Clinical trial results:
A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

Summary

EudraCT number	2015-000966-72
Trial protocol	IT DE AT FR PT ES DK GB
Global end of trial date	08 August 2019

Results information

Result version number	v1
This version publication date	20 November 2020
First version publication date	20 November 2020

Trial information

Trial identification

Sponsor protocol code	221AD301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02477800
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.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	08 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score as compared with placebo in subjects with early Alzheimer's Disease (AD).

Protection of trial subjects:

Written informed consent was obtained from each subject or subject’s legally authorized representative (e.g., legal guardian), as applicable, prior to evaluations performed for eligibility. Subjects or the subject’s legally authorized representative were given adequate time to review the information in the informed consent/assent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 August 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 766
Country: Number of subjects enrolled	Italy: 116
Country: Number of subjects enrolled	Spain: 105
Country: Number of subjects enrolled	Australia: 102
Country: Number of subjects enrolled	Japan: 100
Country: Number of subjects enrolled	Germany: 97
Country: Number of subjects enrolled	Canada: 84
Country: Number of subjects enrolled	United Kingdom: 81
Country: Number of subjects enrolled	France: 60
Country: Number of subjects enrolled	Korea, Republic of: 50
Country: Number of subjects enrolled	Portugal: 47
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	Austria: 9

Worldwide total number of subjects	1653
EEA total number of subjects	538

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)	371
From 65 to 84 years	1272
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 169 investigational sites in Australia, Austria, Canada, Denmark, France, Germany, Italy, Japan, Portugal, Republic of Korea, Spain, Taiwan, the United Kingdom (UK) and the United States (US) from 13 August, 2015 to 04 July, 2018.

Pre-assignment

Screening details:

A total of 1653 subjects with Alzheimer's disease were enrolled and randomised in the study. Of these, 1647 subjects received the study drug in placebo-controlled (PC) period. After completing PC period, 852 subjects entered and dosed in long-term extension (LTE) period and no subjects completed the study due to early termination of the study.

Period 1

Period 1 title	Placebo-Controlled Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (PC Period)

Arm description:

Subjects received BIIB037-matching placebo intravenously (IV), once every 4 weeks in PC period for 1.8 years.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion, once every 4 weeks.

Arm title	BIIB037 Low Dose (PC Period)

Arm description:

Subjects received BIIB037 low dose, IV, once every 4 weeks in PC period for 1.8 years.

Arm type	Experimental
Investigational medicinal product name	BIIB037
Investigational medicinal product code	
Other name	Aducanumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion, once every 4 weeks.

Arm title	BIIB037 High Dose (PC Period)

Arm description:

Subjects received BIIB037 high dose, IV, once every 4 weeks in PC period for 1.8 years.

Arm type	Experimental

Investigational medicinal product name	BIIB037
Investigational medicinal product code	
Other name	Aducanumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion, once every 4 weeks.

Number of subjects in period 1[1]	Placebo (PC Period)	BIIB037 Low Dose (PC Period)	BIIB037 High Dose (PC Period)
Started	545	547	555
Completed	325	325	288
Not completed	220	222	267
Relocation	2	-	-
Adverse Event	16	25	28
Investigator Decision	3	2	1
Study Visit Burden	5	3	11
Disease Progression	1	-	1
Change of Treatment	1	2	1
Consent Withdrawn	26	16	27
Site Terminated By Sponsor	2	1	-
Death	-	3	2
Site Terminated by Investigator	1	1	1
Withdrawal by Parent/Guardian	1	5	3
Lost to follow-up	1	3	3
Reason not Specified	161	161	189

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported in the baseline period is for intent to treat population (545 subjects in placebo arm, 547 subjects in BIIB037 Low Dose arm, 555 subjects in BIIB037 High Dose arm).

Period 2

Period 2 title	Long Term Extension Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	BIIB037 Late Start: Low Dose (LTE Period)

Arm description:

Following PC period, subjects randomized to placebo received BIIB037 low dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.

Arm type	Experimental
Investigational medicinal product name	BIIB037
Investigational medicinal product code	
Other name	Aducanumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion, once every 4 weeks.

Arm title	BIIB037 Late Start: High Dose (LTE Period)

Arm description:

Following PC period, subjects randomized to placebo received BIIB037 high dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.

Arm type	Experimental
Investigational medicinal product name	BIIB037
Investigational medicinal product code	
Other name	Aducanumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion, once every 4 weeks.

Arm title	BIIB037 Early Start: Low Dose (LTE Period)

Arm description:

Following PC period, subjects randomized to low dose BIIB037 continued to receive the same dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.

Arm type	Experimental
Investigational medicinal product name	BIIB037
Investigational medicinal product code	
Other name	Aducanumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion, once every 4 weeks.

Arm title	BIIB037 Early Start: High Dose (LTE Period)

Arm description:

Following PC period, subjects randomized to high dose BIIB037 continued to receive the same dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.

Arm type	Experimental
Investigational medicinal product name	BIIB037
Investigational medicinal product code	
Other name	Aducanumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion, once every 4 weeks.

Number of subjects in period 2[2]	BIIB037 Late Start: Low Dose (LTE Period)	BIIB037 Late Start: High Dose (LTE Period)	BIIB037 Early Start: Low Dose (LTE Period)
Started	150	152	299
Completed	0	0	0
Not completed	150	152	299
Site Terminated By Sponsor	-	-	2
Adverse Event	6	2	4
Death	1	1	1
Withdrawal by Parent/Guardian	1	3	3
Investigator Decision	-	-	-
Lost to follow-up	-	1	3
Study Visit Burden	3	-	2
Disease Progression	3	1	1
Reason not Specified	126	140	270
Consent Withdrawn	10	4	13

Number of subjects in period 2[2]	BIIB037 Early Start: High Dose (LTE Period)
Started	251
Completed	0
Not completed	251
Site Terminated By Sponsor	1
Adverse Event	3
Death	2
Withdrawal by Parent/Guardian	1
Investigator Decision	2
Lost to follow-up	-
Study Visit Burden	2
Disease Progression	-
Reason not Specified	224
Consent Withdrawn	16

Notes:

[2] - 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: 938 subjects completed the PC period, out of which only 852 subjects entered in LTE period. 86 subjects from PC period did not enter LTE period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo (PC Period)
Reporting group description:	
Subjects received BIIB037-matching placebo intravenously (IV), once every 4 weeks in PC period for 1.8 years.	
Reporting group title	BIIB037 Low Dose (PC Period)
Reporting group description:	
Subjects received BIIB037 low dose, IV, once every 4 weeks in PC period for 1.8 years.	
Reporting group title	BIIB037 High Dose (PC Period)
Reporting group description:	
Subjects received BIIB037 high dose, IV, once every 4 weeks in PC period for 1.8 years.	

Reporting group values	Placebo (PC Period)	BIIB037 Low Dose (PC Period)	BIIB037 High Dose (PC Period)
Number of subjects	545	547	555
Age categorical			
Units: subjects			
Age Continuous			
Units: years			
arithmetic mean	69.8	70.4	70.0
standard deviation	± 7.72	± 6.96	± 7.65
Sex: Female, Male			
Units: subjects			
Female	287	284	292
Male	258	263	263
Race			
Units: Subjects			
Asian	55	55	65
Black or African American	5	1	2
Native Hawaiian or other Pacific Islander	0	1	0
White	413	412	413
Not reported due to confidentiality regulations	69	74	72
Other	3	4	3
Ethnicity			
Units: Subjects			
Hispanic or Latino	13	11	13
Not Hispanic or Latino	489	492	499
Not reported due to confidentiality regulations	43	44	43

Reporting group values	Total		
Number of subjects	1647		
Age categorical			
Units: subjects			

Age Continuous Units: years arithmetic mean standard deviation	- 		
Sex: Female, Male Units: subjects			
Female Male	863 784		
Race Units: Subjects			
Asian Black or African American Native Hawaiian or other Pacific Islander White Not reported due to confidentiality regulations Other	175 8 1 1238 215 10		
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Not reported due to confidentiality regulations	37 1480 130		

End points

End points reporting groups

Reporting group title	Placebo (PC Period)
Reporting group description:	
Subjects received BIIB037-matching placebo intravenously (IV), once every 4 weeks in PC period for 1.8 years.	
Reporting group title	BIIB037 Low Dose (PC Period)
Reporting group description:	
Subjects received BIIB037 low dose, IV, once every 4 weeks in PC period for 1.8 years.	
Reporting group title	BIIB037 High Dose (PC Period)
Reporting group description:	
Subjects received BIIB037 high dose, IV, once every 4 weeks in PC period for 1.8 years.	
Reporting group title	BIIB037 Late Start: Low Dose (LTE Period)
Reporting group description:	
Following PC period, subjects randomized to placebo received BIIB037 low dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.	
Reporting group title	BIIB037 Late Start: High Dose (LTE Period)
Reporting group description:	
Following PC period, subjects randomized to placebo received BIIB037 high dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.	
Reporting group title	BIIB037 Early Start: Low Dose (LTE Period)
Reporting group description:	
Following PC period, subjects randomized to low dose BIIB037 continued to receive the same dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.	
Reporting group title	BIIB037 Early Start: High Dose (LTE Period)
Reporting group description:	
Following PC period, subjects randomized to high dose BIIB037 continued to receive the same dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.	

Primary: Change from Baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB) Score at Week 78

End point title	Change from Baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB) Score at Week 78
End point description:	
CDR-SB integrates assessments from 3 domains of cognition (memory, orientation, judgment/problem-solving) and 3 domains of function (community affairs, home/hobbies, personal care). Following caregiver interview and systematic patient examination, the rater assigns a score describing the subject's current performance level in each of these domains of life functioning. Prespecified severity anchors range from none = 0, questionable = 0.5, mild = 1, moderate = 2 to severe = 3 (the personal care domain omits the 0.5 score). "Sum of boxes" scoring methodology sums the score for each of the 6 domains and provides a value ranging from 0 to 18 that can change in increments of 0.5 or greater. Higher scores indicate greater disease severity. Mixed model for repeated measures (MMRM) analysis was used to analyse change from baseline in CDR-SB. A positive change from baseline indicates clinical decline. Intent-to-Treat (ITT) population. n=number of subjects analysed at specific timepoint.	
End point type	Primary
End point timeframe:	
Baseline, Week 78	

End point values	Placebo (PC Period)	BIIB037 Low Dose (PC Period)	BIIB037 High Dose (PC Period)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	545	547	555	
Units: score on a scale				
arithmetic mean (standard error)				
Change at Week 78 (n =333,331,295)	1.56 (± 0.108)	1.38 (± 0.108)	1.59 (± 0.111)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB037 Low Dose

Statistical analysis description:

Adjusted mean for each treatment group (Placebo, BIIB037 Low Dose, BIIB037 High Dose), difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Comparison groups	Placebo (PC Period) v BIIB037 Low Dose (PC Period)
Number of subjects included in analysis	1092
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.225
Method	MMRM Model
Parameter estimate	Difference from Placebo
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.469
upper limit	0.11

Statistical analysis title	Placebo vs BIIB037 High Dose

Statistical analysis description:

Adjusted mean for each treatment group (Placebo, BIIB037 Low Dose, BIIB037 High Dose), difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Comparison groups	Placebo (PC Period) v BIIB037 High Dose (PC Period)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.833
Method	MMRM Model
Parameter estimate	Difference from Placebo
Point estimate	0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.262
upper limit	0.326

Secondary: Change from Baseline in Mini-Mental State Examination (MMSE) Score at Week 78

End point title	Change from Baseline in Mini-Mental State Examination (MMSE) Score at Week 78

End point description:

The MMSE is a widely used performance-based test of global cognitive status. It consists of 11 tasks that assess orientation, word recall, attention and calculation, language abilities, and visuospatial functions. The scores from the 11 tests are combined to obtain the total score, which ranges from 0 to 30, with lower scores over time indicating increasing cognitive impairment. MMRM analysis was used to analyse change from baseline in MMSE. A negative change from baseline indicates clinical decline. ITT is defined as all randomised subjects who had received at least one dose of study treatment (Aducanumab or Placebo). Here, 'n' signifies number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 78

End point values	Placebo (PC Period)	BIIB037 Low Dose (PC Period)	BIIB037 High Dose (PC Period)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	545	547	555	
Units: score on a scale				
arithmetic mean (standard error)				
Change at Week 78 (n=332,334,297)	-3.5 (± 0.21)	-3.3 (± 0.21)	-3.6 (± 0.21)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB037 Low Dose

Statistical analysis description:

Adjusted mean for each treatment group (Placebo, BIIB037 Low Dose, BIIB037 High Dose), difference from Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MMSE as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline MMSE, baseline MMSE by visit interaction, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Comparison groups	Placebo (PC Period) v BIIB037 Low Dose (PC Period)
Number of subjects included in analysis	1092
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4795
Method	MMRM Model
Parameter estimate	Difference from Placebo
Point estimate	0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.74

Statistical analysis title	Placebo vs BIIB037 High Dose

Statistical analysis description:

Adjusted mean for each treatment group (Placebo, BIIB037 Low Dose, BIIB037 High Dose), difference from Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MMSE as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline MMSE, baseline MMSE by visit interaction, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Comparison groups	Placebo (PC Period) v BIIB037 High Dose (PC Period)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8106
Method	MMRM Model
Parameter estimate	Difference from Placebo
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.49

Secondary: Change from Baseline in Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) (ADAS-Cog 13) Score at Week 78

End point title	Change from Baseline in Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) (ADAS-Cog 13) Score at Week 78

End point description:

ADAS-Cog13 comprises both cognitive tasks and clinical ratings of cognitive performance. The scale items capture word recall, ability to follow commands, the ability to correctly copy or draw an image, naming, the ability to interact with everyday objects, orientation, word recognition, memory, comprehension of spoken language, word-finding, and language ability, with a measure for delayed word recall and concentration/distractibility. The total score ranges from 0 to 85. An increase in score over time indicates increasing cognitive impairment. MMRM analysis was used to analyse change from baseline in ADAS-Cog 13. A positive change from baseline indicates clinical decline. ITT is defined as all randomised subjects who had received at least one dose of study treatment (Aducanumab or Placebo). Here, 'n' signifies number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 78

End point values	Placebo (PC Period)	BIIB037 Low Dose (PC Period)	BIIB037 High Dose (PC Period)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	545	547	555	
Units: score on a scale				
arithmetic mean (standard error)				
Change at Week 78 (n=331,332,294)	5.140 (± 0.3783)	4.558 (± 0.3780)	4.552 (± 0.3872)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB037 Low Dose

Statistical analysis description:

Adjusted mean for each treatment group (Placebo,BIIB037 Low Dose,BIIB037 High Dose),difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in ADAS-Cog 13 as dependent variable and with fixed effects of treatment group,categorical visit,treatment-by-visit interaction,baseline ADAS-Cog 13,baseline ADAS-Cog 13 by visit interaction,baseline MMSE,AD symptomatic medication use at baseline,region,and laboratory ApoE status.

Comparison groups	Placebo (PC Period) v BIIB037 Low Dose (PC Period)
Number of subjects included in analysis	1092
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2536
Method	MMRM Model
Parameter estimate	Difference from Placebo
Point estimate	-0.583
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5835
upper limit	0.4181

Statistical analysis title	Placebo vs BIIB037 High Dose

Statistical analysis description:

Adjusted mean for each treatment group (Placebo,BIIB037 Low Dose,BIIB037 High Dose),difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in ADAS-Cog 13 as dependent variable and with fixed effects of treatment group,categorical visit,treatment-by-visit interaction,baseline ADAS-Cog 13,baseline ADAS-Cog 13 by visit interaction,baseline MMSE,AD symptomatic medication use at baseline,region,and laboratory ApoE status.

Comparison groups	Placebo (PC Period) v BIIB037 High Dose (PC Period)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2578
Method	MMRM Model
Parameter estimate	Difference from Placebo
Point estimate	-0.588

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6067
upper limit	0.4309

Secondary: Change from Baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI) Score at Week 78

End point title	Change from Baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI) Score at Week 78

End point description:

The ADCS-ADL-MCI consists of 17 instrumental items (e.g., shopping, preparing meals, using household appliances) and 1 basic item (getting dressed). Ratings reflect caregiver observations about the patient's actual functioning over the previous month and provide an assessment of change in the functional state of the participant over time. The total score ranges from 0 to 53, with lower values over time reflecting functional deterioration. MMRM analysis was used to analyse change from baseline in ADAS-ADL-MCI. A negative change from baseline indicates clinical decline. ITT is defined as all randomised subjects who had received at least one dose of study treatment (Aducanumab or Placebo). Here, 'n' signifies number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 78

End point values	Placebo (PC Period)	BIIB037 Low Dose (PC Period)	BIIB037 High Dose (PC Period)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	545	547	555	
Units: score on a scale				
arithmetic mean (standard error)				
Change at Week 78 (n=331,330,298)	-3.8 (± 0.35)	-3.1 (± 0.35)	-3.1 (± 0.35)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB037 Low Dose

Statistical analysis description:

Adjusted mean for each group (Placebo, BIIB037 Low Dose, BIIB037 High Dose), difference with Placebo,95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in ADCS-ADL-MCI as dependent variable and with fixed effects of treatment group,categorical visit,treatment-by-visit interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by visit interaction, baseline MMSE AD symptomatic medication use at baseline,region, and laboratory ApoE status.

Comparison groups	Placebo (PC Period) v BIIB037 Low Dose (PC Period)

Number of subjects included in analysis	1092
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1225
Method	MMRM Model
Parameter estimate	Difference from Placebo
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	1.64

Statistical analysis title	Placebo vs BIIB037 High Dose

Statistical analysis description:

Adjusted mean for each group (Placebo, BIIB037 Low Dose, BIIB037 High Dose), difference with Placebo,95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in ADCS-ADL-MCI as dependent variable and with fixed effects of treatment group,categorical visit,treatment-by-visit interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by visit interaction, baseline MMSE AD symptomatic medication use at baseline,region, and laboratory ApoE status.

Comparison groups	Placebo (PC Period) v BIIB037 High Dose (PC Period)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1506
Method	MMRM Model
Parameter estimate	Difference from Placebo
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	1.61

Adverse events

Adverse events information

Timeframe for reporting adverse events:

End of study (up to 4 years)

Adverse event reporting additional description:

Safety population was all randomised subjects who received at least one dose of study treatment. In PC period, 5 subjects randomised to placebo, inadvertently received 1 or more doses of active treatment during the PC period. For subjects affected, a subject was counted only once within each system organ class/preferred term/study period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo (PC Period)

Reporting group description:

Subjects received BIIB037 matching placebo intravenously (IV), once every 4 weeks in PC period for 1.5 years.

Reporting group title	BIIB037 High Dose (PC Period)

Reporting group description:

Subjects received BIIB037 high dose, IV, once every 4 weeks in PC period for 1.5 years.

Reporting group title	BIIB037 Low Dose (PC Period)

Reporting group description:

Subjects received BIIB037 low dose, IV, once every 4 weeks in PC period for 1.5 years.

Reporting group title	BIIB037 Late Start: Low Dose (LTE Period)

Reporting group description:

Following PC period, subjects randomized to placebo received BIIB037 low dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.

Reporting group title	BIIB037 Late Start High Dose (LTE Period)

Reporting group description:

Following PC period, subjects randomized to placebo received BIIB037 high dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period

Reporting group title	BIIB037 Early Start: Low Dose (LTE Period)

Reporting group description:

Following PC period, subjects randomized to low dose BIIB037 continued to receive the same dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.

Reporting group title	BIIB037 Early Start: High Dose (LTE Period)

Reporting group description:

Following PC period, subjects randomized to high dose BIIB037 continued to receive the same dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.

Serious adverse events	Placebo (PC Period)	BIIB037 High Dose (PC Period)	BIIB037 Low Dose (PC Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	70 / 540 (12.96%)	79 / 558 (14.16%)	76 / 549 (13.84%)
number of deaths (all causes)	0	2	3
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Adenocarcinoma of colon			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	0 / 549 (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
Breast cancer stage i			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive papillary breast carcinoma			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung adenocarcinoma			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Lymphoma			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	2 / 540 (0.37%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesothelioma			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Metastases to liver			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to peritoneum			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Myeloproliferative neoplasm			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Neurofibrosarcoma			

subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer stage iii			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Pancreatic carcinoma			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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 carcinoma metastatic			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polycythaemia vera			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Prostate cancer stage 0			

subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Transitional cell carcinoma			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Tubular breast carcinoma			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Aortic dissection			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 540 (0.19%)	4 / 558 (0.72%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			

subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Hypotension			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Peripheral artery stenosis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	0 / 549 (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
Chest pain			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Fatigue			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Gait disturbance			

subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	2 / 549 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Incarcerated hernia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Non-cardiac chest pain			
subjects affected / exposed	3 / 540 (0.56%)	2 / 558 (0.36%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Prostatic dysplasia			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
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, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Asthmatic crisis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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

Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Nasal obstruction			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Organising pneumonia			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Pneumothorax			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 540 (0.37%)	3 / 558 (0.54%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary infarction			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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 failure			

subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
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			
Agitation			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Completed suicide			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Delirium			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Generalised anxiety disorder			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Mental status changes			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Persistent depressive disorder			

subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Psychogenic tremor			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Psychotic disorder			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Suicide attempt			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	2 / 549 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood ketone body increased			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Blood pressure increased			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	2 / 540 (0.37%)	0 / 558 (0.00%)	0 / 549 (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
Compression fracture			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Concussion			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Craniocerebral injury			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Exposure to toxic agent			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Extradural haematoma			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Facial bones fracture			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	6 / 540 (1.11%)	4 / 558 (0.72%)	12 / 549 (2.19%)
occurrences causally related to treatment / all	0 / 7	0 / 4	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	2 / 540 (0.37%)	1 / 558 (0.18%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	2 / 549 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			

subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Forearm fracture			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	2 / 540 (0.37%)	0 / 558 (0.00%)	0 / 549 (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
Heat illness			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Humerus fracture			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	2 / 549 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament injury			

subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Limb crushing injury			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Lumbar vertebral fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Meniscus injury			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Postoperative respiratory failure			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Radius fracture			

subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	2 / 549 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	2 / 540 (0.37%)	1 / 558 (0.18%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scapula fracture			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Skull fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Subdural haematoma			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	0 / 549 (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
Subdural haemorrhage			

subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Thermal burn			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Tibia fracture			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Tooth fracture			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Ulna fracture			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Upper limb fracture			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Wrist fracture			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Encephalocele			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Hypertrophic cardiomyopathy			

subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	0 / 549 (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
Angina pectoris			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Arrhythmia			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	6 / 540 (1.11%)	3 / 558 (0.54%)	4 / 549 (0.73%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Bradycardia			

subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle branch block right			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Cardiac arrest			
subjects affected / exposed	0 / 540 (0.00%)	2 / 558 (0.36%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Cardiac failure congestive			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	0 / 549 (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
Coronary artery disease			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	0 / 549 (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
Coronary artery occlusion			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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 stenosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Mitral valve incompetence			

subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Myocardial infarction			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits			
subjects affected / exposed	0 / 540 (0.00%)	2 / 558 (0.36%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amyloid related imaging			

abnormality-oedema/effusion			
subjects affected / exposed	0 / 540 (0.00%)	7 / 558 (1.25%)	2 / 549 (0.36%)
occurrences causally related to treatment / all	0 / 0	9 / 9	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Balance disorder			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Cerebral infarction			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Cerebral ischaemia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	2 / 549 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dementia			

subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
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 alzheimer's type			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Dementia with lewy bodies			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Dystonia			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Focal dyscognitive seizures			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Haemorrhage intracranial			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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 discomfort			

subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Headache			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Ischaemic stroke			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar stroke			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Loss of consciousness			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Myasthenia gravis			

subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Myelitis transverse			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Myoclonus			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Orthostatic intolerance			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Parkinson's disease			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Peroneal nerve palsy			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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			

subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	2 / 549 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 540 (0.37%)	0 / 558 (0.00%)	0 / 549 (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
Superficial siderosis of central nervous system			
subjects affected / exposed	0 / 540 (0.00%)	2 / 558 (0.36%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 540 (0.37%)	5 / 558 (0.90%)	4 / 549 (0.73%)
occurrences causally related to treatment / all	1 / 2	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	2 / 549 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral artery dissection			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Blood and lymphatic system disorders			
Blood loss anaemia			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Leukocytosis			

subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Ear and labyrinth disorders			
Labyrinthine fistula			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Eye disorders			
Cataract			
subjects affected / exposed	2 / 540 (0.37%)	1 / 558 (0.18%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Retinal artery occlusion			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Abdominal pain			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Abdominal pain lower			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Constipation			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Duodenal ulcer			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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 haemorrhage			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	0 / 549 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Haemorrhoids			

subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Inguinal hernia			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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 obstruction			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
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 perforation			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	0 / 549 (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
Large intestinal ulcer			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Large intestine perforation			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Large intestine polyp			

subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Mallory-weiss syndrome			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Melaena			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Obstructive pancreatitis			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	2 / 549 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal ulcer			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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 disorder			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Pancreatitis acute			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
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			
Bile duct stone			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Cholangitis acute			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	0 / 549 (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
Cholelithiasis			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	0 / 549 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Nephrolithiasis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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 colic			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Ureterolithiasis			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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			
Bone pain			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Intervertebral disc compression			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Muscular weakness			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Osteoarthritis			
subjects affected / exposed	0 / 540 (0.00%)	2 / 558 (0.36%)	2 / 549 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Spondylolisthesis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Vertebral osteophyte			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 540 (0.19%)	1 / 558 (0.18%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			

subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Arthritis bacterial			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Bronchitis			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Candida infection			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 540 (0.37%)	0 / 558 (0.00%)	0 / 549 (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
Cholecystitis infective			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Diverticulitis			
subjects affected / exposed	0 / 540 (0.00%)	2 / 558 (0.36%)	0 / 549 (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
Escherichia urinary tract infection			

subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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			
subjects affected / exposed	0 / 540 (0.00%)	2 / 558 (0.36%)	0 / 549 (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
Infection			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Influenza			
subjects affected / exposed	2 / 540 (0.37%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 540 (0.37%)	4 / 558 (0.72%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Post procedural infection			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Post procedural sepsis			

subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Postoperative wound infection			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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
Respiratory tract infection			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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			
subjects affected / exposed	0 / 540 (0.00%)	1 / 558 (0.18%)	0 / 549 (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
Serratia infection			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Urosepsis			

subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Wound infection staphylococcal			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	2 / 540 (0.37%)	0 / 558 (0.00%)	0 / 549 (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
Gout			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Hypoglycaemia			
subjects affected / exposed	1 / 540 (0.19%)	0 / 558 (0.00%)	0 / 549 (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
Hypokalaemia			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	1 / 549 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (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

Serious adverse events	BIIB037 Late Start:	BIIB037 Late Start	BIIB037 Early Start:

	Low Dose (LTE Period)	High Dose (LTE Period)	Low Dose (LTE Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 150 (12.67%)	14 / 152 (9.21%)	35 / 299 (11.71%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Adenocarcinoma of colon			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 i			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Colon cancer			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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

Invasive papillary breast carcinoma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Lung adenocarcinoma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Lymphoma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Malignant melanoma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Mesothelioma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 liver			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 peritoneum			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Myeloproliferative neoplasm			

subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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
Neurofibrosarcoma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Non-small cell lung cancer			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Ovarian cancer stage iii			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 carcinoma			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Polycythaemia vera			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer stage 0			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Tubular breast carcinoma			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			
Aortic aneurysm			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Aortic dissection			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Aortic stenosis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Hypertension			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Hypertensive emergency			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Peripheral artery stenosis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Chest pain			
subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	0 / 299 (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
Fatigue			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated hernia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Prostatic dysplasia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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

Asthmatic crisis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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
Nasal obstruction			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Organising pneumonia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 effusion			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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 aspiration			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Pneumothorax			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	2 / 299 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary infarction			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Respiratory failure			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Completed suicide			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Delirium			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Generalised anxiety disorder			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Persistent depressive disorder			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Psychogenic tremor			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Suicide attempt			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 ketone body increased			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 pressure increased			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			
Cervical vertebral fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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

Compression fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Concussion			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exposure to toxic agent			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Extradural haematoma			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Facial bones fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	4 / 150 (2.67%)	0 / 152 (0.00%)	7 / 299 (2.34%)
occurrences causally related to treatment / all	0 / 5	0 / 0	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			

subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Fibula fracture			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Foot fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Forearm fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Heat illness			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	2 / 299 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 dislocation			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Ligament injury			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Limb crushing injury			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 limb fracture			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Meniscus injury			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Overdose			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Post procedural complication			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative respiratory failure			

subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Rib fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Scapula fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Skull fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Spinal compression fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Spinal fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			

subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Subdural haemorrhage			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Thermal burn			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Tooth fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Ulna fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Wrist fracture			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Congenital, familial and genetic disorders			
Encephalocele			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			
subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	2 / 299 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Arrhythmia			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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 fibrillation			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 complete			

subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Bradycardia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Bundle branch block right			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 arrest			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 congestive			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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
Coronary artery occlusion			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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
Coronary artery stenosis			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Mitral valve incompetence			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Tachycardia			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits			

subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amyloid related imaging abnormality-oedema/effusion			
subjects affected / exposed	2 / 150 (1.33%)	2 / 152 (1.32%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	2 / 2	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Balance disorder			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 infarction			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Cerebrovascular accident			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Dementia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Dementia alzheimer's type			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dementia with lewy bodies			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Dysarthria			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dystonia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Focal dyscognitive seizures			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Haemorrhage intracranial			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head discomfort			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Hypoaesthesia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Lacunar infarction			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Lacunar stroke			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Loss of consciousness			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Migraine			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Myasthenia gravis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Myelitis transverse			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Myoclonus			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
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 disorder			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic intolerance			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Peroneal nerve palsy			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Presyncope			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Seizure			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Superficial siderosis of central nervous system			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Syncope			
subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	2 / 299 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral artery dissection			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			
Blood loss anaemia			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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
Ear and labyrinth disorders			
Labyrinthine fistula			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Diplopia			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Retinal artery occlusion			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain lower			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Constipation			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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
Enteritis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Gastritis			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Haemorrhoids			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Hiatus hernia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Ileus			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Intestinal perforation			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Large intestinal ulcer			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Large intestine perforation			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Large intestine polyp			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Mallory-weiss syndrome			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Melaena			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Obstructive pancreatitis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Oesophageal ulcer			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic disorder			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Cholangitis acute			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Cholecystitis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Cholecystitis acute			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Urticaria			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Nephrolithiasis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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 colic			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Ureterolithiasis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Intervertebral disc compression			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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

Intervertebral disc protrusion			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Muscular weakness			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Osteoarthritis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	2 / 299 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Vertebral osteophyte			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
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			

Appendicitis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Appendicitis perforated			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Arthritis bacterial			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Arthritis infective			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Bronchitis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida infection			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Cellulitis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Cholecystitis infective			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Diverticulitis			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Escherichia urinary tract infection			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Gastroenteritis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Influenza			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Paronychia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Pneumonia			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 299 (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 pneumococcal			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Post procedural sepsis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 299 (0.33%)
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	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Serratia infection			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Staphylococcal infection			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Subcutaneous abscess			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Urinary tract infection			

subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 299 (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
Urosepsis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Wound infection staphylococcal			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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			
Decreased appetite			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Dehydration			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Hypoglycaemia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Hypokalaemia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (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
Hyponatraemia			

subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	1 / 299 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	BIIB037 Early Start: High Dose (LTE Period)		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 251 (9.96%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer stage i			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon cancer			

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric cancer				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Invasive papillary breast carcinoma				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymphoma				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mesothelioma				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to liver				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to peritoneum				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myeloproliferative neoplasm				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neurofibrosarcoma				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-small cell lung cancer				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal adenocarcinoma				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ovarian cancer stage iii				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma metastatic				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Polycythaemia vera				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer stage 0				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transitional cell carcinoma				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tubular breast carcinoma				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic aneurysm				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic dissection				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic stenosis				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertensive emergency				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral artery stenosis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gait disturbance				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Incarcerated hernia				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Benign prostatic hyperplasia				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostatic dysplasia				

subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 251 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthmatic crisis			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasal obstruction			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Organising pneumonia			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			

subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary infarction				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Agitation				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Delirium				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depression				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Generalised anxiety disorder				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Persistent depressive disorder				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychogenic tremor				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood ketone body increased				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood pressure increased				

subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Compression fracture			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Exposure to toxic agent			
subjects affected / exposed	1 / 251 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Extradural haematoma			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Facial bones fracture			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			

subjects affected / exposed	2 / 251 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fibula fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Forearm fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Heat illness				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaw fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament injury				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Limb crushing injury				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meniscus injury				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Overdose				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural complication				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative respiratory failure				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Scapula fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skull fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haemorrhage				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tooth fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ulna fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				

subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Encephalocele				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertrophic cardiomyopathy				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Atrial flutter				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block complete				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bundle branch block right				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery occlusion				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mitral valve incompetence				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus bradycardia				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus node dysfunction				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Amyloid related imaging abnormality-oedema/effusion				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Balance disorder				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carotid artery stenosis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haematoma				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Cerebral infarction				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dementia				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dementia alzheimer's type				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dementia with lewy bodies				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dystonia				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Focal dyscognitive seizures				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Generalised tonic-clonic seizure				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Head discomfort				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	2 / 251 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lacunar infarction				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lacunar stroke				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myasthenia gravis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myelitis transverse				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myoclonus				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorder				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Orthostatic intolerance				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Parkinson's disease				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peroneal nerve palsy				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Superficial siderosis of central nervous system				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				

subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vertebral artery dissection			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Blood loss anaemia			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leukocytosis			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Labyrinthine fistula			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diplopia			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal artery occlusion			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain lower			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulum intestinal			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hiatus hernia				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	2 / 251 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal ulcer				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mallory-weiss syndrome				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstructive pancreatitis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal ulcer				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic disorder				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stone				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis acute				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				

subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal colic			
subjects affected / exposed	1 / 251 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue			

disorders				
Bone pain				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc compression				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rotator cuff syndrome				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spondylolisthesis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vertebral foraminal stenosis				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vertebral osteophyte				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis perforated				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis infective				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Candida infection				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				

subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis infective				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia urinary tract infection				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paronychia				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia pneumococcal				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural infection				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural sepsis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 251 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Serratia infection				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				

subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound infection staphylococcal				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gout				
subjects affected / exposed	0 / 251 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				

subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo (PC Period)	BIIB037 High Dose (PC Period)	BIIB037 Low Dose (PC Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	327 / 540 (60.56%)	410 / 558 (73.48%)	396 / 549 (72.13%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	23 / 540 (4.26%)	36 / 558 (6.45%)	33 / 549 (6.01%)
occurrences (all)	33	49	46
Fall			
subjects affected / exposed	54 / 540 (10.00%)	83 / 558 (14.87%)	70 / 549 (12.75%)
occurrences (all)	74	102	96
Nervous system disorders			
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits			
subjects affected / exposed	34 / 540 (6.30%)	102 / 558 (18.28%)	89 / 549 (16.21%)
occurrences (all)	41	141	129
Amyloid related imaging abnormality-oedema/effusion			
subjects affected / exposed	16 / 540 (2.96%)	195 / 558 (34.95%)	140 / 549 (25.50%)
occurrences (all)	16	308	225
Dizziness			

subjects affected / exposed	54 / 540 (10.00%)	54 / 558 (9.68%)	49 / 549 (8.93%)
occurrences (all)	66	76	71
Headache			
subjects affected / exposed	81 / 540 (15.00%)	115 / 558 (20.61%)	98 / 549 (17.85%)
occurrences (all)	149	173	160
Superficial siderosis of central nervous system			
subjects affected / exposed	10 / 540 (1.85%)	88 / 558 (15.77%)	51 / 549 (9.29%)
occurrences (all)	12	134	77
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	38 / 540 (7.04%)	34 / 558 (6.09%)	30 / 549 (5.46%)
occurrences (all)	45	39	34
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	44 / 540 (8.15%)	52 / 558 (9.32%)	49 / 549 (8.93%)
occurrences (all)	54	66	64
Nausea			
subjects affected / exposed	42 / 540 (7.78%)	40 / 558 (7.17%)	30 / 549 (5.46%)
occurrences (all)	53	49	38
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	33 / 540 (6.11%)	19 / 558 (3.41%)	29 / 549 (5.28%)
occurrences (all)	36	23	31
Psychiatric disorders			
Anxiety			
subjects affected / exposed	28 / 540 (5.19%)	28 / 558 (5.02%)	32 / 549 (5.83%)
occurrences (all)	29	28	34
Depression			
subjects affected / exposed	34 / 540 (6.30%)	34 / 558 (6.09%)	40 / 549 (7.29%)
occurrences (all)	35	35	41
Confusional state			
subjects affected / exposed	0 / 540 (0.00%)	0 / 558 (0.00%)	0 / 549 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	28 / 540 (5.19%)	35 / 558 (6.27%)	27 / 549 (4.92%)
occurrences (all)	38	44	30
Back pain			
subjects affected / exposed	42 / 540 (7.78%)	44 / 558 (7.89%)	26 / 549 (4.74%)
occurrences (all)	45	52	29
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	64 / 540 (11.85%)	68 / 558 (12.19%)	65 / 549 (11.84%)
occurrences (all)	95	90	85
Upper respiratory tract infection			
subjects affected / exposed	49 / 540 (9.07%)	51 / 558 (9.14%)	47 / 549 (8.56%)
occurrences (all)	73	59	59
Urinary tract infection			
subjects affected / exposed	37 / 540 (6.85%)	34 / 558 (6.09%)	30 / 549 (5.46%)
occurrences (all)	43	44	42

Non-serious adverse events	BIIB037 Late Start: Low Dose (LTE Period)	BIIB037 Late Start High Dose (LTE Period)	BIIB037 Early Start: Low Dose (LTE Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 150 (59.33%)	90 / 152 (59.21%)	130 / 299 (43.48%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 150 (2.67%)	6 / 152 (3.95%)	17 / 299 (5.69%)
occurrences (all)	4	6	20
Fall			
subjects affected / exposed	11 / 150 (7.33%)	18 / 152 (11.84%)	28 / 299 (9.36%)
occurrences (all)	14	24	36
Nervous system disorders			
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits			
subjects affected / exposed	23 / 150 (15.33%)	22 / 152 (14.47%)	16 / 299 (5.35%)
occurrences (all)	29	30	19
Amyloid related imaging abnormality-oedema/effusion			
subjects affected / exposed	33 / 150 (22.00%)	43 / 152 (28.29%)	19 / 299 (6.35%)
occurrences (all)	56	65	25
Dizziness			

subjects affected / exposed	6 / 150 (4.00%)	4 / 152 (2.63%)	14 / 299 (4.68%)
occurrences (all)	7	6	18
Headache			
subjects affected / exposed	14 / 150 (9.33%)	19 / 152 (12.50%)	27 / 299 (9.03%)
occurrences (all)	19	42	40
Superficial siderosis of central nervous system			
subjects affected / exposed	15 / 150 (10.00%)	17 / 152 (11.18%)	9 / 299 (3.01%)
occurrences (all)	24	24	9
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 150 (4.00%)	8 / 152 (5.26%)	16 / 299 (5.35%)
occurrences (all)	7	11	18
Nausea			
subjects affected / exposed	5 / 150 (3.33%)	10 / 152 (6.58%)	13 / 299 (4.35%)
occurrences (all)	6	10	14
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 150 (6.00%)	4 / 152 (2.63%)	12 / 299 (4.01%)
occurrences (all)	10	4	13
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 150 (4.67%)	4 / 152 (2.63%)	12 / 299 (4.01%)
occurrences (all)	8	4	13
Depression			
subjects affected / exposed	8 / 150 (5.33%)	5 / 152 (3.29%)	9 / 299 (3.01%)
occurrences (all)	8	5	9
Confusional state			
subjects affected / exposed	5 / 150 (3.33%)	9 / 152 (5.92%)	4 / 299 (1.34%)
occurrences (all)	6	10	5
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 299 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 150 (7.33%)	11 / 152 (7.24%)	20 / 299 (6.69%)
occurrences (all)	13	17	29
Upper respiratory tract infection			
subjects affected / exposed	10 / 150 (6.67%)	12 / 152 (7.89%)	21 / 299 (7.02%)
occurrences (all)	12	15	25
Urinary tract infection			
subjects affected / exposed	12 / 150 (8.00%)	5 / 152 (3.29%)	16 / 299 (5.35%)
occurrences (all)	20	5	28

Non-serious adverse events	BIIB037 Early Start: High Dose (LTE Period)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 251 (48.21%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 251 (1.59%)		
occurrences (all)	5		
Fall			
subjects affected / exposed	22 / 251 (8.76%)		
occurrences (all)	25		
Nervous system disorders			
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits			
subjects affected / exposed	18 / 251 (7.17%)		
occurrences (all)	23		
Amyloid related imaging abnormality-oedema/effusion			
subjects affected / exposed	21 / 251 (8.37%)		
occurrences (all)	27		
Dizziness			

subjects affected / exposed	13 / 251 (5.18%)		
occurrences (all)	14		
Headache			
subjects affected / exposed	24 / 251 (9.56%)		
occurrences (all)	30		
Superficial siderosis of central nervous system			
subjects affected / exposed	14 / 251 (5.58%)		
occurrences (all)	15		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 251 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 251 (3.59%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	6 / 251 (2.39%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 251 (2.39%)		
occurrences (all)	8		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	14 / 251 (5.58%)		
occurrences (all)	15		
Depression			
subjects affected / exposed	9 / 251 (3.59%)		
occurrences (all)	9		
Confusional state			
subjects affected / exposed	3 / 251 (1.20%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	0 / 251 (0.00%) 0 0 / 251 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 15 / 251 (5.98%) 20 20 / 251 (7.97%) 24 14 / 251 (5.58%) 18		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2016	(1) To allow subjects who suspend dosing after a first observance of amyloid-related imaging abnormalities (ARIA) to (a) restart at the same dose (rather than at the next lower dose) after ARIA resolution and (b) titrate up to the originally assigned dose (rather than continue on the next lower dose for the duration of the study), (2) Removed requirement to permanently discontinue treatment after severe symptomatic ARIA or serious ARIA ("other medically important" criteria only); instead, in such subjects, dosing could be suspended and then resumed at the same dose after ARIA and symptoms resolved or stabilized, (3) to clarify dosing and monitoring frequency when ARIA occurs during titration, (4) Regarding the management of recurrent ARIA, the amendment (a) allowed subjects who had suspended dosing after a second episode to restart dosing, after ARIA resolution, at the next lower dose and continue uptitration (rather than remaining on the restart dose) and (b) required treatment discontinuation after 3 ARIA episodes (rather than requiring a third dose reduction with Sponsor approval).
24 March 2017	To allow ApoE ε4 carrier subjects randomised to aducanumab high-dose to receive the same aducanumab high-dose regimen already received by ApoE ε4 noncarriers (i.e., per this amendment, the high dose for carriers was changed from 6 to 10 milligrams per kilograms (mg/kg), which was also the high-dose for noncarriers).
18 September 2017	(1) To update the percentage of primary endpoint data estimated to be available at the time of a potential blinded sample size re-estimation, (2) To provide additional details on the planned sample size re-estimation (including the maximum potential sample size), (3) To add information on an additional concentration and formulation for aducanumab used in the study.
28 June 2018	(1) To reflect the agreement of the data monitoring committee that the characteristics or outcomes of the first event and recurrent events of ARIA were similar, the management of recurrent ARIA was modified so that a third episode of ARIA that requires dose suspension will no longer require study treatment discontinuation, and after recurrent ARIA resolves or stabilizes, dosing will resume at the same dose, (2) To extend the study such that subjects nearing study completion under Protocol Version 5 can continue in the study and receive treatment until either the subject's End of Treatment Visit at Week 338 (an additional 3 years of treatment) or until the last subject has had his or her Week 182 Visit, whichever occurs first, (3) To adjust the sample size from 450 to 535 subjects per treatment group following the blinded sample size re-estimation to ensure adequate power to detect a mean treatment effect of 0.5 for the primary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was halted prematurely based on a prespecified futility analysis and not based on safety concerns. Subjects discontinued due to study termination are included in "Reason not Specified" category in subject disposition tables above.