Clinical trial results:
Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration

Summary

EudraCT number	2019-003851-12
Trial protocol	HU LT LV PT EE AT FR SK BG CZ GB IT
Global end of trial date	06 August 2024

Results information

Result version number	v1 (current)
This version publication date	14 August 2025
First version publication date	14 August 2025

Trial information

Trial identification

Sponsor protocol code	20968

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04423718
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	06 August 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine if treatment with aflibercept 8 mg (HD) at intervals of 12 or 16 weeks provides noninferior BCVA change compared to aflibercept 2 mg every 8 weeks in participants with nAMD.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects and/or their legally authorized representative signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 August 2020
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	Australia: 24
Country: Number of subjects enrolled	China: 101
Country: Number of subjects enrolled	Japan: 98
Country: Number of subjects enrolled	Korea, Republic of: 31
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Bulgaria: 35
Country: Number of subjects enrolled	Czechia: 97
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Georgia: 9
Country: Number of subjects enrolled	Hungary: 84
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Latvia: 24
Country: Number of subjects enrolled	Lithuania: 26

Country: Number of subjects enrolled	Portugal: 18
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Serbia: 1
Country: Number of subjects enrolled	Slovakia: 29
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	Switzerland: 14
Country: Number of subjects enrolled	Ukraine: 16
Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	United States: 295
Worldwide total number of subjects	1012
EEA total number of subjects	391

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)	114
From 65 to 84 years	784
85 years and over	114

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 251 centers in 27 countries/regions with first participant first visit on 20-AUG-2020 and last participant last visit (Week 156) on 07-Aug-2024.

Pre-assignment

Screening details:

Overall, 1395 participants were screened, of whom 383 participants did not complete screening, 1 participant was randomized in error although he/she did not complete screening and had withdrawn consent. A total of 1011 participants were randomized in nearly equal numbers to 1 of the 3 treatment groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Aflibercept 2q8

Arm description:

Participants enrolled in main study received aflibercept 2 mg administered every 8 weeks after 3 initial injections at 4-week intervals up to 96 weeks.

Arm type	Active comparator
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	BAY86-5321)
Other name	Eylea
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Solution in Vial, 2 mg, Aflibercept 2 mg administered every 8 weeks in the double-masked study part (Years 1 and 2).

Arm title	Aflibercep HDq12

Arm description:

Participants enrolled in main study received high dose (HD) aflibercept administered every 12 weeks after 3 initial injections at 4-week intervals, up to 96 weeks.

Arm type	Experimental
Investigational medicinal product name	Aflibercept High Dose
Investigational medicinal product code	BAY86-5321
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Solution in Vial, 8 mg, administered every 16 weeks after an initiation phase. Treatment intervals adjusted according to individual patient response.

Arm title	Aflibercept HDq16

Arm description:

Participants enrolled in main study received high dose (HD) aflibercept administered every 16 weeks after 3 initial injections at 4-week intervals, up to 96 weeks.

Arm type	Experimental

Investigational medicinal product name	Aflibercept High Dose
Investigational medicinal product code	BAY86-5321
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Solution in Vial, 8 mg, administered every 16 weeks after an initiation phase. Treatment intervals adjusted according to individual patient response.

Number of subjects in period 1[1]	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16
Started	336	335	338
Completed	286	291	294
Not completed	50	44	44
Adverse event, serious fatal	11	7	7
COVID-19 pandemic	2	2	2
Physician decision	2	3	1
Consent withdrawn by subject	15	20	20
Adverse event, non-fatal	7	5	7
Other	9	3	2
Lost to follow-up	2	3	4
Lack of efficacy	2	1	-
Protocol deviation	-	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Not all randomized subjected received treatment.

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Aflibercept 2q8 (Week 0-96) / HD (up to week 156)

Arm description:

Participants enrolled in the extension originally assigned to 2q8 in main study and switched to high dose aflibercept every 12 weeks starting at Week 96.

Arm type	Experimental
Investigational medicinal product name	Aflibercept High Dose
Investigational medicinal product code	BAY86-5321
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Solution in Vial, 8 mg, in Year 3, high dose aflibercept administered according to individual patient response. (Experimental)

Arm title	Aflibercep HDq12

Arm description:

Participants enrolled in the extension continued with HD aflibercept at their latest dosing interval at Week 96.

Arm type	Experimental
Investigational medicinal product name	Aflibercept High Dose
Investigational medicinal product code	BAY86-5321
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Solution in Vial, 8 mg, Aflibercept high dose (HD) administered every 12 weeks after an initiation phase. Treatment intervals adjusted according to individual patient response.

Arm title	Aflibercept HDq16

Arm description:

Participants enrolled in the extension continued with HD aflibercept at their latest dosing interval at Week 96.

Arm type	Experimental
Investigational medicinal product name	Aflibercept High Dose
Investigational medicinal product code	BAY86-5321
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Solution in Vial, 8 mg, Aflibercept high dose administered every 16 weeks after an initiation phase. Treatment intervals adjusted according to individual patient response.

Number of subjects in period 2[2]	Aflibercept 2q8 (Week 0-96) / HD (up to week 156)	Aflibercep HDq12	Aflibercept HDq16
Started	208	210	207
Treated	208	210	207
Completed	187	186	191
Not completed	21	24	16
Adverse event, serious fatal	4	7	2
Physician decision	1	-	1
Consent withdrawn by subject	11	11	7
Logistical problems	-	1	1
Adverse event, non-fatal	2	3	1
Decision made by the staff and the patient	1	-	-
Lost to follow-up	-	2	3

Lack of efficacy	2	-	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Not all subjects who completed main study entered extension phase.

Baseline characteristics

Reporting groups	
Reporting group title	Aflibercept 2q8
Reporting group description:	
Participants enrolled in main study received aflibercept 2 mg administered every 8 weeks after 3 initial injections at 4-week intervals up to 96 weeks.	
Reporting group title	Aflibercep HDq12
Reporting group description:	
Participants enrolled in main study received high dose (HD) aflibercept administered every 12 weeks after 3 initial injections at 4-week intervals, up to 96 weeks.	
Reporting group title	Aflibercept HDq16
Reporting group description:	
Participants enrolled in main study received high dose (HD) aflibercept administered every 16 weeks after 3 initial injections at 4-week intervals, up to 96 weeks.	

Reporting group values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16
Number of subjects	336	335	338
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	74.2	74.7	74.5
standard deviation	± 8.8	± 7.9	± 8.5
Sex: Female, Male Units: Participants			
Female	188	182	180
Male	148	153	158
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12	7	9
Not Hispanic or Latino	322	322	326
Unknown or Not Reported	2	6	3
Baseline BCVA measured by the ETDRS letter score			
Visual function of the study eye was assessed at a distance of 4 meters using the Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score. BCVA scale range is 0 (worst) to 100 (best).			
Units: scores on a scale			
arithmetic mean	58.9	59.9	60.0

standard deviation	± 14.0	± 13.4	± 12.4
Baseline choroidal neovascularization (CNV) size			
Units: mm²			
arithmetic mean	6.3593	5.9768	6.5459
standard deviation	± 5.0394	± 4.8306	± 5.5315
Baseline total lesion area			
Units: mm²			
arithmetic mean	6.8647	6.3820	6.8814
standard deviation	± 5.4145	± 5.0664	± 5.6514
Baseline central subfield retinal thickness (CST)			
Units: µm			
arithmetic mean	367.1	370.3	370.7
standard deviation	± 133.6	± 123.7	± 132.7
Baseline NEI-VFQ-25 total score			
NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25 NEI VFQ-25 was a 25-item questionnaire that gave a score on a scale from 0 (worst) to 100 (best = no vision problems)			
Units: scores on a scale			
arithmetic mean	77.8082	76.3575	77.6670
standard deviation	± 14.4206	± 15.1213	± 15.3980

Reporting group values	Total		
Number of subjects	1009		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	550		
Male	459		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	28		
Not Hispanic or Latino	970		
Unknown or Not Reported	11		
Baseline BCVA measured by the ETDRS letter score			
Visual function of the study eye was assessed at a distance of 4 meters using the Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score. BCVA scale range			

is 0 (worst) to 100 (best).			
Units: scores on a scale arithmetic mean standard deviation	- -		
Baseline choroidal neovascularization (CNV) size Units: mm² arithmetic mean standard deviation	- -		
Baseline total lesion area Units: mm² arithmetic mean standard deviation	- -		
Baseline central subfield retinal thickness (CST) Units: µm arithmetic mean standard deviation	- -		
Baseline NEI-VFQ-25 total score			
NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25 NEI VFQ-25 was a 25-item questionnaire that gave a score on a scale from 0 (worst) to 100 (best = no vision problems)			
Units: scores on a scale arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Aflibercept 2q8
Reporting group description:	
Participants enrolled in main study received aflibercept 2 mg administered every 8 weeks after 3 initial injections at 4-week intervals up to 96 weeks.	
Reporting group title	Aflibercep HDq12
Reporting group description:	
Participants enrolled in main study received high dose (HD) aflibercept administered every 12 weeks after 3 initial injections at 4-week intervals, up to 96 weeks.	
Reporting group title	Aflibercept HDq16
Reporting group description:	
Participants enrolled in main study received high dose (HD) aflibercept administered every 16 weeks after 3 initial injections at 4-week intervals, up to 96 weeks.	
Reporting group title	Aflibercept 2q8 (Week 0-96) / HD (up to week 156)
Reporting group description:	
Participants enrolled in the extension originally assigned to 2q8 in main study and switched to high dose aflibercept every 12 weeks starting at Week 96.	
Reporting group title	Aflibercep HDq12
Reporting group description:	
Participants enrolled in the extension continued with HD aflibercept at their latest dosing interval at Week 96.	
Reporting group title	Aflibercept HDq16
Reporting group description:	
Participants enrolled in the extension continued with HD aflibercept at their latest dosing interval at Week 96.	
Subject analysis set title	All Aflibercept HD, main study
Subject analysis set type	Full analysis
Subject analysis set description:	
Included all participants from aflibercept HDq12 and aflibercept HDq16 in main study	
Subject analysis set title	All Aflibercept HD, extension phase
Subject analysis set type	Full analysis
Subject analysis set description:	
Included all participants from aflibercept HDq12 and aflibercept HDq16 in extension phase.	

Primary: Change from baseline in BCVA measured by the ETDRS letter score at Week 48

End point title	Change from baseline in BCVA measured by the ETDRS letter score at Week 48
End point description:	
Visual function of the study eye was assessed at a distance of 4 meters using the ETDRS BCVA letter score. BCVA scale range is 0 (worst) to 100 (best).	
End point type	Primary
End point timeframe:	
At baseline and Week 48	

End point values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	336	335	338	
Units: scores on a scale				
least squares mean (standard error)				
LS mean (SE) change from baseline	7.03 (± 0.74)	6.06 (± 0.77)	5.89 (± 0.72)	

Statistical analyses

Statistical analysis title	HDq12 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercep HDq12
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0009 [1]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.87
upper limit	0.92

Notes:

[1] - Strictly hierarchical testing procedure: Since p-value below significance level 0.025, fixed sequence testing continued with next primary endpoint (HDq16-2q8) / within EMA/PMDA specific hierarchy with secondary endpoint (BCVA at W60, HDq12-2q8)

Statistical analysis title	HDq16 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercept HDq16
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0011 [2]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.97
upper limit	0.69

Notes:

[2] - Strictly hierarchical testing procedure: Since p-value below significance level 0.025, fixed sequence testing continued with secondary endpoint (no IRF no SRF at W16)/within EMA/PMDA specific hierarchy with secondary endpoint (BCVA at W60, HDq16-2q8)

Secondary: Change from baseline in BCVA measured by the ETDRS letter score at Week 60

End point title	Change from baseline in BCVA measured by the ETDRS letter score at Week 60

End point description:

Visual function of the study eye was assessed at a distance of 4 meters using the ETDRS BCVA letter score. BCVA scale range is 0 (worst) to 100 (best).

End point type	Secondary

End point timeframe:

At baseline and Week 60

End point values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	336	335	338	
Units: scores on a scale				
least squares mean (standard error)	7.23 (± 0.68)	6.37 (± 0.74)	6.31 (± 0.66)	

Statistical analyses

Statistical analysis title	HDq12 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercep HDq12
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002 [3]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.57
upper limit	0.84

Notes:

[3] - EMA/PMDA specific hierarchy: i.e. secondary endpoint was tested for EMA/PMDA after primary endpoint (HDq12-2q8). Since p-value below significance level 0.025, EMA/PMDA specific fixed sequence testing continued with next primary endpoint (HDq16-2q8)

Statistical analysis title	HDq16 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercept HDq16
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-0.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.51
upper limit	0.66

Notes:

[4] - EMA/PMDA specific hierarchy: i.e. secondary endpoint was tested after primary endpoint (HDq16-2q8). Since p-value below significance level 0.025, EMA/PMDA specific fixed sequence testing continued with secondary endpoint test (no IRF no SRF at W16)

Secondary: Percentage of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in central subfield at Week 16

End point title	Percentage of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in central subfield at Week 16

End point description:

End point type	Secondary

End point timeframe:

At Week 16

End point values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16	All Aflibercept HD, main study
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	335	333	334	667
Units: Percentage of participants				
number (not applicable)	51.6	61.6	65.0	63.3

Statistical analyses

Statistical analysis title	All HD - 2q8
Comparison groups	Aflibercept 2q8 v All Aflibercept HD, main study
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	11.733
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.263
upper limit	18.204

Notes:

[5] - Strictly hierarchical testing procedure to adjust for multiplicity.

Secondary: Percentage of participants gaining at least 15 letters in BCVA from baseline at Week 48

End point title	Percentage of participants gaining at least 15 letters in BCVA from baseline at Week 48

End point description:

End point type	Secondary

End point timeframe:

At baseline and Week 48

End point values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	335	334	337	
Units: Percentage of participants				
number (not applicable)	22.1	20.7	21.7	

Statistical analyses

Statistical analysis title	HDq16 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercept HDq16
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7611 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-0.939
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.997
upper limit	5.119

Notes:

[6] - Nominal p-value, not adjusted for multiplicity

Statistical analysis title	HDq12 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercep HDq12
Number of subjects included in analysis	669
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5704 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-1.748

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.784
upper limit	4.287

Notes:

[7] - Nominal p-value, not adjusted for multiplicity

Secondary: Percentage of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 48

End point title	Percentage of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 48

End point description:

End point type	Secondary

End point timeframe:

At Week 48

End point values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	335	334	337	
Units: Percentage of participants				
number (not applicable)	57.9	56.9	54.3	

Statistical analyses

Statistical analysis title	HDq16 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercept HDq16
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4834 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-2.221
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.435
upper limit	3.994

Notes:

[8] - Nominal p-value, not adjusted for multiplicity

Statistical analysis title	HDq12 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercep HDq12

Number of subjects included in analysis	669
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9554 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-0.182
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.565
upper limit	6.2

Notes:

[9] - Nominal p-value, not adjusted for multiplicity

Secondary: Change in choroidal neovascularization (CNV) size from baseline to Week 48

End point title	Change in choroidal neovascularization (CNV) size from baseline to Week 48

End point description:

End point type	Secondary

End point timeframe:

At baseline and Week 48

End point values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	336	335	338	
Units: mm^2				
least squares mean (standard error)	-2.43 (± 0.31)	-3.65 (± 0.28)	-2.91 (± 0.29)	

Statistical analyses

Statistical analysis title	HDq16 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercept HDq16
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2076 [10]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-0.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	0.27

Notes:

[10] - Nominal p-value, not adjusted for multiplicity

Statistical analysis title	HDq12 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercep HDq12
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0009 [11]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.94
upper limit	-0.51

Notes:

[11] - Nominal p-value, not adjusted for multiplicity

Secondary: Change in total lesion area from baseline to Week 48

End point title	Change in total lesion area from baseline to Week 48

End point description:

End point type	Secondary

End point timeframe:

At baseline and Week 48

End point values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	336	335	338	
Units: mm^2				
least squares mean (standard error)	0.09 (± 0.22)	-0.46 (± 0.19)	-0.35 (± 0.20)	

Statistical analyses

Statistical analysis title	HDq16 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercept HDq16

Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.087 [12]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	0.06

Notes:

[12] - Nominal p-value, not adjusted for multiplicity

Statistical analysis title	HDq12 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercep HDq12
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0287 [13]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	-0.06

Notes:

[13] - Nominal p-value, not adjusted for multiplicity

Secondary: Percentage of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in the center subfield at Week 48

End point title	Percentage of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in the center subfield at Week 48

End point description:

End point type	Secondary

End point timeframe:

At Week 48

End point values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	335	332	334	
Units: Percentage of participants				
number (not applicable)	59.4	71.1	66.8	

Statistical analyses

Statistical analysis title	HDq16 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercept HDq16
Number of subjects included in analysis	669
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0458 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	7.451
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.142
upper limit	14.76

Notes:

[14] - Nominal p-value, not adjusted for multiplicity

Statistical analysis title	HDq12 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercep HDq12
Number of subjects included in analysis	667
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0015 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	11.725
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.527
upper limit	18.923

Notes:

[15] - Nominal p-value, not adjusted for multiplicity

Secondary: Change from baseline in central subfield retinal thickness (CST) at Week 48

End point title	Change from baseline in central subfield retinal thickness (CST) at Week 48

End point description:

End point type	Secondary
End point timeframe:	
At baseline and Week 48	

End point values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	336	335	338	
Units: µm				
least squares mean (standard error)	-136.25 (± 4.24)	-147.37 (± 4.01)	-146.76 (± 3.76)	

Statistical analyses

Statistical analysis title	HDq16 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercept HDq16
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0321 [16]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-10.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.12
upper limit	-0.9

Notes:

[16] - Nominal p-value, not adjusted for multiplicity

Statistical analysis title	HDq12 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercep HDq12
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0283 [17]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-11.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.06
upper limit	-1.18

Notes:

[17] - Nominal p-value, not adjusted for multiplicity

Secondary: Change from baseline in National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score at Week 48

End point title	Change from baseline in National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score at Week 48

End point description:

NEI VFQ-25 was a 25-item questionnaire that gave a score on a scale from 0 (worst) to 100 (best = no vision problems)

End point type	Secondary

End point timeframe:

At baseline and Week 48

End point values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	336	335	338	
Units: scores on a scale				
least squares mean (standard error)	4.22 (± 0.70)	3.50 (± 0.70)	3.35 (± 0.72)	

Statistical analyses

Statistical analysis title	HDq16 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercept HDq16
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.307 [18]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.55
upper limit	0.8

Notes:

[18] - Nominal p-value, not adjusted for multiplicity

Statistical analysis title	HDq12 - 2q8
Comparison groups	Aflibercept 2q8 v Aflibercep HDq12

Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3817 [19]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.35
upper limit	0.9

Notes:

[19] - Nominal p-value, not adjusted for multiplicity

Secondary: Systemic exposure to aflibercept as assessed by plasma concentrations of free, adjusted bound and total aflibercept from baseline through Week 48

End point title	Systemic exposure to aflibercept as assessed by plasma concentrations of free, adjusted bound and total aflibercept from baseline through Week 48

End point description:

"99999" in following table denotes not calculated (less than 2/3 of values per timepoint are >= Lower level of quantification (LLOQ) for geometric mean calculation).

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	336	335	338	
Units: mg/L				
geometric mean (geometric coefficient of variation)				
Week 4, subjects analyzed in were 287, 295, 299	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
Visit 5, subjects analyzed were 263, 269, 255	0.03 (± 70.29)	0.14 (± 78.69)	0.13 (± 82.50)	
Week 12, subjects analyzed were 292, 291, 302	99999 (± 99999)	0.02 (± 81.35)	0.02 (± 84.06)	
Week 28, subjects analyzed were 268, 291, 283	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
Week 48, subjects analyzed were 265, 275, 273	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of treatment-emergent anti-drug antibodies (ADA) response

End point title	Incidence of treatment-emergent anti-drug antibodies (ADA) response

End point description:

End point type	Secondary

End point timeframe:

Up to week 96

End point values	Aflibercept 2q8	Aflibercep HDq12	Aflibercept HDq16	All Aflibercept HD, main study
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	285	295	295	590
Units: participants				
maximum ADA titers - Low (< 1000)	8	14	13	27
maximum ADA titers - Moderate (1000-10000)	0	0	0	0
maximum ADA titers - High (> 10000)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Through Week 96, from first dosing up to 30 days after last dosing (active or sham procedure). Through Week 156, from first dosing up to 30 days after last dosing

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0/27.0

Reporting groups

Reporting group title	Aflibercept 2q8 (Week 0- 96)

Reporting group description:

Participants enrolled in main study received aflibercept 2 mg administered every 8 weeks after 3 initial injections at 4-week intervals.

Reporting group title	Aflibercept HDq12 (Week 0- 96)

Reporting group description:

Participants enrolled in main study received high dose (HD) aflibercept administered every 12 weeks after 3 initial injections at 4-week intervals. Participants in this group could have their treatment intervals adjusted according to pre-specified dose regimen modification (DRM) criteria.

Reporting group title	Aflibercept HDq16 (Week 0- 96)

Reporting group description:

Participants enrolled in main study received high dose (HD) aflibercept administered every 16 weeks after 3 initial injections at 4-week intervals. Participants in this group could have their treatment intervals adjusted according to pre-specified dose regimen modification (DRM) criteria.

Reporting group title	All Aflibercept HD (Week 0- 96)

Reporting group description:

All participants from aflibercept HDq12 (Week 0-96) and aflibercept HDq16 (Week 0-96).

Reporting group title	Aflibercept 2q8/HD (Week 0- 156)

Reporting group description:

Participants enrolled in the extension originally assigned to 2q8 in main study and switched to high dose aflibercept every 12 weeks starting at Week 96. Participants in this group could have their treatment intervals adjusted in the extension according to pre-specified dose regimen modification (E-DRM) criteria.

Reporting group title	Aflibercept HDq12 (Week 0- 156)

Reporting group description:

Participants enrolled in the extension originally assigned to HDq12 in main study and continued with HD aflibercept at their latest dosing interval at Week 96. Participants in this group could have their treatment intervals adjusted in the extension according to pre-specified dose regimen modification (E-DRM) criteria.

Reporting group title	Aflibercept HDq16 (Week 0- 156)

Reporting group description:

Participants enrolled in the extension originally assigned to HDq16 in main study and continued with HD aflibercept at their latest dosing interval at Week 96. Participants in this group could have their treatment intervals adjusted in the extension according to pre-specified dose regimen modification (E-DRM) criteria.

Reporting group title	All Aflibercept HD (Week 0- 156)

Reporting group description:

All participants from aflibercept HDq12 (Week 0-156) and aflibercept HDq16 (Week 0-156). Participants in this group could have their treatment intervals adjusted in the extension according to pre-specified dose regimen modification (E-DRM) criteria.

Serious adverse events	Aflibercept 2q8 (Week 0- 96)	Aflibercept HDq12 (Week 0- 96)	Aflibercept HDq16 (Week 0- 96)
Total subjects affected by serious adverse events			
subjects affected / exposed	69 / 336 (20.54%)	83 / 335 (24.78%)	72 / 338 (21.30%)
number of deaths (all causes)	12	11	7
number of deaths resulting from adverse events	9	10	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma metastatic			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Adenocarcinoma of colon			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Bladder cancer			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			
subjects affected / exposed	3 / 336 (0.89%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone neoplasm			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Breast cancer			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Breast cancer recurrent			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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 cancer			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Colon neoplasm			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Endometrial cancer			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Hypopharyngeal cancer			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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 and neck cancer			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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 cancer			
subjects affected / exposed	1 / 336 (0.30%)	1 / 335 (0.30%)	2 / 338 (0.59%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung carcinoma cell type unspecified stage IV			

subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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	1 / 336 (0.30%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Malignant peritoneal neoplasm			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Metastatic neoplasm			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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 progression			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Non-small cell lung cancer			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Non-small cell lung cancer stage I			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma recurrent			

subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Penile squamous cell carcinoma			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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	1 / 336 (0.30%)	1 / 335 (0.30%)	0 / 338 (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
Rectal adenocarcinoma			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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			
Giant cell arteritis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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	1 / 336 (0.30%)	2 / 335 (0.60%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Artificial urinary sphincter implant			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Cataract operation			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia repair			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Polypectomy			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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

Chest pain			
subjects affected / exposed	0 / 336 (0.00%)	2 / 335 (0.60%)	1 / 338 (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
Cyst			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Death			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	2 / 338 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Oedema			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Oedema peripheral			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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 swelling			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	1 / 338 (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
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			

Disability			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical dysplasia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Prostatitis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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			
Asthma			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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	1 / 336 (0.30%)	3 / 335 (0.90%)	0 / 338 (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
Cough variant asthma			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	1 / 338 (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
Epistaxis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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 embolism			
subjects affected / exposed	1 / 336 (0.30%)	2 / 335 (0.60%)	1 / 338 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Nasal cyst			

subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary thrombosis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Intraocular pressure increased			
subjects affected / exposed	0 / 336 (0.00%)	2 / 335 (0.60%)	0 / 338 (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
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniofacial fracture			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Alcohol poisoning			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Femur fracture			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	1 / 338 (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
Ligament sprain			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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 limb fracture			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Periprosthetic fracture			

subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	2 / 336 (0.60%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound complication			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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	2 / 336 (0.60%)	0 / 335 (0.00%)	0 / 338 (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
Shoulder fracture			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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 laceration			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Skull fracture			

subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	2 / 338 (0.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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 coronary syndrome			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Acute left ventricular failure			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	1 / 338 (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
Acute myocardial infarction			

subjects affected / exposed	2 / 336 (0.60%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	4 / 338 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 336 (0.00%)	2 / 335 (0.60%)	1 / 338 (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
Aortic valve stenosis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Arrhythmia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 336 (0.30%)	2 / 335 (0.60%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Coronary artery disease			

subjects affected / exposed	0 / 336 (0.00%)	2 / 335 (0.60%)	1 / 338 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 336 (0.00%)	3 / 335 (0.90%)	0 / 338 (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
Cardiac failure chronic			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 336 (0.30%)	1 / 335 (0.30%)	1 / 338 (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 / 1
Cardiac arrest			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Stress cardiomyopathy			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	1 / 338 (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
Myocardial infarction			
subjects affected / exposed	1 / 336 (0.30%)	1 / 335 (0.30%)	3 / 338 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypertensive heart disease			

subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 336 (0.00%)	2 / 335 (0.60%)	0 / 338 (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
Nervous system disorders			
Basal ganglia infarction			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid aneurysm rupture			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Carotid arteriosclerosis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Intracranial mass			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 336 (0.60%)	1 / 335 (0.30%)	1 / 338 (0.30%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed	2 / 336 (0.60%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Loss of consciousness			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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 radiculopathy			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Stroke in evolution			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Sciatica			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Radiculopathy			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Parkinson's disease			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Syncope			

subjects affected / exposed	0 / 336 (0.00%)	2 / 335 (0.60%)	1 / 338 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 336 (0.30%)	1 / 335 (0.30%)	0 / 338 (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
Febrile neutropenia			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypochromic anaemia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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 loss anaemia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Tinnitus			

subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	1 / 338 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular detachment			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Dry age-related macular degeneration			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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	0 / 336 (0.00%)	2 / 335 (0.60%)	2 / 338 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Retinal tear			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Retinal haemorrhage			
subjects affected / exposed	1 / 336 (0.30%)	2 / 335 (0.60%)	2 / 338 (0.59%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			

subjects affected / exposed	1 / 336 (0.30%)	2 / 335 (0.60%)	3 / 338 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Abdominal pain			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Dysphagia			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Diarrhoea			
subjects affected / exposed	0 / 336 (0.00%)	2 / 335 (0.60%)	0 / 338 (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
Dental caries			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Colitis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal strangulated hernia			

subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Enteritis			
subjects affected / exposed	1 / 336 (0.30%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	1 / 336 (0.30%)	1 / 335 (0.30%)	1 / 338 (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
Intestinal obstruction			
subjects affected / exposed	0 / 336 (0.00%)	2 / 335 (0.60%)	0 / 338 (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
Haemorrhoids			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoperitoneum			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival bleeding			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			

subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Oesophagitis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Nausea			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Mesenteric artery thrombosis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Pancreatitis chronic			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Mechanical ileus			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			

subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Umbilical hernia			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	2 / 336 (0.60%)	0 / 335 (0.00%)	0 / 338 (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
Cholelithiasis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	1 / 338 (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
Haemorrhagic cholecystitis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic hepatic cyst			

subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic vascular thrombosis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 336 (0.30%)	1 / 335 (0.30%)	0 / 338 (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
Bladder stenosis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Cystitis haemorrhagic			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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 cyst			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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 impairment			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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 mass			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Ureterolithiasis			

subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Mobility decreased			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exostosis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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

Back pain			
subjects affected / exposed	1 / 336 (0.30%)	1 / 335 (0.30%)	1 / 338 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Osteoarthritis			
subjects affected / exposed	3 / 336 (0.89%)	5 / 335 (1.49%)	3 / 338 (0.89%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteitis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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 pain			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff tear arthropathy			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			

subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	1 / 338 (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
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Appendicitis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	2 / 338 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	2 / 338 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Cellulitis			
subjects affected / exposed	0 / 336 (0.00%)	2 / 335 (0.60%)	0 / 338 (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
Diverticulitis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Endophthalmitis			

subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Erysipelas			
subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Gangrene			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Liver abscess			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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 aspiration			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Pneumonia			
subjects affected / exposed	2 / 336 (0.60%)	5 / 335 (1.49%)	5 / 338 (1.48%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Otitis externa			

subjects affected / exposed	0 / 336 (0.00%)	1 / 335 (0.30%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	2 / 338 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Pneumonia viral			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Urinary tract infection			
subjects affected / exposed	5 / 336 (1.49%)	1 / 335 (0.30%)	2 / 338 (0.59%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic infection			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Staphylococcal sepsis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Sinusitis			

subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Q fever			
subjects affected / exposed	0 / 336 (0.00%)	0 / 335 (0.00%)	1 / 338 (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
Urosepsis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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			
Malnutrition			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Hyponatraemia			
subjects affected / exposed	2 / 336 (0.60%)	0 / 335 (0.00%)	2 / 338 (0.59%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 335 (0.00%)	0 / 338 (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
Hyperglycaemia			
subjects affected / exposed	1 / 336 (0.30%)	1 / 335 (0.30%)	0 / 338 (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

Serious adverse events	All Aflibercept HD	Aflibercept 2q8/HD	Aflibercept HDq12

	(Week 0- 96)	(Week 0- 156)	(Week 0- 156)
Total subjects affected by serious adverse events			
subjects affected / exposed	155 / 673 (23.03%)	49 / 208 (23.56%)	61 / 210 (29.05%)
number of deaths (all causes)	18	4	7
number of deaths resulting from adverse events	14	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma metastatic			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Basal cell carcinoma			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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 neoplasm			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Breast cancer recurrent			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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 neoplasm			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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 cancer			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopharyngeal cancer			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head and neck cancer			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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	3 / 673 (0.45%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung carcinoma cell type unspecified stage IV			

subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Lung neoplasm malignant			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant peritoneal neoplasm			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Neoplasm progression			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Non-small cell lung cancer stage I			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma recurrent			

subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Papillary thyroid cancer			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Penile squamous cell carcinoma			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	2 / 210 (0.95%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Vascular disorders			
Giant cell arteritis			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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 arterial occlusive disease			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Hypertension			
subjects affected / exposed	2 / 673 (0.30%)	0 / 208 (0.00%)	0 / 210 (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
Venous thrombosis limb			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Artificial urinary sphincter implant			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract operation			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia repair			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Polypectomy			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
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	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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

Chest pain			
subjects affected / exposed	3 / 673 (0.45%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cyst			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Death			
subjects affected / exposed	3 / 673 (0.45%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Oedema			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			

Disability			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical dysplasia			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	3 / 673 (0.45%)	1 / 208 (0.48%)	3 / 210 (1.43%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough variant asthma			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 673 (0.30%)	0 / 208 (0.00%)	0 / 210 (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
Epistaxis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 673 (0.45%)	1 / 208 (0.48%)	3 / 210 (1.43%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Pleural effusion			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal cyst			

subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary thrombosis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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			
Adjustment disorder			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Intraocular pressure increased			
subjects affected / exposed	2 / 673 (0.30%)	0 / 208 (0.00%)	2 / 210 (0.95%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Craniofacial fracture			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Fall			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Alcohol poisoning			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Femoral neck fracture			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 673 (0.15%)	1 / 208 (0.48%)	0 / 210 (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
Ligament sprain			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Patella fracture			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			

subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Postoperative wound complication			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Rib fracture			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shoulder fracture			
subjects affected / exposed	0 / 673 (0.00%)	2 / 208 (0.96%)	0 / 210 (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
Skin laceration			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Skull fracture			

subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	2 / 673 (0.30%)	0 / 208 (0.00%)	0 / 210 (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
Subdural haematoma			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Wrist fracture			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	1 / 673 (0.15%)	1 / 208 (0.48%)	0 / 210 (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
Acute myocardial infarction			

subjects affected / exposed	1 / 673 (0.15%)	1 / 208 (0.48%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	4 / 673 (0.59%)	1 / 208 (0.48%)	0 / 210 (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
Angina unstable			
subjects affected / exposed	3 / 673 (0.45%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Arrhythmia			
subjects affected / exposed	1 / 673 (0.15%)	1 / 208 (0.48%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 673 (0.30%)	2 / 208 (0.96%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			

subjects affected / exposed	3 / 673 (0.45%)	1 / 208 (0.48%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	3 / 673 (0.45%)	1 / 208 (0.48%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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	2 / 673 (0.30%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Myocardial ischaemia			
subjects affected / exposed	1 / 673 (0.15%)	1 / 208 (0.48%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	4 / 673 (0.59%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypertensive heart disease			

subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	2 / 673 (0.30%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Basal ganglia infarction			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid aneurysm rupture			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Carotid arteriosclerosis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial mass			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 673 (0.30%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Stroke in evolution			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Sciatica			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Parkinson's disease			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Syncope			

subjects affected / exposed	3 / 673 (0.45%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypochromic anaemia			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood loss anaemia			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Tinnitus			

subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	1 / 673 (0.15%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular detachment			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Dry age-related macular degeneration			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	4 / 673 (0.59%)	2 / 208 (0.96%)	3 / 210 (1.43%)
occurrences causally related to treatment / all	0 / 4	2 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal tear			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal haemorrhage			
subjects affected / exposed	4 / 673 (0.59%)	1 / 208 (0.48%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			

subjects affected / exposed	5 / 673 (0.74%)	1 / 208 (0.48%)	2 / 210 (0.95%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 673 (0.30%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental caries			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Colitis ischaemic			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal strangulated hernia			

subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	2 / 673 (0.30%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	2 / 673 (0.30%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoperitoneum			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Gingival bleeding			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			

subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Mesenteric artery thrombosis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Mechanical ileus			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			

subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Cholangitis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 673 (0.30%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic cholecystitis			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Haemorrhagic hepatic cyst			

subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	1 / 210 (0.48%)
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 vascular thrombosis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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 / 673 (0.15%)	1 / 208 (0.48%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder stenosis			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis haemorrhagic			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cyst			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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 mass			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			

subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 673 (0.00%)	2 / 208 (0.96%)	0 / 210 (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
Mobility decreased			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Exostosis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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

Back pain			
subjects affected / exposed	2 / 673 (0.30%)	1 / 208 (0.48%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Osteoarthritis			
subjects affected / exposed	8 / 673 (1.19%)	2 / 208 (0.96%)	4 / 210 (1.90%)
occurrences causally related to treatment / all	0 / 9	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteitis			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff tear arthropathy			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			

subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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			
Bronchitis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Appendicitis			
subjects affected / exposed	2 / 673 (0.30%)	0 / 208 (0.00%)	0 / 210 (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
COVID-19			
subjects affected / exposed	2 / 673 (0.30%)	1 / 208 (0.48%)	0 / 210 (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
COVID-19 pneumonia			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 673 (0.30%)	0 / 208 (0.00%)	2 / 210 (0.95%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Gangrene			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Herpes zoster			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	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	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Liver abscess			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	10 / 673 (1.49%)	2 / 208 (0.96%)	3 / 210 (1.43%)
occurrences causally related to treatment / all	0 / 10	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Otitis externa			

subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Pyelonephritis acute			
subjects affected / exposed	2 / 673 (0.30%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Pneumonia viral			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 673 (0.45%)	4 / 208 (1.92%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic infection			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Staphylococcal sepsis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			

subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Sepsis			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (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
Q fever			
subjects affected / exposed	1 / 673 (0.15%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 673 (0.00%)	1 / 208 (0.48%)	0 / 210 (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
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 673 (0.30%)	2 / 208 (0.96%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 673 (0.00%)	0 / 208 (0.00%)	0 / 210 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 673 (0.15%)	1 / 208 (0.48%)	1 / 210 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Aflibercept HDq16	All Aflibercept HD	

	(Week 0- 156)	(Week 0- 156)	
Total subjects affected by serious adverse events			
subjects affected / exposed	61 / 207 (29.47%)	122 / 417 (29.26%)	
number of deaths (all causes)	2	9	
number of deaths resulting from adverse events	1	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma metastatic			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Basal cell carcinoma			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone neoplasm			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Breast cancer recurrent			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon neoplasm			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopharyngeal cancer			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head and neck cancer			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	3 / 207 (1.45%)	4 / 417 (0.96%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified stage IV			

subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung neoplasm malignant			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant peritoneal neoplasm			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer stage I			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma recurrent			

subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile squamous cell carcinoma			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 207 (0.00%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Giant cell arteritis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Artificial urinary sphincter implant			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract operation			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia repair			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polypectomy			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest pain			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			

Disability			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 207 (0.48%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 207 (0.00%)	3 / 417 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough variant asthma			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 207 (0.97%)	5 / 417 (1.20%)	
occurrences causally related to treatment / all	2 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nasal cyst			

subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	1 / 207 (0.48%)	3 / 417 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniofacial fracture			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Alcohol poisoning			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			

subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shoulder fracture			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			

subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	2 / 207 (0.97%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 207 (0.48%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 207 (0.48%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 207 (0.48%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 207 (0.48%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	3 / 207 (1.45%)	4 / 417 (0.96%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 207 (0.48%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 207 (0.97%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			

subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Basal ganglia infarction			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid aneurysm rupture			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid arteriosclerosis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial mass			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	3 / 207 (1.45%)	4 / 417 (0.96%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochromic anaemia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			

subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular detachment			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry age-related macular degeneration			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	5 / 207 (2.42%)	8 / 417 (1.92%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	2 / 207 (0.97%)	3 / 417 (0.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			

subjects affected / exposed	2 / 207 (0.97%)	4 / 417 (0.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 207 (0.48%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal strangulated hernia			

subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoperitoneum			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			

subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric artery thrombosis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			

subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 207 (0.48%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic cholecystitis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic hepatic cyst			

subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic vascular thrombosis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder stenosis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal mass			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			

subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exostosis			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	2 / 207 (0.97%)	3 / 417 (0.72%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	3 / 207 (1.45%)	7 / 417 (1.68%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff tear arthropathy			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			

subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	3 / 207 (1.45%)	3 / 417 (0.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 207 (0.00%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			

subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 207 (1.45%)	6 / 417 (1.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			

subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 207 (0.48%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic infection			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 207 (0.48%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Q fever			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 207 (0.48%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 207 (0.97%)	2 / 417 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 207 (0.00%)	0 / 417 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 417 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Aflibercept 2q8 (Week 0- 96)	Aflibercept HDq12 (Week 0- 96)	Aflibercept HDq16 (Week 0- 96)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	179 / 336 (53.27%)	163 / 335 (48.66%)	180 / 338 (53.25%)
Investigations			
Intraocular pressure increased			
subjects affected / exposed	10 / 336 (2.98%)	12 / 335 (3.58%)	11 / 338 (3.25%)
occurrences (all)	19	20	20
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 336 (5.36%)	22 / 335 (6.57%)	23 / 338 (6.80%)
occurrences (all)	21	26	23
Eye disorders			
Cataract			
subjects affected / exposed	22 / 336 (6.55%)	29 / 335 (8.66%)	32 / 338 (9.47%)
occurrences (all)	22	29	33
Retinal haemorrhage			
subjects affected / exposed	19 / 336 (5.65%)	16 / 335 (4.78%)	17 / 338 (5.03%)
occurrences (all)	21	16	20
Visual acuity reduced			
subjects affected / exposed	24 / 336 (7.14%)	21 / 335 (6.27%)	23 / 338 (6.80%)
occurrences (all)	31	24	34
Vitreous floaters			
subjects affected / exposed	16 / 336 (4.76%)	5 / 335 (1.49%)	17 / 338 (5.03%)
occurrences (all)	17	6	19
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 336 (2.98%)	8 / 335 (2.39%)	13 / 338 (3.85%)
occurrences (all)	13	8	14
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 336 (2.38%)	12 / 335 (3.58%)	11 / 338 (3.25%)
occurrences (all)	10	13	12
Back pain			

subjects affected / exposed	21 / 336 (6.25%)	17 / 335 (5.07%)	14 / 338 (4.14%)
occurrences (all)	31	27	15
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 336 (2.98%)	8 / 335 (2.39%)	4 / 338 (1.18%)
occurrences (all)	11	8	4
COVID-19			
subjects affected / exposed	60 / 336 (17.86%)	58 / 335 (17.31%)	70 / 338 (20.71%)
occurrences (all)	64	59	73
Nasopharyngitis			
subjects affected / exposed	30 / 336 (8.93%)	18 / 335 (5.37%)	27 / 338 (7.99%)
occurrences (all)	40	25	31
Urinary tract infection			
subjects affected / exposed	18 / 336 (5.36%)	12 / 335 (3.58%)	14 / 338 (4.14%)
occurrences (all)	20	12	19

Non-serious adverse events	All Aflibercept HD (Week 0- 96)	Aflibercept 2q8/HD (Week 0- 156)	Aflibercept HDq12 (Week 0- 156)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	343 / 673 (50.97%)	136 / 208 (65.38%)	120 / 210 (57.14%)
Investigations			
Intraocular pressure increased			
subjects affected / exposed	23 / 673 (3.42%)	8 / 208 (3.85%)	12 / 210 (5.71%)
occurrences (all)	40	20	21
Vascular disorders			
Hypertension			
subjects affected / exposed	45 / 673 (6.69%)	18 / 208 (8.65%)	21 / 210 (10.00%)
occurrences (all)	49	20	25
Eye disorders			
Cataract			
subjects affected / exposed	61 / 673 (9.06%)	27 / 208 (12.98%)	34 / 210 (16.19%)
occurrences (all)	62	29	37
Retinal haemorrhage			
subjects affected / exposed	33 / 673 (4.90%)	17 / 208 (8.17%)	11 / 210 (5.24%)
occurrences (all)	36	22	11
Visual acuity reduced			
subjects affected / exposed	44 / 673 (6.54%)	16 / 208 (7.69%)	15 / 210 (7.14%)
occurrences (all)	58	23	17

Vitreous floaters			
subjects affected / exposed	22 / 673 (3.27%)	12 / 208 (5.77%)	2 / 210 (0.95%)
occurrences (all)	25	13	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 673 (3.12%)	15 / 208 (7.21%)	6 / 210 (2.86%)
occurrences (all)	22	22	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 673 (3.42%)	7 / 208 (3.37%)	6 / 210 (2.86%)
occurrences (all)	25	9	7
Back pain			
subjects affected / exposed	31 / 673 (4.61%)	14 / 208 (6.73%)	11 / 210 (5.24%)
occurrences (all)	42	24	24
Infections and infestations			
Bronchitis			
subjects affected / exposed	12 / 673 (1.78%)	11 / 208 (5.29%)	7 / 210 (3.33%)
occurrences (all)	12	11	8
COVID-19			
subjects affected / exposed	128 / 673 (19.02%)	50 / 208 (24.04%)	44 / 210 (20.95%)
occurrences (all)	132	59	45
Nasopharyngitis			
subjects affected / exposed	45 / 673 (6.69%)	28 / 208 (13.46%)	20 / 210 (9.52%)
occurrences (all)	56	46	33
Urinary tract infection			
subjects affected / exposed	26 / 673 (3.86%)	17 / 208 (8.17%)	11 / 210 (5.24%)
occurrences (all)	31	20	11

Non-serious adverse events	Aflibercept HDq16 (Week 0- 156)	All Aflibercept HD (Week 0- 156)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	135 / 207 (65.22%)	255 / 417 (61.15%)	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	8 / 207 (3.86%)	20 / 417 (4.80%)	
occurrences (all)	12	33	
Vascular disorders			

Hypertension			
subjects affected / exposed	15 / 207 (7.25%)	36 / 417 (8.63%)	
occurrences (all)	15	40	
Eye disorders			
Cataract			
subjects affected / exposed	33 / 207 (15.94%)	67 / 417 (16.07%)	
occurrences (all)	35	72	
Retinal haemorrhage			
subjects affected / exposed	11 / 207 (5.31%)	22 / 417 (5.28%)	
occurrences (all)	15	26	
Visual acuity reduced			
subjects affected / exposed	14 / 207 (6.76%)	29 / 417 (6.95%)	
occurrences (all)	16	33	
Vitreous floaters			
subjects affected / exposed	18 / 207 (8.70%)	20 / 417 (4.80%)	
occurrences (all)	20	22	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 207 (5.80%)	18 / 417 (4.32%)	
occurrences (all)	16	22	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 207 (6.76%)	20 / 417 (4.80%)	
occurrences (all)	15	22	
Back pain			
subjects affected / exposed	14 / 207 (6.76%)	25 / 417 (6.00%)	
occurrences (all)	15	39	
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 207 (2.90%)	13 / 417 (3.12%)	
occurrences (all)	7	15	
COVID-19			
subjects affected / exposed	59 / 207 (28.50%)	103 / 417 (24.70%)	
occurrences (all)	62	107	
Nasopharyngitis			

subjects affected / exposed	28 / 207 (13.53%)	48 / 417 (11.51%)	
occurrences (all)	38	71	
Urinary tract infection			
subjects affected / exposed	14 / 207 (6.76%)	25 / 417 (6.00%)	
occurrences (all)	20	31	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2020	• Updates were made throughout the protocol to reflect the updated DRM and rescue regimen criteria and activities. • Overall design text was amended to update information on potential dose interval changes during Year 1 and Year 2 • Two additional exploratory endpoints were added. • New text was added to improve characterization of the safety profile of investigational aflibercept and to separate documentation of potential relationship of AEs to commercial or investigational aflibercept.
26 April 2022	• The secondary – other endpoint was modified and updates were made to the exploratory endpoints. • Added text with the description of the additional superiority hypotheses and to describe the power, based on the revised confirmatory testing hierarchy. • Added text to clarify the updated testing strategy on key secondary endpoints.
13 September 2022	• Added language to newly introduce the extension period of the study.
27 February 2023	• Updated text to align the protocol with the proposed HD labeling update which extends the time contraception is needed after the last study drug dose from 3 months to 4 months. • Added text to clarify that exploratory analyses may have been performed before Week 96 (but after the completion of the confirmatory analyses at Week 48 and Week 60) as necessary, e.g. to address health authority requests and queries, as well as to perform editorial corrections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported