



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, APOEε4 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, APOEε4 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, APOEε4 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 (\pm 0.758) | 8.53 (\pm 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, APOEε4 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: | |
| <p>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, APOEε4 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.</p> | |
| 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 (\pm 0.377) | -4.96 (\pm 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: | <p>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, APOEε4 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.</p> |
| 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 (\pm 1.226) | -13.39 (\pm 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: | <p>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, APOEε4 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.</p> |
| 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, APOEε4 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, APOEε4 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, APOEε4 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, APOEε4 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: | |
| <p>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, APOEε4 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.</p> | |
| 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, APOEε4 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, APOEε4 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, APOEε4 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 | | | |

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|--|-----------------|-----------------|--|
| 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 | |

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|---|-----------------|-----------------|--|
| 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 | |

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|---|-----------------|-----------------|--|
| 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 | | | |

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