# 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 | v1 |
| This version publication date | 11 June 2020 |
| First version publication date | 11 June 2020 |

## 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 |
| 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 | 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<br>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<br>Units: Years | | | |
| arithmetic mean | 70.7 | 71.1 | |
| standard deviation | ± 7.9 | ± 7.5 | - |
| Sex: Female, Male<br>Units: | | | |
| Female | 225 | 231 | 456 |
| Male | 174 | 176 | 350 |
| Race/Ethnicity, Customized<br>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<br>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 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, 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 | 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 | 1.3 |
| 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 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 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 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 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 | 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 and domain scores will be calculated (higher scores indicate higher levels of distress). 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 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:

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 | 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:

Screening (Weeks -8 to -1); Day 1 Week 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:

Screening (Weeks -8 to -1); Day 1 Week 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: Change from Baseline to Week 77 in Whole Brain Volume as Determined by Magnetic Resonance Imaging (MRI)

| End point title | Change from Baseline to Week 77 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. The sample sizes at Week 105 were less than 10 and therefore only results at Week 77 are being reported. Data presented below is only for subjects that were included in the actual analysis.

| 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 | 40 | 41 | | |
| Units: Units on a Scale | | | | |
| least squares mean (standard error) | | | | |
| Week 77 | -1.90 (± 0.107) | -1.86 (± 0.105) | | |

### Statistical analyses

| **Statistical analysis title** | Crenezumab versus Placebo |
|---|---|
| Comparison groups | Placebo (Modified ITT) v Crenezumab (Modified ITT) |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.32 |
| upper limit | 0.24 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.144 |

## Secondary: Change from Baseline to Week 77 in Ventricle Volume as Determined by Magnetic Resonance Imaging (MRI)

| End point title | Change from Baseline to Week 77 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. The sample sizes at Week 105 were less than 10 and therefore only results at Week 77 are being reported. Data presented below is only for subjects that were included in the actual analysis.

| 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 | 40 | 41 | | |
| Units: Units on a Scale | | | | |
| least squares mean (standard error) | 15.13 (± 0.783) | 14.54 (± 0.763) | | |

**Statistical analyses**

| **Statistical analysis title** | Crenezumab versus Placebo |
|---|---|
| Comparison groups | Placebo (Modified ITT) v Crenezumab (Modified ITT) |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.51 |
| upper limit | 2.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.065 |

## Secondary: Change from Baseline to Week 77 in Hippocampal Volume as Determined by Magnetic Resonance Imaging (MRI)

| End point title | Change from Baseline to Week 77 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. The sample sizes at Week 105 were less than 10 and therefore only results at

Week 77 are being reported. Data presented below is only for subjects that were included in the actual analysis.

| | |
|---|---|
| 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 | 32 | 33 | | |
| Units: Units on a Scale | | | | |
| least squares mean (standard error) | -5.03 (± 0.281) | -5.18 (± 0.288) | | |

**Statistical analyses**

| **Statistical analysis title** | Crenezumab versus Placebo |
|---|---|
| Comparison groups | Placebo (Modified ITT) v Crenezumab (Modified ITT) |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.64 |
| upper limit | 0.95 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.391 |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| 2 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 | 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 | |
| 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 | |
| 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 | |
| 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<br>subjects affected / exposed<br>occurrences (all) | 25 / 398 (6.28%)<br>32 | 24 / 404 (5.94%)<br>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: