Clinical trial results:
Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Two Year Study to Evaluate the Effect of Subcutaneous RO4909832 on Cognition and Function in Prodromal Alzheimer's Disease and Up to Three Years of an Open-Label Extension with Active Study Treatment

Summary

EudraCT number	2010-019895-66
Trial protocol	GB SE DE IT ES FI NL DK CZ BE PT
Global end of trial date	

Results information

Result version number	v1
This version publication date	15 July 2016
First version publication date	15 July 2016

Trial information

Trial identification

Sponsor protocol code	WN25203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01224106
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	Roche Trial Information Hotline, F. Hoffmann La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann La Roche AG, +41 61 6878333, 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	Interim
Date of interim/final analysis	22 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2015
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of gantenerumab versus placebo on the change in the Clinical Dementia Rating scale Sum of Boxes (CDR-SOB), and the change in an integrated global measure of cognition and functional ability after 2 years of treatment.

Protection of trial subjects:

The Investigator ensured that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever affords the greater protection to the participant. The study fully adhered to the principles outlined in "Guideline for Good Clinical Practice" International Council on Harmonisation (ICH) Tripartite Guideline or with local law if it afforded greater protection to the participant. For studies conducted in the European Union (EU)/European Economic Area (EEA) countries, the Investigator ensured compliance with the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the United States of America (USA) or under United States Investigational New Drug (USIND), the Investigator additionally ensured adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 Code of Federal Regulations, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 33
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Spain: 101
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	United Kingdom: 57
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 51
Country: Number of subjects enrolled	Germany: 55
Country: Number of subjects enrolled	Italy: 55

Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Canada: 58
Country: Number of subjects enrolled	United States: 112
Country: Number of subjects enrolled	Argentina: 36
Country: Number of subjects enrolled	Australia: 49
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	Mexico: 47
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Turkey: 20
Worldwide total number of subjects	797
EEA total number of subjects	418

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)	162
From 65 to 84 years	627
85 years and over	8

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening period was up to 8 weeks. The study consisted of 3 parts. Parts 1 and 2 were terminated. Part 3 is currently ongoing as an open-label extension (OLE) with progressive uptitration to higher doses of active study drug.

Period 1

Period 1 title	Treatment Period (Part 1 and 2) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Parts 1 and 2)

Arm description:

Participants with Alzheimer's disease received placebo by subcutaneous (SC) injection every 4 weeks (q4w) for 104 weeks or approximately 2 years during Part 1 of the study. Participants who completed the Week 104 visit were given an option to continue the treatment received during Part 1 for 2 additional years in Part 2.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received gantenerumab matching placebo SC injection q4w.

Arm title	Gantenerumab 105 mg (Parts 1 and 2)

Arm description:

Participants with Alzheimer's disease received gantenerumab 105 milligrams (mg) by SC injection q4w for 104 weeks or approximately 2 years during Part 1 of the study. Participants who completed the Week 104 visit were given an option to continue the treatment received during Part 1 for 2 additional years in Part 2.

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

Dosage and administration details:

Participants received gantenerumab SC injection q4w.

Arm title	Gantenerumab 225 mg (Parts 1 and 2)

Arm description:

Participants with Alzheimer's disease received gantenerumab 225 mg by SC injection q4w for 104 weeks or approximately 2 years during Part 1 of the study. Participants who completed the Week 104 visit were given an option to continue the treatment received during Part 1 for 2 additional years in Part 2.

Arm type	Experimental

Investigational medicinal product name	Gantenerumab
Investigational medicinal product code	RO4909832
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received gantenerumab SC injection q4w.

Number of subjects in period 1	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)
Started	266	271	260
Completed	187	185	180
Not completed	79	86	80
Physician decision	6	5	4
Sponsor decision to terminate study	62	68	63
Death	3	-	-
Subject/legal guardian decision	7	8	8
Adverse event	-	5	3
Unspecified	-	-	1
Lost to follow-up	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo (Parts 1 and 2)
Reporting group description:	
Participants with Alzheimer's disease received placebo by subcutaneous (SC) injection every 4 weeks (q4w) for 104 weeks or approximately 2 years during Part 1 of the study. Participants who completed the Week 104 visit were given an option to continue the treatment received during Part 1 for 2 additional years in Part 2.	
Reporting group title	Gantenerumab 105 mg (Parts 1 and 2)
Reporting group description:	
Participants with Alzheimer's disease received gantenerumab 105 milligrams (mg) by SC injection q4w for 104 weeks or approximately 2 years during Part 1 of the study. Participants who completed the Week 104 visit were given an option to continue the treatment received during Part 1 for 2 additional years in Part 2.	
Reporting group title	Gantenerumab 225 mg (Parts 1 and 2)
Reporting group description:	
Participants with Alzheimer's disease received gantenerumab 225 mg by SC injection q4w for 104 weeks or approximately 2 years during Part 1 of the study. Participants who completed the Week 104 visit were given an option to continue the treatment received during Part 1 for 2 additional years in Part 2.	

Reporting group values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)
Number of subjects	266	271	260
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	69.5	70.3	71.3
standard deviation	± 7.5	± 7	± 7.1
Gender categorical			
Units: Subjects			
Female	149	152	152
Male	117	119	108

Reporting group values	Total		
Number of subjects	797		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	453		
Male	344		

End points

End points reporting groups

Reporting group title	Placebo (Parts 1 and 2)
Reporting group description:	
Participants with Alzheimer's disease received placebo by subcutaneous (SC) injection every 4 weeks (q4w) for 104 weeks or approximately 2 years during Part 1 of the study. Participants who completed the Week 104 visit were given an option to continue the treatment received during Part 1 for 2 additional years in Part 2.	
Reporting group title	Gantenerumab 105 mg (Parts 1 and 2)
Reporting group description:	
Participants with Alzheimer's disease received gantenerumab 105 milligrams (mg) by SC injection q4w for 104 weeks or approximately 2 years during Part 1 of the study. Participants who completed the Week 104 visit were given an option to continue the treatment received during Part 1 for 2 additional years in Part 2.	
Reporting group title	Gantenerumab 225 mg (Parts 1 and 2)
Reporting group description:	
Participants with Alzheimer's disease received gantenerumab 225 mg by SC injection q4w for 104 weeks or approximately 2 years during Part 1 of the study. Participants who completed the Week 104 visit were given an option to continue the treatment received during Part 1 for 2 additional years in Part 2.	
Subject analysis set title	Placebo Match Gantenerumab 225 mg (Parts 1 and 2)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants receiving placebo matching gantenurumab 225 mg were included in this analysis set.	

Primary: Mean Change From Baseline in Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) Total Score at Week 104

End point title	Mean Change From Baseline in Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) Total Score at Week 104
End point description:	
The CDR-SOB is a global clinical staging instrument that sums 6 clinical ratings: 1) memory, 2) orientation, 3) judgment and problem solving, 4) involvement in community affairs, 5) home and hobbies, and 6) personal care based on the CDR interview. CDR included discussions with the participant and caregiver using a structured format. This scale was administered by a trained and certified global rater who did not have access to any information regarding adverse events experienced by the participant. Total CDR-SOB score is calculated as the sum of the six clinical ratings. The CDR-SOB score range for each domain is 0 to 3. CDR-SOB total score range is 0 (least impairment) to 18 (most impairment); a negative change from baseline indicates an improvement. The intent-to-treat (ITT) population included all participants who had received any dose of study treatment and had at least one post-baseline assessment of CDR-SOB. Number of subjects analyzed included number of participants evaluable.	
End point type	Primary
End point timeframe:	
Baseline, Week 104	

End point values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	105	100	
Units: units on a scale				
arithmetic mean (standard deviation)	1.19 (± 1.68)	1.41 (± 2.02)	1.47 (± 1.89)	

Statistical analyses

Statistical analysis title	Statistical analysis I
Statistical analysis description:	
Distribution of effect size was calculated based on mixed model repeated measure analysis.	
Comparison groups	Gantenerumab 105 mg (Parts 1 and 2) v Placebo (Parts 1 and 2)
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6744
Method	Mixed models analysis
Parameter estimate	effect size
Point estimate	-0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.248
upper limit	0.161

Statistical analysis title	Statistical analysis II
Statistical analysis description:	
Distribution of effect size was calculated based on mixed model repeated measure analysis.	
Comparison groups	Gantenerumab 225 mg (Parts 1 and 2) v Placebo (Parts 1 and 2)
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4494
Method	Mixed models analysis
Parameter estimate	effect size
Point estimate	-0.085
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.304
upper limit	0.135

Secondary: Mean Change From Baseline in Alzheimer Disease Assessment Scale-Cognitive Subscale 11 (ADAS-Cog-11) Scores at Week 104

End point title	Mean Change From Baseline in Alzheimer Disease Assessment

	Scale-Cognitive Subscale 11 (ADAS-Cog-11) Scores at Week 104

End point description:

ADAS-Cog scale evaluates memory, language, and praxis with items such as orientation, word recall, word recognition, object identification, comprehension, and the completion of simple tasks. Analysis of the ADAS-Cog for this study was based upon 11 items: 1) word recall task, 2) naming objects and fingers, 3) following commands, 4) constructional praxis, 5) ideational praxis, 6) orientation, 7) word recognition, 8) remembering test instructions, 9) spoken language ability, 10) word finding difficulty in spontaneous speech, and 11) comprehension. This scale had to be administered by a trained and certified psychometric rater who did not have access to any information regarding adverse events experienced. The ADAS-Cog/11 ranged from 0 to 70 points, with higher scores indicating a greater degree of impairment. A negative change from baseline indicates a decrease in cognitive impairment. ITT population participants evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	104	100	
Units: units on a scale				
arithmetic mean (standard deviation)	3.68 (± 6.64)	3.52 (± 6.28)	3.97 (± 6.89)	

Statistical analyses

Statistical analysis title	Statistical analysis I

Statistical analysis description:

Distribution of effect size based on mixed model repeated measures analysis.

Comparison groups	Gantenerumab 105 mg (Parts 1 and 2) v Placebo (Parts 1 and 2)
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7458
Method	Mixed models analysis
Parameter estimate	effect size
Point estimate	0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.179
upper limit	0.25

Statistical analysis title	Statistical analysis II

Statistical analysis description:

Distribution of effect size based on mixed model repeated measures analysis.

Comparison groups	Gantenerumab 225 mg (Parts 1 and 2) v Placebo (Parts 1 and 2)
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.723
Method	Mixed models analysis
Parameter estimate	effect size
Point estimate	0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.191
upper limit	0.275

Secondary: Mean Change From Baseline in Mini Mental State Exam (MMSE) Score at Week 104

End point title	Mean Change From Baseline in Mini Mental State Exam (MMSE) Score at Week 104

End point description:

The MMSE is a brief, practical screening test for cognitive dysfunction. The test consists of five sections (orientation, registration, attention-calculation, recall, and language); the total score can range from 0 to 30, with a higher score indicating better function. A positive change score indicates improvement. ITT population, number of subjects analyzed is equal to number of participants evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	105	99	
Units: units on a scale				
arithmetic mean (standard deviation)	-2.31 (± 3.23)	-2.46 (± 3.68)	-2.25 (± 3.31)	

Statistical analyses

Statistical analysis title	Statistical analysis I

Statistical analysis description:

Distribution of effect size based on mixed model repeated measures analysis

Comparison groups	Gantenerumab 105 mg (Parts 1 and 2) v Placebo (Parts 1 and 2)

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7973
Method	Mixed models analysis
Parameter estimate	effect size
Point estimate	-0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.242
upper limit	0.186

Statistical analysis title	Statistical analysis II
Statistical analysis description:	
Distribution of effect size based on mixed model repeated measures analysis	
Comparison groups	Gantenerumab 225 mg (Parts 1 and 2) v Placebo (Parts 1 and 2)
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4793
Method	Mixed models analysis
Parameter estimate	effect size
Point estimate	0.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.319

Secondary: Mean Change From Baseline in Cambridge Neuropsychological Test Automated Battery (CANTAB) Composite Score at Week 104

End point title	Mean Change From Baseline in Cambridge Neuropsychological Test Automated Battery (CANTAB) Composite Score at Week 104

End point description:

A composite memory score was created based on a summation of Z-scores (using the baseline population as the standardization distribution) for each of: 'z' Delayed Match to Sample (DMS) percent correct, 'z' Paired Associates Learning (PAL), 'z' First Trial Memory Score (FTMS), 'z' Pattern Recognition Memory (PRM) immediate percent correct, 'z' PRM delayed percent correct and 'z' Spatial Working Memory (SWM) between errors (where SWM between Errors is reverse scored). At subsequent time points, Z scores were calculated as [(time point score - baseline mean)/ baseline SD] (positive). ITT population, number of subjects analyzed is equal to number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)	Placebo Match Gantenerumab 225 mg (Parts 1 and 2)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	90	87	80	73
Units: units on a scale				
arithmetic mean (standard deviation)	-1.72 (± 2.99)	-1.37 (± 2.74)	-1.4 (± 3.11)	-1.93 (± 3.08)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Free and Cued Selective Reminding Test (FCSRT) Score at Week 104

End point title	Mean Change from Baseline in Free and Cued Selective Reminding Test (FCSRT) Score at Week 104

End point description:

FCSRT assesses verbal episodic memory. Performances in free recalls, cued recalls and in a recognition task were analyzed, as the process of encoding is controlled. Participants were asked to remember a list of 16 words. Three tasks of free and cued recalls, as well as 1 recognition task and one delayed recall give the scores. Total recall was obtained by the addition of cued recalls to free recalls. Maximum score is 48 for immediate: 16 words multiplied by (*) 3 corresponding to immediate free recall + immediate cued recall + immediate recognition test. Maximum score is 64 (better score) when delayed recall: 16 words*4. The minimum score is 0 (worse). ITT population, number of subjects analyzed is equal to number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)	Placebo Match Gantenerumab 225 mg (Parts 1 and 2)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	100	102	97	79
Units: units on a scale				
arithmetic mean (standard deviation)	-4.05 (± 8.73)	-4.11 (± 8.57)	-6.42 (± 8.45)	-4.05 (± 8.68)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Functional Activities Questionnaire (FAQ)

Score at Week 104

End point title	Mean Change From Baseline in Functional Activities Questionnaire (FAQ) Score at Week 104

End point description:

Participants completed the FAQ for physical function. Overall scores ranged from 0 (independent) to 30 (dependent) where lower scores represented an improvement in physical function. ITT population, number of subjects analyzed is equal to number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)	Placebo Match Gantenerumab 225 mg (Parts 1 and 2)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	105	104	99	84
Units: units on a scale				
arithmetic mean (standard deviation)	3.59 (± 4.93)	4.89 (± 6.2)	4.03 (± 5.75)	3.6 (± 4.93)

Statistical analyses

Statistical analysis title	Statistical analysis I

Statistical analysis description:

Distribution of effect size based on mixed model repeated measures analysis.

Comparison groups	Placebo (Parts 1 and 2) v Gantenerumab 105 mg (Parts 1 and 2)
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0825
Method	Mixed models analysis
Parameter estimate	effect size
Point estimate	-0.191
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.407
upper limit	0.025

Statistical analysis title	Statistical analysis II

Statistical analysis description:

Distribution of effect size based on mixed model repeated measures analysis.

Comparison groups	Placebo (Parts 1 and 2) v Gantenerumab 225 mg (Parts 1 and 2)

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7171
Method	Mixed models analysis
Parameter estimate	effect size
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.276

Secondary: Mean Change From Baseline in CDR-Global Score at Week 104

End point title	Mean Change From Baseline in CDR-Global Score at Week 104

End point description:

Global CDR is derived from the scores in each of the 6 categories ("box scores") as follows. Memory (M) is considered the primary category and all others are secondary. CDR=M if at least 3 secondary categories are given the same score as M. Whenever 3 or more secondary categories are given a score greater or less than the memory score, CDR = score of majority of secondary categories on whichever side of M has the greater number of secondary categories. When 3 secondary categories are scored on one side of M and two secondary categories are scored on the other side of M, CDR=M. When M = 0.5, CDR = 1 if at least 3 of the other categories are scored one or greater. If M=0.5, CDR cannot be 0; it can only be 0.5 or 1. If M=0, CDR=0 unless there is impairment (0.5 or greater) in 2 or more secondary categories, in which case CDR=0.5. ITT population, number of subjects analyzed is equal to number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)	Placebo Match Gantenerumab 225 mg (Parts 1 and 2)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	104	105	100	83
Units: units on a scale				
arithmetic mean (standard deviation)	0.1 (± 0.29)	0.18 (± 0.36)	0.14 (± 0.33)	0.1 (± 0.31)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Neuropsychiatric Inventory (NPI) Questionnaire Score at Week 104

End point title	Mean Change from Baseline in Neuropsychiatric Inventory (NPI) Questionnaire Score at Week 104

End point description:

The NPI is a retrospective (to 1 month) caregiver-informant interview assessing frequency and severity of 12 neuropsychiatric symptom domains. The NPI score is based on the sum of the severity ratings (0=absent, 1=mild, 3=severe). The 12 symptom domains include delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, nighttime behavioral disturbances, and appetite/eating abnormalities. The NPI severity score is based on severity ratings (0=absent, 1=mild to 3=severe). ITT population, number of subjects analyzed is equal to number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)	Placebo Match Gantenerumab 225 mg (Parts 1 and 2)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	103	105	99	82
Units: units on a scale				
arithmetic mean (standard deviation)	0.6 (± 3.22)	0.39 (± 2.57)	0.34 (± 2.84)	0.72 (± 3.35)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Cerebrospinal Fluid Biomarkers (Phosphorylated-tau [p-tau], Amyloid Beta 1-42 [Abeta 1-42], Total tau [t-tau]) at Week 104

End point title	Percent Change from Baseline in Cerebrospinal Fluid Biomarkers (Phosphorylated-tau [p-tau], Amyloid Beta 1-42 [Abeta 1-42], Total tau [t-tau]) at Week 104

End point description:

CSF biomarker phospho-tau (p-tau) is an indicator of neuronal injury and neurodegeneration. An elevation in levels of tau, as well as specific p-tau species, is thought to be a marker for progressive cellular degeneration in AD. ITT population, number of subjects analyzed is equal to number of participants evaluable for this end point. "n" represents number of participants evaluable for the specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)	Placebo Match Gantenerumab 225 mg (Parts 1 and 2)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	263	264	254	211
Units: percent change				
arithmetic mean (standard deviation)				

p-tau (n=72,71,66,56)	2.77 (± 20.69)	-4.78 (± 11.9)	-7.34 (± 10.09)	2.84 (± 23.19)
t-tau (n=72,71,66,56)	3.43 (± 19.95)	-1.36 (± 12.89)	-2.12 (± 11.01)	3.46 (± 22.32)
Abeta (n=69,64,65,56)	4.87 (± 36.14)	2.45 (± 24.57)	15.2 (± 45.24)	4.3 (± 39.31)

Statistical analyses

Statistical analysis title	Statistical analysis I
Statistical analysis description:	
Statistical analysis of the Abeta 1-42 CSF biomarker between "Placebo (Parts 1 and 2)" and "Gantenerumab 105 mg (Parts 1 and 2)" treatment arms at Week 104.	
Comparison groups	Placebo (Parts 1 and 2) v Gantenerumab 105 mg (Parts 1 and 2)
Number of subjects included in analysis	527
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9734
Method	Mixed models analysis

Statistical analysis title	Statistical analysis II
Statistical analysis description:	
Statistical analysis of the Abeta 1-42 CSF biomarker between "Placebo (Parts 1 and 2)" and "Gantenerumab 225 mg (Parts 1 and 2)" treatment arms at Week 104.	
Comparison groups	Placebo (Parts 1 and 2) v Gantenerumab 225 mg (Parts 1 and 2)
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0629
Method	Mixed models analysis

Statistical analysis title	Statistical analysis III
Statistical analysis description:	
Statistical analysis of the p-tau CSF biomarker between "Placebo (Parts 1 and 2)" and "Gantenerumab 105 mg (Parts 1 and 2)" treatment arms at Week 104.	
Comparison groups	Placebo (Parts 1 and 2) v Gantenerumab 105 mg (Parts 1 and 2)
Number of subjects included in analysis	527
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0084
Method	Mixed models analysis

Statistical analysis title	Statistical analysis IV

Statistical analysis description:

Statistical analysis of the p-tau CSF biomarker between "Placebo (Parts 1 and 2)" and "Gantenerumab 225 mg (Parts 1 and 2)" treatment arms at Week 104.

Comparison groups	Placebo (Parts 1 and 2) v Gantenerumab 225 mg (Parts 1 and 2)
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Mixed models analysis

Statistical analysis title	Statistical analysis V

Statistical analysis description:

Statistical analysis of the t-tau CSF biomarker between "Placebo (Parts 1 and 2)" and "Gantenerumab 105 mg (Parts 1 and 2)" treatment arms at Week 104.

Comparison groups	Placebo (Parts 1 and 2) v Gantenerumab 105 mg (Parts 1 and 2)
Number of subjects included in analysis	527
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0903
Method	Mixed models analysis

Statistical analysis title	Statistical analysis VI

Statistical analysis description:

Statistical analysis of the t-tau CSF biomarker between "Placebo (Parts 1 and 2)" and "Gantenerumab 225 mg (Parts 1 and 2)" treatment arms at Week 104.

Comparison groups	Placebo (Parts 1 and 2) v Gantenerumab 225 mg (Parts 1 and 2)
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0434
Method	Mixed models analysis

Secondary: Percent Change from Baseline in Hippocampal Volume at Week 104

End point title	Percent Change from Baseline in Hippocampal Volume at Week 104

End point description:

Change from baseline in hippocampal right volume (HRV) and hippocampal left volume (HLV) were analyzed at Week 104 using magnetic resonance imaging. ITT population. Number of subjects analyzed is equal to number of participants evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)	Placebo Match Gantenerumab 225 mg (Parts 1 and 2)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	131	124	119	107
Units: percent change				
arithmetic mean (standard deviation)				
HRV	-7.61 (± 4.03)	-7.52 (± 3.96)	-7.34 (± 3.84)	-7.7 (± 4.01)
HLV	-7.8 (± 4.28)	-7.76 (± 3.74)	-7.27 (± 3.78)	-8.12 (± 4.19)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Cortical Composite Sustained Uptake Volume Ratio (SUVr) in Different Brain Regions at Week 156

End point title	Percent Change From Baseline in Cortical Composite Sustained Uptake Volume Ratio (SUVr) in Different Brain Regions at Week 156

End point description:

The different regions of the brain that were analyzed included cerebellum gray, whole cerebellum, composite white matter, subcortical white matter, pons and composite reference. ITT population. Number of subjects analyzed is equal to number of participants evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 156

End point values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)	Placebo Match Gantenerumab 225 mg (Parts 1 and 2)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	6	4	10	4
Units: percent change				
arithmetic mean (standard deviation)				
cerebellum gray	6.26 (± 9.1)	2.7 (± 10.59)	-8.36 (± 9.11)	5.95 (± 11.13)
whole cerebellum	5.41 (± 7.13)	2.07 (± 8.65)	-8.44 (± 8.06)	5.17 (± 8.66)
composite white matter	2.75 (± 3.18)	-0.87 (± 2.95)	-4.86 (± 6.35)	3.07 (± 2.07)
subcortical white matter	4.83 (± 4.95)	1.69 (± 4.45)	-0.42 (± 8.26)	4.59 (± 0.55)
pons	1.72 (± 2.51)	-2.83 (± 3.39)	-6.99 (± 5.65)	2.1 (± 2.73)
composite reference	4.5 (± 3.48)	1.19 (± 5.63)	-6.75 (± 6.1)	4.46 (± 4.49)

Statistical analyses

No statistical analyses for this end point

Secondary: Gantenerumab Plasma Concentration at Different Time Points

End point title	Gantenerumab Plasma Concentration at Different Time Points[1]

End point description:

ITT population. Number of subjects analysed is equal to number of participants evaluable for this end point. "n" represents number of participants evaluable for the specified category.

End point type	Secondary

End point timeframe:

Prior to injections at Weeks 1, 8, 20, 44, 53, 68, 100, 101

Notes:

[1] - 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 end point is related to gantenerumab plasma concentration thus, placebo arm is not included.

End point values	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	227		
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Week 1 (n=239,227)	3.56 (± 2.36)	7.4 (± 4.28)		
Week 8 (n=237,225)	2.87 (± 1.84)	5.92 (± 3.16)		
Week 20 (n=228,220)	3.7 (± 2.15)	7.66 (± 4.14)		
Week 44 (n=212,199)	4.08 (± 2.44)	8.22 (± 4.51)		
Week 53 (n=195,185)	6.77 (± 3.94)	15 (± 9.34)		
Week 68 (n=165,155)	3.95 (± 2.35)	8.91 (± 4.86)		
Week 100 (n=98,86)	4.35 (± 2.34)	9.4 (± 4.69)		
Week 101 (n=95,77)	7.32 (± 3.53)	16.63 (± 7.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Dementia

End point title	Time to Onset of Dementia

End point description:

Data for this endpoint is available only in figures and the same is uploaded as an attachment.

End point type	Secondary

End point timeframe:

Every 6 months to up to 3 years (1096 days)

End point values	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: days				
number (not applicable)				

Notes:

[2] - Data for this endpoint is available only in figure and the same is uploaded as an attachment.

[3] - Data for this endpoint is available only in figure and the same is uploaded as an attachment.

[4] - Data for this endpoint is available only in figure and the same is uploaded as an attachment.

Attachments (see zip file)	Time to onset of dementia/image.png

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to approximately 5 years (Until data cut-off date of 22 June 2015)	
Adverse event reporting additional description:	
Safety evaluable population	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Placebo (Parts 1 and 2)
Reporting group description:	
Participants with Alzheimer's disease received placebo by SC injection q4w for 104 weeks or approximately 2 years during Part 1 of the study. Participants who completed the Week 104 visit were given an option to continue the treatment received during Part 1 for 2 additional years in Part 2.	
Reporting group title	Gantenerumab 105 mg (Parts 1 and 2)
Reporting group description:	
Participants with Alzheimer's disease received gantenerumab 105 mg by SC injection q4w for 104 weeks or approximately 2 years during Part 1 of the study. Participants who completed the Week 104 visit were given an option to continue the treatment received during Part 1 for 2 additional years in Part 2.	
Reporting group title	Gantenerumab 225 mg (Parts 1 and 2)
Reporting group description:	
Participants with Alzheimer's disease received gantenerumab 225 mg by SC injection q4w for 104 weeks or approximately 2 years during Part 1 of the study. Participants who completed the Week 104 visit were given an option to continue the treatment received during Part 1 for 2 additional years in Part 2.	

Serious adverse events	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 266 (20.68%)	48 / 271 (17.71%)	46 / 260 (17.69%)
number of deaths (all causes)	6	0	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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

Benign ovarian tumour			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Biliary cancer metastatic			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Bladder cancer			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone sarcoma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer stage II			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal tract adenoma			

subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioma			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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 adenocarcinoma			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukaemia			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			

subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal neoplasm benign			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasmacytoma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	2 / 266 (0.75%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal oncocytoma			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell carcinoma			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Tongue neoplasm malignant stage unspecified			

subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Malignant hypertension			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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 artery aneurysm			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee arthroplasty			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal decompression			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral dilation procedure			

subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type I hypersensitivity			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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

Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystocele			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Prostatomegaly			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Delirium			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Pulmonary embolism			
subjects affected / exposed	1 / 266 (0.38%)	1 / 271 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			

subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Behavioral and psychological symptoms of dementia			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Major depression			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Suicide attempt			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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			

Ankle fracture			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Fall			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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 / 266 (0.38%)	1 / 271 (0.37%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			

subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Lower limb fracture			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Post procedural haematuria			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation mucositis			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	2 / 266 (0.75%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			

subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Spinal fracture			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 266 (0.38%)	1 / 271 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Upper limb fracture			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention postoperative			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Angina unstable			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Atrial fibrillation			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial thrombosis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 266 (0.00%)	2 / 271 (0.74%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 266 (0.75%)	0 / 271 (0.00%)	0 / 260 (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
Myocardial rupture			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Sinus arrest			
subjects affected / exposed	1 / 266 (0.38%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Nervous system disorders			
Amyotrophic lateral sclerosis			

subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Balance disorder			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar infarction			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Dementia with Lewy bodies			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoparesis			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			

subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Radial nerve palsy			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retrograde amnesia			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 266 (0.75%)	1 / 271 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamic infarction			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Transient global amnesia			

subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 266 (0.38%)	1 / 271 (0.37%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 266 (0.00%)	2 / 271 (0.74%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Abdominal pain			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Diarrhoea			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Diverticulum intestinal haemorrhagic			

subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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 haemorrhage			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Gastritis			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	2 / 266 (0.75%)	1 / 271 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic mass			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Cholelithiasis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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			
Bladder obstruction			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis reactive			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Osteoarthritis			
subjects affected / exposed	1 / 266 (0.38%)	1 / 271 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal column stenosis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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			
Abdominal abscess			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Atypical pneumonia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bacterial sepsis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Cellulitis			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			

subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lyme disease			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection bacterial			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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	1 / 266 (0.38%)	1 / 271 (0.37%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			

subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Subcutaneous abscess			
subjects affected / exposed	0 / 266 (0.00%)	0 / 271 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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			
Dehydration			
subjects affected / exposed	1 / 266 (0.38%)	0 / 271 (0.00%)	0 / 260 (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
Diabetes mellitus			
subjects affected / exposed	0 / 266 (0.00%)	1 / 271 (0.37%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo (Parts 1 and 2)	Gantenerumab 105 mg (Parts 1 and 2)	Gantenerumab 225 mg (Parts 1 and 2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	163 / 266 (61.28%)	188 / 271 (69.37%)	189 / 260 (72.69%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	28 / 266 (10.53%)	23 / 271 (8.49%)	27 / 260 (10.38%)
occurrences (all)	42	32	38

Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 266 (6.77%)	11 / 271 (4.06%)	20 / 260 (7.69%)
occurrences (all)	20	11	23
Nervous system disorders			
ARIA-E			
subjects affected / exposed	2 / 266 (0.75%)	18 / 271 (6.64%)	34 / 260 (13.08%)
occurrences (all)	2	20	36
ARIA-H			
subjects affected / exposed	31 / 266 (11.65%)	58 / 271 (21.40%)	36 / 260 (13.85%)
occurrences (all)	51	92	64
Dizziness			
subjects affected / exposed	21 / 266 (7.89%)	21 / 271 (7.75%)	26 / 260 (10.00%)
occurrences (all)	21	27	35
Headache			
subjects affected / exposed	36 / 266 (13.53%)	34 / 271 (12.55%)	25 / 260 (9.62%)
occurrences (all)	50	47	36
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 266 (3.01%)	7 / 271 (2.58%)	15 / 260 (5.77%)
occurrences (all)	8	7	20
Injection site erythema			
subjects affected / exposed	3 / 266 (1.13%)	29 / 271 (10.70%)	35 / 260 (13.46%)
occurrences (all)	3	133	114
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 266 (4.89%)	15 / 271 (5.54%)	15 / 260 (5.77%)
occurrences (all)	18	22	18
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 266 (4.89%)	11 / 271 (4.06%)	13 / 260 (5.00%)
occurrences (all)	14	13	13
Psychiatric disorders			
Anxiety			
subjects affected / exposed	18 / 266 (6.77%)	20 / 271 (7.38%)	16 / 260 (6.15%)
occurrences (all)	23	20	16
Depression			

subjects affected / exposed	13 / 266 (4.89%)	23 / 271 (8.49%)	25 / 260 (9.62%)
occurrences (all)	14	23	25
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 266 (7.89%)	12 / 271 (4.43%)	16 / 260 (6.15%)
occurrences (all)	29	14	17
Back pain			
subjects affected / exposed	26 / 266 (9.77%)	16 / 271 (5.90%)	26 / 260 (10.00%)
occurrences (all)	33	18	31
Musculoskeletal pain			
subjects affected / exposed	16 / 266 (6.02%)	6 / 271 (2.21%)	5 / 260 (1.92%)
occurrences (all)	18	7	5
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 266 (3.76%)	10 / 271 (3.69%)	14 / 260 (5.38%)
occurrences (all)	10	12	18
Influenza			
subjects affected / exposed	13 / 266 (4.89%)	13 / 271 (4.80%)	15 / 260 (5.77%)
occurrences (all)	14	18	17
Nasopharyngitis			
subjects affected / exposed	17 / 266 (6.39%)	30 / 271 (11.07%)	20 / 260 (7.69%)
occurrences (all)	34	40	35
Upper respiratory tract infection			
subjects affected / exposed	11 / 266 (4.14%)	13 / 271 (4.80%)	18 / 260 (6.92%)
occurrences (all)	14	15	21
Urinary tract infection			
subjects affected / exposed	25 / 266 (9.40%)	16 / 271 (5.90%)	22 / 260 (8.46%)
occurrences (all)	37	25	38

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2011	- An overall benefit-risk assessment subsection was added; information about the ribonucleic acid (RNA) sampling was added to the optional responsible conduct of research (RCR) sampling; age range for inclusion was changed from 50-85 to 50-80; text were added for contraception requirements for women of childbearing potential; and inclusion criteria were amended to allow for screening of participants with abnormal memory function based on the FCSRT-Immediate Recall (IR) up to one month prior to the first screening visit. - Experience at sites indicated that several participants fail screening solely for right bundle branch block (RBBB). As electrocardiogram (ECG) monitoring study was also used to collect data for this biological investigational drug in order to obtain regulatory waiver for a thorough QT study, the possibility to allow RBBB participants who may not be included in QTc analysis was reviewed again with the conclusion that RBBB participants can be enrolled. - One of the exclusion criteria was reformatted to more clearly quantify the amount of use permitted for some agents; information regarding the Columbia-Suicide Severity Rating Scale (C-SSRS) test was added; instructions were added to be followed in the event of a second occurrence of 2 new microbleeds on a single magnetic resonance imaging (MRI), and explanation of the procedures to be followed if a new microbleed is seen on an MRI. - Analysis plan was clarified to mention that analysis may include measurement of beta amyloid pyroglutamate and cerebrospinal fluid (CSF) biomarkers; and information regarding missed dose, and information regarding analysis and sample collection of anti-drug antibody (ADA) was added.
14 March 2012	- The sample size was updated; requirements for post-screening CDR global score and FCSRT-IR evaluations were added; requirements for separate interim data review committee or a separate group performing unblinded analysis were removed. - A negative pregnancy test requirement prior to start of treatment was extended for throughout the duration of treatment for women of child bearing potential. It was added that women of child-bearing potential must have a pregnancy test done at the site prior to each dose. - A paragraph requesting investigators to report increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with an increase in total bilirubin or jaundice as an serious adverse event (SAE) to the Sponsor due to regulatory reasons.
15 February 2013	- Information regarding two interim analysis, an administrative interim analysis and a subsequent futility analysis, was added; text regarding sensitivity analysis and subgroup analysis were added - The primary efficacy comparison of the high dose gantenerumab arm to the placebo arm was changed so that only placebo participants with APOE 0e4 or APOE 1e4 were to be included in the analysis, and not the ones with APOE 2e4. - Part 2 (extension) of the study was added; procedures to follow in the event of amyloid related imaging abnormalities-hemosiderin deposits (ARIA-H) findings and abnormal manetic resonance imaging (MRI) findings were updated to reflect extension of the study. - Information regarding the use of symptomatic treatment for Alzheimer's disease during the study was updated; frequency for testing of the primary endpoint (CDR) as well as the ADAS-cog and MMSE was updated to every 3 months through Year 4 from every 3 months through Year 2; details regarding availability of blinded interim safety data in the Investigator Brochure (IB) was added; and the information on possible analysis of concentration effect relationship using PK data was added.

17 July 2014	- Relevant protocol sections were updated to better align with the independent MRI Review Committee (MRI-C) Charter that was revised. Guidance was added with regard to the reset of MRI schedules after withheld and then restarted dosing due to MRI findings. - Requirements for a final follow-up visit for safety and limited efficacy evaluations at 52 weeks after the final dose. The reporting period for adverse events (AEs) was updated accordingly. - CSF biomarkers, Abeta1−42, t-tau, and p-tau, were changed to secondary objective from exploratory objectives. Clarification about MRI volumetric measures was also added. - Guidance was added for the shelf life of reconstituted investigational medicinal product (IMP) prepared under aseptic and non-aseptic conditions. - Reporting period for pregnancies was adjusted to take into account 5 half-lives of study medication, in agreement with the standard operating procedure (SOP) for safety report process of the Sponsor. Information regarding precautionary measures were added in the case of abnormally low neutrophils (moderate to severe neutropenia) to align WN25203 with other gantenerumab protocols.
16 September 2015	Based on the futility analysis findings, Part 1 and 2 of the study was terminated in December 2014. The OLE, Part 3 was added to test gantenerumab at higher doses expected to have a clinically relevant effect. Revised dosing titration schemes were imposed for the OLE to manage risks of ARIA. This amendment also provides updated safety assessments and updated formulation information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 December 2014	Based on the futility analysis findings, dosing in Part 1 and 2 of the study was terminated on 19 December 2014. However, due to the observed effect of gantenerumab on amyloid plaques, further higher doses than previously studied in Part 1 and 2 of are being explored in Part 3 to evaluate the potential benefit for gantenerumab to slow the progression of AD.	16 September 2015

Notes:

Limitations and caveats

None reported