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 (± 0.15)	2.82 (± 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 (± 0.49)	6.66 (± 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 (± 0.33)	5.86 (± 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 (± 0.53)	-7.43 (± 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

	MRI

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 (± 2.768)	-48.00 (± 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 neurograinin				
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	5 / 474 (1.05%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	5	1	0
Pharyngitis			
subjects affected / exposed	5 / 474 (1.05%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	7	0	1
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	4 / 474 (0.84%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	4	0	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	4 / 501 (0.80%)		
occurrences (all)	4		
Hypertension			
subjects affected / exposed	34 / 501 (6.79%)		
occurrences (all)	38		
Varicose vein			
subjects affected / exposed	1 / 501 (0.20%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	75 / 501 (14.97%)		
occurrences (all)	319		
Fatigue			
subjects affected / exposed	15 / 501 (2.99%)		
occurrences (all)	17		
Reproductive system and breast disorders			
Pruritus genital			
subjects affected / exposed	0 / 501 (0.00%)		
occurrences (all)	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) Anxiety subjects affected / exposed occurrences (all) Confusional state subjects affected / exposed occurrences (all)	 0 / 501 (0.00%) 0 26 / 501 (5.19%) 31 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) Periorbital haematoma subjects affected / exposed occurrences (all) Head injury subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all) Bone fissure subjects affected / exposed occurrences (all) Skin laceration subjects affected / exposed occurrences (all)	 5 / 501 (1.00%) 8 0 / 501 (0.00%) 0 6 / 501 (1.20%) 6 47 / 501 (9.38%) 74 1 / 501 (0.20%) 1 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)	33 / 501 (6.59%) 35		
Amyloid related imaging abnormality-oedema/effusion subjects affected / exposed occurrences (all)	114 / 501 (22.75%) 162		
Cerebral haemorrhage subjects affected / exposed occurrences (all)	4 / 501 (0.80%) 5		
Dizziness subjects affected / exposed occurrences (all)	39 / 501 (7.78%) 54		
Headache subjects affected / exposed occurrences (all)	64 / 501 (12.77%) 118		
Syncope subjects affected / exposed occurrences (all)	14 / 501 (2.79%) 17		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	22 / 501 (4.39%) 38		
Diarrhoea subjects affected / exposed occurrences (all)	39 / 501 (7.78%) 44		
Constipation			

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 approachfor 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