Clinical trial results:
A Randomized, Double-Masked, Active-Controlled Phase 2/3 Study of the Efficacy and Safety of High-Dose Aflibercept in Patients with Diabetic Macular Edema

Summary

EudraCT number	2019-003643-30
Trial protocol	GB DE HU CZ
Global end of trial date	18 June 2024

Results information

Result version number	v1 (current)
This version publication date	04 July 2025
First version publication date	04 July 2025

Trial information

Trial identification

Sponsor protocol code	VGFTe-HD-DME-1934

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04429503
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, United States, 10591
Public contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc, 001 8447346643, clinicaltrials@regeneron.com
Scientific contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc, 001 8447346643, clinicaltrials@regeneron.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	18 June 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to determine if treatment with high-dose aflibercept (HD) at intervals of 12 or 16 weeks provides non-inferior best corrected visual acuity (BCVA) compared to aflibercept dosed every 8 weeks. The secondary objectives of the study are as follows: - To determine the effect of HD vs. aflibercept on anatomic and other visual measures of response - To evaluate the safety, immunogenicity, and pharmacokinetics (PK) of aflibercept

Protection of trial subjects:

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 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	Canada: 10
Country: Number of subjects enrolled	Czechia: 38
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 77
Country: Number of subjects enrolled	Japan: 74
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 452
Worldwide total number of subjects	658
EEA total number of subjects	118

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)	369
From 65 to 84 years	285
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 970 participants were screened and 660 participants were randomized, of whom 658 participants received at least 1 dose of study treatment in the study eye. Only one study eye per participant was analyzed within the study.

Period 1

Period 1 title	Main Study (Up to Wk 96)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Aflibercept 2 mg every 8 weeks (2q8)

Arm description:

Participants received 2 milligrams (mg) aflibercept every 8 weeks (2q8), following 5 initial monthly doses

Arm type	Active comparator
Investigational medicinal product name	aflibercept
Investigational medicinal product code	
Other name	EYLEA
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

2 mg every 8 weeks (2q8)

Arm title	High-dose (HD) aflibercept every 12 weeks (HDq12)

Arm description:

Participants received HD aflibercept (8 mg) every 12 weeks (HDq12) following 3 initial monthly doses

Arm type	Experimental
Investigational medicinal product name	HD aflibercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

8 mg aflibercept every 12 weeks (HDq12)

Arm title	HD aflibercept every 16 weeks (HDq16)

Arm description:

Participants received HD aflibercept (8mg) every 16 weeks (HDq16) following 3 initial monthly doses

Arm type	Experimental
Investigational medicinal product name	HD aflibercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:
8 mg aflibercept every 16 weeks (HDq16)

Number of subjects in period 1	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)
Started	167	328	163
Completed Week 48	157	300	156
Completed Week 60	155	289	152
Completed Week 96	139	256	139
Completed	139	256	139
Not completed	28	72	24
Decision by the investigator/sponsor	2	9	2
Adverse event, serious fatal	9	18	5
Consent withdrawn by subject	9	17	8
Adverse event, non-fatal	1	8	2
Lost to follow-up	5	19	7
Non-compliance with protocol by the subject	2	1	-

Period 2

Period 2 title	Extension Phase (Wk 96 to Wk 156)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:
12 weeks double-blind then open-label through week 156

Arms

Are arms mutually exclusive?	Yes
Arm title	2q8/HD aflibercept (extension)

Arm description:
Participants receiving aflibercept 2q8 switched to HD in the extension phase

Arm type	Experimental

Investigational medicinal product name	HD aflibercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

8 mg HD aflibercept

Arm title	HDq12 aflibercept (extension)

Arm description:

Participants continued to receive HDq12 aflibercept during the extension phase

Arm type	Experimental
Investigational medicinal product name	HD aflibercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

8 mg aflibercept every 12 weeks (HDq12)

Arm title	HDq16 aflibercept (extension)

Arm description:

Participants continued to receive HDq16 aflibercept during the extension phase

Arm type	Experimental
Investigational medicinal product name	HD aflibercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

8 mg aflibercept every 16 weeks (HDq16)

Number of subjects in period 2[1]	2q8/HD aflibercept (extension)	HDq12 aflibercept (extension)	HDq16 aflibercept (extension)
Started	70	130	65
Completed	58	103	49
Not completed	12	27	16
Adverse event, serious fatal	2	7	2
Decision by the investigator/sponsor	-	3	2
Consent withdrawn by subject	5	10	5
Adverse event, non-fatal	1	1	1
Lost to follow-up	3	6	6
Protocol deviation	1	-	-

Notes:

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

Justification: Not all participants from main phase continued to extension phase.

Baseline characteristics

Reporting groups	
Reporting group title	Aflibercept 2 mg every 8 weeks (2q8)
Reporting group description:	
Participants received 2 milligrams (mg) aflibercept every 8 weeks (2q8), following 5 initial monthly doses	
Reporting group title	High-dose (HD) aflibercept every 12 weeks (HDq12)
Reporting group description:	
Participants received HD aflibercept (8 mg) every 12 weeks (HDq12) following 3 initial monthly doses	
Reporting group title	HD aflibercept every 16 weeks (HDq16)
Reporting group description:	
Participants received HD aflibercept (8mg) every 16 weeks (HDq16) following 3 initial monthly doses	

Reporting group values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)
Number of subjects	167	328	163
Age categorical Units: Subjects			
Adults (≥18 years)	167	328	163
Age Continuous Units: Years			
arithmetic mean	63.0	62.1	61.9
standard deviation	± 9.78	± 11.13	± 9.50
Sex: Female, Male Units: Participants			
Female	75	118	64
Male	92	210	99
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	31	54	34
Not Hispanic or Latino	133	266	126
Unknown or Not Reported	3	8	3
Race/Ethnicity, Customized			
Race			
Units: Subjects			
American Indian or Alaska Native	0	2	0
Asian	30	48	23
Black or African American	18	35	9
Native Hawaiian or Other Pacific Islander	0	1	0
White	112	231	128
Multiple	0	1	0
Other	4	6	1
Not Reported	3	4	2
Best Corrected Visual Acuity (BCVA) in the Study Eye			
Early Treatment Diabetic Retinopathy Study (ETDRS) letter score; Only one study eye per participant was analyzed within the study			
Units: Letters			

arithmetic mean	61.5	63.6	61.4
standard deviation	± 11.22	± 10.10	± 11.76

Reporting group values	Total		
Number of subjects	658		
Age categorical Units: Subjects			
Adults (≥18 years)	658		
Age Continuous Units: Years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: Participants			
Female	257		
Male	401		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	119		
Not Hispanic or Latino	525		
Unknown or Not Reported	14		
Race/Ethnicity, Customized			
Race			
Units: Subjects			
American Indian or Alaska Native	2		
Asian	101		
Black or African American	62		
Native Hawaiian or Other Pacific Islander	1		
White	471		
Multiple	1		
Other	11		
Not Reported	9		
Best Corrected Visual Acuity (BCVA) in the Study Eye			
Early Treatment Diabetic Retinopathy Study (ETDRS) letter score; Only one study eye per participant was analyzed within the study			
Units: Letters arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Aflibercept 2 mg every 8 weeks (2q8)
Reporting group description:	
Participants received 2 milligrams (mg) aflibercept every 8 weeks (2q8), following 5 initial monthly doses	
Reporting group title	High-dose (HD) aflibercept every 12 weeks (HDq12)
Reporting group description:	
Participants received HD aflibercept (8 mg) every 12 weeks (HDq12) following 3 initial monthly doses	
Reporting group title	HD aflibercept every 16 weeks (HDq16)
Reporting group description:	
Participants received HD aflibercept (8mg) every 16 weeks (HDq16) following 3 initial monthly doses	
Reporting group title	2q8/HD aflibercept (extension)
Reporting group description:	
Participants receiving aflibercept 2q8 switched to HD in the extension phase	
Reporting group title	HDq12 aflibercept (extension)
Reporting group description:	
Participants continued to receive HDq12 aflibercept during the extension phase	
Reporting group title	HDq16 aflibercept (extension)
Reporting group description:	
Participants continued to receive HDq16 aflibercept during the extension phase	

Primary: Change from baseline in Best Corrected Visual Acuity (BCVA) (Early Treatment Diabetic Retinopathy Study [ETDRS] letter score) in the Study Eye at week 48

End point title	Change from baseline in Best Corrected Visual Acuity (BCVA) (Early Treatment Diabetic Retinopathy Study [ETDRS] letter score) in the Study Eye at week 48
End point description:	
Visual function of the study eye was assessed at a distance of 4 meters at every study visit using the Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score. BCVA scale range is 0 (worst) to 100 (best). Full analysis set (FAS): All randomized participants who received at least 1 dose of study drug; it was based on the treatment assigned to the participant at baseline (as randomized); Only one study eye per participant was analyzed within the study.	
End point type	Primary
End point timeframe:	
Baseline, Week 48	

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	328	163	
Units: Letters				
least squares mean (standard error)	8.67 (± 0.73)	8.10 (± 0.61)	7.23 (± 0.71)	

Statistical analyses

Statistical analysis title	aflibercept 2Q8, HDQ16
Comparison groups	Aflibercept 2 mg every 8 weeks (2q8) v HD aflibercept every 16 weeks (HDq16)
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0031
Method	Mixed Model for Repeated Measurements
Parameter estimate	LS Mean Difference
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.27
upper limit	0.39

Statistical analysis title	aflibercept 2Q8, HDQ12
Comparison groups	Aflibercept 2 mg every 8 weeks (2q8) v High-dose (HD) aflibercept every 12 weeks (HDq12)
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed Model for Repeated Measurements
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	1.13

Secondary: Percentage of participants with a ≥2 step improvement from baseline in Diabetic Retinopathy Severity Scale (DRSS) score at week 48

End point title	Percentage of participants with a ≥2 step improvement from baseline in Diabetic Retinopathy Severity Scale (DRSS) score at week 48

End point description:

The DRSS was assessed according to the following scale: 10 = Diabetic retinopathy (DR) absent, 14 = DR questionable, 15 = DR questionable, 20 = Micro-aneurysms only, 35 = Mild Non-proliferative

diabetic retinopathy (NPDR), 43 = Moderate NPDR, 47 = Moderately severe NPDR, 53 = Severe NPDR, 61 = Mild Proliferative diabetic retinopathy (PDR), 65 = Moderate PDR, 71 = High-risk PDR, 75 = High-risk PDR, 81 = Advanced PDR: fundus partially obscured, center of macula attached, 85 = Advanced PDR: posterior fundus obscured, or center of macula detached, 90 = cannot grade, even sufficiently for level 81 or 85. Full analysis set (FAS): All randomized participants who received at least 1 dose of study drug; it was based on the treatment assigned to the participant at baseline (as randomized); Only one study eye per participant was analyzed within the study,

End point type	Secondary
End point timeframe:	
Baseline, Week 48	

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	310	153	
Units: Percentage of Participants				
number (not applicable)	26.6	29.0	19.6	

Statistical analyses

Statistical analysis title	aflibercept 2Q8, HDQ12
Comparison groups	Aflibercept 2 mg every 8 weeks (2q8) v High-dose (HD) aflibercept every 12 weeks (HDq12)
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted Difference (%)
Point estimate	1.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.61
upper limit	10.57

Statistical analysis title	aflibercept 2Q8, HDQ16
Comparison groups	Aflibercept 2 mg every 8 weeks (2q8) v HD aflibercept every 16 weeks (HDq16)
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted Difference (%)
Point estimate	-7.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.88
upper limit	1.84

Secondary: Percentage of participants gaining ≥15 letters in BCVA from baseline at week 48

End point title	Percentage of participants gaining ≥15 letters in BCVA from baseline at week 48

End point description:

Visual function of the study eye was assessed at a distance of 4 meters at every study visit using the Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score. BCVA scale range is 0 (worst) to 100 (best). Only one study eye per participant was analyzed within the study. Full analysis set (FAS): All randomized participants who received at least 1 dose of study drug; it was based on the treatment assigned to the participant at baseline (as randomized).

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165	326	163	
Units: Percentage of Participants				
number (not applicable)	23.0	18.7	16.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with BCVA ≥69 letters at week 48

End point title	Percentage of participants with BCVA ≥69 letters at week 48

End point description:

Visual function of the study eye was assessed at a distance of 4 meters at every study visit using the Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score. BCVA scale range is 0 (worst) to 100 (best). Full analysis set (FAS): All randomized participants who received at least 1 dose of study drug; it was based on the treatment assigned to the participant at baseline (as randomized)

End point type	Secondary

End point timeframe:

At Week 48

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165	326	163	
Units: Percentage of Participants				
number (not applicable)	63.0	65.3	62.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants without fluid at foveal center at week 48

End point title	Percentage of participants without fluid at foveal center at week 48

End point description:

Retinal fluid status was evaluated using spectral domain optical coherence tomography (SD-OCT) on the study eye. Full analysis set (FAS): All randomized participants who received at least 1 dose of study drug; it was based on the treatment assigned to the participant at baseline (as randomized)

End point type	Secondary

End point timeframe:

At Week 48

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165	325	162	
Units: Percentage of Participants				
number (not applicable)	54.5	58.5	43.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Central Retinal Thickness (CRT) in the Study Eye at week 48

End point title	Change from baseline in Central Retinal Thickness (CRT) in the Study Eye at week 48

End point description:

Central Retinal Thickness (CRT) was measured in the study eye by spectral domain optical coherence

tomography (SD-OCT). Full analysis set (FAS): All randomized participants who received at least 1 dose of study drug; it was based on the treatment assigned to the participant at baseline (as randomized). Only one study eye per participant was analyzed within the study.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	328	163	
Units: Microns				
least squares mean (standard error)	-164.85 (± 8.79)	-176.77 (± 5.73)	-148.84 (± 9.45)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants without leakage on Fluorescein Angiography (FA) at week 48

End point title	Percentage of participants without leakage on Fluorescein Angiography (FA) at week 48

End point description:

Leakage is the release of fluorescein dye from diseased retinal vessels. Full analysis set (FAS): All randomized participants who received at least 1 dose of study drug; it was based on the treatment assigned to the participant at baseline (as randomized)

End point type	Secondary

End point timeframe:

At Week 48

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	162	303	152	
Units: Percentage of Participants				
number (not applicable)	2.5	7.6	0.7	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Vision-specific quality of life is assessed with the NEI VFQ-25 (National Eye Institute Visual Function Questionnaire), i.e. a 25-item questionnaire that gives a score on a scale from 0 (worst) to 100 (best = no vision problems). Full analysis set (FAS): All randomized participants who received at least 1 dose of study drug; it was based on the treatment assigned to the participant at baseline (as randomized)

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	328	163	
Units: Score on a Scale				
least squares mean (standard error)	2.82 (± 1.10)	4.06 (± 0.80)	2.94 (± 0.93)	

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic pharmacokinetics (PK) of aflibercept as assessed by plasma concentrations through week 48

End point title	Systemic pharmacokinetics (PK) of aflibercept as assessed by plasma concentrations through week 48

End point description:

Concentrations of Free Aflibercept in Plasma by Time and Treatment Group; Pharmacokinetic analysis set (PKAS): All treated participants who received any amount of study drug and had at least 1 non-missing free or bound aflibercept measurement following the first dose of study drug as applicable. The PKAS is based on the actual treatment received (as treated) rather than as randomized.

End point type	Secondary

End point timeframe:

Through Week 48

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	328	163	
Units: milligram/Litre (mg/L)				
arithmetic mean (standard deviation)	0.00102 (± 0.00580)	0.0111 (± 0.0157)	0.00105 (± 0.00477)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in BCVA in the Study Eye in participants with both baseline and week 48 BCVA

End point title	Change from baseline in BCVA in the Study Eye in participants with both baseline and week 48 BCVA

End point description:

Visual function of the study eye was assessed at a distance of 4 meters at every study visit using the Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score. BCVA scale range is 0 (worst) to 100 (best). (Per Statistical Analysis Plan (SAP) Version 2.0 Appendix 10.9 for US Only); Full Analysis Set (FAS) - for participants who had both baseline BCVA and week 48 BCVA; Only one study eye per participant was analyzed within the study

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	291	154	
Units: Letters				
arithmetic mean (standard deviation)	9.11 (± 8.94)	9.14 (± 8.35)	9.11 (± 7.30)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from 8-weeks post initial treatment phase in BCVA in the Study Eye in participants with both 8-weeks post initial treatment phase BCVA and week 48 BCVA

End point title	Change from 8-weeks post initial treatment phase in BCVA in the Study Eye in participants with both 8-weeks post initial treatment phase BCVA and week 48 BCVA

End point description:

Visual function of the study eye was assessed at a distance of 4 meters at every study visit using the Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score. BCVA scale range is 0 (worst) to 100 (best). (Per SAP Version 2.0 Appendix 10.9 for US Only); Full Analysis Set (FAS) - for participants who had both BCVA at 8 weeks post initial treatment and week 48 BCVA; Only one study eye per participant was analyzed within the study

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	282	153	
Units: Letters				
arithmetic mean (standard deviation)	1.63 (± 6.65)	1.68 (± 5.54)	1.64 (± 4.75)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in BCVA (region-specific analysis) in the Study Eye at week 60

End point title	Change from baseline in BCVA (region-specific analysis) in the Study Eye at week 60

End point description:

Visual function of the study eye was assessed at a distance of 4 meters at every study visit using the Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score. BCVA scale range is 0 (worst) to 100 (best). FAS: All randomized participants who received at least 1 dose of study drug; it was based on the treatment assigned to the participant at baseline (as randomized); Here, Number of Participants Analyzed = Number of participants with week 60 data. Only one study eye per participant was analyzed within the study

End point type	Secondary

End point timeframe:

Baseline, Week 60

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	328	163	
Units: Letters				
least squares mean (standard error)	9.40 (± 0.77)	8.52 (± 0.63)	7.64 (± 0.75)	

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of immunogenicity to aflibercept by measuring the incidence of treatment-emergent anti-drug antibodies (ADA) response through week 96

End point title	Assessment of immunogenicity to aflibercept by measuring the incidence of treatment-emergent anti-drug antibodies (ADA) response through week 96

End point description:

Number of participants with pre-existing immunoreactivity and treatment-emergent ADA response reported; ADA analysis set (AAS): All treated participants who received any amount of study drug and had at least 1 non-missing anti-aflibercept antibody result following the first dose of study drug. The AAS is based on the actual treatment received (as treated) rather than as randomized

End point type	Secondary

End point timeframe:

Through Week 96

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	151	289	150	
Units: Participants				
Pre-existing Immunoreactivity	4	11	2	
Treatment-Emergent	2	7	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any treatment-emergent adverse event (TEAE) through week 96

End point title	Number of participants with any treatment-emergent adverse event (TEAE) through week 96

End point description:

A TEAE is an AE starting after the first dose of study drug to the last dose of study drug (active or sham) plus 30 days. Additionally, for patients who are still participating in the study (ie, have not been withdrawn and are continuing in the extension phase of the study) as of the week 96 visit all AEs up through the date of the week 96 visit were considered treatment-emergent. Safety analysis set (SAF): All randomized participants who received any study treatment; it was based on the treatment received (as treated)

End point type	Secondary
End point timeframe: Through Week 96	

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	328	163	
Units: Participants	134	277	143	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any serious TEAE through week 96

End point title	Number of participants with any serious TEAE through week 96

End point description:

A TEAE is an AE starting after the first dose of study drug to the last dose of study drug (active or sham) plus 30 days. Additionally, for patients who are still participating in the study (ie, have not been withdrawn and are continuing in the extension phase of the study) as of the week 96 visit all AEs up through the date of the week 96 visit were considered treatment-emergent. Safety analysis set (SAF): All randomized participants who received any study treatment; it was based on the treatment received (as treated)

End point type	Secondary
End point timeframe: Through Week 96	

End point values	Aflibercept 2 mg every 8 weeks (2q8)	High-dose (HD) aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	328	163	
Units: Participants	46	81	44	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any TEAE through week 156

End point title	Number of participants with any TEAE through week 156

End point description:

TEAEs are defined as AEs starting after the first dose of study drug to the last dose of study drug (active or sham) plus 30 days or week 156 visit, whichever is later. Extension Safety Analysis Set (eSAF): All participants in the SAF who enrolled in the extension phase and completed the extension baseline visit.

End point type	Secondary

End point timeframe:

Through Week 156

End point values	2q8/HD aflibercept (extension)	HDq12 aflibercept (extension)	HDq16 aflibercept (extension)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	130	65	
Units: Participants	64	122	59	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any serious TEAE through week 156

End point title	Number of participants with any serious TEAE through week 156

End point description:

Extension Safety Analysis Set (eSAF): All participants in the SAF who enrolled in the extension phase and completed the extension baseline visit.

End point type	Secondary

End point timeframe:

Through Week 156

End point values	2q8/HD aflibercept (extension)	HDq12 aflibercept (extension)	HDq16 aflibercept (extension)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	130	65	
Units: Participants	27	41	22	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first study treatment through week 156	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0/27.0
Reporting groups	
Reporting group title	Aflibercept 2 mg every 8 weeks (2q8)
Reporting group description: (baseline through week 96)	
Reporting group title	HD aflibercept every 12 weeks (HDq12)
Reporting group description: (baseline through week 96)	
Reporting group title	HD aflibercept every 16 weeks (HDq16)
Reporting group description: (baseline through week 96)	
Reporting group title	2q8/HD aflibercept (extension)
Reporting group description: Participants receiving aflibercept 2q8 switched to HD upon entry into the extension phase (week 96 through week 156)	
Reporting group title	HDq12 aflibercept (extension)
Reporting group description: Participants continued to receive HDq12 aflibercept during the extension phase (week 96 through 156)	
Reporting group title	HDq16 aflibercept (extension)
Reporting group description: Participants continued to receive HDq16 aflibercept during the extension phase (week 96 through 156)	

Serious adverse events	Aflibercept 2 mg every 8 weeks (2q8)	HD aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 167 (27.54%)	84 / 328 (25.61%)	45 / 163 (27.61%)
number of deaths (all causes)	9	18	5
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Rectal adenocarcinoma			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Plasma cell myeloma			
subjects affected / exposed	1 / 167 (0.60%)	1 / 328 (0.30%)	0 / 163 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal neoplasm			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
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 cancer metastatic			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
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 cancer			

subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Neuroendocrine carcinoma			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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 metastatic			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric cancer			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Metastasis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive breast carcinoma			

subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
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 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
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 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 167 (0.00%)	2 / 328 (0.61%)	0 / 163 (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
Arteriosclerosis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Haematoma			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Hypertensive emergency			
subjects affected / exposed	1 / 167 (0.60%)	1 / 328 (0.30%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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 / 167 (0.60%)	1 / 328 (0.30%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive urgency			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
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 / 167 (0.60%)	0 / 328 (0.00%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral venous disease			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Thrombosis prophylaxis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Skin neoplasm excision			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	1 / 167 (0.60%)	3 / 328 (0.91%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
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	1 / 167 (0.60%)	3 / 328 (0.91%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 0
Sudden death			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (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
Asthenia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organ failure			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
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			
Scrotal oedema			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
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			
Pulmonary embolism			
subjects affected / exposed	0 / 167 (0.00%)	2 / 328 (0.61%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute respiratory failure			
subjects affected / exposed	2 / 167 (1.20%)	2 / 328 (0.61%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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 fibrosis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
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 oedema			
subjects affected / exposed	0 / 167 (0.00%)	2 / 328 (0.61%)	0 / 163 (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

Hypoxia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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 / 167 (0.60%)	1 / 328 (0.30%)	0 / 163 (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
Respiratory distress			
subjects affected / exposed	0 / 167 (0.00%)	2 / 328 (0.61%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Haemoptysis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Psychiatric disorders			
Stress			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device failure			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Intraocular pressure increased Study Eye			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Intraocular pressure increased Fellow Eye			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 167 (0.60%)	1 / 328 (0.30%)	0 / 163 (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
Head injury			

subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Alcohol poisoning			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
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 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Femoral neck fracture			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	2 / 167 (1.20%)	0 / 328 (0.00%)	0 / 163 (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
Upper limb fracture			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Subdural haematoma			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			

subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
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	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
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 pseudoaneurysm			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
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 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			

subjects affected / exposed	3 / 167 (1.80%)	5 / 328 (1.52%)	3 / 163 (1.84%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Cardiac failure			
subjects affected / exposed	1 / 167 (0.60%)	2 / 328 (0.61%)	0 / 163 (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
Cardiac arrest			
subjects affected / exposed	3 / 167 (1.80%)	3 / 328 (0.91%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 2	0 / 0
Acute left ventricular failure			
subjects affected / exposed	3 / 167 (1.80%)	2 / 328 (0.61%)	0 / 163 (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
Acute myocardial infarction			
subjects affected / exposed	2 / 167 (1.20%)	10 / 328 (3.05%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 2	0 / 10	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 167 (0.60%)	1 / 328 (0.30%)	0 / 163 (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
Coronary artery disease			
subjects affected / exposed	2 / 167 (1.20%)	3 / 328 (0.91%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			

subjects affected / exposed	0 / 167 (0.00%)	2 / 328 (0.61%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 167 (0.00%)	3 / 328 (0.91%)	0 / 163 (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
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
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 congestive			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Left ventricular failure			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Supraventricular tachycardia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			

subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Ventricular extrasystoles			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 167 (0.00%)	3 / 328 (0.91%)	5 / 163 (3.07%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic neuropathy			

subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 167 (0.60%)	1 / 328 (0.30%)	0 / 163 (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
Syncope			
subjects affected / exposed	1 / 167 (0.60%)	1 / 328 (0.30%)	0 / 163 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
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 encephalopathy			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamus haemorrhage			

subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Embolic stroke			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Occipital lobe stroke			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 167 (0.60%)	1 / 328 (0.30%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract Fellow Eye			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal haemorrhage Fellow Eye			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Diabetic retinopathy Fellow Eye			
subjects affected / exposed	1 / 167 (0.60%)	3 / 328 (0.91%)	0 / 163 (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
Vitreous haemorrhage Fellow Eye			
subjects affected / exposed	2 / 167 (1.20%)	1 / 328 (0.30%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal artery occlusion Fellow Eye			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tractional retinal detachment Fellow Eye			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cataract subcapsular Study Eye			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Retinal detachment Study Eye			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage Study Eye			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcerative keratitis Study Eye			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiretinal membrane Fellow Eye			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract nuclear Study Eye			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Retinal neovascularisation Study Eye			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract Study Eye			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal tear Study Eye			

subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcerative keratitis Fellow Eye			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 167 (0.60%)	1 / 328 (0.30%)	0 / 163 (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
Ileus			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal fluid collection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumoperitoneum			

subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	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 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			

subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute cholecystitis necrotic			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 167 (0.00%)	2 / 328 (0.61%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Blister			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 167 (1.20%)	7 / 328 (2.13%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Azotaemia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Diabetic nephropathy			

subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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 kidney disease			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Renal failure			
subjects affected / exposed	0 / 167 (0.00%)	2 / 328 (0.61%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
End stage renal disease			
subjects affected / exposed	1 / 167 (0.60%)	3 / 328 (0.91%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
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	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			

subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Neuropathic arthropathy			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exostosis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (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	0 / 167 (0.00%)	1 / 328 (0.30%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			

subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral lesion			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 167 (0.00%)	6 / 328 (1.83%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Pneumonia			
subjects affected / exposed	1 / 167 (0.60%)	6 / 328 (1.83%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	3 / 167 (1.80%)	3 / 328 (0.91%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Citrobacter sepsis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Bronchitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Diabetic foot infection			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Diabetic gangrene			

subjects affected / exposed	1 / 167 (0.60%)	1 / 328 (0.30%)	0 / 163 (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
Localised infection			
subjects affected / exposed	0 / 167 (0.00%)	2 / 328 (0.61%)	0 / 163 (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
Osteomyelitis			
subjects affected / exposed	0 / 167 (0.00%)	2 / 328 (0.61%)	0 / 163 (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
Osteomyelitis acute			
subjects affected / exposed	1 / 167 (0.60%)	1 / 328 (0.30%)	0 / 163 (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
Cellulitis			
subjects affected / exposed	2 / 167 (1.20%)	1 / 328 (0.30%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	2 / 167 (1.20%)	0 / 328 (0.00%)	0 / 163 (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
Sepsis			
subjects affected / exposed	4 / 167 (2.40%)	2 / 328 (0.61%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (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
Necrotising fasciitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Septic shock			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (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
Wound infection staphylococcal			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis gangrenous			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
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			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			

subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
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 Study Eye			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
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			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 167 (0.00%)	2 / 328 (0.61%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			

subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (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
Hyperkalaemia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	3 / 163 (1.84%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketoacidosis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 167 (1.20%)	0 / 328 (0.00%)	0 / 163 (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
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 167 (0.00%)	1 / 328 (0.30%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 167 (0.00%)	0 / 328 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	2q8/HD aflibercept (extension)	HDq12 aflibercept (extension)	HDq16 aflibercept (extension)

Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 70 (38.57%)	46 / 130 (35.38%)	23 / 65 (35.38%)
number of deaths (all causes)	2	7	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 cancer			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Plasma cell myeloma			
subjects affected / exposed	1 / 70 (1.43%)	1 / 130 (0.77%)	0 / 65 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 cancer			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal neoplasm			

subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 cancer metastatic			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 cancer			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine carcinoma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer metastatic			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric cancer			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Squamous cell carcinoma of lung			

subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastasis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive breast carcinoma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Penile squamous cell carcinoma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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			
Aortic stenosis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Haematoma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			

subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (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
Peripheral vascular disorder			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Hypertensive urgency			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral venous disease			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Thrombosis prophylaxis			

subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Skin neoplasm excision			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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			
Chest pain			
subjects affected / exposed	1 / 70 (1.43%)	1 / 130 (0.77%)	0 / 65 (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
Oedema peripheral			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 70 (1.43%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Sudden death			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 organ dysfunction syndrome			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organ failure			

subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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			
Hypersensitivity			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Scrotal oedema			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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			
Pulmonary embolism			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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	1 / 70 (1.43%)	2 / 130 (1.54%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			

subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 oedema			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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 / 70 (1.43%)	1 / 130 (0.77%)	0 / 65 (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
Respiratory distress			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Haemoptysis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Stress			

subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 70 (1.43%)	1 / 130 (0.77%)	0 / 65 (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
Product issues			
Device failure			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraocular pressure increased Study Eye			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraocular pressure increased Fellow Eye			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 injury			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Alcohol poisoning			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
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 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
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 limb fracture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Post procedural haemorrhage			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Lower limb fracture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			

subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Limb injury			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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			
Myocardial infarction			
subjects affected / exposed	1 / 70 (1.43%)	4 / 130 (3.08%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 70 (1.43%)	1 / 130 (0.77%)	1 / 65 (1.54%)
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	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Acute left ventricular failure			
subjects affected / exposed	2 / 70 (2.86%)	1 / 130 (0.77%)	0 / 65 (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
Acute myocardial infarction			
subjects affected / exposed	1 / 70 (1.43%)	2 / 130 (1.54%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			

subjects affected / exposed	1 / 70 (1.43%)	1 / 130 (0.77%)	0 / 65 (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
Coronary artery disease			
subjects affected / exposed	2 / 70 (2.86%)	1 / 130 (0.77%)	0 / 65 (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
Coronary artery occlusion			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	2 / 70 (2.86%)	0 / 130 (0.00%)	0 / 65 (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
Atrioventricular block second degree			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 70 (0.00%)	3 / 130 (2.31%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			

subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			

subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 70 (1.43%)	3 / 130 (2.31%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Diabetic neuropathy			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 70 (1.43%)	2 / 130 (1.54%)	0 / 65 (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
Syncope			
subjects affected / exposed	1 / 70 (1.43%)	1 / 130 (0.77%)	0 / 65 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 70 (0.00%)	2 / 130 (1.54%)	0 / 65 (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
Carpal tunnel syndrome			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 encephalopathy			

subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamus haemorrhage			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Presyncope			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cerebral infarction			

subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Occipital lobe stroke			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 70 (1.43%)	2 / 130 (1.54%)	0 / 65 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract Fellow Eye			
subjects affected / exposed	2 / 70 (2.86%)	0 / 130 (0.00%)	0 / 65 (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
Retinal haemorrhage Fellow Eye			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Diabetic retinopathy Fellow Eye			
subjects affected / exposed	1 / 70 (1.43%)	2 / 130 (1.54%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage Fellow Eye			
subjects affected / exposed	2 / 70 (2.86%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Retinal artery occlusion Fellow Eye			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tractional retinal detachment Fellow Eye			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract subcapsular Study Eye			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment Study Eye			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage Study Eye			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcerative keratitis Study Eye			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiretinal membrane Fellow Eye			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract nuclear Study Eye			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Retinal neovascularisation Study Eye			

subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract Study Eye			
subjects affected / exposed	2 / 70 (2.86%)	0 / 130 (0.00%)	0 / 65 (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
Retinal tear Study Eye			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcerative keratitis Fellow Eye			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal fluid collection			

subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumoperitoneum			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 acute			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 cholecystitis necrotic			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 disorder			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 70 (0.00%)	4 / 130 (3.08%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Blister			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 / 70 (1.43%)	4 / 130 (3.08%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Azotaemia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Diabetic nephropathy			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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 kidney disease			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Renal failure			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
End stage renal disease			
subjects affected / exposed	1 / 70 (1.43%)	2 / 130 (1.54%)	0 / 65 (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
Nephrotic syndrome			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			

subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 retention			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathic arthropathy			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exostosis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (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	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Spondylolisthesis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Vertebral lesion			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
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			
COVID-19			
subjects affected / exposed	0 / 70 (0.00%)	3 / 130 (2.31%)	0 / 65 (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
Pneumonia			
subjects affected / exposed	0 / 70 (0.00%)	4 / 130 (3.08%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COVID-19 pneumonia			
subjects affected / exposed	2 / 70 (2.86%)	1 / 130 (0.77%)	0 / 65 (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
Citrobacter sepsis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Diabetic foot infection			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Diabetic gangrene			
subjects affected / exposed	2 / 70 (2.86%)	1 / 130 (0.77%)	0 / 65 (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
Localised infection			
subjects affected / exposed	0 / 70 (0.00%)	3 / 130 (2.31%)	0 / 65 (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
Osteomyelitis			
subjects affected / exposed	0 / 70 (0.00%)	4 / 130 (3.08%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis acute			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	1 / 70 (1.43%)	1 / 130 (0.77%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis			

subjects affected / exposed	3 / 70 (4.29%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Septic shock			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis gangrenous			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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			

subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 Study Eye			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
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 bacteraemia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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
Wound infection			

subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (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			
Hypoglycaemia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 70 (1.43%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 70 (1.43%)	1 / 130 (0.77%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketoacidosis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 70 (2.86%)	0 / 130 (0.00%)	0 / 65 (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
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 70 (0.00%)	1 / 130 (0.77%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Aflibercept 2 mg every 8 weeks (2q8)	HD aflibercept every 12 weeks (HDq12)	HD aflibercept every 16 weeks (HDq16)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 167 (58.68%)	190 / 328 (57.93%)	116 / 163 (71.17%)
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 167 (13.17%)	35 / 328 (10.67%)	31 / 163 (19.02%)
occurrences (all)	31	38	34
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 167 (2.99%)	5 / 328 (1.52%)	6 / 163 (3.68%)
occurrences (all)	7	6	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 167 (0.60%)	6 / 328 (1.83%)	6 / 163 (3.68%)
occurrences (all)	1	6	6
Investigations			
Intraocular pressure increased Study Eye			
subjects affected / exposed	7 / 167 (4.19%)	9 / 328 (2.74%)	2 / 163 (1.23%)
occurrences (all)	13	12	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 167 (2.40%)	2 / 328 (0.61%)	2 / 163 (1.23%)
occurrences (all)	4	3	3
Cardiac disorders			

Coronary artery disease			
subjects affected / exposed	4 / 167 (2.40%)	5 / 328 (1.52%)	1 / 163 (0.61%)
occurrences (all)	4	5	1
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 167 (2.40%)	13 / 328 (3.96%)	4 / 163 (2.45%)
occurrences (all)	5	16	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 167 (2.99%)	12 / 328 (3.66%)	9 / 163 (5.52%)
occurrences (all)	5	12	9
Eye disorders			
Cataract Fellow Eye			
subjects affected / exposed	8 / 167 (4.79%)	17 / 328 (5.18%)	14 / 163 (8.59%)
occurrences (all)	8	17	14
Cataract Study Eye			
subjects affected / exposed	5 / 167 (2.99%)	18 / 328 (5.49%)	18 / 163 (11.04%)
occurrences (all)	5	19	18
Vitreous floaters Study Eye			
subjects affected / exposed	6 / 167 (3.59%)	19 / 328 (5.79%)	7 / 163 (4.29%)
occurrences (all)	6	20	8
Diabetic retinopathy Fellow Eye			
subjects affected / exposed	5 / 167 (2.99%)	5 / 328 (1.52%)	9 / 163 (5.52%)
occurrences (all)	5	6	9
Conjunctival haemorrhage Study Eye			
subjects affected / exposed	6 / 167 (3.59%)	18 / 328 (5.49%)	8 / 163 (4.91%)
occurrences (all)	7	18	9
Eye pain Study Eye			
subjects affected / exposed	4 / 167 (2.40%)	10 / 328 (3.05%)	3 / 163 (1.84%)
occurrences (all)	4	10	3
Punctate keratitis Study Eye			
subjects affected / exposed	1 / 167 (0.60%)	5 / 328 (1.52%)	7 / 163 (4.29%)
occurrences (all)	1	5	7
Retinal haemorrhage Study Eye			
subjects affected / exposed	1 / 167 (0.60%)	0 / 328 (0.00%)	6 / 163 (3.68%)
occurrences (all)	1	0	7
Vision blurred Study Eye			

subjects affected / exposed	5 / 167 (2.99%)	4 / 328 (1.22%)	2 / 163 (1.23%)
occurrences (all)	5	4	2
Visual acuity reduced Study Eye			
subjects affected / exposed	4 / 167 (2.40%)	6 / 328 (1.83%)	2 / 163 (1.23%)
occurrences (all)	4	9	2
Visual impairment Study Eye			
subjects affected / exposed	1 / 167 (0.60%)	6 / 328 (1.83%)	3 / 163 (1.84%)
occurrences (all)	1	6	3
Diabetic retinal oedema Fellow Eye			
subjects affected / exposed	6 / 167 (3.59%)	15 / 328 (4.57%)	8 / 163 (4.91%)
occurrences (all)	7	17	8
Vitreous detachment Study Eye			
subjects affected / exposed	7 / 167 (4.19%)	16 / 328 (4.88%)	5 / 163 (3.07%)
occurrences (all)	7	16	5
Vitreous floaters Fellow Eye			
subjects affected / exposed	4 / 167 (2.40%)	4 / 328 (1.22%)	8 / 163 (4.91%)
occurrences (all)	4	4	9
Vitreous detachment Fellow Eye			
subjects affected / exposed	7 / 167 (4.19%)	7 / 328 (2.13%)	5 / 163 (3.07%)
occurrences (all)	7	8	5
Punctate keratitis Fellow Eye			
subjects affected / exposed	0 / 167 (0.00%)	3 / 328 (0.91%)	4 / 163 (2.45%)
occurrences (all)	0	3	5
Vitreous haemorrhage Fellow Eye			
subjects affected / exposed	5 / 167 (2.99%)	7 / 328 (2.13%)	6 / 163 (3.68%)
occurrences (all)	5	10	7
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 167 (1.80%)	6 / 328 (1.83%)	9 / 163 (5.52%)
occurrences (all)	3	6	12
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 167 (1.20%)	8 / 328 (2.44%)	6 / 163 (3.68%)
occurrences (all)	2	8	6
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	5 / 167 (2.99%)	11 / 328 (3.35%)	5 / 163 (3.07%)
occurrences (all)	6	12	5
Infections and infestations			
COVID-19			
subjects affected / exposed	15 / 167 (8.98%)	40 / 328 (12.20%)	26 / 163 (15.95%)
occurrences (all)	16	41	27
Nasopharyngitis			
subjects affected / exposed	9 / 167 (5.39%)	21 / 328 (6.40%)	10 / 163 (6.13%)
occurrences (all)	11	24	12
Urinary tract infection			
subjects affected / exposed	10 / 167 (5.99%)	9 / 328 (2.74%)	7 / 163 (4.29%)
occurrences (all)	12	13	8
Influenza			
subjects affected / exposed	6 / 167 (3.59%)	5 / 328 (1.52%)	3 / 163 (1.84%)
occurrences (all)	6	5	3
Upper respiratory tract infection			
subjects affected / exposed	1 / 167 (0.60%)	8 / 328 (2.44%)	3 / 163 (1.84%)
occurrences (all)	1	8	3
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	6 / 167 (3.59%)	8 / 328 (2.44%)	8 / 163 (4.91%)
occurrences (all)	7	8	8
Hypercholesterolaemia			
subjects affected / exposed	2 / 167 (1.20%)	10 / 328 (3.05%)	7 / 163 (4.29%)
occurrences (all)	2	10	7
Hyperlipidaemia			
subjects affected / exposed	2 / 167 (1.20%)	9 / 328 (2.74%)	5 / 163 (3.07%)
occurrences (all)	2	9	5

Non-serious adverse events	2q8/HD aflibercept (extension)	HDq12 aflibercept (extension)	HDq16 aflibercept (extension)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 70 (71.43%)	99 / 130 (76.15%)	50 / 65 (76.92%)
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 70 (8.57%)	21 / 130 (16.15%)	13 / 65 (20.00%)
occurrences (all)	10	22	13

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 70 (5.71%)	2 / 130 (1.54%)	1 / 65 (1.54%)
occurrences (all)	5	3	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 70 (2.86%)	4 / 130 (3.08%)	4 / 65 (6.15%)
occurrences (all)	2	5	4
Investigations			
Intraocular pressure increased Study Eye			
subjects affected / exposed	5 / 70 (7.14%)	2 / 130 (1.54%)	2 / 65 (3.08%)
occurrences (all)	15	2	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	5 / 70 (7.14%)	1 / 130 (0.77%)	1 / 65 (1.54%)
occurrences (all)	5	1	2
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	4 / 70 (5.71%)	2 / 130 (1.54%)	1 / 65 (1.54%)
occurrences (all)	4	2	1
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 70 (4.29%)	8 / 130 (6.15%)	1 / 65 (1.54%)
occurrences (all)	4	8	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 70 (2.86%)	5 / 130 (3.85%)	3 / 65 (4.62%)
occurrences (all)	2	5	3
Eye disorders			
Cataract Fellow Eye			
subjects affected / exposed	7 / 70 (10.00%)	18 / 130 (13.85%)	8 / 65 (12.31%)
occurrences (all)	7	19	8
Cataract Study Eye			
subjects affected / exposed	8 / 70 (11.43%)	18 / 130 (13.85%)	10 / 65 (15.38%)
occurrences (all)	8	18	10
Vitreous floaters Study Eye			

subjects affected / exposed	3 / 70 (4.29%)	8 / 130 (6.15%)	4 / 65 (6.15%)
occurrences (all)	3	9	4
Diabetic retinopathy Fellow Eye			
subjects affected / exposed	2 / 70 (2.86%)	3 / 130 (2.31%)	5 / 65 (7.69%)
occurrences (all)	2	3	5
Conjunctival haemorrhage Study Eye			
subjects affected / exposed	2 / 70 (2.86%)	4 / 130 (3.08%)	3 / 65 (4.62%)
occurrences (all)	3	5	4
Eye pain Study Eye			
subjects affected / exposed	2 / 70 (2.86%)	3 / 130 (2.31%)	4 / 65 (6.15%)
occurrences (all)	2	3	5
Punctate keratitis Study Eye			
subjects affected / exposed	1 / 70 (1.43%)	3 / 130 (2.31%)	5 / 65 (7.69%)
occurrences (all)	1	3	5
Retinal haemorrhage Study Eye			
subjects affected / exposed	1 / 70 (1.43%)	1 / 130 (0.77%)	5 / 65 (7.69%)
occurrences (all)	1	1	6
Vision blurred Study Eye			
subjects affected / exposed	4 / 70 (5.71%)	2 / 130 (1.54%)	2 / 65 (3.08%)
occurrences (all)	4	2	2
Visual acuity reduced Study Eye			
subjects affected / exposed	4 / 70 (5.71%)	1 / 130 (0.77%)	1 / 65 (1.54%)
occurrences (all)	4	1	1
Visual impairment Study Eye			
subjects affected / exposed	0 / 70 (0.00%)	4 / 130 (3.08%)	4 / 65 (6.15%)
occurrences (all)	0	4	4
Diabetic retinal oedema Fellow Eye			
subjects affected / exposed	5 / 70 (7.14%)	8 / 130 (6.15%)	3 / 65 (4.62%)
occurrences (all)	6	8	3
Vitreous detachment Study Eye			
subjects affected / exposed	3 / 70 (4.29%)	8 / 130 (6.15%)	2 / 65 (3.08%)
occurrences (all)	3	8	2
Vitreous floaters Fellow Eye			
subjects affected / exposed	2 / 70 (2.86%)	3 / 130 (2.31%)	5 / 65 (7.69%)
occurrences (all)	2	3	7
Vitreous detachment Fellow Eye			

subjects affected / exposed	3 / 70 (4.29%)	4 / 130 (3.08%)	4 / 65 (6.15%)
occurrences (all)	3	4	4
Punctate keratitis Fellow Eye			
subjects affected / exposed	0 / 70 (0.00%)	0 / 130 (0.00%)	4 / 65 (6.15%)
occurrences (all)	0	0	5
Vitreous haemorrhage Fellow Eye			
subjects affected / exposed	6 / 70 (8.57%)	8 / 130 (6.15%)	3 / 65 (4.62%)
occurrences (all)	10	11	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 70 (2.86%)	2 / 130 (1.54%)	2 / 65 (3.08%)
occurrences (all)	2	2	2
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 70 (0.00%)	5 / 130 (3.85%)	4 / 65 (6.15%)
occurrences (all)	0	5	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 70 (5.71%)	4 / 130 (3.08%)	2 / 65 (3.08%)
occurrences (all)	5	4	2
Infections and infestations			
COVID-19			
subjects affected / exposed	6 / 70 (8.57%)	19 / 130 (14.62%)	15 / 65 (23.08%)
occurrences (all)	6	22	18
Nasopharyngitis			
subjects affected / exposed	5 / 70 (7.14%)	16 / 130 (12.31%)	4 / 65 (6.15%)
occurrences (all)	7	21	7
Urinary tract infection			
subjects affected / exposed	4 / 70 (5.71%)	8 / 130 (6.15%)	1 / 65 (1.54%)
occurrences (all)	6	10	1
Influenza			
subjects affected / exposed	5 / 70 (7.14%)	5 / 130 (3.85%)	7 / 65 (10.77%)
occurrences (all)	6	5	7
Upper respiratory tract infection			
subjects affected / exposed	0 / 70 (0.00%)	3 / 130 (2.31%)	5 / 65 (7.69%)
occurrences (all)	0	3	5
Metabolism and nutrition disorders			

Diabetes mellitus			
subjects affected / exposed	4 / 70 (5.71%)	3 / 130 (2.31%)	5 / 65 (7.69%)
occurrences (all)	5	3	5
Hypercholesterolaemia			
subjects affected / exposed	0 / 70 (0.00%)	5 / 130 (3.85%)	4 / 65 (6.15%)
occurrences (all)	0	5	4
Hyperlipidaemia			
subjects affected / exposed	3 / 70 (4.29%)	2 / 130 (1.54%)	4 / 65 (6.15%)
occurrences (all)	3	2	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2019	The purpose of this amendment was to address feedback received from European Union (EU) regulatory agencies as part of the Voluntary Harmonisation Procedure (VHP).
14 February 2020	The primary purpose of this amendment was to update study design details regarding Dose Regimen Modification (DRM) assessments.
07 May 2020	The primary purposes for this amendment were to clarify the machine-specific values for central retinal thickness defined in the inclusion criteria for the reading center's determination of eligibility, and to describe the continuity plan for conducting clinical study activities and study oversight activities during the public health emergency due to Coronavirus Disease 2019 (COVID-19).
28 April 2022	The primary purpose for this amendment was to simplify and extend the confirmatory testing hierarchy.
14 September 2022	The primary purpose for this amendment was to add an optional 1 year extension phase to the current study at select countries and sites.
27 February 2023	The primary purpose of this amendment was to extend contraception requirements based on proposed aflibercept HD labeling language updates.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported