Clinical trial results:
A Phase III, Multicenter, Randomised, Double-Masked, Sham-Controlled Study to assess the Efficacy and Safety of Lampalizumab Administered Intravitreally to Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

Summary

EudraCT number	2014-000106-35
Trial protocol	HU DE IT AT DK GB SE NL ES BE PT SK FR
Global end of trial date	23 January 2018

Results information

Result version number	v1 (current)
This version publication date	02 February 2019
First version publication date	02 February 2019

Trial information

Trial identification

Sponsor protocol code	GX29185

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02247531
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of intravitreal injections of 10-mg lampalizumab administered every 4 weeks (Q4W) or every 6 weeks (Q6W) in complement factor I (CFI)-profile biomarker-positive and CFI-profile biomarker-negative subjects compared with sham control.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 553
Country: Number of subjects enrolled	France: 57
Country: Number of subjects enrolled	Germany: 55
Country: Number of subjects enrolled	United Kingdom: 54
Country: Number of subjects enrolled	Austria: 38
Country: Number of subjects enrolled	Italy: 35
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Switzerland: 10
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	Turkey: 10
Country: Number of subjects enrolled	Slovakia: 8
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Peru: 10
Country: Number of subjects enrolled	Mexico: 4

Country: Number of subjects enrolled	Argentina: 2
Worldwide total number of subjects	975
EEA total number of subjects	360

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)	53
From 65 to 84 years	716
85 years and over	206

Subject disposition

Recruitment

Recruitment details:

A total of 975 subjects were randomised to the study at 144 study sites across 22 countries. The study was terminated early by the Sponsor due to lack of efficacy.

Pre-assignment

Screening details:

This study enrolled subjects with bilateral Geographic Atrophy (GA) secondary to Age-Related Macular Degeneration (AMD) and no signs of prior or active choroidal neovascularisation (CNV), age >= 50 years with a valid complement factor I (CFI)-profile biomarker result.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sham Comparator

Arm description:

Subjects received sham comparator once every 4 weeks (Q4W) or once every 6 weeks (Q6W) starting at the Day 1 visit.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Lampalizumab Q4W

Arm description:

Subjects received 10 mg (milligrams) dose of lampalizumab by intravitreal injection Q4W starting at the Day 1 visit.

Arm type	Experimental
Investigational medicinal product name	Lampalizumab
Investigational medicinal product code	RO5490249
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Lampalizumab was administered at a dose of 10 milligrams (mg) as an intravitreal injection Q4W starting at the Day 1 visit.

Arm title	Lampalizumab Q6W

Arm description:

Subjects received 10 mg dose of lampalizumab by intravitreal injection Q6W starting at the Day 1 visit.

Arm type	Experimental
Investigational medicinal product name	Lampalizumab
Investigational medicinal product code	RO5490249
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Lampalizumab was administered at a dose of 10 mg as an intravitreal injection Q6W starting at the Day 1 visit.

Number of subjects in period 1	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W
Started	321	330	324
Completed	215	205	214
Not completed	106	125	110
Physician decision	-	2	2
Adverse Event	3	4	9
Death	8	9	5
Other	2	3	4
Non-compliance	2	2	-
Withdrawal by Subject	26	31	25
Study Terminated by Sponsor	64	66	62
Lost to follow-up	1	8	3

Baseline characteristics

Reporting groups	
Reporting group title	Sham Comparator
Reporting group description:	
Subjects received sham comparator once every 4 weeks (Q4W) or once every 6 weeks (Q6W) starting at the Day 1 visit.	
Reporting group title	Lampalizumab Q4W
Reporting group description:	
Subjects received 10 mg (milligrams) dose of lampalizumab by intravitreal injection Q4W starting at the Day 1 visit.	
Reporting group title	Lampalizumab Q6W
Reporting group description:	
Subjects received 10 mg dose of lampalizumab by intravitreal injection Q6W starting at the Day 1 visit.	

Reporting group values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W
Number of subjects	321	330	324
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	77.6	77.3	78.7
standard deviation	± 8.3	± 7.8	± 8.0
Sex: Female, Male Units: Subjects			
Female	191	197	190
Male	130	133	134
Geographic Atrophy (GA) Area, as Assessed by Fundus Autofluoresence (FAF)			
At baseline the area of GA was assessed by FAF. Intent-to-treat (ITT) population included all the subjects who were randomised to the study. Overall number of baseline subjects for GA area in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 321, 330, and 324, respectively.			
Units: millimetre square (mm^2)			
arithmetic mean	7.554	8.308	8.498
standard deviation	± 3.983	± 3.916	± 4.260
Number of Absolute Scotomatous Points as Assessed by Mesopic Micrometry			
Scotomatous points were the testing points on microperimetry examination that were centered on the macula and reported a lack of retinal sensitivity within the range tested. Mesopic microperimetry assessments were performed post-dilation on the study eye only, and the data was forwarded to the central reading centre. Overall number of baseline subjects for number of scotomatous points in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 48, 58, and 55, respectively.			
Units: number of absolute scotomatous points			
arithmetic mean	23.2	28.2	27.9
standard deviation	± 13.5	± 17.3	± 14.4
Macular Sensitivity as Assessed by Mesopic Microperimetry			
Mesopic microperimetry was used to assess macular sensitivity and assessments were performed post-			

dilation on the study eye only, and the data was forwarded to the central reading centre. Overall number of baseline subjects for macular sensitivity in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 48, 57, and 54, respectively.			
Units: decibel (dB)			
arithmetic mean	6.5	5.7	5.3
standard deviation	± 3.3	± 3.8	± 3.2
Best Corrected Visual Acuity (BCVA) Score as Assessed by Early Treatment Diabetic Retinopathy Study			
BCVA score was based on number of letters read correctly on ETDRS visual acuity chart assessed at starting distance of 4 metres. BCVA score testing was performed prior to dilating the eyes. BCVA score ranges from 0 to 100 letters in the study eye. The lower the number of letters read correctly on the eye chart, the worse the vision (or visual acuity). ITT population included all the subjects who were randomised to the study. Overall number of baseline subjects for BCVA score in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 319, 330, and 321, respectively.			
Units: letters			
arithmetic mean	66.1	66.0	65.7
standard deviation	± 9.8	± 9.6	± 9.8
Low Luminance Visual Acuity (LLVA) as Assessed by ETDRS Chart Under Low Luminance Conditions			
LLVA was measured by placing a 2.0-log-unit neutral density filter over best correction for that eye and having the subjects read the normally illuminated ETDRS chart. Assessment was performed prior to dilating the eyes. The LLVA score was based on number of letters read correctly on the ETDRS visual acuity chart assessed at a starting distance of 4 m. ITT population included all the subjects who were randomised to the study. Overall number of baseline subjects for LLVA score in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 310, 322, and 310, respectively.			
Units: letters			
arithmetic mean	36.8	36.1	35.8
standard deviation	± 16.5	± 17.5	± 16.8
Binocular Reading Speed as Assessed by Minnesota Low-Vision Reading Test or Radner Reading Charts			
MNRead acuity cards were suitable for measuring reading speed of normal and low-vision subjects. Sentences that could not be read should be recorded as 0 for time and 10 for errors. Radner Reading Cards were suitable for measuring reading speed, visual acuity, and critical print size. Test stopped when reading time was longer than 20 seconds. ITT population included all subjects who were randomised to the study. Overall number of baseline subjects for binocular reading speed in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 298, 303, and 302, respectively.			
Units: words per minute (wpm)			
arithmetic mean	105.16	104.38	99.75
standard deviation	± 56.94	± 54.35	± 56.56
Monocular Maximum Reading Speed as Assessed by MNRead Charts or Radner Reading Charts			
MNRead acuity cards were suitable for measuring reading speed of normal and low-vision subjects. Sentences that could not be read should be recorded as 0 for time and 10 for errors. Radner Reading Cards were suitable for measuring reading speed, visual acuity, and critical print size. Test stopped when reading time was longer than 20 seconds. ITT population included all subjects who were randomised to the study. Overall number of baseline subjects for monocular reading speed in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 300, 310, and 304, respectively.			
Units: wpm			
arithmetic mean	81.20	80.38	74.52
standard deviation	± 57.48	± 53.70	± 50.11
National Eye Institute Visual Functioning Questionnaire 25-item (NEI VFQ-25) Version Composite Score			
It included 25 items based on which overall composite VFQ score and 12 subscales (general vision,near vision,distance vision,ocular pain,social functioning,mental health,roll difficulties,dependency,driving,color vision and peripheral vision) were derived. For each subscale and			

100, higher score represents better functioning. ITT population included all subjects who were randomised to study. Overall number of baseline subjects for NEI-VFQ-25 score in reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 283, 299, and 296, respectively.			
Units: score on a scale			
arithmetic mean	64.84	62.88	64.03
standard deviation	± 15.80	± 17.50	± 17.65
NEI VFQ-25 Near Activity Subscale Score			
NEI-VFQ-25 questionnaire included 25 items based on which near activities were measured. Near activities are defined as reading ordinary print in newspapers, performing work requiring near vision, or finding something on crowded shelf. Response to each question converted to 0-100 score. Higher score represents better functioning. ITT population included all subjects who were randomised to study. Overall number of baseline subjects for NEI VFQ-25 near activity subscale score in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 283, 299, and 296, respectively.			
Units: score on a scale			
arithmetic mean	53.89	51.68	53.24
standard deviation	± 19.91	± 21.92	± 22.07
NEI VFQ-25 Distance Activity Subscale Score			
NEI-VFQ-25 questionnaire included 25 items based on which distance activities was measured. Distance activities are defined as reading street signs or names on stores, and going down stairs, steps, or curbs. Response to each question converted to 0-100 score. A higher score represents better functioning. ITT population included all subjects who were randomised to the study. Overall number of baseline subjects for NEI VFQ-25 distance activity subscale score in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 283, 299, and 296, respectively.			
Units: score on a scale			
arithmetic mean	62.68	58.57	60.95
standard deviation	± 21.41	± 22.03	± 21.55
Mean Functional Reading Independence (FRI) Index			
FRI was an interviewer-administered questionnaire with 7 items on functional reading activities most relevant to GA AMD subjects. It has one total index score. For each reading activity performed in the past 7 days, subjects were asked about the extent to which they required vision aids, adjustments in activity, or help from another subject. ITT population included all subjects who were randomised to the study. Overall number of baseline subjects for FRI index in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 278, 296, and 293, respectively.			
Units: score on a scale			
arithmetic mean	2.70	2.66	2.64
standard deviation	± 0.79	± 0.82	± 0.87
GA Area in Complement Factor I (CFI) Positive Subjects			
For CFI profile, positive biomarker status refers to the presence of the risk allele at CFI and at least one risk allele at CFH or risk locus containing both C2/CFB. ITT population included all subjects who were randomised to study. Overall number of baseline CFI positive subjects for GA area in reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 194, 199, and 194, respectively.			
Units: mm^2			
arithmetic mean	7.491	8.183	8.652
standard deviation	± 4.068	± 3.835	± 4.250
GA Area in CFI Negative Subjects			
For CFI profile, negative biomarker status refers to the absence of the risk allele at CFI and at least one risk allele at CFH or risk locus containing both C2/CFB. ITT population included all subjects who were randomized to study. Overall number of baseline CFI negative subjects for GA area in reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 127, 131, and 130, respectively.			
Units: mm^2			
arithmetic mean	7.650	8.499	8.268
standard deviation	± 3.862	± 4.044	± 4.281

Reporting group values	Total		
Number of subjects	975		

Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: Subjects			
Female	578		
Male	397		
Geographic Atrophy (GA) Area, as Assessed by Fundus Autofluoresence (FAF)			
At baseline the area of GA was assessed by FAF. Intent-to-treat (ITT) population included all the subjects who were randomised to the study. Overall number of baseline subjects for GA area in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 321, 330, and 324, respectively.			
Units: millimetre square (mm^2) arithmetic mean standard deviation	 -		
Number of Absolute Scotomatous Points as Assessed by Mesopic Micrometry			
Scotomatous points were the testing points on microperimetry examination that were centered on the macula and reported a lack of retinal sensitivity within the range tested. Mesopic microperimetry assessments were performed post-dilation on the study eye only, and the data was forwarded to the central reading centre. Overall number of baseline subjects for number of scotomatous points in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 48, 58, and 55, respectively.			
Units: number of absolute scotomatous points arithmetic mean standard deviation	 -		
Macular Sensitivity as Assessed by Mesopic Microperimetry			
Mesopic microperimetry was used to assess macular sensitivity and assessments were performed post-dilation on the study eye only, and the data was forwarded to the central reading centre. Overall number of baseline subjects for macular sensitivity in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 48, 57, and 54, respectively.			
Units: decibel (dB) arithmetic mean standard deviation	 -		
Best Corrected Visual Acuity (BCVA) Score as Assessed by Early Treatment Diabetic Retinopathy Study			
BCVA score was based on number of letters read correctly on ETDRS visual acuity chart assessed at starting distance of 4 metres. BCVA score testing was performed prior to dilating the eyes. BCVA score ranges from 0 to 100 letters in the study eye. The lower the number of letters read correctly on the eye chart, the worse the vision (or visual acuity). ITT population included all the subjects who were randomised to the study. Overall number of baseline subjects for BCVA score in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 319, 330, and 321, respectively.			
Units: letters arithmetic mean standard deviation	 -		
Low Luminance Visual Acuity (LLVA) as Assessed by ETDRS Chart Under Low Luminance Conditions			
LLVA was measured by placing a 2.0-log-unit neutral density filter over best correction for that eye and having the subjects read the normally illuminated ETDRS chart. Assessment was performed prior to			

dilating the eyes. The LLVA score was based on number of letters read correctly on the ETDRS visual acuity chart assessed at a starting distance of 4 m. ITT population included all the subjects who were randomised to the study. Overall number of baseline subjects for LLVA score in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 310, 322, and 310, respectively.			
Units: letters arithmetic mean standard deviation	- 		
Binocular Reading Speed as Assessed by Minnesota Low-Vision Reading Test or Radner Reading Charts			
MNRead acuity cards were suitable for measuring reading speed of normal and low-vision subjects. Sentences that could not be read should be recorded as 0 for time and 10 for errors. Radner Reading Cards were suitable for measuring reading speed, visual acuity, and critical print size. Test stopped when reading time was longer than 20 seconds. ITT population included all subjects who were randomised to the study. Overall number of baseline subjects for binocular reading speed in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 298, 303, and 302, respectively.			
Units: words per minute (wpm) arithmetic mean standard deviation	- 		
Monocular Maximum Reading Speed as Assessed by MNRead Charts or Radner Reading Charts			
MNRead acuity cards were suitable for measuring reading speed of normal and low-vision subjects. Sentences that could not be read should be recorded as 0 for time and 10 for errors. Radner Reading Cards were suitable for measuring reading speed, visual acuity, and critical print size. Test stopped when reading time was longer than 20 seconds. ITT population included all subjects who were randomised to the study. Overall number of baseline subjects for monocular reading speed in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 300, 310, and 304, respectively.			
Units: wpm arithmetic mean standard deviation	- 		
National Eye Institute Visual Functioning Questionnaire 25-item (NEI VFQ-25) Version Composite Score			
It included 25 items based on which overall composite VFQ score and 12 subscales (general vision,near vision,distance vision,ocular pain,social functioning,mental health,roll difficulties,dependency,driving,color vision and peripheral vision) were derived. For each subscale and total score, score range is 0 to 100, higher score represents better functioning. ITT population included all subjects who were randomised to study. Overall number of baseline subjects for NEI-VFQ-25 score in reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 283, 299, and			
Units: score on a scale arithmetic mean standard deviation	- 		
NEI VFQ-25 Near Activity Subscale Score			
NEI-VFQ-25 questionnaire included 25 items based on which near activities were measured. Near activities are defined as reading ordinary print in newspapers, performing work requiring near vision, or finding something on crowded shelf. Response to each question converted to 0-100 score. Higher score represents better functioning. ITT population included all subjects who were randomised to study. Overall number of baseline subjects for NEI VFQ-25 near activity subscale score in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 283, 299, and 296, respectively.			
Units: score on a scale arithmetic mean standard deviation	- 		
NEI VFQ-25 Distance Activity Subscale Score			
NEI-VFQ-25 questionnaire included 25 items based on which distance activities was measured. Distance activities are defined as reading street signs or names on stores, and going down stairs, steps, or curbs. Response to each question converted to 0-100 score. A higher score represents better functioning. ITT population included all subjects who were randomised to the study. Overall number of baseline subjects			

for NEI VFQ-25 distance activity subscale score in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 283, 299, and 296, respectively.			
Units: score on a scale arithmetic mean standard deviation	-		
Mean Functional Reading Independence (FRI) Index			
FRI was an interviewer-administered questionnaire with 7 items on functional reading activities most relevant to GA AMD subjects. It has one total index score. For each reading activity performed in the past 7 days, subjects were asked about the extent to which they required vision aids, adjustments in activity, or help from another subject. ITT population included all subjects who were randomised to the study. Overall number of baseline subjects for FRI index in the reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 278, 296, and 293, respectively.			
Units: score on a scale arithmetic mean standard deviation	-		
GA Area in Complement Factor I (CFI) Positive Subjects			
For CFI profile, positive biomarker status refers to the presence of the risk allele at CFI and at least one risk allele at CFH or risk locus containing both C2/CFB. ITT population included all subjects who were randomised to study. Overall number of baseline CFI positive subjects for GA area in reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 194, 199, and 194, respectively.			
Units: mm^2 arithmetic mean standard deviation	-		
GA Area in CFI Negative Subjects			
For CFI profile, negative biomarker status refers to the absence of the risk allele at CFI and at least one risk allele at CFH or risk locus containing both C2/CFB. ITT population included all subjects who were randomized to study. Overall number of baseline CFI negative subjects for GA area in reporting groups; Sham Comparator, Lampalizumab Q4W, and Lampalizumab Q6W were 127, 131, and 130, respectively.			
Units: mm^2 arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Sham Comparator
Reporting group description:	
Subjects received sham comparator once every 4 weeks (Q4W) or once every 6 weeks (Q6W) starting at the Day 1 visit.	
Reporting group title	Lampalizumab Q4W
Reporting group description:	
Subjects received 10 mg (milligrams) dose of lampalizumab by intravitreal injection Q4W starting at the Day 1 visit.	
Reporting group title	Lampalizumab Q6W
Reporting group description:	
Subjects received 10 mg dose of lampalizumab by intravitreal injection Q6W starting at the Day 1 visit.	

Primary: Change From Baseline in Geographic Atropy (GA) Area, as Assessed by Fundus Autofluoresence (FAF) at Week 48

End point title	Change From Baseline in Geographic Atropy (GA) Area, as Assessed by Fundus Autofluoresence (FAF) at Week 48
End point description:	
The change in GA lesion area was measured by FAF and analysis of FAF images was performed by the central reading centre. A positive change from baseline indicates an increase in size of GA lesion area (worsening; disease progression). The intent-to-treat (ITT) population included all the subjects who were randomised to the study. Subjects analysed in this endpoint were those included in mixed-effect model repeated measures (MMRM) analysis.	
End point type	Primary
End point timeframe:	
Baseline, Week 48	

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	291	293	291	
Units: millimetre square (mm^2)				
arithmetic mean (standard error)	1.932 (± 0.056)	2.089 (± 0.056)	2.019 (± 0.056)	

Statistical analyses

Statistical analysis title	Lampalizumab Q4W vs Sham Comaparator
Statistical analysis description:	
Week 48: MMRM analysis uses change as response variable and included treatment group, visit, treatment−by−visit interaction, baseline GA area, lesion location, contiguity, biomarker status, modified baseline BCVA and sex.	
Comparison groups	Lampalizumab Q4W v Sham Comparator

Number of subjects included in analysis	584
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0479
Method	MMRM
Parameter estimate	Difference in Adjusted Means
Point estimate	0.157
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.313

Statistical analysis title	Lampalizumab Q6W vs Sham Comparator

Statistical analysis description:

Week 48: MMRM analysis uses change as response variable and included treatment group, visit, treatment−by−visit interaction, baseline GA area, lesion location, contiguity, biomarker status, modified baseline BCVA and sex.

Comparison groups	Sham Comparator v Lampalizumab Q6W
Number of subjects included in analysis	582
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2739
Method	MMRM
Parameter estimate	Difference in Adjusted Means
Point estimate	0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.069
upper limit	0.243

Primary: Change From Baseline in GA Area in Complement Factor I (CFI) Positive and Negative Subjects at Week 48

End point title	Change From Baseline in GA Area in Complement Factor I (CFI) Positive and Negative Subjects at Week 48

End point description:

For CFI profile, positive or negative biomarker status refers to the presence (carrier) or absence of the risk allele at CFI and at least one risk allele at complement factor H (CFH) or risk locus containing both complement component 2 and complement factor B (C2/CFB). The change in GA lesion area was measured by FAF and analysis of FAF images was performed by the central reading centre. A positive change from baseline indicates an increase in size of GA lesion area (worsening; disease progression). ITT population included all the subjects who were randomised to the study. Reported here are data for CFI-positive and CFI-negative subjects within the ITT population. Here, "n" is the number of subjects who were analysed for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	321	330	324	
Units: mm^2				
arithmetic mean (standard error)				
CFI-Positive Subjects (n=176, 183, 172)	2.007 (± 0.074)	2.057 (± 0.072)	2.032 (± 0.073)	
CFI-Negative Subjects (n=115, 110, 119)	1.809 (± 0.087)	2.149 (± 0.087)	1.991 (± 0.085)	

Statistical analyses

Statistical analysis title	Lampalizumab Q4W vs Sham Comparator

Statistical analysis description:

CFI Positive: MMRM analysis uses change as response variable and included treatment group, visit, treatment−by−visit interaction, baseline GA area, lesion location, contiguity, biomarker status, modified baseline BCVA and sex.

Comparison groups	Sham Comparator v Lampalizumab Q4W
Number of subjects included in analysis	651
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6333
Method	MMRM
Parameter estimate	Difference in Adjusted Means
Point estimate	0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.153
upper limit	0.252

Statistical analysis title	Lampalizumab Q6W vs Sham Comparator

Statistical analysis description:

CFI Positive: MMRM analysis uses change as response variable and included treatment group, visit, treatment−by−visit interaction, baseline GA area, lesion location, contiguity, biomarker status, modified baseline BCVA and sex.

Comparison groups	Sham Comparator v Lampalizumab Q6W
Number of subjects included in analysis	645
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8105
Method	MMRM
Parameter estimate	Difference in Adjusted Means
Point estimate	0.025

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.23

Statistical analysis title	Lampalizumab Q4W vs Sham Comparator

Statistical analysis description:

CFI Negative: MMRM analysis uses change as response variable and included treatment group, visit, treatment−by−visit interaction, baseline GA area, lesion location, contiguity, biomarker status, modified baseline BCVA and sex.

Comparison groups	Sham Comparator v Lampalizumab Q4W
Number of subjects included in analysis	651
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0063
Method	MMRM
Parameter estimate	Difference in Adjusted Means
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.097
upper limit	0.584

Statistical analysis title	Lampalizumab Q6W vs Sham Comparator

Statistical analysis description:

CFI Negative: MMRM analysis uses change as response variable and included treatment group, visit, treatment−by−visit interaction, baseline GA area, lesion location, contiguity, biomarker status, modified baseline BCVA and sex.

Comparison groups	Sham Comparator v Lampalizumab Q6W
Number of subjects included in analysis	645
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1359
Method	MMRM
Parameter estimate	Difference in Adjusted Means
Point estimate	0.182
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.058
upper limit	0.422

Secondary: Change From Baseline in Number of Absolute Scotomatous Points

Assessed by Mesopic Microperimetry at Week 48

End point title	Change From Baseline in Number of Absolute Scotomatous Points Assessed by Mesopic Microperimetry at Week 48

End point description:

Scotomatous points were the testing points on microperimetry examination that were centered on the macula and reported a lack of retinal sensitivity within the range tested. Mesopic microperimetry assessments were performed post-dilation on the study eye only, and the data was forwarded to the central reading centre. A positive change from baseline indicates an increase in the number of absolute scotomatous points (more lack of retinal sensitivity); disease worsening. The microperimetry analysis population consisted of all subjects who met the microperimetry eligibility criteria assessed by the reading centre (subjects at selected sites only; subjects grouped according to treatment assigned at randomisation). Subjects analysed in this end point were those included in MMRM analysis. The data was collected up to Week 48 instead of Week 96, due to early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	42	43	
Units: number of absolute scotomatous points				
arithmetic mean (standard error)	5.4 (± 1.6)	5.0 (± 1.5)	6.7 (± 1.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Macular Sensitivity as Assessed by Mesopic Microperimetry at Week 48

End point title	Change From Baseline in Macular Sensitivity as Assessed by Mesopic Microperimetry at Week 48

End point description:

Mesopic microperimetry was used to assess macular sensitivity and assessments were performed post-dilation on the study eye only, and the data was forwarded to the central reading center. A negative change from baseline indicates a decrease in the mean macular sensitivity; disease worsening. Data were collected up to Week 48 instead of Week 96, due to early termination of the study. ITT population included all the subjects who were randomised to the study. Subjects analysed in this endpoint were those included in the MMRM analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	41	42	
Units: decibel (dB)				
arithmetic mean (standard error)	-0.99 (± 0.36)	-0.89 (± 0.34)	-1.25 (± 0.35)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Best Corrected Visual Acuity (BCVA) Score as Assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) Chart at Week 48

End point title	Change From Baseline in Best Corrected Visual Acuity (BCVA) Score as Assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) Chart at Week 48

End point description:

BCVA score was based on the number of letters read correctly on the ETDRS visual acuity chart assessed at a starting distance of 4 metres (m). A decrease in the VA score indicates a worsening of visual acuity. BCVA score testing was performed prior to dilating the eyes. BCVA score ranges from 0 to 100 letters in the study eye. The lower the number of letters read correctly on the eye chart, the worse the vision (or visual acuity). A negative change from baseline indicates a decrease in the visual acuity; disease worsening. ITT population included all the subjects who were randomized to the study. Subjects analysed in this end point were those included in MMRM analysis. The data was collected up to Week 48 instead of Week 96, due to early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	288	286	287	
Units: letters				
arithmetic mean (standard error)	-5.3 (± 0.7)	-4.6 (± 0.7)	-5.1 (± 0.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Less Than 15 Letters Loss From Baseline in BCVA Score at Week 48

End point title	Percentage of Subjects with Less Than 15 Letters Loss From Baseline in BCVA Score at Week 48

End point description:

Loss of less than 15 letters from baseline was assessed by the ETDRS chart at a starting distance of 4 m. BCVA was measured using an eye chart and was reported as the number of letters read correctly (ranging from 0 to 100 letters). The lower the number of letters read correctly on the eye chart, the

worse the vision (or visual acuity). ITT population included all the subjects who were randomized to the study. The data was collected up to Week 48 instead of Week 96, due to early termination of the study.

End point type	Secondary

End point timeframe:

Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	288	286	287	
Units: percentage of subjects				
number (confidence interval 95%)	86.8 (82.9 to 90.7)	87.8 (84.0 to 91.6)	86.4 (82.4 to 90.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Low Luminance Visual Acuity (LLVA) as Assessed by ETDRS Chart Under Low Luminance Conditions at Week 48

End point title	Change From Baseline in Low Luminance Visual Acuity (LLVA) as Assessed by ETDRS Chart Under Low Luminance Conditions at Week 48

End point description:

The LLVA was measured by placing a 2.0-log-unit neutral density filter over the best correction for that eye and having the subject read the normally illuminated ETDRS chart. The assessment was performed prior to dilating the eyes. A negative change from baseline indicates a decrease in the visual acuity; disease worsening. Data were collected up to Week 48 instead of Week 96, due to early termination of the study. ITT population included all the subjects who were randomised to the study. Subjects analysed in this endpoint were those included in the MMRM analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	274	278	274	
Units: letters				
arithmetic mean (standard error)	-2.5 (± 0.6)	-2.6 (± 0.6)	-3.6 (± 0.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Less Than 15 Letters Loss From Baseline in LLVA Score at Week 48

End point title	Percentage of Subjects with Less Than 15 Letters Loss From Baseline in LLVA Score at Week 48

End point description:

Loss of less than 15 letters from baseline was assessed by the ETDRS chart at a starting distance of 4 m. Data were collected up to Week 48 instead of Week 96, due to early termination of the study. ITT population included all the subjects who were randomised to the study.

End point type	Secondary

End point timeframe:

Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	274	278	274	
Units: percentage of subjects				
number (confidence interval 95%)	87.6 (83.7 to 91.5)	89.9 (86.4 to 93.5)	86.9 (82.9 to 90.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Binocular Reading Speed as Assessed by Minnesota Low-Vision Reading Test (MNRead) Charts or Radner Reading Charts at Week 48

End point title	Change From Baseline in Binocular Reading Speed as Assessed by Minnesota Low-Vision Reading Test (MNRead) Charts or Radner Reading Charts at Week 48

End point description:

MNRead acuity cards were continuous-text reading-acuity cards suitable for measuring the reading acuity and reading speed of normal and low-vision subjects. The MNRead acuity cards consisted of single, simple sentences with equal numbers of characters. A stopwatch was used to record time to a tenth of a second. Sentences that could not be read or were not attempted due to vision should be recorded as 0 for time and 10 for errors. The Radner Reading Cards were suitable for measuring reading speed, reading visual acuity, and critical print size. The reading test was stopped when the reading time was longer than 20 seconds or when the subject was making severe errors. A negative change from baseline indicates a decrease in the binocular reading speed; disease worsening. Reported here is the ITT population included in MMRM analysis. The data was collected up to Week 48 instead of Week 96, due to early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	261	255	266	
Units: words per minute (wpm)				
arithmetic mean (standard error)	-15.27 (± 2.33)	-13.92 (± 2.36)	-14.20 (± 2.31)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Monocular Maximum Reading Speed as Assessed by MNRead Charts or Radner Reading Charts at Week 48

End point title	Change From Baseline in Monocular Maximum Reading Speed as Assessed by MNRead Charts or Radner Reading Charts at Week 48

End point description:

MNRead acuity cards were continuous-text reading-acuity cards suitable for measuring reading acuity and reading speed of normal and low-vision participants. A stopwatch was used to record time to a tenth of a second. Sentences that could not be read or were not attempted due to vision should be recorded as 0 for time and 10 for errors. Radner Reading Cards were suitable for measuring reading speed, reading visual acuity, and critical print size. Reading test was stopped when reading time was longer than 20 seconds or when participant was making severe errors. A negative change from baseline indicates a decrease in the monocular reading speed; disease worsening. The data was collected up to Week 48 instead of Week 96, due to early termination of the study. ITT population included all the subjects who were randomised to the study. Subjects analysed in this endpoint were those included in the MMRM analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	264	272	
Units: wpm				
arithmetic mean (standard error)	-16.58 (± 2.30)	-16.46 (± 2.30)	-18.30 (± 2.27)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in National Eye Institute Visual Functioning Questionnaire 25-item (NEI VFQ-25) Version Composite Score at Week 48

End point title	Change From Baseline in National Eye Institute Visual Functioning Questionnaire 25-item (NEI VFQ-25) Version Composite Score at Week 48

End point description:

NEI-VFQ-25 questionnaire included 25 items based on which overall composite VFQ score and 12 subscales were derived: near activities, distance activities, general health, general vision, ocular pain, vision−specific social functioning, vision−specific mental health, vision−specific role difficulties, vision−specific dependency, driving, color vision and peripheral vision. Response to each question converted to 0-100 score. Each subscale or total score is the average of items contributing to the score. For each subscale and total score the score range is 0 to 100 with a higher score representing better functioning. A negative change from baseline indicates a decrease in the visual functioning; disease worsening. Data were collected up to Week 48 instead of Week 96, due to early termination of the study. ITT population included all the subjects who were randomised to the study. Subjects analysed in this endpoint were those included in the MMRM analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	251	259	265	
Units: score on a scale				
arithmetic mean (standard error)	-2.08 (± 0.74)	-0.86 (± 0.73)	-1.05 (± 0.72)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in NEI VFQ-25 Near Activity Subscale Score at Week 48

End point title	Change from Baseline in NEI VFQ-25 Near Activity Subscale Score at Week 48

End point description:

NEI-VFQ-25 questionnaire included 25 items based on which near activities were measured. Near activities are defined as reading ordinary print in newspapers, performing work or hobbies requiring near vision, or finding something on a crowded shelf. Response to each question converted to 0-100 score. A higher score represents better functioning. A negative change from baseline indicates a decrease in the near visual activities; disease worsening. ITT population included all the subjects who were randomized to the study. Subjects analysed in this end point were those included in MMRM analysis. The data was collected up to Week 48 instead of Week 96, due to early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	251	259	265	
Units: score on a scale				
arithmetic mean (standard error)	-4.12 (± 0.91)	-1.49 (± 0.89)	-1.93 (± 0.88)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in NEI VFQ-25 Distance Activity Subscale Score at Week 48

End point title	Change from Baseline in NEI VFQ-25 Distance Activity Subscale Score at Week 48

End point description:

NEI-VFQ-25 questionnaire included 25 items based on which distance activities were measured. Distance activities are defined as reading street signs or names on stores, and going down stairs, steps, or curbs. Response to each question converted to 0-100 score. A higher score represents better functioning. A negative change from baseline indicates a decrease in the distance visual activities; disease worsening. ITT population included all the subjects who were randomized to the study. Subjects analysed in this end point were those included in MMRM analysis. The data was collected up to Week 48 instead of Week 96, due to early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	251	259	265	
Units: score on a scale				
arithmetic mean (standard error)	-2.83 (± 1.04)	-1.80 (± 1.03)	-2.24 (± 1.01)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Functional Reading Independence (FRI) Index at Week 48

End point title	Change From Baseline in Mean Functional Reading Independence (FRI) Index at Week 48

End point description:

The FRI was an interviewer-administered questionnaire with 7 items on functional reading activities most relevant to GA AMD subjects. It has one total index score. The index score is an ordinal scale with higher levels representing higher FRI. For each FRI Index reading activity performed in the past 7 days, subjects were asked about the extent to which they required vision aids, adjustments in the activity, or help from another subject. A negative change from baseline indicates a decrease in the FRI; disease worsening. ITT population included all the subjects who were randomized to the study. Subjects analysed in this end point were those included in MMRM analysis. The data was collected up to Week 48 instead of Week 96, due to early termination of the study.

End point type	Secondary

End point timeframe:
Baseline, Week 48

End point values	Sham Comparator	Lampalizumab Q4W	Lampalizumab Q6W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	248	257	260	
Units: score on a scale				
arithmetic mean (standard error)	-0.16 (± 0.04)	-0.12 (± 0.04)	-0.14 (± 0.04)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to approximately 2 years	
Adverse event reporting additional description:	
Safety population included all subjects who received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Sham Comparator
Reporting group description:	
Subjects received sham comparator Q4W or Q6W starting at the Day 1 visit.	
Reporting group title	Lampalizumab Q6W
Reporting group description:	
Subjects received 10 mg dose of lampalizumab by intravitreal injection Q6W starting at the Day 1 visit.	
Reporting group title	Lampalizumab Q4W
Reporting group description:	
Subjects received 10 mg dose of lampalizumab by intravitreal injection Q4W starting at the Day 1 visit.	

Serious adverse events	Sham Comparator	Lampalizumab Q6W	Lampalizumab Q4W
Total subjects affected by serious adverse events			
subjects affected / exposed	99 / 318 (31.13%)	111 / 323 (34.37%)	113 / 329 (34.35%)
number of deaths (all causes)	9	7	10
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B−cell lymphoma			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Bone cancer			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Breast cancer			

subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Breast cancer metastatic			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Cervix carcinoma stage IV			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Colon neoplasm			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatic cancer			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal cancer stage I			

subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Lip squamous cell carcinoma			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm of unknown primary site			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Metastases to central nervous system			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Neoplasm malignant			

subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Oesophageal cancer metastatic			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
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	0 / 318 (0.00%)	2 / 323 (0.62%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Salivary gland neoplasm			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestine carcinoma metastatic			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the vulva			

subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval cancer stage 0			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Waldenstrom’s macroglobulinaemia			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
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	0 / 318 (0.00%)	0 / 323 (0.00%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
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	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasculitis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Hypertension			
subjects affected / exposed	0 / 318 (0.00%)	2 / 323 (0.62%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Fracture treatment			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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

Chest pain			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication associated with device			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Death			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	3 / 329 (0.91%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 3
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Stent-graft endoleak			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
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 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Endometrial hyperplasia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Prostatomegaly			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	7 / 329 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Dyspnoea			
subjects affected / exposed	0 / 318 (0.00%)	2 / 323 (0.62%)	0 / 329 (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
Haemoptysis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia aspiration			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumothorax			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary embolism			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
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 hypertension			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus polyp			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Mental disorder			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			

Device malfunction			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
International normalised ratio abnormal			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Intraocular pressure increased			
subjects affected / exposed	1 / 318 (0.31%)	8 / 323 (2.48%)	10 / 329 (3.04%)
occurrences causally related to treatment / all	0 / 1	6 / 20	7 / 22
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acetabulum fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Ankle fracture			

subjects affected / exposed	2 / 318 (0.63%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Comminuted fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	5 / 318 (1.57%)	5 / 323 (1.55%)	4 / 329 (1.22%)
occurrences causally related to treatment / all	0 / 7	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
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	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Fracture displacement			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			

subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Hip fracture			
subjects affected / exposed	2 / 318 (0.63%)	2 / 323 (0.62%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated incisional hernia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Incomplete spinal fusion			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Laceration			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Pelvic fracture			

subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
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 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Pubis fracture			
subjects affected / exposed	3 / 318 (0.94%)	0 / 323 (0.00%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Rib fracture			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	0 / 329 (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
Spinal compression fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Sternal fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			

subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Tendon rupture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Upper limb fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain herniation			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Corneal abrasion			
subjects affected / exposed	0 / 318 (0.00%)	2 / 323 (0.62%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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 disorders			

Acute myocardial infarction			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 318 (0.00%)	3 / 323 (0.93%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 318 (0.31%)	2 / 323 (0.62%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	2 / 318 (0.63%)	0 / 323 (0.00%)	0 / 329 (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
Arrhythmia			
subjects affected / exposed	2 / 318 (0.63%)	0 / 323 (0.00%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	6 / 318 (1.89%)	2 / 323 (0.62%)	7 / 329 (2.13%)
occurrences causally related to treatment / all	0 / 7	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Atrioventricular block complete			
subjects affected / exposed	2 / 318 (0.63%)	1 / 323 (0.31%)	0 / 329 (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
Atrioventricular block second degree			

subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
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 dissociation			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 318 (0.31%)	2 / 323 (0.62%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	4 / 318 (1.26%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardiac disorder			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 318 (0.00%)	2 / 323 (0.62%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure congestive			
subjects affected / exposed	4 / 318 (1.26%)	8 / 323 (2.48%)	3 / 329 (0.91%)
occurrences causally related to treatment / all	0 / 5	0 / 8	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	2 / 318 (0.63%)	2 / 323 (0.62%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			

subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Left ventricular dysfunction			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Left ventricular failure			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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 prolapse			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 318 (0.63%)	1 / 323 (0.31%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
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 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			

subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Ventricular tachycardia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Balance disorder			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Carotid artery disease			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Carotid artery stenosis			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	0 / 329 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Cerebral infarction			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebral ischaemia			

subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 318 (0.63%)	1 / 323 (0.31%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
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			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Haemorrhagic stroke			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatic encephalopathy			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IIIrd nerve paralysis			

subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lumbar radiculopathy			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Memory impairment			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 318 (0.63%)	1 / 323 (0.31%)	6 / 329 (1.82%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoacusis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Vertigo			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	3 / 329 (0.91%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness transient			
subjects affected / exposed	0 / 318 (0.00%)	2 / 323 (0.62%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 0	2 / 3	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Choroidal neovascularisation			
subjects affected / exposed	1 / 318 (0.31%)	2 / 323 (0.62%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dry age−related macular degeneration			
subjects affected / exposed	0 / 318 (0.00%)	3 / 323 (0.93%)	3 / 329 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glaucoma			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	0 / 329 (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
Neovascular age−related macular degeneration			
subjects affected / exposed	2 / 318 (0.63%)	4 / 323 (1.24%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Open angle glaucoma			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic ischaemic neuropathy			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Ulcerative keratitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Uveitic glaucoma			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			

subjects affected / exposed	10 / 318 (3.14%)	18 / 323 (5.57%)	13 / 329 (3.95%)
occurrences causally related to treatment / all	0 / 14	1 / 19	1 / 17
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Vitreous floaters			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Vitreous haemorrhage			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Cataract			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior capsule opacification			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Visual acuity reduced transiently			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			

subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn’s disease			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Enteritis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	0 / 329 (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
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
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 inguinal hernia			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
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 haemorrhage			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Pancreatitis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			

subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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			
Cholecystitis			
subjects affected / exposed	3 / 318 (0.94%)	1 / 323 (0.31%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Hepatic cirrhosis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
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 acute			

subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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			
Skin necrosis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 318 (0.31%)	2 / 323 (0.62%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cyst			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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 urinary tract symptoms			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Nephrolithiasis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pollakiuria			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	1 / 318 (0.31%)	2 / 323 (0.62%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costochondritis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Joint swelling			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	2 / 318 (0.63%)	1 / 323 (0.31%)	0 / 329 (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
Musculoskeletal chest pain			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	4 / 318 (1.26%)	1 / 323 (0.31%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	0 / 329 (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
Rotator cuff syndrome			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			

subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 318 (0.31%)	1 / 323 (0.31%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Cystitis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	2 / 318 (0.63%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometritis			

subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Endophthalmitis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	4 / 329 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal sepsis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Erysipelas			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Infectious pleural effusion			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			

subjects affected / exposed	0 / 318 (0.00%)	2 / 323 (0.62%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Localised infection			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Periorbital cellulitis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Pharyngitis streptococcal			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	7 / 318 (2.20%)	5 / 323 (1.55%)	3 / 329 (0.91%)
occurrences causally related to treatment / all	0 / 8	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia mycoplasmal			

subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 318 (0.94%)	1 / 323 (0.31%)	3 / 329 (0.91%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 318 (0.00%)	3 / 323 (0.93%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Vaginal infection			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Device related infection			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Lower respiratory tract infection			

subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 318 (0.31%)	2 / 323 (0.62%)	2 / 329 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Fluid overload			
subjects affected / exposed	0 / 318 (0.00%)	1 / 323 (0.31%)	0 / 329 (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
Gout			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 318 (0.00%)	0 / 323 (0.00%)	1 / 329 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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
Hypovolaemia			

subjects affected / exposed	1 / 318 (0.31%)	0 / 323 (0.00%)	0 / 329 (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

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

Non-serious adverse events	Sham Comparator	Lampalizumab Q6W	Lampalizumab Q4W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	227 / 318 (71.38%)	253 / 323 (78.33%)	268 / 329 (81.46%)
Investigations			
Intraocular pressure increased			
subjects affected / exposed	7 / 318 (2.20%)	39 / 323 (12.07%)	50 / 329 (15.20%)
occurrences (all)	14	72	85
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	41 / 318 (12.89%)	28 / 323 (8.67%)	47 / 329 (14.29%)
occurrences (all)	50	41	58
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 318 (8.18%)	22 / 323 (6.81%)	27 / 329 (8.21%)
occurrences (all)	26	23	30
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 318 (3.46%)	9 / 323 (2.79%)	20 / 329 (6.08%)
occurrences (all)	11	11	26
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	84 / 318 (26.42%)	97 / 323 (30.03%)	112 / 329 (34.04%)
occurrences (all)	205	228	268
Eye pain			
subjects affected / exposed	30 / 318 (9.43%)	36 / 323 (11.15%)	55 / 329 (16.72%)
occurrences (all)	50	93	87
Vitreous detachment			
subjects affected / exposed	24 / 318 (7.55%)	31 / 323 (9.60%)	37 / 329 (11.25%)
occurrences (all)	33	41	49
Cataract			

subjects affected / exposed	25 / 318 (7.86%)	25 / 323 (7.74%)	23 / 329 (6.99%)
occurrences (all)	41	36	35
Retinal haemorrhage			
subjects affected / exposed	14 / 318 (4.40%)	22 / 323 (6.81%)	24 / 329 (7.29%)
occurrences (all)	18	31	38
Dry eye			
subjects affected / exposed	16 / 318 (5.03%)	16 / 323 (4.95%)	19 / 329 (5.78%)
occurrences (all)	26	31	32
Vitreous floaters			
subjects affected / exposed	5 / 318 (1.57%)	26 / 323 (8.05%)	29 / 329 (8.81%)
occurrences (all)	8	33	35
Blepharitis			
subjects affected / exposed	11 / 318 (3.46%)	15 / 323 (4.64%)	26 / 329 (7.90%)
occurrences (all)	20	25	55
Vision blurred			
subjects affected / exposed	15 / 318 (4.72%)	12 / 323 (3.72%)	18 / 329 (5.47%)
occurrences (all)	24	17	27
Posterior capsule opacification			
subjects affected / exposed	11 / 318 (3.46%)	11 / 323 (3.41%)	20 / 329 (6.08%)
occurrences (all)	16	14	26
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 318 (1.57%)	8 / 323 (2.48%)	18 / 329 (5.47%)
occurrences (all)	5	8	20
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 318 (3.14%)	10 / 323 (3.10%)	26 / 329 (7.90%)
occurrences (all)	11	12	26
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	17 / 318 (5.35%)	14 / 323 (4.33%)	22 / 329 (6.69%)
occurrences (all)	20	14	22
Arthralgia			
subjects affected / exposed	16 / 318 (5.03%)	14 / 323 (4.33%)	18 / 329 (5.47%)
occurrences (all)	20	14	19
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	46 / 318 (14.47%)	36 / 323 (11.15%)	45 / 329 (13.68%)
occurrences (all)	65	39	62
Bronchitis			
subjects affected / exposed	16 / 318 (5.03%)	32 / 323 (9.91%)	25 / 329 (7.60%)
occurrences (all)	19	43	29
Urinary tract infection			
subjects affected / exposed	22 / 318 (6.92%)	14 / 323 (4.33%)	33 / 329 (10.03%)
occurrences (all)	34	20	44
Influenza			
subjects affected / exposed	13 / 318 (4.09%)	14 / 323 (4.33%)	23 / 329 (6.99%)
occurrences (all)	13	16	28
Upper respiratory tract infection			
subjects affected / exposed	20 / 318 (6.29%)	13 / 323 (4.02%)	19 / 329 (5.78%)
occurrences (all)	25	15	20

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2014	Protocol was amended to allow investigator site staff to perform telephone administration of the patient-reported outcome (PRO) assessments on the study subjects in countries where law and/or regulation prohibit the use of a third-party Sponsor contracted call centre to perform the telephone administration of the PRO assessments.
04 September 2014	Protocol was amended to reflect that the microperimetry assessment should be performed post-dilation.
18 November 2014	Protocol was amended to include additional inclusion/exclusion criteria to enhance subject safety and to comply with health authority requests, enabling the protocol to be conducted globally.
06 March 2015	Protocol was amended to change the telephone-based collection of patient-reported outcome questionnaires (National Eye Institute Visual Functioning Questionnaire 25-item Version and Functional Reading Independence Index) to an on-site, in-person administration format. The screening period was extended from 21 days to 28 days. To reduce the chance of user error, the sham vial appropriate handing was clarified. This amendment included small revisions and clarifications to the inclusion and exclusion criteria. The protocol expanded on use of Lucentis (at the discretion of the investigator) in either eye for any ocular condition for which it was approved in a country.
24 September 2015	Planned total sample size was updated to provide a more accurate number of planned global sites. Section Subjects included guidance regarding the procedure for handling subjects who needed an extended screening period to prevent unnecessary re-screening. In the inclusion criteria contraceptive methods for women of childbearing potential and men as well as definition of women of childbearing potential were harmonised with current international recommendations. In the exclusion criteria concurrent systemic conditions were updated to include treatment for localised in addition to systemic infection. Ongoing prophylactic use of antimicrobial therapy should be discussed with Medical Monitor. Additional details regarding the masked and unmasked roles were added. In Permitted Therapy, updated instructions were given in the event that Lucentis treatment was given at the same visit as a study eye treatment with lampalizumab/sham to help ensure subject safety. Safety Plan was updated to include transient vision loss as a potential ocular safety issue currently thought to be associated with the route of administration to help ensure subject safety. More detailed guidance was provided for the assessment of causality of adverse events. Clarified the pre-treatment procedures for subjects undergoing treatment or sham injections to help ensure subject safety. Preparation and administration of lampalizumab injection was revised to include equivalent study treatment supplies (needles) available outside of the United States and to further clarify the steps required to prepare and administer a lampalizumab injection to help ensure subject safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

23 January 2018	The study was terminated early by the Sponsor due to lack of efficacy of the compound.	-

Notes:

Limitations and caveats

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

This study was terminated early by the Sponsor. Thus, not all subjects in this study completed the full duration of treatment.

Notes: