



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 with Option for up to an Additional Two Years of Treatment and 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	10 September 2020

Results information

Result version number	v2
This version publication date	24 September 2021
First version publication date	15 July 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	WN25203
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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, CH4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 September 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of Subcutaneous RO4909832 on Cognition and Function in Prodromal Alzheimer's Disease

Protection of trial subjects:

All study subjects were required to sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 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	Argentina: 36
Country: Number of subjects enrolled	Australia: 49
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Canada: 58
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	Czechia: 8
Country: Number of subjects enrolled	Germany: 55
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Spain: 101
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 51
Country: Number of subjects enrolled	United Kingdom: 57
Country: Number of subjects enrolled	Italy: 55
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Mexico: 47
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	Russian Federation: 17
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	Turkey: 20
Country: Number of subjects enrolled	United States: 112
Worldwide total number of subjects	797
EEA total number of subjects	361

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)	156
From 65 to 84 years	630
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 128 centers in 24 countries.

Pre-assignment

Screening details:

A total of 799 subjects were randomised in this study. Of these, 797 subjects were enrolled and received at least one dose of any study drug (represented the Safety population) during the Double-Blind Treatment (DBT) Phase of the study. From the DBT Phase, a total of 154 subjects (at 53 sites) enrolled into Open-Label Extension Phase of the study.

Period 1

Period 1 title	Double-Blind Treatment Phase
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:

Subjects with Alzheimer's disease received Placebo by SC injection every 4 weeks (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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 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)
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Arm description:

Subjects with Alzheimer's disease received Gantenerumab 105 mg by SC injection every 4 weeks (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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	
Other name	
Pharmaceutical forms	Powder 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)
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Arm description:

Subjects with Alzheimer's disease received Gantenerumab 225 mg by SC injection every 4 weeks (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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	
Other name	
Pharmaceutical forms	Powder 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
Adverse event, serious fatal	3	-	-
Physician decision	6	5	4
Participant/legal guardian decision	7	8	8
Adverse event, non-fatal	-	5	3
Parts 1 and 2 Termination by Sponsor	62	68	63
Unspecified	-	-	1
Lost to follow-up	1	-	1

Period 2

Period 2 title	Open-Label Extension (OLE) Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)

Arm description:

Subjects with Alzheimer's disease who had received Placebo by SC injection in Part 1 or Part 2, now received Gantenerumab at doses up to 1200 mg by SC injection every 4 weeks (Q4W) for up to 5 additional years.

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

Dosage and administration details:

Participants received gantenerumab SC injection Q4W.

Arm title	Gant Up to 1200 mg (Part 3 OLE)
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Arm description:

Subjects with Alzheimer's disease who had received Gantenerumab by SC injection in Part 1 or Part 2, now received Gantenerumab at doses up to 1200 mg by SC injection every 4 weeks (Q4W) for up to 5 additional years.

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

Dosage and administration details:

Participants received gantenerumab SC injection Q4W.

Number of subjects in period 2^[1]	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)
Started	49	105
Completed	33	71
Not completed	16	34
Adverse event, serious fatal	1	3
Physician decision	2	7
Consent withdrawn by subject	6	15
Adverse event, non-fatal	2	6
Unspecified	5	3

Notes:

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

Justification: Out of the 797 subjects that enrolled into the Double-Blind Treatment phase of this study and entire study, a subset (154) subjects moved into the OLE phase.

Baseline characteristics

Reporting groups

Reporting group title	Placebo (Parts 1 and 2)
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Reporting group description:

Subjects with Alzheimer's disease received Placebo by SC injection every 4 weeks (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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)
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Reporting group description:

Subjects with Alzheimer's disease received Gantenerumab 105 mg by SC injection every 4 weeks (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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)
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Reporting group description:

Subjects with Alzheimer's disease received Gantenerumab 225 mg by SC injection every 4 weeks (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	59	57	40
From 65-84 years	202	210	218
85 years and over	5	4	2
Age Continuous			
Parts 1, 2 and 3 of the study			
Units: years			
arithmetic mean	69.5	70.3	71.3
standard deviation	± 7.5	± 7.0	± 7.1
Sex: Female, Male			
Parts 1, 2 and 3 of the study.			
Units: Participants			
Female	149	152	152
Male	117	119	108
Race/Ethnicity, Customized			
Parts 1, 2 and 3 of the study (Race).			
Units: Subjects			
American Indian or Alaska native	1	6	5
Asian	9	4	7

Black	1	2	2
White	239	252	239
Not Available	16	7	7
Race/Ethnicity, Customized			
Parts 1, 2 and 3 of the study (Ethnicity).			
Units: Subjects			
Non-Hispanic	217	221	210
Hispanic	41	39	47
Unknown	8	11	3

Reporting group values	Total		
Number of subjects	797		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	156		
From 65-84 years	630		
85 years and over	11		
Age Continuous			
Parts 1, 2 and 3 of the study			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Parts 1, 2 and 3 of the study.			
Units: Participants			
Female	453		
Male	344		
Race/Ethnicity, Customized			
Parts 1, 2 and 3 of the study (Race).			
Units: Subjects			
American Indian or Alaska native	12		
Asian	20		
Black	5		
White	730		
Not Available	30		
Race/Ethnicity, Customized			
Parts 1, 2 and 3 of the study (Ethnicity).			
Units: Subjects			
Non-Hispanic	648		
Hispanic	127		
Unknown	22		

Subject analysis sets

Subject analysis set title	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with Alzheimer's disease who had received Placebo by SC injection in Part 1 or Part 2, now received Gantenerumab at doses up to 1200 mg by SC injection every 4 weeks (Q4W) for 5 additional years.

Subject analysis set title	Gant Up to 1200 mg (Part 3 OLE)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with Alzheimer's disease who had received Gantenerumab by SC injection in Part 1 or Part 2, now received Gantenerumab at doses up to 1200 mg by SC injection every 4 weeks (Q4W) for 5 additional years.

Subject analysis set title	Placebo Match Gantenerumab 225 mg (Parts 1 and 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with Alzheimer's disease received matching Placebo to Gantenerumab 225 mg by SC injection Q4W for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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	Gant 1200 mg (Part 3 OLE)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with Alzheimer's disease who had received Gantenerumab by SC injection in Part 1 or Part 2, now received Gantenerumab at a dose of 1200 mg by SC injection every 4 weeks (Q4W) for 5 additional years.

Reporting group values	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)	Placebo Match Gantenerumab 225 mg (Parts 1 and 2)
Number of subjects	49	105	107
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)	0	9	
From 65-84 years	46	92	
85 years and over	3	4	
Age Continuous			
Parts 1, 2 and 3 of the study			
Units: years			
arithmetic mean	75.5	73.7	
standard deviation	± 5.8	± 7.3	±
Sex: Female, Male			
Parts 1, 2 and 3 of the study.			
Units: Participants			
Female	27	64	
Male	22	41	

Race/Ethnicity, Customized			
Parts 1, 2 and 3 of the study (Race).			
Units: Subjects			
American Indian or Alaska native	0	3	
Asian	2	0	
Black	0	0	
White	42	101	
Not Available	5	1	
Race/Ethnicity, Customized			
Parts 1, 2 and 3 of the study (Ethnicity).			
Units: Subjects			
Non-Hispanic	39	88	
Hispanic	10	17	
Unknown	0	0	

Reporting group values	Gant 1200 mg (Part 3 OLE)		
Number of subjects	99		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Parts 1, 2 and 3 of the study			
Units: years			
arithmetic mean			
standard deviation	±		
Sex: Female, Male			
Parts 1, 2 and 3 of the study.			
Units: Participants			
Female			
Male			
Race/Ethnicity, Customized			
Parts 1, 2 and 3 of the study (Race).			
Units: Subjects			
American Indian or Alaska native			
Asian			
Black			
White			
Not Available			
Race/Ethnicity, Customized			
Parts 1, 2 and 3 of the study (Ethnicity).			
Units: Subjects			
Non-Hispanic			

Hispanic			
Unknown			

End points

End points reporting groups

Reporting group title	Placebo (Parts 1 and 2)
Reporting group description: Subjects with Alzheimer's disease received Placebo by SC injection every 4 weeks (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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: Subjects with Alzheimer's disease received Gantenerumab 105 mg by SC injection every 4 weeks (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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: Subjects with Alzheimer's disease received Gantenerumab 225 mg by SC injection every 4 weeks (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)
Reporting group description: Subjects with Alzheimer's disease who had received Placebo by SC injection in Part 1 or Part 2, now received Gantenerumab at doses up to 1200 mg by SC injection every 4 weeks (Q4W) for up to 5 additional years.	
Reporting group title	Gant Up to 1200 mg (Part 3 OLE)
Reporting group description: Subjects with Alzheimer's disease who had received Gantenerumab by SC injection in Part 1 or Part 2, now received Gantenerumab at doses up to 1200 mg by SC injection every 4 weeks (Q4W) for up to 5 additional years.	
Subject analysis set title	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects with Alzheimer's disease who had received Placebo by SC injection in Part 1 or Part 2, now received Gantenerumab at doses up to 1200 mg by SC injection every 4 weeks (Q4W) for 5 additional years.	
Subject analysis set title	Gant Up to 1200 mg (Part 3 OLE)
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects with Alzheimer's disease who had received Gantenerumab by SC injection in Part 1 or Part 2, now received Gantenerumab at doses up to 1200 mg by SC injection every 4 weeks (Q4W) for 5 additional years.	
Subject analysis set title	Placebo Match Gantenerumab 225 mg (Parts 1 and 2)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with Alzheimer's disease received matching Placebo to Gantenerumab 225 mg by SC injection Q4W for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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	Gant 1200 mg (Part 3 OLE)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with Alzheimer's disease who had received Gantenerumab by SC injection in Part 1 or Part 2, now received Gantenerumab at a dose of 1200 mg by SC injection every 4 weeks (Q4W) for 5 additional years.	

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

End point title	Mean Change From Baseline in Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) Total Score at Week 104 (Double-Blind Treatment Phase)
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End point description:

The CDR (Clinical Dementia Rating) is obtained through semi-structured interviews of participants and informants, and cognitive functioning is rated in six domains of functioning: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a five-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment. The CDR-SOB (Clinical Dementia Rating-Sum of Boxes) is based on summing each of the domain box scores with total scores ranging from 0-18, where lower total scores represent better outcomes and higher total scores represent worse outcomes.

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: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 104	1.19 (± 1.68)	1.41 (± 2.02)	1.47 (± 1.89)	

Statistical analyses

Statistical analysis title	Statistical Analysis I
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	
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
Comparison groups	Placebo (Parts 1 and 2) v Gantenerumab 225 mg (Parts 1 and 2)

	2)
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	
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

Primary: Number of Subjects with Adverse Events (AEs) or Serious Adverse Events (SAEs) (OLE Phase)

End point title	Number of Subjects with Adverse Events (AEs) or Serious Adverse Events (SAEs) (OLE Phase) ^[1]
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End point description:

An Adverse Event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events.

End point type	Primary
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End point timeframe:

Baseline up until a maximum of 4.5 years

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 analyses were performed, as the OLE phase in reality only had 1 arm with all subjects receiving Gantenerumab (up to 1200mg).

End point values	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	105		
Units: Subjects				
number (not applicable)				
AEs	46	100		
SAEs	18	28		

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean Change From Baseline in Alzheimer Disease Assessment Scale-Cognitive Subscale 11 (ADAS-Cog-11) Scores at Week 104 (Double-Blind Treatment Phase)
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End point description:

The ADAS-Cog-11 assesses multiple cognitive domains including memory, comprehension, praxis, orientation, and spontaneous speech. Most of these are assessed by tests although some are rated by the clinician on a 5-point scale. The score range for ADAS-Cog-11 is from 0 to 70 with higher scores representing severe dysfunction.

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: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 104	3.68 (± 6.64)	3.52 (± 6.28)	3.97 (± 6.89)	

Statistical analyses

Statistical analysis title	Statistical Analysis I
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	
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
Comparison groups	Placebo (Parts 1 and 2) v Gantenerumab 225 mg (Parts 1 and 2)

Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	
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: Time to Onset of Dementia at Week 104 (Double-Blind Treatment Phase)

End point title	Time to Onset of Dementia at Week 104 (Double-Blind Treatment Phase)
End point description:	Time to Onset of Dementia was defined as the time interval between the first treatment date and the date that participant is assessed as having Alzheimer-type dementia by investigators.
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	91	95	91	
Units: Days				
median (confidence interval 95%)	63.64 (56.63 to 69.82)	62.98 (56.00 to 69.16)	70.64 (63.34 to 76.65)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean Change From Baseline in Cambridge Neuropsychological Test Automated Battery (CANTAB) Composite Score at Week 104 (Double-Blind Treatment Phase)
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End point description:

The CANTAB is a computerised assessment battery consisting of tests for neuropsychological function. 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).

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: Composite Score				
arithmetic mean (standard deviation)				
Week 104	-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 (Double-Blind Treatment Phase)

End point title	Mean Change from Baseline in Free and Cued Selective Reminding Test (FCSRT) Score at Week 104 (Double-Blind Treatment Phase)
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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).

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: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 104	-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 (Double-Blind Treatment Phase)

End point title	Mean Change From Baseline in Functional Activities Questionnaire (FAQ) Score at Week 104 (Double-Blind Treatment Phase)
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.	
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: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 104	3.59 (± 4.93)	4.89 (± 6.2)	4.03 (± 5.75)	3.6 (± 4.93)

Statistical analyses

Statistical analysis title	Statistical Analysis II
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	
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

Statistical analysis title	Statistical Analysis I
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	
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

Secondary: Mean Change From Baseline in CDR-Global Score at Week 104 (Double-Blind Treatment Phase)

End point title	Mean Change From Baseline in CDR-Global Score at Week 104 (Double-Blind Treatment Phase)
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.	
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: Scores on a Scale				

arithmetic mean (standard deviation)				
Week 104	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 (Double-Blind Treatment Phase)

End point title	Mean Change from Baseline in Neuropsychiatric Inventory (NPI) Questionnaire Score at Week 104 (Double-Blind Treatment Phase)
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).	
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: Scores 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: Percentage 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 (Double-Blind Treatment Phase)

End point title	Percentage 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 (Double-Blind Treatment Phase)
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.	
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	72	71	66	56
Units: Percentage Change				
arithmetic mean (standard deviation)				
p-tau	2.77 (± 20.69)	-4.78 (± 11.9)	-7.34 (± 10.09)	2.84 (± 23.19)
t-tau	3.43 (± 19.95)	-1.36 (± 12.89)	-2.12 (± 11.01)	3.46 (± 22.32)
Abeta	4.87 (± 36.14)	2.45 (± 24.57)	15.2 (± 45.24)	4.3 (± 39.31)

Statistical analyses

Statistical analysis title	Statistical Analysis I
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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	143
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9734
Method	Mixed models analysis

Statistical analysis title	Statistical Analysis II
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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	138
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0629
Method	Mixed models analysis

Statistical analysis title	Statistical Analysis III
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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	143
Analysis specification	Pre-specified
Analysis type	
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	138
Analysis specification	Pre-specified
Analysis type	
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	143
Analysis specification	Pre-specified
Analysis type	
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)
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Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0434
Method	Mixed models analysis

Secondary: Percentage Change from Baseline in Hippocampal Volume at Week 104 (Double-Blind Treatment Phase)

End point title	Percentage Change from Baseline in Hippocampal Volume at Week 104 (Double-Blind Treatment Phase)
End point description:	Change from baseline in hippocampal right volume (HRV) and hippocampal left volume (HLV) were analysed at Week 104 using magnetic resonance imaging.
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: Percentage Change				
arithmetic mean (standard deviation)				
HRV (Week 104)	-7.61 (± 4.03)	-7.52 (± 3.96)	-7.34 (± 3.84)	-7.7 (± 4.01)
HLV (Week 104)	-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: Percentage Change From Baseline in Cortical Composite Sustained Uptake Volume Ratio (SUVR) in Different Brain Regions at Week 156 (Double-Blind Treatment Phase)

End point title	Percentage Change From Baseline in Cortical Composite Sustained Uptake Volume Ratio (SUVR) in Different Brain Regions at Week 156 (Double-Blind Treatment Phase)
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.
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: Percentage Change				
arithmetic mean (standard deviation)				
Cerebellum gray (Week 156)	6.26 (± 9.1)	2.7 (± 10.59)	-8.36 (± 9.11)	5.95 (± 11.13)
Whole Cerebellum (Week 156)	5.41 (± 7.13)	2.07 (± 8.65)	-8.44 (± 8.06)	5.17 (± 8.66)
Composite White Matter (Week 156)	2.75 (± 3.18)	-0.87 (± 2.95)	-4.86 (± 6.35)	3.07 (± 2.07)
Subcortical White Matter (Week 156)	4.83 (± 4.95)	1.69 (± 4.45)	-0.42 (± 8.26)	4.59 (± 0.55)
Pons (Week 156)	1.72 (± 2.51)	-2.83 (± 3.39)	-6.99 (± 5.65)	2.1 (± 2.73)
Composite Reference (Week 156)	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 Concentrations at Different Time Points (Double-Blind Treatment Phase)

End point title	Gantenerumab Plasma Concentrations at Different Time Points (Double-Blind Treatment Phase) ^[2]
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End point description:

The PK analyses includes tabulation of plasma concentration data and summarisation of plasma concentrations by visits with subjects grouped according to treatment received. Descriptive summary statistics for the Arithmetic Mean and Standard Deviation are presented below. (n=X; n=X) indicates the number of subjects analysed at each timepoint.

End point type	Secondary
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End point timeframe:

Pre-Dose: Weeks 8, 20, 44, 68 and 100; Post-Dose: Weeks 1, 53 and 101

Notes:

[2] - 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: This analysis was only performed on the 'Double-Blind Treatment Phase' arms and hence why not all arms are presented.

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: µg/ml (micrograms per milliliter)				
arithmetic mean (standard deviation)				
Week 1 (Post-Dose) (n=239; n=227)	3.56 (± 2.36)	7.4 (± 4.28)		
Week 8 (Pre-Dose) (n=237; n=225)	2.87 (± 1.84)	5.92 (± 3.16)		
Week 20 (Pre-Dose) (n=228; n=220)	3.7 (± 2.15)	7.66 (± 4.14)		
Week 44 (Pre-Dose) (n=212; n=199)	4.08 (± 2.44)	8.22 (± 4.51)		
Week 53 (Post-Dose) (n=195; n=185)	6.77 (± 3.94)	15 (± 9.34)		

Week 68 (Pre-Dose) (n=165; n=155)	3.95 (± 2.35)	8.91 (± 4.86)		
Week 100 (Pre-Dose) (n=98; n=86)	4.35 (± 2.34)	9.4 (± 4.69)		
Week 101 (Post-Dose) (n=95; n=77)	7.32 (± 3.53)	16.63 (± 7.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Mini Mental State Exam (MMSE) Score at Week 104 (Double-Blind Treatment Phase)

End point title	Mean Change From Baseline in Mini Mental State Exam (MMSE) Score at Week 104 (Double-Blind Treatment Phase)
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.	
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: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 104	-2.31 (± 3.23)	-2.46 (± 3.68)	-2.25 (± 3.31)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events (AEs) or Serious Adverse Events (SAEs) (Double-Blind Treatment Phase)

End point title	Number of Subjects with Adverse Events (AEs) or Serious Adverse Events (SAEs) (Double-Blind Treatment Phase)
End point description: An Adverse Event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events.	
End point type	Secondary
End point timeframe: Baseline through end of study (up to approximately 4.5 years)	

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	266	271	260	
Units: Subjects				
number (not applicable)				
AEs	250	241	240	
SAEs	55	48	46	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Anti-Drug Antibodies (ADAs) (Double-Blind Treatment Phase)

End point title	Percentage of Subjects with Anti-Drug Antibodies (ADAs) (Double-Blind Treatment Phase)
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End point description:

Subjects were considered positive or negative for ADA based on their baseline and post-baseline sample results. The number and percentage of subjects with confirmed positive ADA levels were determined for Gantenerumab and Placebo groups. The prevalence of ADA at baseline was calculated as the proportion of subjects with confirmed positive ADA levels at baseline relative to the total number of subjects with a sample available at baseline. The incidence of treatment-emergent ADAs was determined as the proportion of subjects with confirmed post-baseline positive ADAs relative to the total number of subjects that had at least one post-baseline sample available for ADA analysis. (n=X; n=X; n=X) indicates the number of subjects analysed at each timepoint.

End point type	Secondary
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End point timeframe:

Baseline through end of study (up to approximately 4.5 years)

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	259	266	256	
Units: Percentage of Subjects				
number (not applicable)				
Baseline ADAs (n=259; n=266; n=256)	5.8	7.5	5.5	
Treatment Emergent ADAs (n=259; n=258; n=250)	5.0	7.0	6.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) Total Score at Week 156 (OLE Phase)

End point title	Mean Change From Baseline in Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) Total Score at Week 156 (OLE Phase)
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End point description:

The CDR (Clinical Dementia Rating) is obtained through semi-structured interviews of participants and informants, and cognitive functioning is rated in six domains of functioning: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a five-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment. The CDR-SOB (Clinical Dementia Rating-Sum of Boxes) is based on summing each of the domain box scores with total scores ranging from 0-18, where lower total scores represent better outcomes and higher total scores represent worse outcomes.

End point type	Secondary
End point timeframe:	
Baseline, Week 156	

End point values	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	52		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 156	3.3 (\pm 2.4)	2.8 (\pm 3.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Alzheimer Disease Assessment Scale-Cognitive Subscale 11 (ADAS-Cog-11) Scores at Week 156 (OLE Phase)

End point title	Mean Change From Baseline in Alzheimer Disease Assessment Scale-Cognitive Subscale 11 (ADAS-Cog-11) Scores at Week 156 (OLE Phase)
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End point description:

The ADAS-Cog-11 assesses multiple cognitive domains including memory, comprehension, praxis, orientation, and spontaneous speech. Most of these are assessed by tests although some are rated by the clinician on a 5-point scale. The score range for ADAS-Cog-11 is from 0 to 70 with higher scores representing severe dysfunction.

End point type	Secondary
End point timeframe:	
Baseline, Week 156	

End point values	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	51		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 156	5.8 (± 7.3)	8.9 (± 9.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Alzheimer Disease Assessment Scale-Cognitive Subscale 13 (ADAS-Cog-13) Scores at Week 156 (OLE Phase)

End point title	Mean Change From Baseline in Alzheimer Disease Assessment Scale-Cognitive Subscale 13 (ADAS-Cog-13) Scores at Week 156 (OLE Phase)
End point description: The ADAS-Cog-13 assesses multiple cognitive domains including memory, comprehension, praxis, orientation, and spontaneous speech. The score range for ADAS-Cog-13 is from 0 to 85 with higher scores representing severe dysfunction.	
End point type	Secondary
End point timeframe: Baseline, Week 156	

End point values	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	51		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 156	8.0 (± 8.2)	10.4 (± 10.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Dementia at Week 156 (OLE Phase)

End point title	Time to Onset of Dementia at Week 156 (OLE Phase)
End point description:	
Time to Onset of Dementia was defined as the time interval between the first treatment date and the date that participant is assessed as having Alzheimer-type dementia by investigators.	
End point type	Secondary
End point timeframe:	
Baseline, Week 156	

End point values	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	14		
Units: Days				
median (confidence interval 95%)	38.18 (9.90 to 66.97)	50.82 (32.04 to 66.87)		

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 156 (OLE Phase)

End point title	Mean Change from Baseline in Free and Cued Selective Reminding Test (FCSRT) Score at Week 156 (OLE Phase)
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).	
End point type	Secondary
End point timeframe:	
Baseline, Week 156	

End point values	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	51		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 156	-7.7 (± 9.3)	-4.1 (± 8.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Functional Activities Questionnaire (FAQ) Score at Week 156 (OLE Phase)

End point title	Mean Change From Baseline in Functional Activities Questionnaire (FAQ) Score at Week 156 (OLE Phase)
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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.

End point type	Secondary
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End point timeframe:

Baseline, Week 156

End point values	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	52		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 156	8.1 (± 5.3)	6.8 (± 6.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in CDR-Global Score at Week 156 (OLE Phase)

End point title	Mean Change From Baseline in CDR-Global Score at Week 156 (OLE Phase)
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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.

End point type	Secondary
End point timeframe:	
Baseline, Week 156	

End point values	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	52		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 156	0.6 (± 0.6)	0.5 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in Hippocampal Volume at Week 152 (OLE Phase)

End point title	Percentage Change from Baseline in Hippocampal Volume at Week 152 (OLE Phase)
End point description:	
Change from baseline in hippocampal right volume (HRV) and hippocampal left volume (HLV) were analysed at Week 152 using magnetic resonance imaging.	
End point type	Secondary
End point timeframe:	
Baseline, Week 152	

End point values	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	51		
Units: Percentage Change				
arithmetic mean (standard deviation)				
HRV (Week 156)	16.7 (± 8.4)	16.1 (± 8.2)		
HLV (Week 156)	16.2 (± 13.0)	18.0 (± 8.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in Cortical Composite Sustained Uptake Volume Ratio (SUVR) in Different Brain Regions at Week 156 (OLE Phase)

End point title	Percentage Change From Baseline in Cortical Composite Sustained Uptake Volume Ratio (SUVR) in Different Brain Regions at Week 156 (OLE Phase)
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.	
End point type	Secondary
End point timeframe: Baseline, Week 156	

End point values	Gant Up to 1200 mg (Part 3 OLE)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Percentage Change				
arithmetic mean (standard deviation)				
Cerebellum gray (Week 156)	-0.2 (\pm 0.2)			
Composite Reference (Week 156)	-41.4 (\pm 29.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Gantenerumab Plasma Concentrations at Different Time Points (OLE Phase)

End point title	Gantenerumab Plasma Concentrations at Different Time Points (OLE Phase)
End point description: The PK analyses includes tabulation of plasma concentration data and summarisation of plasma concentrations by visits with subjects grouped according to treatment received. Descriptive summary statistics for the Arithmetic Mean and Standard Deviation are presented below. (n=X) indicates the number of subjects analysed at each timepoint.	
End point type	Secondary
End point timeframe: Pre-Dose: Weeks 64, 100, 104, 136, 156 and 208; Post-Dose: Week 101	

End point values	Gant 1200 mg (Part 3 OLE)			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: µg/ml (micrograms per milliliter)				
arithmetic mean (standard deviation)				
Week 64 (Pre-Dose) (n=99)	33.0 (± 21.7)			
Week 100 (Pre-Dose) (n=89)	39.2 (± 22.7)			
Week 101 (Post-Dose) (n=88)	80.5 (± 37.8)			
Week 104 (Pre-Dose) (n=91)	40.5 (± 22.5)			
Week 136 (Pre-Dose) (n=83)	45.2 (± 22.4)			
Week 156 (Pre-Dose) (n=93)	39.6 (± 28.2)			
Week 208 (Pre-Dose) (n=26)	37.1 (± 29.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Mini Mental State Exam (MMSE) Score at Week 156 (OLE Phase)

End point title	Mean Change From Baseline in Mini Mental State Exam (MMSE) Score at Week 156 (OLE Phase)
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.	
End point type	Secondary
End point timeframe: Baseline, Week 156	

End point values	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	53		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 156	-4.3 (± 4.3)	-4.7 (± 4.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Anti-Drug Antibodies (ADAs) (OLE Phase)

End point title	Percentage of Subjects with Anti-Drug Antibodies (ADAs) (OLE Phase)
End point description:	
Subjects were considered positive or negative for ADA based on their baseline and post-baseline sample results. The number and percentage of subjects with confirmed positive ADA levels were determined. The prevalence of ADA at baseline was calculated as the proportion of subjects with confirmed positive ADA levels at baseline relative to the total number of subjects with a sample available at baseline. The incidence of treatment-emergent ADAs was determined as the proportion of subjects with confirmed post-baseline positive ADAs relative to the total number of subjects that had at least one post-baseline sample available for ADA analysis. (n=X; n=X) indicates the number of subjects analysed at each timepoint.	
End point type	Secondary
End point timeframe:	
Baseline through end of study (up to approximately 4.5 years)	

End point values	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)	Gant Up to 1200 mg (Part 3 OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	104		
Units: Percentage of Subjects				
number (not applicable)				
Baseline ADAs (n=49; n=104)	2.0	5.8		
Treatment Emergent ADAs (n=46; n=102)	2.2	2.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up until a maximum of 9.75 years

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Gantenerumab 105 mg (Parts 1 and 2)
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Reporting group description:

Subjects with Alzheimer's disease received Gantenerumab 105 mg by SC injection every 4 weeks (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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	Placebo (Parts 1 and 2)
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Reporting group description:

Subjects with Alzheimer's disease received Placebo by SC injection every 4 weeks (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)
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Reporting group description:

Subjects with Alzheimer's disease who had received Placebo by SC injection in Part 1 or Part 2, now received Gantenerumab at doses up to 1200 mg by SC injection every 4 weeks (Q4W) for up to 5 additional years.

Reporting group title	Gant Up to 1200 mg (Part 3 OLE)
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Reporting group description:

Subjects with Alzheimer's disease who had received Gantenerumab by SC injection in Part 1 or Part 2, now received Gantenerumab at doses up to 1200 mg by SC injection every 4 weeks (Q4W) for up to 5 additional years.

Reporting group title	Gantenerumab 225 mg (Parts 1 and 2)
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Reporting group description:

Subjects with Alzheimer's disease received Gantenerumab 225 mg by SC injection every 4 weeks (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study. Subjects 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	Gantenerumab 105 mg (Parts 1 and 2)	Placebo (Parts 1 and 2)	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 271 (17.71%)	55 / 266 (20.68%)	18 / 49 (36.73%)
number of deaths (all causes)	0	6	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary cancer metastatic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Breast cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Colon cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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 cancer metastatic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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 neoplasm malignant			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metastases to bone				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Myelodysplastic syndrome				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Plasmacytoma				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Prostate cancer				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	2 / 266 (0.75%)	0 / 49 (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	
Small cell carcinoma				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0	
Basal cell carcinoma				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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	
Benign ovarian tumour				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Bladder cancer alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Bladder transitional cell carcinoma alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Bone sarcoma alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer stage II alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal tract adenoma alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioma alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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

Intestinal adenocarcinoma alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Intraductal proliferative breast lesion alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal neoplasm benign alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Rectal adenocarcinoma alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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 oncocytoma alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Tongue neoplasm malignant stage unspecified alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral artery aneurysm			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Malignant hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Hip arthroplasty alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Knee arthroplasty alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal decompression alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Urethral dilation procedure alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Rotator cuff repair			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral caruncle removal			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
General disorders and administration site conditions			
Chest pain alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Malaise			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Asthenia			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			

subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Type I hypersensitivity			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Reproductive system and breast disorders			
Prostatomegaly			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign prostatic hyperplasia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Ovarian cyst			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Respiratory, thoracic and mediastinal disorders			
Delirium			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Pulmonary embolism			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	1 / 266 (0.38%)	0 / 49 (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
Haemothorax			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Agitation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Behavioral and psychological symptoms of dementia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Major depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Suicide attempt			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropsychiatric symptoms			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Suicidal behaviour			

subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood pressure increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Body temperature increased			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	2 / 49 (4.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	1 / 266 (0.38%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Post lumbar puncture syndrome alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Rib fracture alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	1 / 266 (0.38%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ankle fracture alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 271 (0.00%) 0 / 0 0 / 0	 1 / 266 (0.38%) 0 / 1 0 / 0	 0 / 49 (0.00%) 0 / 0 0 / 0
Femur fracture alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 271 (0.00%) 0 / 0 0 / 0	 1 / 266 (0.38%) 0 / 1 0 / 0	 0 / 49 (0.00%) 0 / 0 0 / 0
Humerus fracture alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 271 (0.00%) 0 / 0 0 / 0	 0 / 266 (0.00%) 0 / 0 0 / 0	 0 / 49 (0.00%) 0 / 0 0 / 0
Laceration alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 271 (0.00%) 0 / 0 0 / 0	 0 / 266 (0.00%) 0 / 0 0 / 0	 0 / 49 (0.00%) 0 / 0 0 / 0
Ligament rupture alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 271 (0.00%) 0 / 0 0 / 0	 1 / 266 (0.38%) 0 / 1 0 / 0	 0 / 49 (0.00%) 0 / 0 0 / 0
Lower limb fracture alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 271 (0.37%) 0 / 1 0 / 0	 0 / 266 (0.00%) 0 / 0 0 / 0	 0 / 49 (0.00%) 0 / 0 0 / 0
Meniscus injury alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Post procedural haematuria alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Radiation mucositis alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Radius fracture alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	2 / 266 (0.75%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Spinal fracture alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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

Urinary retention postoperative alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle strain			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Mitral valve incompetence alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	2 / 266 (0.75%)	0 / 49 (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
Supraventricular tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Acute coronary syndrome			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Angina pectoris			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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 unstable			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial fibrillation			

alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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	
Atrial thrombosis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Atrioventricular block second degree				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Cardiac ventricular thrombosis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Coronary artery disease				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 271 (0.74%)	0 / 266 (0.00%)	0 / 49 (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				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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	
Sinus arrest				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 271 (0.37%)	1 / 266 (0.38%)	0 / 49 (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
Arrhythmia			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebellar infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Balance disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia with Lewy bodies			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Epilepsy			

alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Partial seizures				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Retrograde amnesia				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Seizure				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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	
Subarachnoid haemorrhage				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0	
Thalamic infarction				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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	
Amyotrophic lateral sclerosis				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Monoparesis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Presyncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Radial nerve palsy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	2 / 266 (0.75%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Transient global amnesia alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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 ischaemic attack alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	1 / 266 (0.38%)	0 / 49 (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
ARIA-E			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech disorder			

subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 271 (0.74%)	0 / 266 (0.00%)	0 / 49 (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
Visual impairment			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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

Gastric ulcer alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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	
Inguinal hernia alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 271 (0.37%)	2 / 266 (0.75%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Abdominal distension alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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	
Abdominal pain alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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	
Diarrhoea alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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	
Diverticulum intestinal haemorrhagic alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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	
Gastritis alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Hiatus hernia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic mass			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Umbilical hernia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Constipation			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Cholelithiasis			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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 and urinary disorders			
Bladder obstruction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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
Haematuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Diabetes insipidus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	1 / 266 (0.38%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis reactive			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Rotator cuff syndrome			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Osteitis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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

Pelvic abscess				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Sepsis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Urinary tract infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Appendicitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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	
Bacterial sepsis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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	
Cellulitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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	
Cholecystitis infective				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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 viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lyme disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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

Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	1 / 266 (0.38%)	0 / 49 (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
Post procedural infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Subcutaneous abscess			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 266 (0.38%)	0 / 49 (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
Diabetes mellitus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 266 (0.00%)	0 / 49 (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

Serious adverse events	Gant Up to 1200 mg (Part 3 OLE)	Gantenerumab 225 mg (Parts 1 and 2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 105 (26.67%)	46 / 260 (17.69%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary cancer metastatic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 105 (0.95%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Plasmacytoma alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Prostate cancer alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Small cell carcinoma alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Basal cell carcinoma alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Benign ovarian tumour alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bladder cancer alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bladder transitional cell carcinoma alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bone sarcoma				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Breast cancer stage II				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastrointestinal tract adenoma				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Glioma				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intestinal adenocarcinoma				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intraductal proliferative breast lesion				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Pharyngeal neoplasm benign alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal oncocytoma alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue neoplasm malignant stage unspecified alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral artery aneurysm alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hip arthroplasty			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal decompression alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral dilation procedure alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff repair			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral caruncle removal			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type I hypersensitivity			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatomegaly			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystocele			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Delirium			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 105 (2.86%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Behavioral and psychological symptoms of dementia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Major depression alternative assessment type: Non-systematic subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt alternative assessment type: Non-systematic subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropsychiatric symptoms subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations Blood pressure increased alternative assessment type: Non-systematic subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased alternative assessment type: Non-systematic subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			

subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 105 (3.81%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post lumbar puncture syndrome			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 105 (0.95%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Laceration				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ligament rupture				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lower limb fracture				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Meniscus injury				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Post procedural haematuria				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Radiation mucositis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Radius fracture				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention postoperative			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 105 (0.95%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Angina unstable alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Arteriosclerosis coronary artery alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Atrial fibrillation alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Atrial thrombosis alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Atrioventricular block second degree alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cardiac ventricular thrombosis alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial rupture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			

alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cerebral haemorrhage				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	1 / 1		
Dementia with Lewy bodies				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Epilepsy				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 105 (1.90%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 2	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Partial seizures				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Retrograde amnesia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Seizure				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amyotrophic lateral sclerosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Presyncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radial nerve palsy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARIA-E			
subjects affected / exposed	2 / 105 (1.90%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Generalised tonic-clonic seizure subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders Deafness unilateral subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders Retinal detachment alternative assessment type: Non- systematic			

subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic mass			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder obstruction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Diabetes insipidus			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Abdominal abscess				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Atypical pneumonia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pelvic abscess				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Sepsis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Urinary tract infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Appendicitis				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bacterial sepsis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cellulitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cholecystitis infective				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cystitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Erysipelas				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastroenteritis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Gastroenteritis viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 105 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			

subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 105 (0.00%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Gantenerumab 105 mg (Parts 1 and 2)	Placebo (Parts 1 and 2)	Plac (Parts 1 + 2) switched to Gant Up to 1200mg (Part 3 OLE)
Total subjects affected by non-serious adverse events subjects affected / exposed	188 / 271 (69.37%)	163 / 266 (61.28%)	40 / 49 (81.63%)
Investigations Weight decreased subjects affected / exposed occurrences (all)	0 / 271 (0.00%) 0	0 / 266 (0.00%) 0	2 / 49 (4.08%) 2
Injury, poisoning and procedural complications Fall alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all) Skin laceration subjects affected / exposed occurrences (all)	23 / 271 (8.49%) 32 0 / 271 (0.00%) 0 0 / 271 (0.00%) 0	28 / 266 (10.53%) 42 0 / 266 (0.00%) 0 0 / 266 (0.00%) 0	13 / 49 (26.53%) 20 4 / 49 (8.16%) 4 0 / 49 (0.00%) 0
Vascular disorders Hypertension alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	11 / 271 (4.06%) 11	18 / 266 (6.77%) 20	2 / 49 (4.08%) 2
Nervous system disorders Dizziness alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Headache alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) ARIA-E alternative assessment type: Non-systematic	21 / 271 (7.75%) 27 34 / 271 (12.55%) 47 ARIA-E alternative assessment type: Non-systematic	21 / 266 (7.89%) 21 36 / 266 (13.53%) 50 ARIA-E alternative assessment type: Non-systematic	4 / 49 (8.16%) 5 7 / 49 (14.29%) 11 ARIA-E alternative assessment type: Non-systematic

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ARIA-H</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>18 / 271 (6.64%)</p> <p>20</p> <p>58 / 271 (21.40%)</p> <p>92</p>	<p>2 / 266 (0.75%)</p> <p>2</p> <p>31 / 266 (11.65%)</p> <p>51</p>	<p>12 / 49 (24.49%)</p> <p>21</p> <p>7 / 49 (14.29%)</p> <p>12</p>
<p>General disorders and administration site conditions</p> <p>Fatigue</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Injection site erythema</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 271 (2.58%)</p> <p>7</p> <p>29 / 271 (10.70%)</p> <p>133</p>	<p>8 / 266 (3.01%)</p> <p>8</p> <p>3 / 266 (1.13%)</p> <p>3</p>	<p>0 / 49 (0.00%)</p> <p>0</p> <p>17 / 49 (34.69%)</p> <p>196</p>
<p>Eye disorders</p> <p>Cataract</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 271 (0.00%)</p> <p>0</p>	<p>0 / 266 (0.00%)</p> <p>0</p>	<p>4 / 49 (8.16%)</p> <p>5</p>
<p>Gastrointestinal disorders</p> <p>Diarrhoea</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>15 / 271 (5.54%)</p> <p>22</p> <p>0 / 271 (0.00%)</p> <p>0</p>	<p>13 / 266 (4.89%)</p> <p>18</p> <p>0 / 266 (0.00%)</p> <p>0</p>	<p>3 / 49 (6.12%)</p> <p>3</p> <p>5 / 49 (10.20%)</p> <p>5</p>
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Productive cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>11 / 271 (4.06%)</p> <p>13</p> <p>0 / 271 (0.00%)</p> <p>0</p>	<p>13 / 266 (4.89%)</p> <p>14</p> <p>0 / 266 (0.00%)</p> <p>0</p>	<p>5 / 49 (10.20%)</p> <p>5</p> <p>3 / 49 (6.12%)</p> <p>3</p>

Psychiatric disorders Anxiety alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Depression alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Agitation subjects affected / exposed occurrences (all) Confusional state subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all)	 20 / 271 (7.38%) 20 23 / 271 (8.49%) 23 0 / 271 (0.00%) 0 0 / 271 (0.00%) 0 0 / 271 (0.00%) 0	 18 / 266 (6.77%) 23 13 / 266 (4.89%) 14 0 / 266 (0.00%) 0 0 / 266 (0.00%) 0 0 / 266 (0.00%) 0	 2 / 49 (4.08%) 2 0 / 49 (0.00%) 0 3 / 49 (6.12%) 4 5 / 49 (10.20%) 5 1 / 49 (2.04%) 1
Musculoskeletal and connective tissue disorders Arthralgia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Back pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Musculoskeletal pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Osteoporosis subjects affected / exposed occurrences (all)	 12 / 271 (4.43%) 14 16 / 271 (5.90%) 18 6 / 271 (2.21%) 7 0 / 271 (0.00%) 0	 21 / 266 (7.89%) 29 26 / 266 (9.77%) 33 16 / 266 (6.02%) 18 0 / 266 (0.00%) 0	 2 / 49 (4.08%) 2 2 / 49 (4.08%) 2 0 / 49 (0.00%) 0 3 / 49 (6.12%) 3
Infections and infestations			

Bronchitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 271 (3.69%)	10 / 266 (3.76%)	3 / 49 (6.12%)
occurrences (all)	12	10	3
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 271 (4.80%)	13 / 266 (4.89%)	3 / 49 (6.12%)
occurrences (all)	18	14	4
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	30 / 271 (11.07%)	17 / 266 (6.39%)	7 / 49 (14.29%)
occurrences (all)	40	34	7
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 271 (4.80%)	11 / 266 (4.14%)	5 / 49 (10.20%)
occurrences (all)	15	14	5
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	16 / 271 (5.90%)	25 / 266 (9.40%)	4 / 49 (8.16%)
occurrences (all)	25	37	6
Herpes Zoster			
subjects affected / exposed	0 / 271 (0.00%)	0 / 266 (0.00%)	4 / 49 (8.16%)
occurrences (all)	0	0	4

Non-serious adverse events	Gant Up to 1200 mg (Part 3 OLE)	Gantenerumab 225 mg (Parts 1 and 2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 105 (82.86%)	189 / 260 (72.69%)	
Investigations			
Weight decreased			
subjects affected / exposed	6 / 105 (5.71%)	0 / 260 (0.00%)	
occurrences (all)	7	0	
Injury, poisoning and procedural complications			
Fall			
alternative assessment type: Non-systematic			

<p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>17 / 105 (16.19%)</p> <p>29</p>	<p>27 / 260 (10.38%)</p> <p>38</p>	
<p>Contusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 105 (4.76%)</p> <p>5</p>	<p>0 / 260 (0.00%)</p> <p>0</p>	
<p>Skin laceration</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 105 (6.67%)</p> <p>8</p>	<p>0 / 260 (0.00%)</p> <p>0</p>	
<p>Vascular disorders</p> <p>Hypertension</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 105 (7.62%)</p> <p>11</p>	<p>20 / 260 (7.69%)</p> <p>23</p>	
<p>Nervous system disorders</p> <p>Dizziness</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ARIA-E</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ARIA-H</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>14 / 105 (13.33%)</p> <p>18</p> <p>12 / 105 (11.43%)</p> <p>18</p> <p>29 / 105 (27.62%)</p> <p>45</p> <p>17 / 105 (16.19%)</p> <p>44</p>	<p>26 / 260 (10.00%)</p> <p>35</p> <p>25 / 260 (9.62%)</p> <p>36</p> <p>34 / 260 (13.08%)</p> <p>36</p> <p>36 / 260 (13.85%)</p> <p>64</p>	
<p>General disorders and administration site conditions</p> <p>Fatigue</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 105 (0.00%)</p> <p>0</p>	<p>15 / 260 (5.77%)</p> <p>20</p>	

Injection site erythema alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	36 / 105 (34.29%) 359	35 / 260 (13.46%) 114	
Eye disorders Cataract subjects affected / exposed occurrences (all)	2 / 105 (1.90%) 3	0 / 260 (0.00%) 0	
Gastrointestinal disorders Diarrhoea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	11 / 105 (10.48%) 14 6 / 105 (5.71%) 9	15 / 260 (5.77%) 18 0 / 260 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all)	8 / 105 (7.62%) 12 0 / 105 (0.00%) 0	13 / 260 (5.00%) 13 0 / 260 (0.00%) 0	
Psychiatric disorders Anxiety alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Depression alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Agitation subjects affected / exposed occurrences (all)	7 / 105 (6.67%) 8 0 / 105 (0.00%) 0 8 / 105 (7.62%) 10	16 / 260 (6.15%) 16 25 / 260 (9.62%) 25 0 / 260 (0.00%) 0	

Confusional state subjects affected / exposed occurrences (all)	8 / 105 (7.62%) 8	0 / 260 (0.00%) 0	
Irritability subjects affected / exposed occurrences (all)	6 / 105 (5.71%) 9	0 / 260 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	8 / 105 (7.62%) 8	16 / 260 (6.15%) 17	
Back pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	10 / 105 (9.52%) 10	26 / 260 (10.00%) 31	
Musculoskeletal pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 105 (0.00%) 0	5 / 260 (1.92%) 5	
Osteoporosis subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1	0 / 260 (0.00%) 0	
Infections and infestations Bronchitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	7 / 105 (6.67%) 9	14 / 260 (5.38%) 18	
Influenza alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	7 / 105 (6.67%) 8	15 / 260 (5.77%) 17	
Nasopharyngitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	15 / 105 (14.29%) 23	20 / 260 (7.69%) 35	

Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 105 (9.52%)	18 / 260 (6.92%)	
occurrences (all)	19	21	
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 105 (14.29%)	22 / 260 (8.46%)	
occurrences (all)	25	38	
Herpes Zoster			
subjects affected / exposed	1 / 105 (0.95%)	0 / 260 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2011	<p>Following updates were made:</p> <p>[1] An overall benefit-risk assessment subsection was added; information about the RNA sampling was added to the optional 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 subjects with abnormal memory function based on the FCSRT-IR up to one month prior to the first screening visit;</p> <p>[2] Experience at sites indicated that several subjects fail screening solely for right bundle branch block (RBBB). As 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 patients who may not be included in QTc analysis was reviewed again with the conclusion that RBBB patients can be enrolled;</p> <p>[3] Exclusion 35 was reformatted to more clearly quantify the amount of use permitted for some agents; information regarding the 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 MRI, and explanation of the procedures to be followed if a new microbleed is seen on an MRI;</p> <p>[4] Analysis plan was clarified to mention that analysis may include measurement of beta amyloid pyroglutamate and CSF biomarkers; and Information regarding missed dose, and information regarding analysis and sample collection of ADA was added.</p>
14 March 2012	<p>Following updates were made:</p> <p>[1] 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;</p> <p>[2] 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;</p> <p>[3] A paragraph requesting investigators to report increases in ALT or AST in combination with an increase in total bilirubin or jaundice as an SAE to the Sponsor due to regulatory reasons.</p>
15 February 2013	<p>Following updates were made:</p> <p>[1] 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;</p> <p>[2] The primary efficacy comparison of the high dose gantenerumab arm to the placebo arm was changed so that only placebo subjects with APOE 0ε4 or APOE 1ε4 were to be included in the analysis, and not the ones with APOE 2ε4;</p> <p>[3] Part 2 (extension) of the study was added; procedures to follow in the event of ARIA-H findings and abnormal MRI findings were updated to reflect extension of the study;</p> <p>[4] Information regarding the use of symptomatic treatment for AD 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 IB was added; and the information on possible analysis of concentration-effect relationship using PK data was added.</p>

17 July 2014	<p>Following updates were made:</p> <p>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;</p> <p>[2] Requirements for a final follow-up visit for safety and limited efficacy evaluations at 52 weeks after the final dose. The reporting period for AEs was updated accordingly;</p> <p>[3] Cerebrospinal fluid biomarkers, Aβ1–42, T-tau, and P-tau, were changed to secondary objective from exploratory objectives. Clarification about MRI volumetric measures was also added.</p> <p>[4] Guidance was added for the shelf life of reconstituted IMP prepared under aseptic and non-aseptic conditions.</p> <p>[5] Reporting period for pregnancies was adjusted to take into account 5 half-lives of study medication, in agreement with the SOP for safety report process of the Sponsor.</p> <p>[6] Information regarding precautionary measures were added in the case of abnormally low neutrophils (moderate to severe neutropenia) to align WN25203 with other gantenerumab protocols.</p>
16 September 2015	<p>Following updates were made:</p> <p>[1] 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.</p>
09 July 2018	<p>Updated to allow subjects to continue receiving open-label gantenerumab until July 2020, at which time anticipated results from other relevant monoclonal antibody treatments targeting amyloid-beta will be available. Additional updates include: [1] Gantenerumab information has been updated; [2] MRI findings were updated; [3] Clarification of OLE phase objectives; [4] Storage parameters of solution at ambient temperature have been adjusted and [5] Conditions for recording MRI observations have been adjusted.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 December 2014	<p>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.</p>	16 September 2015

Notes:

Limitations and caveats

None reported