



Clinical trial results:

A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, and Safety Study of Gantenerumab in Patients With Early (Prodromal to Mild) Alzheimer's Disease

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2017-001365-24 |
| Trial protocol | ES GB DK BE PT PL NL SE FI HR |
| Global end of trial date | 28 November 2022 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 13 April 2024 |
| First version publication date | 08 October 2023 |
| Version creation reason | • Correction of full data set Update in OM description. |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | WN39658 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03444870 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| 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 | 28 November 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 November 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy and safety of gantenerumab administered by subcutaneous (SC) injection compared with placebo.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form (ICF).

Background therapy:

Participants were allowed to take standard of care symptomatic treatment throughout the study i.e., cholinesterase inhibitors and/or memantine.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 22 August 2018 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 62 |
| Country: Number of subjects enrolled | Belgium: 10 |
| Country: Number of subjects enrolled | Chile: 46 |
| Country: Number of subjects enrolled | Denmark: 18 |
| Country: Number of subjects enrolled | Spain: 155 |
| Country: Number of subjects enrolled | Finland: 23 |
| Country: Number of subjects enrolled | United Kingdom: 54 |
| Country: Number of subjects enrolled | Croatia: 1 |
| Country: Number of subjects enrolled | Japan: 64 |
| Country: Number of subjects enrolled | Korea, Republic of: 54 |
| Country: Number of subjects enrolled | Mexico: 50 |
| Country: Number of subjects enrolled | Netherlands: 8 |
| Country: Number of subjects enrolled | Poland: 127 |
| Country: Number of subjects enrolled | Portugal: 32 |
| Country: Number of subjects enrolled | Singapore: 10 |
| Country: Number of subjects enrolled | Sweden: 24 |
| Country: Number of subjects enrolled | Turkey: 3 |
| Country: Number of subjects enrolled | United States: 234 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 975 |
| EEA total number of subjects | 398 |

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) | 167 |
| From 65 to 84 years | 771 |
| 85 years and over | 37 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in the study across 151 investigative sites in 18 countries from 22 August 2018 to 28 November 2022.

Pre-assignment

Screening details:

A total of 975 participants with early (prodromal to mild) Alzheimer's Disease (AD) were randomized to either the gantenerumab (n=498) or placebo arm (n=477) to enter the double-blind treatment (DBT) period.

Period 1

| | |
|------------------------------|-------------------------------|
| Period 1 title | Double-blind Treatment 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: DBT |

Arm description:

Participants received, gantenerumab matching placebo, subcutaneous (SC) injections, every four weeks (Q4W) up to Week 36 and then every two weeks (Q2W) up to Week 114 of the DBT period.

| | |
|--|------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Gantenerumab matching placebo administered as SC injections, Q4W up to Week 36 and then Q2W up to Week 114 of the DBT period.

| | |
|------------------|-------------------|
| Arm title | Gantenerumab: DBT |
|------------------|-------------------|

Arm description:

Participants received gantenerumab, SC injections with gradual up-titration starting at a dose of 120 milligrams (mg), Q4W for 3 doses, followed by 255 mg, Q4W for 3 doses, and 510 mg, Q4W for 3 doses. Following this, from Week 36 onwards, participants received gantenerumab, SC injections, at a dose of 510 mg, Q2W up to Week 114 of the DBT period.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Gantenerumab |
| Investigational medicinal product code | RO4909832 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Gantenerumab administered as SC injections with gradual up titration starting at a dose of 120 mg, Q4W for 3 doses, followed by 255 mg, Q4W for 3 doses, and 510 mg, Q4W for 3 doses. After Week 36, gantenerumab, SC injections, at a dose of 510 mg, Q2W up to Week 114 of the DBT period.

| Number of subjects in period 1 | Placebo: DBT | Gantenerumab: DBT |
|--------------------------------|--------------|-------------------|
| Started | 477 | 498 |
| Completed | 397 | 372 |
| Not completed | 80 | 126 |
| Adverse event, serious fatal | 5 | 7 |
| Consent withdrawn by subject | 54 | 79 |
| Physician decision | 5 | 6 |
| Adverse event, non-fatal | 5 | 19 |
| Protocol Deviation | 1 | 2 |
| Reason Not Specified | 9 | 11 |
| Lost to follow-up | - | 1 |
| Lack of efficacy | 1 | 1 |

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Open-label Extension Period |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Participants were blinded to previous treatment assignments through a blinded titration period.

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo (DBT) to Gantenerumab: Open-label Extension (OLE) |

Arm description:

Participants who received gantenerumab matching placebo in the DBT period received gantenerumab SC injections with gradual up titration starting at a dose of 120 mg, Q4W for 3 doses, followed by 255 mg, Q4W for 3 doses, and then at a dose of 510 mg, Q4W up to Week 34 of the OLE period. To maintain the blind to previous treatment assignment, participants received Q2W, SC injections, with alternate doses containing gantenerumab matching placebo.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Gantenerumab |
| Investigational medicinal product code | RO4909832 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Gantenerumab SC injections with gradual up titration starting at a dose of 120 mg, Q4W for 3 doses, followed by 255 mg, Q4W for 3 doses, and then at a dose of 510 mg, Q4W up to Week 34 of the OLE period. To maintain the blind to previous treatment assignment, participants received Q2W, SC injections, with alternate doses containing gantenerumab matching placebo.

| | |
|------------------|---|
| Arm title | Gantenerumab (DBT) to Gantenerumab: OLE |
|------------------|---|

Arm description:

Participants who received gantenerumab in the DBT period continued receiving gantenerumab, SC injections, 510 mg, Q2W up to Week 34 of the OLE period.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Gantenerumab |
| Investigational medicinal product code | RO4909832 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Gantenerumab, SC injections, 510 mg, Q2W up to Week 34 of the OLE period.

| Number of subjects in period 2^[1] | Placebo (DBT) to Gantenerumab: Open-label Extension (OLE) | Gantenerumab (DBT) to Gantenerumab: OLE |
|---|---|---|
| Started | 13 | 14 |
| Completed | 8 | 13 |
| Not completed | 5 | 1 |
| Consent withdrawn by subject | 2 | 1 |
| Reason Not Specified | 3 | - |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Participants who completed the DBT Period enrolled into the OLE Period or choose to enter the safety follow up or rolled over to PostGraduate OLE (WN42171) study.

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Placebo: DBT |
|-----------------------|--------------|

Reporting group description:

Participants received, gantenerumab matching placebo, subcutaneous (SC) injections, every four weeks (Q4W) up to Week 36 and then every two weeks (Q2W) up to Week 114 of the DBT period.

| | |
|-----------------------|-------------------|
| Reporting group title | Gantenerumab: DBT |
|-----------------------|-------------------|

Reporting group description:

Participants received gantenerumab, SC injections with gradual up-titration starting at a dose of 120 milligrams (mg), Q4W for 3 doses, followed by 255 mg, Q4W for 3 doses, and 510 mg, Q4W for 3 doses. Following this, from Week 36 onwards, participants received gantenerumab, SC injections, at a dose of 510 mg, Q2W up to Week 114 of the DBT period.

| Reporting group values | Placebo: DBT | Gantenerumab: DBT | Total |
|------------------------|--------------|-------------------|-------|
| Number of subjects | 477 | 498 | 975 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|-------|-------|-----|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 71.8 | 71.6 | |
| standard deviation | ± 7.4 | ± 7.8 | - |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 285 | 288 | 573 |
| Male | 192 | 210 | 402 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 13 | 13 | 26 |
| Asian | 75 | 56 | 131 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 4 | 5 | 9 |
| White | 385 | 424 | 809 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 119 | 112 | 231 |
| Not Hispanic or Latino | 358 | 386 | 744 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Clinical Dementia Rating-Sum of Boxes (CDR-SB) | | | |
| CDR was derived by semi-structured interview with participant & informant & rated impairment across 6 domains: memory,orientation,judgment & problem solving,community affairs,home & hobbies & personal care on 5-point scale for which 0=no impairment, 0.5=questionable impairment & 1, 2 & 3=mild,moderate,severe impairment respectively. CDR-SB is based on summing each domain box scores with total score ranging 0-18 with higher scores=greater cognitive & functional impairment. ITT analysis set included all participants randomised during global phase who received at least 1 dose of study drug. | | | |
| Units: score on a scale | | | |

| | | | |
|--------------------|--------|--------|---|
| arithmetic mean | 3.52 | 3.67 | |
| standard deviation | ± 1.54 | ± 1.61 | - |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo: DBT |
| Reporting group description: Participants received, gantenerumab matching placebo, subcutaneous (SC) injections, every four weeks (Q4W) up to Week 36 and then every two weeks (Q2W) up to Week 114 of the DBT period. | |
| Reporting group title | Gantenerumab: DBT |
| Reporting group description: Participants received gantenerumab, SC injections with gradual up-titration starting at a dose of 120 milligrams (mg), Q4W for 3 doses, followed by 255 mg, Q4W for 3 doses, and 510 mg, Q4W for 3 doses. Following this, from Week 36 onwards, participants received gantenerumab, SC injections, at a dose of 510 mg, Q2W up to Week 114 of the DBT period. | |
| Reporting group title | Placebo (DBT) to Gantenerumab: Open-label Extension (OLE) |
| Reporting group description: Participants who received gantenerumab matching placebo in the DBT period received gantenerumab SC injections with gradual up titration starting at a dose of 120 mg, Q4W for 3 doses, followed by 255 mg, Q4W for 3 doses, and then at a dose of 510 mg, Q4W up to Week 34 of the OLE period. To maintain the blind to previous treatment assignment, participants received Q2W, SC injections, with alternate doses containing gantenerumab matching placebo. | |
| Reporting group title | Gantenerumab (DBT) to Gantenerumab: OLE |
| Reporting group description: Participants who received gantenerumab in the DBT period continued receiving gantenerumab, SC injections, 510 mg, Q2W up to Week 34 of the OLE period. | |
| Subject analysis set title | Gantenerumab: DBT |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Participants received gantenerumab, SC injections with gradual up-titration starting at a dose of 120 mg, Q4W for 3 doses, followed by 255 mg, Q4W for 3 doses, and 510 mg, Q4W for 3 doses. Following this, from Week 36 onwards, participants received gantenerumab, SC injections, at a dose of 510 mg, Q2W up to Week 114 of the DBT period. | |

Primary: DBT Period: Change From Baseline to Week 116 in Global Outcome, as Measured by CDR-SB

| | |
|--|---|
| End point title | DBT Period: Change From Baseline to Week 116 in Global Outcome, as Measured by CDR-SB |
| End point description: CDR was derived through semi-structured interview with the participant and an appropriate informant, and it rated impairment across six domains: memory, orientation, judgment, and problem solving, community affairs, home and hobbies, and personal care on a 5-point scale for which 0=no impairment, 0.5=questionable impairment, and 1, 2, and 3=mild, moderate, and severe impairment, respectively. The CDR-SB is based on summing each of the domain box scores with total score ranging from 0-18 with higher scores reflecting greater cognitive and functional impairment. A negative change from baseline indicates improvement. ITT analysis set included all participants randomised during the global phase, who received at least one dose of study drug. Overall number analysed is the number of participants with data available for analysis. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 116 | |

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 477 | 497 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | 3.01 (\pm 0.15) | 2.82 (\pm 0.14) | | |

Statistical analyses

| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
|--|----------------------------------|
| Statistical analysis description: | |
| Change from Baseline was calculated based on ANCOVA analysis model which included the following covariates and stratification factors =Treatment + Baseline (BL) + Geographic Region + Disease Stage + AD Medication at BL + Apolipoprotein E, Allele e4 (APOE e4) + Baseline ADAS COG13 + Baseline Alzheimer Disease Cooperative Study Group-Activities of Daily Living (ADCS-ADL). | |
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 974 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2998 |
| Method | ANCOVA |
| Parameter estimate | Difference in Adjusted mean |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.55 |
| upper limit | 0.17 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.18 |

Primary: OLE Period: Number of Participants with Adverse Events (AEs)

| | |
|-----------------|--|
| End point title | OLE Period: Number of Participants with Adverse Events |
|-----------------|--|

End point description:

An adverse event is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. OLE safety-evaluable set included all participants randomized during the global enrollment phase who received at least one dose of study drug and who entered the OLE period.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From day of first dose in OLE period up to 14 weeks after the last OLE dose (up to 48 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical comparison was planned.

| End point values | Placebo (DBT) to Gantenerumab : Open-label Extension (OLE) | Gantenerumab (DBT) to Gantenerumab : OLE | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 14 | | |
| Units: participants | 8 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Primary: OLE Period: Number of Participants With Change from Baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) Score

| | |
|-----------------|--|
| End point title | OLE Period: Number of Participants With Change from Baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) Score ^[2] |
|-----------------|--|

End point description:

C-SSRS=assessment tool used to assess lifetime suicidality of participant and any new instances of suicidality. Structured interview prompts recollection of suicidal ideation, including intensity of ideation, behavior& attempts with actual/potential lethality. Responses to categories: yes/no[Wish to be Dead;Non-specific Active Suicidal Thoughts; Active Suicidal Ideation with Any Methods without Intent to Act;Active Suicidal Ideation with Some Intent to Act, without Specific Plan;Active Suicidal Ideation with Specific Plan &Intent, Preparatory Acts &Behavior; Aborted Attempt; Interrupted Attempt; Actual Attempt (non-fatal)]; Completed Suicide. Suicidal ideation/behavior is indicated by a "yes" answer to any of the listed categories. Score=0, if no suicide risk is present. Score=1/higher indicates suicidal ideation/behavior. OLE safety-evaluable set=all participants randomized during global enrollment phase who received at least one dose of study drug & who entered OLE period.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From day of first dose in OLE period up to 14 weeks after the last OLE dose (up to 48 weeks)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical comparison was planned.

| End point values | Placebo (DBT) to Gantenerumab : Open-label Extension (OLE) | Gantenerumab (DBT) to Gantenerumab : OLE | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 13 | | |
| Units: participants | | | | |
| Suicidal Ideation: Passive | 1 | 0 | | |
| Suicidal Ideation: Active-Method, No Intent/Plan | 1 | 0 | | |
| Suicidal Ideation: No Event | 10 | 13 | | |
| Suicidal Behavior: No Event | 12 | 13 | | |
| Self-injurious Behavior Without Intent: No Event | 12 | 13 | | |

Statistical analyses

No statistical analyses for this end point

Primary: OLE Period : Number of Participants with Amyloid-Related Imaging Abnormalities-Haemosiderin deposition (ARIA-H) Confirmed by MRI

| | |
|-----------------|---|
| End point title | OLE Period : Number of Participants with Amyloid-Related Imaging Abnormalities-Haemosiderin deposition (ARIA-H) Confirmed by MRI ^[3] |
|-----------------|---|

End point description:

ARIA are an identified risk with anti-amyloid antibodies, including gantenerumab. These changes can be identified on brain MRI. ARIA-H (H for hemosiderosis) are small foci of signal loss observed on MRI sequences sensitive for paramagnetic tissue properties and comprise cerebral microbleeds (small foci of bleeding in the brain parenchyma) and leptomeningeal hemosiderosis (small foci of bleeding on the surface of the brain). These changes also occur sporadically in AD. MRI Safety-evaluable analysis set included all participants in the Safety-evaluable analysis set who had at least one post-baseline safety MRI scan.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From day of first dose in OLE period up to 14 weeks after the last OLE dose (up to 48 weeks)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical comparison was planned.

| End point values | Placebo (DBT) to Gantenerumab : Open-label Extension (OLE) | Gantenerumab (DBT) to Gantenerumab : OLE | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 14 | | |
| Units: participants | 2 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Primary: OLE Period: Number of Participants with Amyloid-Related Imaging Abnormalities-Edema (ARIA-E) Confirmed by Magnetic Resonance Imaging (MRI)

| | |
|-----------------|---|
| End point title | OLE Period: Number of Participants with Amyloid-Related Imaging Abnormalities-Edema (ARIA-E) Confirmed by Magnetic Resonance Imaging (MRI) ^[4] |
|-----------------|---|

End point description:

ARIA are an identified risk with anti-amyloid antibodies, including gantenerumab. These changes can be identified on brain MRI. In ARIA-E, (E for oedema or effusion), oedema can be seen in different areas of the brain on MRI, representing fluid leakage into the brain parenchyma or sulcal spaces. MRI Safety-

evaluable analysis set included all participants in the Safety-evaluable analysis set who had at least one post-baseline safety MRI scan.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From day of first dose in OLE period up to 14 weeks after the last OLE dose (up to 48 weeks)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical comparison was planned.

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | Placebo (DBT) to Gantenerumab : Open-label Extension (OLE) | Gantenerumab (DBT) to Gantenerumab : OLE | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 14 | | |
| Units: participants | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Primary: OLE Period: Number of Participants with Injection-Site Reactions

| | |
|-----------------|---|
| End point title | OLE Period: Number of Participants with Injection-Site Reactions ^[5] |
|-----------------|---|

End point description:

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product or other protocol-imposed intervention, regardless of attribution. Local injection reactions (or injection site reactions) are defined as AEs related to the injection site that occur during or within 24 hours after study drug administration that are judged to be related to the study drug injection. OLE safety-evaluable set included all participants randomized during the global enrollment phase who received at least one dose of study drug and who entered the OLE period.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From day of first dose in OLE period up to 14 weeks after the last OLE dose (up to 48 weeks)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical comparison was planned.

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | Placebo (DBT) to Gantenerumab : Open-label Extension (OLE) | Gantenerumab (DBT) to Gantenerumab : OLE | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 14 | | |
| Units: participants | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: DBT Period: Change from Baseline to Week 116 in Alzheimer Disease Assessment Scale-Cognition Subscale 13 (ADAS-Cog13) Score

| | |
|-----------------|---|
| End point title | DBT Period: Change from Baseline to Week 116 in Alzheimer Disease Assessment Scale-Cognition Subscale 13 (ADAS-Cog13) Score |
|-----------------|---|

End point description:

The ADAS-Cog13 total score includes all of the items in the ADAS-Cog11 in addition to delayed word recall and the number cancellation. For the ADAS-cog 13 the range is 0-85 (score range for Delayed Word Recall [DWR] score is 0-10 and for Number Cancellation [NC] is 0-5, thus the score is ADAS-cog 11[0-70] plus the scores for DWR and NC). A higher score indicates worse performance. A negative change from baseline indicates improvement in cognitive function. ITT analysis set included all participants randomised during the global phase, who received at least one dose of study drug. Overall number analysed is the number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 116

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 491 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | 7.94 (\pm 0.49) | 6.66 (\pm 0.42) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
|----------------------------|---------------------------------|

Statistical analysis description:

Change from BL was calculated based on ANCOVA analysis model which included the following covariates and stratification factors = Treatment + Baseline + Geographical Region + Disease Stage + AD Medication at BL + APOE e4

| | |
|---|----------------------------------|
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 966 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0273 |
| Method | ANCOVA |
| Parameter estimate | Difference in adjusted mean |
| Point estimate | -1.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.41 |
| upper limit | -0.14 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.58 |

Secondary: DBT Period: Change From Baseline to Week 116 in Alzheimer's Disease Cooperative Study- Activities of Daily Living (ADCS-ADL) Total Score

| | |
|-----------------|--|
| End point title | DBT Period: Change From Baseline to Week 116 in Alzheimer's Disease Cooperative Study- Activities of Daily Living (ADCS-ADL) Total Score |
|-----------------|--|

End point description:

ADCS-ADL is a 23-item rater-administered, observer-reported outcome (ObsRO) that captures a participant's ability to perform basic activities of daily living (e.g., eating and toileting) and more complex ADL or instrumental activities of daily living (iADL, e.g., using the telephone, managing finances, preparing a meal). Total score ranges from 0-78, with higher scores reflecting better functioning. A positive change from baseline indicates improvement. ITT analysis set included all participants randomised during the global phase, who received at least one dose of study drug. Overall number analysed is the number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 116

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|----------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 496 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | -9.26 (± 0.62) | -8.44 (± 0.58) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
|----------------------------|---------------------------------|

Statistical analysis description:

Change from BL was calculated based on ANCOVA analysis model which included the following covariates and stratification factors = Treatment + Baseline + Region + Disease Stage + AD Medication at BL + APOE e4

| | |
|---|----------------------------------|
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 971 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2918 |
| Method | ANCOVA |
| Parameter estimate | Difference in adjusted mean |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 2.34 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.78 |

Secondary: DBT Period: Change From Baseline to Week 116 in Functional Activities Questionnaire (FAQ) Score

| | |
|-----------------|---|
| End point title | DBT Period: Change From Baseline to Week 116 in Functional Activities Questionnaire (FAQ) Score |
|-----------------|---|

End point description:

FAQ is a rater-administered ObsRO (informant-based measure) that measures a participant's functional ability to perform complex higher-order activities. The observer provides performance ratings of the target person on ten complex higher-order activities. Total score that ranges from 0-30, with higher scores reflecting greater functional impairment. A negative change from baseline indicates improvement. ITT analysis set included all participants randomised during the global phase, who received at least one dose of study drug. Overall number analysed is the number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 116

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 476 | 496 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | 6.72 (\pm 0.33) | 5.86 (\pm 0.31) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
|----------------------------|---------------------------------|

Statistical analysis description:

Change from BL was calculated based on ANCOVA analysis model which included the following covariates and stratification factors = Treatment + Baseline + Geographical Region + Disease Stage + AD Medication at BL + APOE e4.

| | |
|---|----------------------------------|
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 972 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0438 |
| Method | ANCOVA |
| Parameter estimate | Difference in adjusted mean |
| Point estimate | -0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.7 |
| upper limit | -0.02 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.43 |

Secondary: DBT Period: Change From Baseline to Week 116 in Mini-Mental State Examination (MMSE) Total Score

| | |
|-----------------|--|
| End point title | DBT Period: Change From Baseline to Week 116 in Mini-Mental State Examination (MMSE) Total Score |
|-----------------|--|

End point description:

MMSE is a rater-administered performance-based outcome (PerfO) that includes a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment. The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. Total score ranges from 0-30, with lower scores indicating greater impairment. A positive change from baseline indicates improvement. ITT analysis set included all participants randomised during the global phase, who received at least one dose of study drug. Overall number analysed is the number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 116

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|----------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 477 | 497 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | -4.53 (± 0.22) | -4.00 (± 0.20) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
|----------------------------|---------------------------------|

Statistical analysis description:

Change from Baseline was calculated based on ANCOVA analysis model which included the following covariates and stratification factors =Treatment + Baseline + Geographic Region + Disease Stage + AD Medication at BL + APOE e4.

| | |
|---|----------------------------------|
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 974 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0566 |
| Method | ANCOVA |
| Parameter estimate | Difference in adjusted mean |
| Point estimate | 0.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.01 |
| upper limit | 1.06 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.27 |

Secondary: DBT Period: Change From Baseline to Week 116 in Alzheimer Disease Assessment Scale-Cognition Subscale 11 (ADAS-Cog11) Score

| | |
|-----------------|---|
| End point title | DBT Period: Change From Baseline to Week 116 in Alzheimer Disease Assessment Scale-Cognition Subscale 11 (ADAS-Cog11) Score |
|-----------------|---|

End point description:

The ADAS-Cog11 was designed to measure cognitive symptom change in participants with AD, consisted of 11 tasks. Standard 11 items (& score range) were: word recall (0-10), commands (0-5), constructional praxis (0-5), naming objects & fingers (0-5), ideational praxis (0-5), orientation (0-8), word recognition (0-12), spoken language ability (0-5), comprehension of spoken language (0-5), word-finding difficulty (0-5) & remembering test instructions (0-5). Test included 7 performance items & 4 clinician-rated items. ADAS-Cog11 total score=sum of all 11 individual items, with a total score ranging from 0 (no impairment)-70 (severe impairment). Higher scores indicated more severe cognitive impairment. A negative change from baseline indicates improvement. ITT analysis set was used. Overall number analyzed is number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 116

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|----------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 491 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | 6.97 (± 0.46) | 5.77 (± 0.38) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
|----------------------------|---------------------------------|

Statistical analysis description:

Change from BL was calculated based on ANCOVA analysis model which included the following covariates and stratification factors = Treatment + Baseline + Geographical Region + Disease Stage + AD Medication at BL + APOE e4.

| | |
|---|----------------------------------|
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 966 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.026 |
| Method | ANCOVA |
| Parameter estimate | Difference in adjusted mean |
| Point estimate | -1.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.24 |
| upper limit | -0.14 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.53 |

Secondary: DBT Period: Change From Baseline to Week 116 in Verbal Fluency Task (VFT) Score

| | |
|-----------------|---|
| End point title | DBT Period: Change From Baseline to Week 116 in Verbal Fluency Task (VFT) Score |
|-----------------|---|

End point description:

VFT is a rater administered PerFO that measures speed and flexibility of verbal thought with a total score that ranges from 0-99 (lower scores indicating lower performance). A positive change from baseline indicates improvement. ITT analysis set included all participants randomised during the global phase, who received at least one dose of study drug. Overall number analysed is the number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 116

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|----------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 477 | 497 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | -2.68 (± 0.22) | -2.71 (± 0.21) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
|----------------------------|---------------------------------|

Statistical analysis description:

Change from BL was calculated based on ANCOVA analysis model which included the following covariates and stratification factors = Treatment + Baseline + Geographical Region + Disease Stage + AD Medication at BL + APOE e4.

| | |
|---|----------------------------------|
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 974 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9086 |
| Method | ANCOVA |
| Parameter estimate | Difference in adjusted mean |
| Point estimate | -0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.59 |
| upper limit | 0.52 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.28 |

Secondary: DBT Period: Change from Baseline to Week 116 in the Coding (Digit Symbol Substitution Test [DSST]) Subtest

| | |
|-----------------|--|
| End point title | DBT Period: Change from Baseline to Week 116 in the Coding (Digit Symbol Substitution Test [DSST]) Subtest |
|-----------------|--|

End point description:

Coding, also called DSST is a rater administered Perfo that measures speed of processing and associative memory with a total score that ranges from 0-135 (lower scores indicating lower performance). The DSST was adapted from the Wechsler Adult Intelligence Scale. The 120-second version of the test was used in this study. Positive change from baseline indicates improvement. ITT analysis set included all participants randomised during the global phase, who received at least one dose of study drug. Overall number analysed is the number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 116

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|----------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 497 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | -6.90 (± 0.59) | -5.49 (± 0.55) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
|----------------------------|---------------------------------|

Statistical analysis description:

Change from BL was calculated based on ANCOVA analysis model which included the following covariates and stratification factors = Treatment + Baseline + Geographical Region + Disease Stage + AD Medication at BL + APOE e4.

| | |
|---|----------------------------------|
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 972 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0629 |
| Method | ANCOVA |
| Parameter estimate | Difference in adjusted mean |
| Point estimate | 1.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.08 |
| upper limit | 2.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.76 |

Secondary: DBT Period: Change From Baseline to Week 116 in Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-iADL) Instrumental Score

| | |
|-----------------|--|
| End point title | DBT Period: Change From Baseline to Week 116 in Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-iADL) Instrumental Score |
|-----------------|--|

End point description:

The ADCS-iADL measures activities such as using the telephone, shopping 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. Positive change from baseline indicates improvement. ITT analysis set included all participants randomised during the global phase, who received at least one dose of study drug. Overall number analysed is the number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 116

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 496 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | -8.22 (\pm 0.53) | -7.43 (\pm 0.49) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
|----------------------------|---------------------------------|

Statistical analysis description:

Change from BL was calculated based on ANCOVA analysis model which included the following covariates and stratification factors = Treatment + Baseline + Geographical Region + Disease Stage + AD Medication at BL + APOE e4.

| | |
|---|----------------------------------|
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 971 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2348 |
| Method | ANCOVA |
| Parameter estimate | Difference in adjusted mean |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | 2.09 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.66 |

Secondary: DBT Period: Number of Participants With Change from Baseline in C-SSRS Score

| | |
|-----------------|---|
| End point title | DBT Period: Number of Participants With Change from Baseline in C-SSRS Score ^[6] |
|-----------------|---|

End point description:

C-SSRS=assessment tool used to assess lifetime suicidality of a participant & any new instances of suicidality. Categories have binary responses (yes/no) & include Wish to be Dead; Non-specific Active Suicidal Thoughts; Active Suicidal Ideation with Any Methods without Intent to Act; Active Suicidal Ideation with Some Intent to Act, without Specific Plan; Active Suicidal Ideation with Specific Plan & Intent, Preparatory Acts & Behavior; Aborted Attempt; Interrupted Attempt; Actual Attempt (non-fatal); Completed Suicide. Suicidal ideation/behavior indicated by a "yes" answer to any listed categories. 0= no suicide risk is present. Score of 1/higher= suicidal ideation/behavior. Safety-evaluable set=all participants randomised during global phase who received at least one dose of study drug. 3 participants randomized to placebo received at least one dose of gantenerumab & were considered in gantenerumab arm for safety evaluable set. Categories with non-zero values are only reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Day 1 up to 14 weeks after the last dose of blinded study drug (up to 128 weeks)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint represents data for DBT period only.

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|--|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 464 | 483 | | |
| Units: participants | | | | |
| Suicidal Ideation: Passive | 20 | 12 | | |
| Suicidal Ideation: Active-Nonspecific | 4 | 2 | | |
| Suicidal Ideation: Active-Method, No Intent/Plan | 2 | 2 | | |
| Suicidal Ideation: Active-Method & Intent; No Plan | 1 | 1 | | |
| Suicidal Ideation: Active-Method, Intent & Plan | 0 | 2 | | |
| Suicidal Ideation: No Event | 437 | 464 | | |
| Suicidal Behavior: No Event | 464 | 483 | | |
| Self-injurious Behavior, No Suicidal Intent | 0 | 2 | | |
| Self-injurious Behavior Without Intent: No Event | 464 | 481 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: DBT Period: Number of Participants with AEs

| | |
|-----------------|--|
| End point title | DBT Period: Number of Participants with AEs ^[7] |
|-----------------|--|

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant administered a

pharmaceutical product, regardless of causal attribution. Safety-evaluable set included all participants randomised during the global phase who received at least one dose of study drug. In the DBT period, three participants randomized to placebo arm received at least one dose of gantenerumab and were considered in the gantenerumab arm for safety evaluable set.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Day 1 up to 14 weeks after the last dose of blinded study drug (up to 128 weeks) | |

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: The endpoint represents data for DBT period only.

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|-----------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 474 | 501 | | |
| Units: participants | 409 | 451 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: DBT Period: Number of Participants with ARIA-E Confirmed by MRI

| | |
|-----------------|---|
| End point title | DBT Period: Number of Participants with ARIA-E Confirmed by MRI |
|-----------------|---|

End point description:

ARIA are an identified risk with anti-amyloid antibodies, including gantenerumab. These changes can be identified on brain MRI. In ARIA-E, (E for oedema or effusion), oedema can be seen in different areas of the brain on MRI, representing fluid leakage into the brain parenchyma or sulcal spaces. MRI Safety-evaluable analysis set included all participants in the Safety-evaluable analysis set who had at least one post-baseline safety MRI scan.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Day 1 up to 14 weeks after the last dose of blinded study drug (up to 128 weeks) | |

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|-----------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 470 | 496 | | |
| Units: participants | 18 | 128 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: DBT Period : Number of Participants with ARIA-H Confirmed by MRI

| | |
|-----------------|--|
| End point title | DBT Period : Number of Participants with ARIA-H Confirmed by |
|-----------------|--|

End point description:

ARIA are an identified risk with anti-amyloid antibodies, including gantenerumab. These changes can be identified on brain MRI. ARIA-H (H for hemosiderosis) are small foci of signal loss observed on MRI sequences sensitive for paramagnetic tissue properties and comprise cerebral microbleeds (small foci of bleeding in the brain parenchyma) and leptomeningeal hemosiderosis (small foci of bleeding on the surface of the brain). These changes also occur sporadically in AD. MRI Safety-evaluable analysis set included all participants in the Safety-evaluable analysis set who had at least one post-baseline safety MRI scan.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Day 1 up to 14 weeks after the last dose of blinded study drug (up to 128 weeks)

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|-----------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 470 | 496 | | |
| Units: participants | 57 | 109 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: DBT Period: Number of Participants With Anti-Drug Antibodies (ADA) to Gantenerumab

| | |
|-----------------|--|
| End point title | DBT Period: Number of Participants With Anti-Drug Antibodies (ADA) to Gantenerumab |
|-----------------|--|

End point description:

Number of participants with positive results for ADA against gantenerumab at any post-baseline (PB) assessment time-points were reported. Participant with ADA assay result from at least 1 post-baseline sample = PB evaluable participant. Treatment Emergent ADA = participant with negative/missing baseline ADA result(s) & at least 1 positive PB ADA result. ADA-evaluable analysis set included participants who received at least one dose of study drug and who provided at least one post-baseline ADA sample. In the DBT period, three participants randomized to placebo arm received at least one dose of gantenerumab and were considered in the gantenerumab arm. As pre-specified in the protocol, ADA data for studies WN29922 and WN39658 from the OLE period will be reported when the results for study WN42171 will be posted.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Day 1 up to 14 weeks after the last dose of blinded study drug (up to 128 weeks)

| End point values | Gantenerumab : DBT | | | |
|--|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 501 | | | |
| Units: participants | | | | |
| Number of Participants with Treatment-emergent ADA | 12 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Brain Amyloid Load as Measured by Amyloid Positron Emission Tomography (PET) Scan in a Subset of Participants

| | |
|-----------------|---|
| End point title | Change from Baseline in Brain Amyloid Load as Measured by Amyloid Positron Emission Tomography (PET) Scan in a Subset of Participants |
|-----------------|---|

End point description:

Brain amyloid load over time was assessed using [18F] florbetaben or [18F] flutemetamol tracers. These are PET radioligand selective to amyloid. Amyloid PET burden was measured in composite region of interest by using standardized uptake value ratio (SUVR) mapped to centiloid scale. Centiloid scale anchor points are 0 & 100, where 0=high-certainty amyloid negative scan & 100=amount of global amyloid deposition found in typical AD scan. Amyloid-PET-modified-ITT (mITT) included all participants in ITT analysis set who participated in the Amyloid PET sub-study and who had at least 1 Amyloid PET scan with valid quantitative measurement performed with either florbetaben or flutemetamol who did not withdraw from the Amyloid PET substudy before randomisation. Overall number analysed is number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 116

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|----------------------------------|---------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 40 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | 8.46 (\pm 2.768) | -48.00 (\pm 2.845) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
|----------------------------|---------------------------------|

Statistical analysis description:

Change from BL was calculated based on mixed-effect model of repeated measure which included the following covariates and stratification factors = Baseline + APOE e4 status + Type of Tracer + Analysis Visit + Treatment + Treatment*Analysis Visit + Analysis Visit*Baseline.

| | |
|-------------------|----------------------------------|
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
|-------------------|----------------------------------|

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Difference in adjusted means |
| Point estimate | -56.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -64.36 |
| upper limit | -48.56 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.976 |

Secondary: DBT Period: Number of Participants with Injection-Site Reactions

| | |
|-----------------|---|
| End point title | DBT Period: Number of Participants with Injection-Site Reactions ^[8] |
|-----------------|---|

End point description:

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product or other protocol-imposed intervention, regardless of attribution. Local injection reactions (or injection site reactions) are defined as AEs related to the injection site that occur during or within 24 hours after study drug administration that are judged to be related to the study drug injection. Safety-evaluable set included all participants randomised during the global phase who received at least one dose of study drug. In the DBT period, three participants randomized to placebo arm received at least one dose of gantenerumab and were considered in the gantenerumab arm for safety evaluable set.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Day 1 up to 14 weeks after the last dose of blinded study drug (up to 128 weeks)

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: The endpoint represents data for DBT period only.

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|-----------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 474 | 501 | | |
| Units: participants | 31 | 75 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Brain Tau Load, as Measured by Tau PET Scan in a Subset of Participants

| | |
|-----------------|---|
| End point title | Change From Baseline in Brain Tau Load, as Measured by Tau PET Scan in a Subset of Participants |
|-----------------|---|

End point description:

Change in tau load represents amount of neurofibrillary tau pathology present in brain assessed using PET Scan. [18F] GTP1 (RO6880276) = tau PET radioligand. Tau load was measured using SUVR in four composite target ROIs(both left & right): Temporal composite target region included; Medial temporal composite region not including hippocampus; Frontal lobe; Parietal lobe. Inferior cerebellar grey matter = reference region for calculating SUVRs for all four target regionsAs pre-specified in protocol/SAP single tau PET substudy analyzed participants from 2 studies i.e. WN29922 & WN39658, hence data for Tau PET was analyzed at pooled level of WN29922 & WN39658. These studies had identical study design & enrolled an Early AD population. Tau-PET-mITT analysis set= all participants in ITT set who participated in Tau PET sub-study & who had at least one Tau PET scan with valid quantitative measurement & who did not withdraw from Tau PET substudy before randomization.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 116 | |

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|---------------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 48 | | |
| Units: SUVR | | | | |
| arithmetic mean (standard error) | | | | |
| ROI: Temporal Composite Region | 0.12 (± 0.018) | 0.13 (± 0.014) | | |
| ROI: Medial Temporal Composite Region | 0.08 (± 0.014) | 0.09 (± 0.011) | | |
| ROI: Frontal Lobe | 0.08 (± 0.012) | 0.08 (± 0.009) | | |
| ROI: Parietal Lobe | 0.09 (± 0.020) | 0.09 (± 0.016) | | |

Statistical analyses

| | |
|--|-----------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
| Statistical analysis description: | |
| Temporal Composite Region: Change from BL was calculated based on mixed-effect model of repeated measure which included the following covariates and stratification factors = Baseline + APOE e4 status + Study + Analysis Visit + Treatment + Treatment*Analysis Visit + Analysis Visit*Baseline. | |
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7816 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Difference in adjusted mean |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.04 |
| upper limit | 0.05 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.023 |

| | |
|--|-----------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
| Statistical analysis description: | |
| Parietal Lobe: Change from BL was calculated based on mixed-effect model of repeated measure which included the following covariates and stratification factors = Baseline + APOE e4 status + Study + Analysis Visit + Treatment + Treatment*Analysis Visit + Analysis Visit*Baseline. | |
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9022 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Difference in adjusted means |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.05 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.026 |

| | |
|---|---|
| Statistical analysis title | Frontal Lobe: Placebo: DBT, Gantenerumab: DBT |
| Statistical analysis description: | |
| Frontal Lobe: Change from BL was calculated based on mixed-effect model of repeated measure which included the following covariates and stratification factors = Baseline + APOE e4 status + Study + Analysis Visit + Treatment + Treatment*Analysis Visit + Analysis Visit*Baseline. | |
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7754 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Difference in adjusted means |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03 |
| upper limit | 0.03 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.015 |

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
|-----------------------------------|---------------------------------|

Statistical analysis description:

Medial Temporal Composite Region: Change from BL was calculated based on mixed-effect model of repeated measure which included the following covariates and stratification factors = Baseline + APOE e4 status + Study + Analysis Visit + Treatment + Treatment*Analysis Visit + Analysis Visit*Baseline.

| | |
|---|-----------------------------------|
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6203 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Difference in adjusted means |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03 |
| upper limit | 0.05 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.018 |

Secondary: DBT Period: Percent Change From Baseline in Cerebrospinal Fluid (CSF) Marker of Disease in a Subset of Participants - Neurofilament Light Chain (NFL)

| | |
|-----------------|---|
| End point title | DBT Period: Percent Change From Baseline in Cerebrospinal Fluid (CSF) Marker of Disease in a Subset of Participants - Neurofilament Light Chain (NFL) |
|-----------------|---|

End point description:

NFL is a neuronal cytoplasmic protein highly expressed in large, myelinated axons. Its levels increase in CSF and blood proportionally to the degree of axonal damage in a variety of neurological disorders, including AD. CSF modified ITT analysis set included all participants in the ITT analysis set who had at least one valid quantitative CSF measurement. Overall number analyzed is the number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 116

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|--|-----------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72 | 74 | | |
| Units: percent change in NFL | | | | |
| geometric mean (confidence interval 95%) | 25.5 (15.83 to 35.97) | 8.9 (0.60 to 17.83) | | |

Statistical analyses

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Placebo: DBT vs Gantenerumab: DBT |
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 146 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.014 |
| Method | ANCOVA |
| Parameter estimate | Percent Difference in Geometric Mean |
| Point estimate | -13.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.51 |
| upper limit | -2.87 |

Secondary: DBT Period: Percent Change From Baseline in CSF Marker of Disease in a Subset of Participants - Neurogranin

| | |
|------------------------|--|
| End point title | DBT Period: Percent Change From Baseline in CSF Marker of Disease in a Subset of Participants - Neurogranin |
| End point description: | CSF modified ITT analysis set included all participants in the ITT analysis set who had at least one valid quantitative CSF measurement. Overall number analyzed is the number of participants with data available for analysis. |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 116 | |

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|--|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72 | 72 | | |
| Units: percent change in neurogranin | | | | |
| geometric mean (confidence interval 95%) | -6.1 (-11.99 to 0.12) | -19.6 (-24.66 to -14.30) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Placebo: DBT vs Gantenerumab: DBT |
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 144 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Percent Difference in Geometric Mean |
| Point estimate | -6.21 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.88 |
| upper limit | -2.87 |

Secondary: DBT Period: Percent Change From Baseline in CSF Marker of Disease in a Subset of Participants - Total Tau (tTau)

| | |
|-----------------|--|
| End point title | DBT Period: Percent Change From Baseline in CSF Marker of Disease in a Subset of Participants - Total Tau (tTau) |
|-----------------|--|

End point description:

CSF biomarker tTau has been considered as a general marker of neurodegeneration. CSF phospho-tau is an indicator of neuronal injury and neurodegeneration. CSF modified ITT analysis set included all participants in the ITT analysis set who had at least one valid quantitative CSF measurement. Overall number analysed is the number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 116

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|--|---------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72 | 71 | | |
| Units: percent change in tTau | | | | |
| geometric mean (confidence interval 95%) | 1.8 (-4.46 to 8.45) | -16.4 (-21.55 to -10.87) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |

Secondary: DBT Period: Percent Change From Baseline in CSF Marker of Disease in a Subset of Participants - Phosphorylated Tau (pTau-181)

| | |
|-----------------|---|
| End point title | DBT Period: Percent Change From Baseline in CSF Marker of Disease in a Subset of Participants - Phosphorylated Tau (pTau-181) |
|-----------------|---|

End point description:

CSF phospho-tau is an indicator of neuronal injury and neurodegeneration. CSF biomarker tTau has

been considered as a general marker of neurodegeneration. An elevation in levels of pTau species, is thought to be a marker for progressive cellular degeneration in AD. CSF modified ITT analysis set included all participants in the ITT analysis set who had at least one valid quantitative CSF measurement. Overall number analysed is the number of participants with data available for analysis.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 116 | |

| End point values | Placebo: DBT | Gantenerumab : DBT | | |
|--|---------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 71 | 70 | | |
| Units: percent change in pTau-181 | | | | |
| geometric mean (confidence interval 95%) | 0.1 (-6.50 to 7.16) | -20.9 (-26.17 to -15.31) | | |

Statistical analyses

| Statistical analysis title | Placebo: DBT, Gantenerumab: DBT |
|---|----------------------------------|
| Comparison groups | Placebo: DBT v Gantenerumab: DBT |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

DBT Period: Day 1 to 14 weeks post last dose of study drug (up to 128 weeks); OLE Period: Day 1 (OLE) to 14 weeks post last OLE dose (up to 48 weeks)

Deaths: DBT: Day 1 to end of study (approx. 164 weeks); OLE: OLE Day 1 to end of study (approx. 86 weeks)

Adverse event reporting additional description:

Safety-evaluable set=all participants randomized during global phase who received at least one dose of study drug.3 participants in placebo received at least one dose of gantenerumab &were represented in gantenerumab arm;OLE safety set=all participants randomized during global enrollment &who received at least one dose of drug &entered OLE period.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Placebo: DBT |
|-----------------------|--------------|

Reporting group description:

Participants received, gantenerumab matching placebo, SC injections, Q4W up to Week 36 and then Q2W up to Week 114 of the DBT period.

| | |
|-----------------------|---|
| Reporting group title | Gantenerumab (DBT) to Gantenerumab: OLE |
|-----------------------|---|

Reporting group description:

Participants who received gantenerumab in the DBT period continued receiving gantenerumab, SC injections, 510 mg, Q2W up to Week 34 of the OLE period.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Placebo (DBT) to Gantenerumab: OLE |
|-----------------------|------------------------------------|

Reporting group description:

Participants who received gantenerumab matching placebo in the DBT period received gantenerumab SC injections with gradual up titration starting at a dose of 120 mg, Q4W for 3 doses, followed by 255 mg, Q4W for 3 doses, and then at a dose of 510 mg, Q4W up to Week 34 of the OLE period. To maintain the blind to previous treatment assignment, participants received Q2W, SC injections, with alternate doses containing gantenerumab matching placebo.

| | |
|-----------------------|-------------------|
| Reporting group title | Gantenerumab: DBT |
|-----------------------|-------------------|

Reporting group description:

Participants received gantenerumab, SC injections with gradual up-titration starting at a dose of 120 mg, Q4W for 3 doses, followed by 255 mg, Q4W for 3 doses, and 510 mg, Q4W for 3 doses. Following this, from Week 36 onwards, participants received gantenerumab, SC injections, at the a dose of 510 mg, Q2W up to Week 114 of the DBT period.

| Serious adverse events | Placebo: DBT | Gantenerumab (DBT) to Gantenerumab: OLE | Placebo (DBT) to Gantenerumab: OLE |
|---|-------------------|---|------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 63 / 474 (13.29%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| number of deaths (all causes) | 5 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive breast carcinoma | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer metastatic | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteric cancer | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Haematoma | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden cardiac death | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Prostatitis | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Alcoholism | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delusion | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Mental status changes | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| SARS-CoV-2 test positive | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Avulsion fracture | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back injury | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Fall | | | |
| subjects affected / exposed | 5 / 474 (1.05%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acetabulum fracture | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple injuries | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic fracture | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bundle branch block left | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Chronic coronary syndrome | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus arrhythmia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Focal dyscognitive seizures | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral paralysis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacunar infarction | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Normal pressure hydrocephalus | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haematoma | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertebrobasilar stroke | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 3 / 474 (0.63%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Speech disorder | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vestibular disorder | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal vein occlusion | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------|----------------|----------------|
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |

| | | | |
|---|-----------------|----------------|----------------|
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylitis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Chronic sinusitis | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asymptomatic COVID-19 | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 3 / 474 (0.63%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis bacterial | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Helicobacter gastritis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Labyrinthitis | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periodontitis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suspected COVID-19 | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 474 (0.63%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-------------------|--|--|
| Serious adverse events | Gantenerumab: DBT | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 61 / 501 (12.18%) | | |
| number of deaths (all causes) | 7 | | |
| number of deaths resulting from adverse events | 0 | | |

| | | | |
|---|-----------------|--|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder cancer | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Invasive breast carcinoma | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate cancer metastatic | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ureteric cancer | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|-----------------|--|--|
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 2 / 501 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Reproductive system and breast disorders | | | |
| Prostatitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemothorax | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Alcoholism | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Delusion | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Psychotic disorder | | | |
| subjects affected / exposed | 2 / 501 (0.40%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| SARS-CoV-2 test positive | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Avulsion fracture | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Back injury | | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fall | | | | |
| subjects affected / exposed | 3 / 501 (0.60%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acetabulum fracture | | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femur fracture | | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hand fracture | | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Head injury | | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hip fracture | | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Patella fracture | | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Injury | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 2 / 501 (0.40%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple fractures | | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple injuries | | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Humerus fracture | | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Radius fracture | | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rib fracture | | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Road traffic accident | | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal compression fracture | | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Traumatic fracture | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 2 / 501 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 2 / 501 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bundle branch block left | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardio-respiratory arrest | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic coronary syndrome | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinus arrhythmia | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Focal dyscognitive seizures | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalopathy | | | |
| subjects affected / exposed | 2 / 501 (0.40%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral ischaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Peripheral paralysis | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 2 / 501 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lacunar infarction | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Normal pressure hydrocephalus | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haematoma | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertebrobasilar stroke | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 2 / 501 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Speech disorder | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 2 / 501 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vestibular disorder | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |

| | | | |
|---|-----------------|--|--|
| Retinal vein occlusion | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spondylitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Chronic sinusitis | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asymptomatic COVID-19 | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COVID-19 | | | |
| subjects affected / exposed | 3 / 501 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocarditis bacterial | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Helicobacter gastritis | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 501 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Labyrinthitis | | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Periodontitis | | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 4 / 501 (0.80%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia viral | | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Postoperative wound infection | | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis | | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonitis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Suspected COVID-19 | | | |
| subjects affected / exposed | 2 / 501 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 501 (0.80%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Placebo: DBT | Gantenerumab (DBT) to Gantenerumab: OLE | Placebo (DBT) to Gantenerumab: OLE |
|---|--------------------|---|------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 296 / 474 (62.45%) | 6 / 14 (42.86%) | 8 / 13 (61.54%) |
| Vascular disorders | | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 35 / 474 (7.38%) | 0 / 14 (0.00%) | 2 / 13 (15.38%) |
| occurrences (all) | 40 | 0 | 2 |
| Varicose vein | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Injection site reaction | | | |
| subjects affected / exposed | 31 / 474 (6.54%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 58 | 5 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 12 / 474 (2.53%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 15 | 1 | 0 |
| Reproductive system and breast disorders | | | |
| Pruritus genital | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 4 / 474 (0.84%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Psychiatric disorders | | | |
| Aggression | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 4 | 0 | 1 |
| Anxiety | | | |

| | | | |
|--|------------------|----------------|-----------------|
| subjects affected / exposed | 22 / 474 (4.64%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 23 | 0 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 5 / 474 (1.05%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 6 | 0 | 1 |
| Investigations | | | |
| Blood pressure diastolic decreased | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Skin abrasion | | | |
| subjects affected / exposed | 9 / 474 (1.90%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 12 | 0 | 1 |
| Periorbital haematoma | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Head injury | | | |
| subjects affected / exposed | 7 / 474 (1.48%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 7 | 0 | 1 |
| Fall | | | |
| subjects affected / exposed | 47 / 474 (9.92%) | 1 / 14 (7.14%) | 2 / 13 (15.38%) |
| occurrences (all) | 58 | 1 | 3 |
| Bone fissure | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin laceration | | | |
| subjects affected / exposed | 9 / 474 (1.90%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 10 | 0 | 1 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 0 | 1 |
| Nervous system disorders | | | |

| | | | | |
|---|-----------------------------|-------------------|----------------|----------------|
| Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits | subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| | occurrences (all) | 2 | 0 | 0 |
| Amyloid related imaging abnormality-oedema/effusion | subjects affected / exposed | 12 / 474 (2.53%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| | occurrences (all) | 15 | 1 | 0 |
| Cerebral haemorrhage | subjects affected / exposed | 0 / 474 (0.00%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| | occurrences (all) | 0 | 1 | 0 |
| Dizziness | subjects affected / exposed | 29 / 474 (6.12%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| | occurrences (all) | 36 | 0 | 1 |
| Headache | subjects affected / exposed | 50 / 474 (10.55%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| | occurrences (all) | 64 | 0 | 0 |
| Syncope | subjects affected / exposed | 9 / 474 (1.90%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| | occurrences (all) | 9 | 0 | 1 |
| Gastrointestinal disorders | | | | |
| Vomiting | subjects affected / exposed | 13 / 474 (2.74%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| | occurrences (all) | 20 | 0 | 1 |
| Diarrhoea | subjects affected / exposed | 25 / 474 (5.27%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| | occurrences (all) | 33 | 1 | 0 |
| Constipation | subjects affected / exposed | 15 / 474 (3.16%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| | occurrences (all) | 16 | 0 | 1 |
| Oesophagitis | subjects affected / exposed | 0 / 474 (0.00%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| | occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | | |
| Arthritis | | | | |

| | | | |
|-----------------------------------|-------------------|----------------|----------------|
| subjects affected / exposed | 3 / 474 (0.63%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 3 | 0 | 1 |
| Arthralgia | | | |
| subjects affected / exposed | 42 / 474 (8.86%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 49 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 32 / 474 (6.75%) | 1 / 14 (7.14%) | 1 / 13 (7.69%) |
| occurrences (all) | 39 | 1 | 1 |
| Osteoporosis | | | |
| subjects affected / exposed | 4 / 474 (0.84%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 25 / 474 (5.27%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 27 | 0 | 0 |
| Infections and infestations | | | |
| Dacryocystitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 2 |
| COVID-19 | | | |
| subjects affected / exposed | 30 / 474 (6.33%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 31 | 1 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 3 | 0 | 1 |
| Groin infection | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 49 / 474 (10.34%) | 0 / 14 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 62 | 0 | 2 |
| Urinary tract infection | | | |
| subjects affected / exposed | 26 / 474 (5.49%) | 1 / 14 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 38 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 24 / 474 (5.06%) | 0 / 14 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 26 | 0 | 0 |

| | | | |
|--|----------------------|---------------------|---------------------|
| Suspected COVID-19 subjects affected / exposed occurrences (all) | 5 / 474 (1.05%) 5 | 1 / 14 (7.14%) 1 | 0 / 13 (0.00%) 0 |
| Pharyngitis subjects affected / exposed occurrences (all) | 5 / 474 (1.05%) 7 | 0 / 14 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all) | 4 / 474 (0.84%) 4 | 0 / 14 (0.00%) 0 | 1 / 13 (7.69%) 1 |

| | | | |
|---|--------------------------|--|--|
| Non-serious adverse events | Gantenerumab: DBT | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 358 / 501 (71.46%) | | |
| Vascular disorders Orthostatic hypotension subjects affected / exposed occurrences (all) | 4 / 501 (0.80%) 4 | | |
| Hypertension subjects affected / exposed occurrences (all) | 34 / 501 (6.79%) 38 | | |
| Varicose vein subjects affected / exposed occurrences (all) | 1 / 501 (0.20%) 1 | | |
| General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all) | 75 / 501 (14.97%) 319 | | |
| Fatigue subjects affected / exposed occurrences (all) | 15 / 501 (2.99%) 17 | | |
| Reproductive system and breast disorders Pruritus genital subjects affected / exposed occurrences (all) | 0 / 501 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|------------------------|--|--|
| Epistaxis subjects affected / exposed occurrences (all) | 5 / 501 (1.00%) 6 | | |
| Psychiatric disorders Aggression subjects affected / exposed occurrences (all) | 0 / 501 (0.00%) 0 | | |
| Anxiety subjects affected / exposed occurrences (all) | 26 / 501 (5.19%) 31 | | |
| Confusional state subjects affected / exposed occurrences (all) | 13 / 501 (2.59%) 14 | | |
| Investigations Blood pressure diastolic decreased subjects affected / exposed occurrences (all) | 0 / 501 (0.00%) 0 | | |
| Injury, poisoning and procedural complications Skin abrasion subjects affected / exposed occurrences (all) | 5 / 501 (1.00%) 8 | | |
| Periorbital haematoma subjects affected / exposed occurrences (all) | 0 / 501 (0.00%) 0 | | |
| Head injury subjects affected / exposed occurrences (all) | 6 / 501 (1.20%) 6 | | |
| Fall subjects affected / exposed occurrences (all) | 47 / 501 (9.38%) 74 | | |
| Bone fissure subjects affected / exposed occurrences (all) | 1 / 501 (0.20%) 1 | | |
| Skin laceration subjects affected / exposed occurrences (all) | 10 / 501 (2.00%) 15 | | |

| | | | |
|---|---|--|--|
| Spinal compression fracture subjects affected / exposed occurrences (all) | 2 / 501 (0.40%) 2 | | |
| Cardiac disorders Arrhythmia subjects affected / exposed occurrences (all) | 2 / 501 (0.40%) 2 | | |
| Nervous system disorders Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits subjects affected / exposed occurrences (all) Amyloid related imaging abnormality-oedema/effusion subjects affected / exposed occurrences (all) Cerebral haemorrhage subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all) | 33 / 501 (6.59%) 35 114 / 501 (22.75%) 162 4 / 501 (0.80%) 5 39 / 501 (7.78%) 54 64 / 501 (12.77%) 118 14 / 501 (2.79%) 17 | | |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation | 22 / 501 (4.39%) 38 39 / 501 (7.78%) 44 | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 11 / 501 (2.20%) | | |
| occurrences (all) | 12 | | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 3 / 501 (0.60%) | | |
| occurrences (all) | 3 | | |
| Arthralgia | | | |
| subjects affected / exposed | 39 / 501 (7.78%) | | |
| occurrences (all) | 47 | | |
| Back pain | | | |
| subjects affected / exposed | 29 / 501 (5.79%) | | |
| occurrences (all) | 33 | | |
| Osteoporosis | | | |
| subjects affected / exposed | 6 / 501 (1.20%) | | |
| occurrences (all) | 6 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 15 / 501 (2.99%) | | |
| occurrences (all) | 18 | | |
| Infections and infestations | | | |
| Dacryocystitis | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences (all) | 1 | | |
| COVID-19 | | | |
| subjects affected / exposed | 36 / 501 (7.19%) | | |
| occurrences (all) | 36 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 501 (0.20%) | | |
| occurrences (all) | 1 | | |
| Groin infection | | | |
| subjects affected / exposed | 0 / 501 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasopharyngitis | | | |

| | | | |
|------------------------------------|------------------|--|--|
| subjects affected / exposed | 45 / 501 (8.98%) | | |
| occurrences (all) | 53 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 32 / 501 (6.39%) | | |
| occurrences (all) | 34 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 29 / 501 (5.79%) | | |
| occurrences (all) | 38 | | |
| Suspected COVID-19 | | | |
| subjects affected / exposed | 8 / 501 (1.60%) | | |
| occurrences (all) | 8 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 4 / 501 (0.80%) | | |
| occurrences (all) | 4 | | |
| Metabolism and nutrition disorders | | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 2 / 501 (0.40%) | | |
| occurrences (all) | 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 11 February 2018 | The purpose of this protocol amendment was to present the results of the relative bioavailability study (WP40052) and to adjust the dosing regimen of GRADUATE II according to these results. No participants were enrolled in the study at the time of implementation of the updated protocol. In addition, the entry criteria of the study population were revised to increase the homogeneity of the study population and to better target the appropriate study population. |
| 21 January 2020 | The purpose of this protocol update was to update the sample size of the study. While protocol wording allowed an increase in total enrollment up to 1,140 participants based on factors external to the study, the Sponsor clarified that upon initial learnings from external studies, a decision was made to increase the power of the study. Thus, the sample size was increased from 760 participants to 1,016 (508 patients randomized to gantenerumab and 508 randomized to placebo). In addition, the protocol was amended to allow the first patients enrolled in the study to enroll in an OLE as planned. Details on this procedure and the OLE schedule of activities was also added. |
| 28 May 2020 | The purpose of this protocol amendment was to respond to the COVID-19 pandemic due to the SARS-CoV-2 virus. This amendment extended the double-blind treatment period (originally 104 weeks) by 12 weeks in order to mitigate the impact of missed administrations and preserve the scientific integrity of the study by enabling more participants to receive study drug at the initially intended exposures. The continuing impact of the COVID-19 pandemic on study procedures was closely monitored and, if there were greater than anticipated disruptions to study drug administration, the amendment also allowed the option of further extending the double blind treatment period by another 12 weeks (to 128 weeks). For the same reason, the upper limit of the sample size was increased from 1140 to 1322 participants. This further extension of the double-blind treatment period to 128 weeks was not implemented, nor was the sample size increased. |
| 04 August 2021 | The purpose of this protocol amendment was to update the list of exploratory endpoints for the double-blind treatment period of the study and introduce the estimands approach for the primary analysis to align with the addendum to ICH E9 guidance (ICH E9). An update of the overall benefit-risk summary to address the impact of the COVID-19 pandemic was also made. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|---|--------------|
| 11 November 2022 | Following results of a pre-planned primary analysis of the safety and efficacy of Gant in Graduate I&II (WN29922/WN39658) a decision was made to terminate development of Gantenerumab for treatment of prodromal/mild/early stage Alzheimer's disease. | - |

Notes:

Limitations and caveats

None reported