Clinical trial results:
Phase II, Multicenter, Open-Label, Single Arm Study to Evaluate the Pharmacodynamic Effects of Once Weekly Administration of Gantenerumab in Participants with Early (Prodromal to Mild) Alzheimer's Disease.

Summary

EudraCT number	2020-001384-87
Trial protocol	GB DE BE FR IT
Global end of trial date	15 March 2023

Results information

Result version number	v2 (current)
This version publication date	13 April 2024
First version publication date	26 January 2024
Version creation reason	• Correction of full data set Updated statement to justify presentation in single arm.

Trial information

Trial identification

Sponsor protocol code	WN29722

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04592341
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	15 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 March 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the pharmacodynamic (PD) effect of a once a week (Q1W) dosing regimen of gantenerumab on brain amyloid load as determined by positron emission tomography (PET) imaging in participants with early (prodromal to mild) AD

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Poland: 29
Worldwide total number of subjects	192
EEA total number of subjects	134

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)	44
From 65 to 84 years	148
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in this study at 33 investigative centers in the United States, Poland, Spain, Belgium, France, Germany, Italy, and the United Kingdom from 18 November 2020 up to 15 March 2023.

Pre-assignment

Screening details:

This was a single-arm study and all participants received gantenerumab according to predefined universal up-titration scheme. Data was collected and reported in single arm for each participant who started treatment as specified and either completed or discontinued study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Gantenerumab

Arm description:

Participants received gantenerumab, subcutaneous (SC) injections with gradual up-titration starting at a dose of 120 milligrams (mg), every four weeks (Q4W) on Day 1, Week 4, and Week 8, then 255 mg, Q4W on Weeks 12, 16, and 20, and then 255 mg every 2 weeks (Q2W) for 12 weeks (Weeks 24, 26, 28, 30, 32, and 34), followed by 255 mg every week (Q1W) up to Week 104 (Weeks 36 to 104).

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

Dosage and administration details:

Gantenerumab was administered by SC injection, at a dose of 120 mg Q4W (Day 1, Week 4, and Week 8), then 255 mg Q4W (Weeks 12, 16, and 20), and then 255 mg Q2W for 12 weeks (Weeks 24, 26, 28, 30, 32, and 34), followed by the target dose of 255 mg Q1W (Weeks 36 to 104).

Number of subjects in period 1	Gantenerumab
Started	192
Completed	116
Not completed	76
Physician decision	5
Other	4
Death	1
Adverse event	5
Withdrawal by Subject	53
Study Terminated by Sponsor	5

Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Gantenerumab
Reporting group description:	
Participants received gantenerumab, subcutaneous (SC) injections with gradual up-titration starting at a dose of 120 milligrams (mg), every four weeks (Q4W) on Day 1, Week 4, and Week 8, then 255 mg, Q4W on Weeks 12, 16, and 20, and then 255 mg every 2 weeks (Q2W) for 12 weeks (Weeks 24, 26, 28, 30, 32, and 34), followed by 255 mg every week (Q1W) up to Week 104 (Weeks 36 to 104).	

Reporting group values	Gantenerumab	Total	
Number of subjects	192	192	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	44	44	
From 65-84 years	148	148	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	70.5		
standard deviation	± 8.1	-	
Gender Categorical Units: subjects			
Female	97	97	
Male	95	95	
Race Units: Subjects			
Asian	1	1	
Black or African American	2	2	
White	176	176	
Unknown	13	13	
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	179	179	
Not Reported	10	10	
Unknown	1	1	

End points

End points reporting groups

Reporting group title	Gantenerumab

Reporting group description:

Participants received gantenerumab, subcutaneous (SC) injections with gradual up-titration starting at a dose of 120 milligrams (mg), every four weeks (Q4W) on Day 1, Week 4, and Week 8, then 255 mg, Q4W on Weeks 12, 16, and 20, and then 255 mg every 2 weeks (Q2W) for 12 weeks (Weeks 24, 26, 28, 30, 32, and 34), followed by 255 mg every week (Q1W) up to Week 104 (Weeks 36 to 104).

Primary: Change from Baseline in Brain Amyloid Load at Week 104 as Measured by [18F] Florbetaben Positron Emission Tomography (PET) Scan

End point title	Change from Baseline in Brain Amyloid Load at Week 104 as Measured by [18F] Florbetaben Positron Emission Tomography (PET) Scan[1]

End point description:

Screening amyloid PET scan was considered baseline evaluation.Brain amyloid load was quantified in terms of Standardized Uptake Value Ratio (SUVR),defined as ratio of tracer uptake in cortical composite target region of interest(ROI)to tracer uptake in reference ROI.Composite region: frontal,parietal,temporal,posterior cingulate cortex,anterior cingulate cortex. Reference ROI (whole cerebellum) was represented by weighted average of Cerebellum Ventral,Cerebellum Dorsal (left/right), Cerebellar White Matter.SUVR linearly transformed to standardized Centiloid Scale (CL) using formula CL=175.6xSUVR-174.2.CL ranges from <0 to >100, anchor points are 0=high-certainty amyloid negative scan and 100=amount of global amyloid deposition found in typical AD scan. ITT population set participants were included. Number analyzed is the number of participants with data available for analysis at the specified timepoint.

End point type	Primary

End point timeframe:

Baseline, Week 104

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	Gantenerumab			
Subject group type	Reporting group			
Number of subjects analysed	192			
Units: centiloid				
arithmetic mean (standard deviation)				
Baseline (n=192)	101.80 (± 29.80)			
Change from Baseline at Week 104 (n=12)	-35.48 (± 16.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Responses to Home Administration Questionnaire (HAQ) by Caregiver or Study Partner

End point title	Responses to Home Administration Questionnaire (HAQ) by

	Caregiver or Study Partner

End point description:

HAQ comprised 4 items completed by study partner capturing confidence (Q1), convenience (Q2), ease of use (Q3), and overall satisfaction (Q4) with administering medication. Response options Q1: Not at all confident, somewhat confident, confident, very confident; Q2: Not at all convenient, somewhat convenient, convenient, very convenient; Q3: Not at all easy, somewhat easy, easy, very easy; Q4:Not at all satisfied, somewhat satisfied, satisfied, very satisfied. Opportunity for Home Dosing Safety-Evaluable Analysis Set (OH-SE) included all participants of the SE analysis set who did not discontinue the study drug before week (W) 26. Number analyzed is the number of participants with data available for analysis at the specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 36, 52, 76, 104

End point values	Gantenerumab			
Subject group type	Reporting group			
Number of subjects analysed	163			
Units: participants				
W36:Q1:Not at all confident (n=72)	0			
W36:Q1:Somewhat confident(n=72)	10			
W36:Q1:Confident (n=72)	33			
W36:Q1:Very confident (n=72)	29			
W52:Q1:Not at all confident (n=148)	0			
W52:Q1:Somewhat confident(n=148)	10			
W52:Q1:Confident (n=148)	46			
W52:Q1:Very confident (n=148)	92			
W76:Q1:Not at all confident (n=126)	1			
W76:Q1:Somewhat confident (n=126)	5			
W76:Q1:Confident (n=126)	34			
W76:Q1:Very Confident (n=126)	86			
W104:Q1:Not at all confident (n=29)	0			
W104:Q1:Somewhat confident (n=29)	2			
W104:Q1:Confident (n=29)	6			
W104:Q1:Very Confident (n=29)	21			
W36:Q2:Not at all convenient (n=72)	1			
W36:Q2:Somewhat convenient (n=72)	2			
W36:Q2:Convenient (n=72)	13			
W36:Q2:Very convenient (n=72)	56			
W52:Q2:Not at all convenient (n=148)	0			
W52:Q2:Somewhat convenient (n=148)	5			
W52:Q2:Convenient (n=148)	38			
W52:Q2:Very convenient (n=148)	105			
W76:Q2:Not at all convenient (n=126)	0			
W76:Q2:Somewhat convenient (n=126)	3			
W76:Q2:Convenient (n=126)	23			
W76:Q2:Very convenient (n=126)	100			
W104:Q2:Not at all convenient (n=29)	0			
W104:Q2:Somewhat convenient (n=29)	1			
W104:Q2:Convenient (n=29)	5			
W104:Q2:Very convenient (n=29)	23			

W36:Q3:Not at all easy (n=72)	0			
W36:Q3:Somewhat easy (n=72)	10			
W36:Q3: Easy (n=72)	31			
W36:Q3:Very easy (n=72)	31			
W52:Q3:Not at all easy (n=148)	1			
W52:Q3:Somewhat easy (n=148)	17			
W52:Q3: Easy (n=148)	45			
W52:Q3:Very easy (n=148)	85			
W76:Q3:Not at all easy (n=126)	0			
W76:Q3:Somewhat easy (n=126)	7			
W76:Q3: Easy (n=126)	37			
W76:Q3:Very easy (n=126)	82			
W104:Q3:Not at all easy (n=29)	0			
W104:Q3:Somewhat easy (n=29)	3			
W104:Q3: Easy (n=29)	5			
W104:Q3:Very easy (n=29)	21			
W36:Q4:Not at all satisfied (n=72)	0			
W36:Q4:Somewhat satisfied (n=72)	3			
W36:Q4:Satisfied (n=72)	26			
W36:Q4:Very satisfied (n=72)	43			
W52:Q4:Not at all satisfied (n=148)	0			
W52:Q4:Somewhat satisfied (n=148)	8			
W52:Q4: Satisfied (n=148)	44			
W52:Q4:Very satisfied (n=148)	96			
W76:Q4:Not at all satisfied (n=126)	0			
W76:Q4:Somewhat satisfied (n=126)	3			
W76:Q4:Satisfied (n=126)	38			
W76:Q4:Very satisfied (n=126)	85			
W104:Q4:Not at all satisfied (n=29)	0			
W104:Q4:Somewhat satisfied (n=29)	0			
W104:Q4:Satisfied (n=29)	8			
W104:Q4:Very satisfied (n=29)	21			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

AE: any untoward medical occurrence in participant administered pharmaceutical product, which does not necessarily have causal relationship with treatment. Any unfavorable, unintended sign, symptom, or disease temporally associated with use of medicinal product, whether or not considered related to it. SAE: any AE that was fatal, life threatening, required prolonged inpatient hospitalization, resulted in significant disability or resulted in a congenital anomaly to mother exposed to study treatment. This was a single-arm study and all participants received gantenerumab according to predefined universal up-titration scheme as follows: 120 mg Q4W (Day 1, Week (W) 4, and W8), then 255 mg Q4W (W 12, 16, and 20), then 255 mg Q2W for 12 weeks (W 24, 26, 28, 30, 32, and 34), followed by target dose of 255 mg Q1W (W 36 to 104). Data was collected and reported in single arm for each participant who started treatment as specified and either completed or discontinued study. Safety Evaluable set.

End point type	Secondary

End point timeframe:

From day of first dose up to 16 weeks after the last dose (up to 120 weeks)

End point values	Gantenerumab			
Subject group type	Reporting group			
Number of subjects analysed	192			
Units: participants				
number (not applicable)				
AEs	178			
SAEs	26			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Suicidal Ideation or Suicidal Behavior as Measured Using Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Participants With Suicidal Ideation or Suicidal Behavior as Measured Using Columbia-Suicide Severity Rating Scale (C-SSRS)

End point description:

C-SSRS=assess lifetime suicidality of participant as well as any new instances of suicidality.Structured interview prompts recollection of suicidal ideation (intensity of ideation, behavior, & attempts with actual/potential lethality).Categories have binary responses (yes/no) & include Wish to be Dead; Non-specific Active Suicidal Thoughts; Active Suicidal Ideation with Any Methods(Not Plan)without Intent to Act; Active Suicidal Ideation with Some Intent to Act, without Specific Plan; Active Suicidal Ideation with Specific Plan and Intent, Preparatory Acts and Behavior; Aborted Attempt; Interrupted Attempt; Actual Attempt (non-fatal);Completed Suicide. Suicidal ideation/behavior indicated by yes answer to any of listed categories. Score 0=no suicide risk. Score 1 or higher= suicidal ideation or behavior. Categories with non-zero values are only reported.Safety Evaluable population was analyzed.Number of participants analyzed is number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

From day of first dose up to 16 weeks after the last dose (up to 120 weeks)

End point values	Gantenerumab			
Subject group type	Reporting group			
Number of subjects analysed	191			
Units: participants				
Suicidal Ideation: Passive	6			
Suicidal Ideation: Active-Nonspecific	1			
Suicidal Ideation: Active-Method, No Intent/Plan	3			
Suicidal Ideation: Active-Method, Intent, and Plan	1			
Suicidal Ideation: No Event	180			

Suicidal Behavior: No Event	191			
Self-injurious Behavior Without Intent: No Event	191			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Amyloid-Related Imaging Abnormalities-Haemosiderin deposition (ARIA-H) Confirmed by Magnetic Resonance Imaging (MRI)

End point title	Number of Participants with Amyloid-Related Imaging Abnormalities-Haemosiderin deposition (ARIA-H) Confirmed by Magnetic Resonance Imaging (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 of the SE analysis set who had at least one post-baseline MRI assessment.

End point type	Secondary

End point timeframe:

From day of first dose up to 16 weeks after the last dose (up to 120 weeks)

End point values	Gantenerumab			
Subject group type	Reporting group			
Number of subjects analysed	192			
Units: participants	44			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants with Amyloid-Related Imaging Abnormalities-Edema (ARIA-E) Confirmed by Magnetic Resonance Imaging (MRI)

End point description:

ARIA are an identified risk with anti-amyloid antibodies, including gantenerumab. These changes can be identified on brain MRI. The occurrences of imaging abnormalities in vasogenic edema and sulcal effusions (ARIA-E) were evaluated. MRI Safety-Evaluable Analysis Set included all participants of the SE analysis set who had at least one post-baseline MRI assessment.

End point type	Secondary

End point timeframe:

From day of first dose up to 16 weeks after the last dose (up to 120 weeks)

End point values	Gantenerumab			
Subject group type	Reporting group			
Number of subjects analysed	192			
Units: participants	44			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Injection-Site Reactions (ISR)

End point title	Number of Participants with Injection-Site Reactions (ISR)

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. Injection reactions (local and systemic) were defined as AEs that occured during or within 24 hours after study drug administration that were judged to be related to the study drug injection. Safety Evaluable population included all participants enrolled who received at least one dose of study treatment, whether prematurely withdrawn from the study or not.

End point type	Secondary

End point timeframe:

From day of first dose up to 16 weeks after the last dose (up to 120 weeks)

End point values	Gantenerumab			
Subject group type	Reporting group			
Number of subjects analysed	192			
Units: participants	44			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Brain Amyloid Based on Different Dosing Frequency

End point title	Change in Brain Amyloid Based on Different Dosing Frequency

End point description:

The change from baseline at Week 52 using the once-weekly dosing frequency was analysed using the centiloid scale. The centiloid scale anchor points are 0 and 100, where 0 represents a high-certainty amyloid negative scan and 100 represents the amount of global amyloid deposition found in a typical AD scan. The range of centiloid values can be below 0 (negative) and greater than 100. ITT population set, included all enrolled participants (i.e., who gave informed consent, did not fail screening, and had at least one Amyloid PET scan with a valid quantitative measurement performed with either florbetaben or flutemetamol), whether or not the participant received the assigned treatment. Overall number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Gantenerumab			
Subject group type	Reporting group			
Number of subjects analysed	149			
Units: centiloid				
arithmetic mean (standard deviation)	-26.19 (± 17.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Anti-Drug Antibodies to Gantenerumab

End point title	Number of Participants With Treatment-emergent Anti-Drug Antibodies to Gantenerumab

End point description:

A participant with an ADA assay result from at least one post-baseline sample was defined as a post-baseline evaluable participant. Treatment Emergent ADA was defined as a participant with a negative or missing baseline ADA result(s) and at least one positive post-baseline ADA result, or a participant with a positive ADA result at baseline who has at least one post-baseline titer results with at least a >2.5-fold increase in titer compared to baseline greater than the baseline titer result. Safety Evaluable population included all participants enrolled who received at least one dose of study treatment, whether prematurely withdrawn from the study or not. Overall number analyzed is the number of participants with an ADA assay result from at least one post-baseline sample.

End point type	Secondary

End point timeframe:

From day of first dose up to 16 weeks after the last dose (up to 120 weeks)

End point values	Gantenerumab			
Subject group type	Reporting group			
Number of subjects analysed	191			
Units: participants				
number (not applicable)	26			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Subcutaneous (SC) Gantenerumab at specified timepoints

End point title	Plasma Concentration of Subcutaneous (SC) Gantenerumab at specified timepoints

End point description:

PK evaluable population included only participants that received the previous 6, 4, 6 or 6 planned doses at weeks 24, 36, 52 and 76, respectively. Overall number analyzed was the number of participants with data available for analysis. Number Analyzed was the number of participants with data available for analyses at the specified timepoint.

End point type	Secondary

End point timeframe:

Day 4 of Week 1, Week 24, 36, 52, and 76

End point values	Gantenerumab			
Subject group type	Reporting group			
Number of subjects analysed	190			
Units: microgram per milliliter				
geometric mean (geometric coefficient of variation)				
Day 4 of Week 1 (n=190)	5.24 (± 73.3)			
Week 24 (n=166)	11.9 (± 52.0)			
Week 36 (n=147)	28.8 (± 50.2)			
Week 52 (n=129)	71.4 (± 49.0)			
Week 76 (n=84)	63.6 (± 50.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From day of first dose up to 16 weeks after the last dose (up to 120 weeks)

Adverse event reporting additional description:

Safety Evaluable population. This was single-arm study and all participants received gantenerumab according to predefined universal up-titration scheme. Data was collected and reported in single arm for each participant who started treatment as specified and either completed or discontinued study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	GANTENERUMAB

Reporting group description:

Participants received gantenerumab, SC injections with gradual up-titration starting at a dose of 120 mg, Q4W on Day 1, Week 4, and Week 8, then 255 mg, Q4W on Weeks 12, 16, and 20, and then 255 mg Q2W for 12 weeks (Weeks 24, 26, 28, 30, 32, and 34), followed by 255 mg Q1W up to Week 104 (Weeks 36 to 104).

Serious adverse events	GANTENERUMAB		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 192 (13.54%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic neoplasm			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour inflammation			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal adenocarcinoma			

subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal carcinoma				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Alcohol poisoning				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Giant cell arteritis				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac arrest				
subjects affected / exposed	1 / 192 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Amyloid related imaging abnormality-oedema/effusion			
subjects affected / exposed	3 / 192 (1.56%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Cerebellar ischaemia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Partial seizures			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cholesterolosis bulbi			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoporotic fracture			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			

subjects affected / exposed	2 / 192 (1.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 192 (1.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral discitis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	GANTENERUMAB		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	144 / 192 (75.00%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	22 / 192 (11.46%)		
occurrences (all)	30		
Product dose omission issue			
subjects affected / exposed	12 / 192 (6.25%)		
occurrences (all)	13		
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 192 (7.29%)		
occurrences (all)	18		
Headache			
subjects affected / exposed	32 / 192 (16.67%)		
occurrences (all)	42		
Amyloid related imaging abnormality-oedema/effusion			
subjects affected / exposed	40 / 192 (20.83%)		
occurrences (all)	50		
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits			
subjects affected / exposed	17 / 192 (8.85%)		
occurrences (all)	30		
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	44 / 192 (22.92%)		
occurrences (all)	135		

Eye disorders Cataract subjects affected / exposed occurrences (all)	 10 / 192 (5.21%) 12		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 14 / 192 (7.29%) 18 10 / 192 (5.21%) 11		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	 11 / 192 (5.73%) 12		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 47 / 192 (24.48%) 48 10 / 192 (5.21%) 12 13 / 192 (6.77%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2021	• The planned sample size (approximately 150 participants) was corrected to the final sample size of 192 participants. • Language were added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours.
16 May 2022	• The study was updated to include the optional 2-year extension. The schedule of assessments until Week 103 remains unchanged and the benefit-risk profile of gantenerumab remains unchanged. • The secondary and biomarker endpoints was updated to include a change from baseline to Week 208. • The change from baseline up to Week 208 in deposited amyloid as measured by brain amyloid PET centiloid levels was added as an exploratory biomarker endpoint. • The change from baseline to Week 208 was included for the exploratory efficacy scales and home administration questionnaire. • The Medical Monitor was changed, and the Medical Monitor contact information was deleted from Emergency Medical Contacts to avoid the inclusion of outdated telephone numbers in the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 March 2023	On 14 November 2022, the Sponsor announced that the pivotal GRADUATE I and GRADUATE II studies did not meet their primary endpoint of slowing clinical decline in participants with early AD. As a result, the GRADUATION study was terminated by the Sponsor, and last participant last visit (LPLV) was on 15 March 2023.	-

Notes:

Limitations and caveats

None reported