo treated participants 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. 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	90	87		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	-4.63 (± 0.377)	-4.96 (± 0.383)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	177
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	-0.62
upper limit	1.29
Variability estimate	Standard error of the mean
Dispersion value	0.486

Secondary: Change from Baseline to Week 105 on function as assessed by the ADCS-ADL total score

End point title	Change from Baseline to Week 105 on function as assessed by the 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 participants 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 105 between Crenezumab and Placebo treated participants 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. 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	90	88		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	-11.51 (± 1.226)	-13.39 (± 1.242)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.43
upper limit	5.18
Variability estimate	Standard error of the mean
Dispersion value	1.679

Secondary: Change from Baseline to Week 105 on function as assessed by the ADCS-instrumental (ADCS-iADL) subscore

End point title	Change from Baseline to Week 105 on function as assessed by the ADCS-instrumental (ADCS-iADL) subscore

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 105 between Crenezumab and Placebo treated participants 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. 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	90	88		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	-9.22 (± 0.967)	-10.44 (± 0.979)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.35
upper limit	3.79
Variability estimate	Standard error of the mean
Dispersion value	1.306

Secondary: Change from Baseline to Week 105 on a measure of dependence derived from the ADCS-ADL score

End point title	Change from Baseline to Week 105 on a measure of dependence derived from the ADCS-ADL score

End point description:

Please note that for this Outcome Measure, no participants 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 105

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
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 105 assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q)

End point title	Change from Baseline to Week 105 assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q)

End point description:

The NPI-Q is an informant-based instrument that 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 and eating abnormalities. The severity of each neuropsychiatric symptom is rated on a 3-point scale (mild, moderate and marked) while the distress is rated on a 6-point scale (no distress, minimal, mild, moderate, severe, extreme or very severe). The total severity score ranges from 0 to 36 and the total distress score ranges from 0 to 60. The difference in mean change from Baseline to Week 105 between Crenezumab and Placebo treated participants 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 105

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84[5]	87[6]		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	1.02 (± 0.562)	1.55 (± 0.556)		

Notes:

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

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

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.95
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.723

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 participants who have dementia. The QoL-AD consists of 13 items covering aspects of participants' 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 105 between Crenezumab and Placebo treated participants 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. Data presented below is only for subjects that were included in the actual analysis.

End point type	Secondary

End point timeframe:

Baseline up to Week 105

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90	86		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	-1.69 (± 0.501)	-2.08 (± 0.513)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	1.6

Variability estimate	Standard error of the mean
Dispersion value	0.609

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 and domain scores will be calculated (higher scores indicate higher levels of distress). The difference in mean change from Baseline to Week 105 between Crenezumab and Placebo treated participants 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. Data presented below is only for subjects that were included in the actual analysis.

End point type	Secondary

End point timeframe:

Baseline up to Week 105

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	87		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	22.72 (± 5.135)	24.11 (± 5.106)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.64
upper limit	10.86
Variability estimate	Standard error of the mean
Dispersion value	6.214

Secondary: EQ-5D Questionnaire Domain Score for Participants

End point title	EQ-5D Questionnaire Domain Score for Participants

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 105 between Crenezumab and Placebo treated participants 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. Data presented below is only for subjects that were included in the actual analysis.

End point type	Secondary

End point timeframe:

Baseline up to Week 105

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	87		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	-4.54 (± 1.732)	-6.35 (± 1.761)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.64
upper limit	6.27
Variability estimate	Standard error of the mean
Dispersion value	2.26

Secondary: EQ-5D Questionnaire Domain Score for Caregivers

End point title	EQ-5D Questionnaire Domain Score 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 105 between Crenezumab and Placebo treated participants 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. Data presented below is only for subjects that were included in the actual analysis.

End point type	Secondary

End point timeframe:

Baseline up to Week 105

End point values	Placebo (Modified ITT)	Crenezumab (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	88		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	-3.16 (± 1.713)	-4.09 (± 1.721)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.45
upper limit	5.32
Variability estimate	Standard error of the mean
Dispersion value	2.222

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 participant 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:

Up to Week 105

End point values	Placebo (Safety)	Crenezumab (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	405	404		
Units: Percentage				
number (not applicable)				
AEs	83.2	85.9		
SAEs	15.6	16.6		

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:

Participants were considered positive or negative for ADA based on their baseline and post-baseline sample results. The number and percentage of subjects with confirmed positive ADA levels were determined for Crenezumab and Placebo groups. The prevalence of ADA at baseline was calculated as the proportion of subjects with confirmed positive ADA levels at baseline relative to the total number of subjects with a sample available at baseline. The incidence of treatment-emergent ADAs was determined as the proportion of subjects with confirmed post-baseline positive ADAs relative to the total number of subjects that had at least one post-baseline sample available for ADA analysis. Data below is only for subjects included in the actual analysis. (Pla = X; Cre = X) represents number of subjects analysed at each timepoint for both arms.

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	385	404		
Units: Percentage				
number (not applicable)				
Baseline ADAs (Pla = 385; Cre = 404)	0.3	0.2		

Treatment Emergent ADAs (Pla = 382; Cre = 397)	0.5	0.5		

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 37 and 105. 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, 37 (Pre-dose), 53, 77 and 105 (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	392			
Units: ug/mL				
arithmetic mean (standard deviation)				
Week 1 Day 1 Predose (n = 392)	999 (± 999)			
Week 1 Day 1 Postdose (n = 74)	1350 (± 319)			
Week 13 Predose (n = 388)	345 (± 146)			
Week 13 Postdose (n = 384)	1580 (± 487)			
Week 25 Predose (n = 378)	369 (± 130)			
Week 25 Postdose (n = 54)	1700 (± 443)			
Week 37 Predose (n = 366)	368 (± 152)			
Week 53 Predose (n = 363)	393 (± 164)			
Week 53 Postdose (n = 60)	1800 (± 420)			
Week 77 Predose (n = 263)	410 (± 261)			
Week 77 Postdose (n = 50)	1790 (± 496)			
Week 105 (n = 89)	408 (± 186)			

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 a Post-dose sample was only collected at Week 13. (n = X) refers to Number of Subjects analysed at each timepoint.

End point type	Secondary

End point timeframe:

Screening (Weeks -8 to -1); Day 1 Week 1; Weeks 13, 25, 53, 77 and 105

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	101			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1 Day 1 Predose (n = 101)	0.377 (± 0.136)			
Week 13 Predose (n = 20)	44.6 (± 10.0)			
Week 13 Postdose (n = 21)	44.3 (± 9.5)			
Week 25 Predose (n = 46)	46.4 (± 10.1)			
Week 53 Predose (n = 94)	48.8 (± 10.7)			
Week 77 (n = 40)	47.5 (± 12.2)			
Week 105 Predose (n = 38)	48.6 (± 14.0)			

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 a Post-dose sample was only collected at Week 13. (n = X) refers to Number of Subjects analysed at each timepoint.

End point type	Secondary

End point timeframe:

Screening (Weeks -8 to -1); Day 1 Week 1; Weeks 13, 25, 53, 77 and 105

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	101			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1 Day 1 Predose (n = 101)	0.0335 (± 0.00812)			
Week 13 Predose (n = 20)	2.72 (± 0.553)			
Week 13 Postdose (n = 21)	2.71 (± 0.602)			
Week 25 Predose (n = 46)	2.73 (± 0.55)			
Week 53 Predose (n = 94)	2.87 (± 0.589)			
Week 77 Predose (n = 40)	2.79 (± 0.68)			
Week 105 Predose (n = 38)	2.87 (± 0.818)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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	180	172		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	-2.66 (± 0.091)	-2.65 (± 0.092)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.22
Variability estimate	Standard error of the mean
Dispersion value	0.116

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

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

End point description:

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	189	181		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	22.29 (± 0.907)	23.57 (± 0.912)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.72
upper limit	1.17
Variability estimate	Standard error of the mean
Dispersion value	1.245

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

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

End point description:

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	169	160		
Units: Units on a Scale				
least squares mean (standard error)				
Week 105	-6.57 (± 0.200)	-6.97 (± 0.203)		

Statistical analyses

Statistical analysis title	Crenezumab versus Placebo
Comparison groups	Placebo (Modified ITT) v Crenezumab (Modified ITT)
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.89
Variability estimate	Standard error of the mean
Dispersion value	0.253

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
3 years, 2 months	
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	63 / 405 (15.56%)	67 / 404 (16.58%)	
number of deaths (all causes)	5	8	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA			
subjects affected / exposed	0 / 405 (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	
ADENOCARCINOMA GASTRIC			
subjects affected / exposed	0 / 405 (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 / 1	
BREAST CANCER			
subjects affected / exposed	1 / 405 (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	
DIFFUSE LARGE B-CELL LYMPHOMA			

subjects affected / exposed	1 / 405 (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	
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	0 / 405 (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 ADENOCARCINOMA			
subjects affected / exposed	0 / 405 (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	1 / 405 (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	
LYMPHOPROLIFERATIVE DISORDER			
subjects affected / exposed	0 / 405 (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 / 1	
PROSTATE CANCER			
subjects affected / exposed	0 / 405 (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	
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	0 / 405 (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	
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	1 / 405 (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	
Surgical and medical procedures			

CORONARY ARTERY BYPASS			
subjects affected / exposed	1 / 405 (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 NEOPLASM EXCISION			
subjects affected / exposed	1 / 405 (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	
URETHRAL STENT INSERTION			
subjects affected / exposed	1 / 405 (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	
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	0 / 405 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	1 / 405 (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	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	2 / 405 (0.49%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	1 / 405 (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	
Reproductive system and breast disorders			
OVARIAN CYST			

subjects affected / exposed	0 / 405 (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	
Respiratory, thoracic and mediastinal disorders			
ACUTE INTERSTITIAL PNEUMONITIS			
subjects affected / exposed	0 / 405 (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 / 1	
PNEUMONIA ASPIRATION			
subjects affected / exposed	1 / 405 (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	
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 405 (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	
Psychiatric disorders			
ACUTE PSYCHOSIS			
subjects affected / exposed	1 / 405 (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	
AGITATION			
subjects affected / exposed	1 / 405 (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	
DELIRIUM			
subjects affected / exposed	1 / 405 (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	0 / 405 (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	

HALLUCINATION, VISUAL			
subjects affected / exposed	0 / 405 (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	
PERSONALITY CHANGE			
subjects affected / exposed	0 / 405 (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	
SCHIZOPHRENIA			
subjects affected / exposed	1 / 405 (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	
Product issues			
DEVICE FAILURE			
subjects affected / exposed	0 / 405 (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			
CLAVICLE FRACTURE			
subjects affected / exposed	0 / 405 (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	
CONCUSSION			
subjects affected / exposed	0 / 405 (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	
FACIAL BONES FRACTURE			
subjects affected / exposed	1 / 405 (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	
FALL			
subjects affected / exposed	1 / 405 (0.25%)	4 / 404 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

FEMUR FRACTURE			
subjects affected / exposed	1 / 405 (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	
HIP FRACTURE			
subjects affected / exposed	0 / 405 (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	
RADIUS FRACTURE			
subjects affected / exposed	0 / 405 (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	
RIB FRACTURE			
subjects affected / exposed	1 / 405 (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	
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	1 / 405 (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 LACERATION			
subjects affected / exposed	0 / 405 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKULL FRACTURED BASE			
subjects affected / exposed	0 / 405 (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	
SOFT TISSUE INJURY			
subjects affected / exposed	1 / 405 (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	
SUBDURAL HAEMATOMA			

subjects affected / exposed	3 / 405 (0.74%)	4 / 404 (0.99%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
SUBDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 405 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRAUMATIC INTRACRANIAL HAEMORRHAGE			
subjects affected / exposed	0 / 405 (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	
ULNA FRACTURE			
subjects affected / exposed	0 / 405 (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	
UPPER LIMB FRACTURE			
subjects affected / exposed	0 / 405 (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	
WRIST FRACTURE			
subjects affected / exposed	2 / 405 (0.49%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	1 / 405 (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	
ANGINA UNSTABLE			
subjects affected / exposed	1 / 405 (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	
ATRIAL FLUTTER			

subjects affected / exposed	1 / 405 (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	
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	1 / 405 (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	
BRADYCARDIA			
subjects affected / exposed	2 / 405 (0.49%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	1 / 405 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
CARDIAC FAILURE ACUTE			
subjects affected / exposed	0 / 405 (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 / 1	
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 405 (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	
MYOCARDIAL INFARCTION			
subjects affected / exposed	2 / 405 (0.49%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	0 / 405 (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			
CAROTID ARTERY STENOSIS			

subjects affected / exposed	1 / 405 (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	
CENTRAL NERVOUS SYSTEM LESION			
subjects affected / exposed	1 / 405 (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	
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	1 / 405 (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	
CEREBRAL ISCHAEMIA			
subjects affected / exposed	0 / 405 (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	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 405 (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	
CEREBROVASCULAR DISORDER			
subjects affected / exposed	0 / 405 (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	
DEMENTIA ALZHEIMER'S TYPE			
subjects affected / exposed	1 / 405 (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	
DEPRESSED LEVEL OF CONSCIOUSNESS			
subjects affected / exposed	0 / 405 (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	
HYDROCEPHALUS			

subjects affected / exposed	0 / 405 (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	
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 405 (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	
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	2 / 405 (0.49%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAESTHESIA			
subjects affected / exposed	1 / 405 (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	
SEIZURE			
subjects affected / exposed	0 / 405 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	1 / 405 (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	
SYNCOPE			
subjects affected / exposed	4 / 405 (0.99%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 405 (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 disorders			

ABDOMINAL DISCOMFORT			
subjects affected / exposed	0 / 405 (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	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 405 (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	
CHRONIC GASTRITIS			
subjects affected / exposed	1 / 405 (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	
COLITIS			
subjects affected / exposed	1 / 405 (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	
COLITIS ISCHAEMIC			
subjects affected / exposed	1 / 405 (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 / 405 (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	
DIVERTICULUM			
subjects affected / exposed	0 / 405 (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	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 405 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL PERFORATION			

subjects affected / exposed	1 / 405 (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 ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 405 (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	
GASTROINTESTINAL VASCULAR MALFORMATION			
subjects affected / exposed	0 / 405 (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	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 405 (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	
INGUINAL HERNIA			
subjects affected / exposed	0 / 405 (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 GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 405 (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	
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 405 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS ACUTE			
subjects affected / exposed	1 / 405 (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	

CHOLELITHIASIS			
subjects affected / exposed	1 / 405 (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			
ANGIOEDEMA			
subjects affected / exposed	1 / 405 (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	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROLITHIASIS			
subjects affected / exposed	1 / 405 (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	
Endocrine disorders			
AUTOIMMUNE THYROIDITIS			
subjects affected / exposed	1 / 405 (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	
HYPERPARATHYROIDISM PRIMARY			
subjects affected / exposed	0 / 405 (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			
ARTHRALGIA			
subjects affected / exposed	0 / 405 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHRITIS			

subjects affected / exposed	0 / 405 (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 / 405 (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	
LUMBAR SPINAL STENOSIS			
subjects affected / exposed	0 / 405 (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	
OSTEOARTHRITIS			
subjects affected / exposed	2 / 405 (0.49%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYSTEMIC SCLERODERMA			
subjects affected / exposed	0 / 405 (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	
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 405 (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	
CELLULITIS			
subjects affected / exposed	1 / 405 (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	
DIVERTICULITIS			
subjects affected / exposed	3 / 405 (0.74%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			

subjects affected / exposed	0 / 405 (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	
HERPES ZOSTER			
subjects affected / exposed	0 / 405 (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	
PERITONITIS			
subjects affected / exposed	0 / 405 (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	
PERITONSILLAR ABSCESS			
subjects affected / exposed	0 / 405 (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	3 / 405 (0.74%)	5 / 404 (1.24%)	
occurrences causally related to treatment / all	1 / 3	2 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
PNEUMONIA BACTERIAL			
subjects affected / exposed	0 / 405 (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	
PYELONEPHRITIS			
subjects affected / exposed	0 / 405 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN INFECTION			
subjects affected / exposed	0 / 405 (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	
TUBERCULOSIS OF CENTRAL NERVOUS SYSTEM			

subjects affected / exposed	0 / 405 (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	
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 405 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	1 / 405 (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	
VIRAL INFECTION			
subjects affected / exposed	1 / 405 (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 / 405 (0.00%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC KETOACIDOSIS			
subjects affected / exposed	2 / 405 (0.49%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Crenezumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	214 / 405 (52.84%)	225 / 404 (55.69%)	
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	11 / 405 (2.72%)	22 / 404 (5.45%)	
occurrences (all)	11	22	
Injury, poisoning and procedural			

complications			
FALL			
subjects affected / exposed	33 / 405 (8.15%)	42 / 404 (10.40%)	
occurrences (all)	42	60	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	22 / 405 (5.43%)	27 / 404 (6.68%)	
occurrences (all)	22	29	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	27 / 405 (6.67%)	23 / 404 (5.69%)	
occurrences (all)	34	28	
HEADACHE			
subjects affected / exposed	45 / 405 (11.11%)	39 / 404 (9.65%)	
occurrences (all)	60	48	
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	26 / 405 (6.42%)	25 / 404 (6.19%)	
occurrences (all)	42	27	
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	22 / 405 (5.43%)	7 / 404 (1.73%)	
occurrences (all)	26	8	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	21 / 405 (5.19%)	28 / 404 (6.93%)	
occurrences (all)	24	31	
DEPRESSION			
subjects affected / exposed	27 / 405 (6.67%)	28 / 404 (6.93%)	
occurrences (all)	27	28	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	31 / 405 (7.65%)	26 / 404 (6.44%)	
occurrences (all)	36	38	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	13 / 405 (3.21%)	21 / 404 (5.20%)	
occurrences (all)	13	21	

NASOPHARYNGITIS			
subjects affected / exposed	33 / 405 (8.15%)	40 / 404 (9.90%)	
occurrences (all)	41	50	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	29 / 405 (7.16%)	33 / 404 (8.17%)	
occurrences (all)	38	36	
URINARY TRACT INFECTION			
subjects affected / exposed	22 / 405 (5.43%)	20 / 404 (4.95%)	
occurrences (all)	29	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2015	Following updates were made: [1] Clarification to background information on Crenezumab; [2] Update to data on dose rationale; [3] Addition of section describing exploratory substudies; [4] Clarification that the Independent Data Monitoring Committee may evaluate any planned interim efficacy or futility analyses; [5] Update to Inclusion Criteria; [6] Explanation for procedure for blinding around PK samples; [7] Clarification of Patient Centred Outcomes language; [8] Clarification of procedure around Brain MRI; [9] Updates to Safety Information and [10] Update to Primary Efficacy Endpoint rationale.
10 March 2018	Following updates were made: [1] Restructuring and clarification of Secondary Efficacy, Pharmacokinetic and Biomarker Objectives/Endpoints; [2] Revisions to Statistical Considerations and Analysis Plan and [3] Minor updates made to other sections including Background on Alzheimer's Disease, Biomarkers section, Overall Benefit-Risk Summary, Overview of Study Design, Permitted Therapy, PD Biomarkers, 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

None reported