Clinical trial results:
A Double-Masked, Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap-Eye in Patients with Diabetic Macular Edema (DME).

Summary

EudraCT number	2008-008200-40
Trial protocol	AT
Global end of trial date	07 September 2010

Results information

Result version number	v1 (current)
This version publication date	23 May 2019
First version publication date	23 May 2019

Trial information

Trial identification

Sponsor protocol code	VGFT-OD-0706

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00789477
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Road, Tarrytown, United States, 10591
Public contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc., 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	30 November 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 September 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to explore the effect of various doses and dose intervals of intravitreally (IVT)-administered VEGF Trap-Eye on the best-corrected visual acuity (BCVA) in subjects with diabetic macular edema (DME).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 December 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 206
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Canada: 5
Worldwide total number of subjects	219
EEA total number of subjects	8

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)	129
From 65 to 84 years	86

85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Subjects with clinically significant DME with central involvement and a BCVA of 20/40 to 20/320 (letter score of 73 to 24) in the study eye were eligible to enter the study. Out of 284 screened, a total of 221 subjects were randomized at 39 centers in the US, Canada, & Austria. Of the 221 randomized subjects, 219 were treated.

Pre-assignment

Screening details:

Subjects were screened at visit 1 (day -21 to day -1). Eligible subjects were enrolled and randomized on day 1 (visit 2), and received treatment (active/sham) at each study visit every 4 weeks (day 1 [visit 2] to week 52 [visit 16]).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Laser Photocoagulation

Arm description:

Focal laser using modified Early Treatment Diabetic Retinopathy Study (ETDRS) technique at week 1, and 1 week after visits at which the subject met laser re-treatment criteria to the end of the study (week 52) starting at week 16 (visit 7); laser re-treatment was permitted no more than once every 16 weeks ± 3 days. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the laser group received sham injection at visit 2 (day 1) and at every study visit starting at week 4 (visit 4).

Arm type	Reference treatment

No investigational medicinal product assigned in this arm

Arm title	Intravitreal Aflibercept Injection (IAI) 0.5q4

Arm description:

0.5 mg Intravitreal Aflibercept Injection (IAI;VEGF Trap-Eye;EYLEA®;BAY86-5321) administered every 4 weeks (0.5q4) to week 52. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	BAY86-5321
Other name	EYLEA®; VEGF Trap-Eye
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal aflibercept injection administered at the site by IVT injection using standard ophthalmic techniques.

Arm title	Intravitreal Aflibercept Injection (IAI) 2q4

Arm description:

2 mg Intravitreal Aflibercept Injection (IAI;VEGF Trap-Eye;EYLEA®;BAY86-5321) administered every 4 weeks (2q4) to week 52. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	BAY86-5321
Other name	EYLEA®; VEGF Trap-Eye
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal aflibercept injection administered at the site by IVT injection using standard ophthalmic techniques.

Arm title	Intravitreal Aflibercept Injection (IAI) 2q8

Arm description:

2 mg Intravitreal Aflibercept Injection (IAI;VEGF Trap-Eye;EYLEA®;BAY86-5321) administered every 4 weeks for 3 visits (day 1, week 4 and week 8), followed by 2 mg dosing every 8 weeks (2q8) through week 52 and sham injections at alternating visits (when study drug was not to be administered). All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	BAY86-5321
Other name	EYLEA®; VEGF Trap-Eye
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal aflibercept injection administered at the site by IVT injection using standard ophthalmic techniques.

Arm title	Intravitreal Aflibercept Injection (IAI) 2PRN

Arm description:

2 mg Intravitreal Aflibercept Injection (IAI; VEGF Trap-Eye; EYLEA®;BAY86-5321) administered every 4 weeks for 3 visits (day 1, week 4 and week 8), followed by 2 mg dosing PRN (as-needed) according to the VEGF Trap-Eye re-treatment criteria to week 52 and sham injections at visits at which VEGF Trap-Eye re-treatment criteria were not met. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	BAY86-5321
Other name	EYLEA®; VEGF Trap-Eye
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal aflibercept injection administered at the site by IVT injection using standard ophthalmic techniques.

Number of subjects in period 1	Laser Photocoagulation	Intravitreal Aflibercept Injection (IAI) 0.5q4	Intravitreal Aflibercept Injection (IAI) 2q4
Started	44	44	44
Completed	32	37	32
Not completed	12	7	12
Adverse event, serious fatal	1	1	2
Consent withdrawn by subject	2	2	4
PI treating non-study eye with disallowed med.	1	-	-
Adverse event, non-fatal	3	3	1
Home hospice care	-	-	-
Developed CRVO in study eye-may receive avastin	1	-	-
Did not return for Visit 18	1	-	-
Lost to follow-up	-	1	4
Too many missed visits	-	-	1
Protocol deviation	1	-	-
Lack of efficacy	2	-	-

Number of subjects in period 1	Intravitreal Aflibercept Injection (IAI) 2q8	Intravitreal Aflibercept Injection (IAI) 2PRN
Started	42	45
Completed	34	36
Not completed	8	9
Adverse event, serious fatal	2	-
Consent withdrawn by subject	2	4
PI treating non-study eye with disallowed med.	-	-
Adverse event, non-fatal	-	-
Home hospice care	1	-
Developed CRVO in study eye-may receive avastin	-	-
Did not return for Visit 18	-	-
Lost to follow-up	2	5
Too many missed visits	-	-
Protocol deviation	1	-
Lack of efficacy	-	-

Baseline characteristics

Reporting groups

Reporting group title	Laser Photocoagulation

Reporting group description:

Focal laser using modified Early Treatment Diabetic Retinopathy Study (ETDRS) technique at week 1, and 1 week after visits at which the subject met laser re-treatment criteria to the end of the study (week 52) starting at week 16 (visit 7); laser re-treatment was permitted no more than once every 16 weeks ± 3 days. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the laser group received sham injection at visit 2 (day 1) and at every study visit starting at week 4 (visit 4).

Reporting group title	Intravitreal Aflibercept Injection (IAI) 0.5q4

Reporting group description:

0.5 mg Intravitreal Aflibercept Injection (IAI;VEGF Trap-Eye;EYLEA®;BAY86-5321) administered every 4 weeks (0.5q4) to week 52. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Reporting group title	Intravitreal Aflibercept Injection (IAI) 2q4

Reporting group description:

2 mg Intravitreal Aflibercept Injection (IAI;VEGF Trap-Eye;EYLEA®;BAY86-5321) administered every 4 weeks (2q4) to week 52. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Reporting group title	Intravitreal Aflibercept Injection (IAI) 2q8

Reporting group description:

2 mg Intravitreal Aflibercept Injection (IAI;VEGF Trap-Eye;EYLEA®;BAY86-5321) administered every 4 weeks for 3 visits (day 1, week 4 and week 8), followed by 2 mg dosing every 8 weeks (2q8) through week 52 and sham injections at alternating visits (when study drug was not to be administered). All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Reporting group title	Intravitreal Aflibercept Injection (IAI) 2PRN

Reporting group description:

2 mg Intravitreal Aflibercept Injection (IAI; VEGF Trap-Eye; EYLEA®;BAY86-5321) administered every 4 weeks for 3 visits (day 1, week 4 and week 8), followed by 2 mg dosing PRN (as-needed) according to the VEGF Trap-Eye re-treatment criteria to week 52 and sham injections at visits at which VEGF Trap-Eye re-treatment criteria were not met. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Reporting group values	Laser Photocoagulation	Intravitreal Aflibercept Injection (IAI) 0.5q4	Intravitreal Aflibercept Injection (IAI) 2q4
Number of subjects	44	44	44
Age categorical			
Full analysis set (FAS)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0

Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	24	24	29
From 65-84 years	20	18	13
85 years and over	0	2	2
Age continuous			
Units: years			
arithmetic mean	64.0	62.3	62.1
standard deviation	± 8.12	± 10.70	± 10.50
Gender categorical			
Units: Subjects			
Male	27	24	27
Female	17	20	17
Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score			
Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985) at 4 meters.			
Units: letters correctly read			
arithmetic mean	57.6	59.3	59.9
standard deviation	± 12.47	± 11.16	± 10.07
Central Retinal Thickness (CRT)			
Retinal and lesion characteristics will be evaluated using time domain Optical Coherence Tomography (OCT) on the study eye.			
Units: microns			
arithmetic mean	440.6	426.1	456.6
standard deviation	± 145.41	± 128.9	± 134.95

Reporting group values	Intravitreal Aflibercept Injection (IAI) 2q8	Intravitreal Aflibercept Injection (IAI) 2PRN	Total
Number of subjects	42	45	219
Age categorical			
Full analysis set (FAS)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	22	30	129
From 65-84 years	20	15	86
85 years and over	0	0	4
Age continuous			
Units: years			
arithmetic mean	62.5	60.7	
standard deviation	± 11.49	± 8.66	-
Gender categorical			
Units: Subjects			
Male	22	29	129
Female	20	16	90

Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score			
Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985) at 4 meters.			
Units: letters correctly read			
arithmetic mean	58.8	59.6	
standard deviation	± 12.23	± 11.06	-
Central Retinal Thickness (CRT)			
Retinal and lesion characteristics will be evaluated using time domain Optical Coherence Tomography (OCT) on the study eye.			
Units: microns			
arithmetic mean	434.8	426.6	
standard deviation	± 111.83	± 152.37	-

End points

End points reporting groups

Reporting group title	Laser Photocoagulation

Reporting group description:

Focal laser using modified Early Treatment Diabetic Retinopathy Study (ETDRS) technique at week 1, and 1 week after visits at which the subject met laser re-treatment criteria to the end of the study (week 52) starting at week 16 (visit 7); laser re-treatment was permitted no more than once every 16 weeks ± 3 days. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the laser group received sham injection at visit 2 (day 1) and at every study visit starting at week 4 (visit 4).

Reporting group title	Intravitreal Aflibercept Injection (IAI) 0.5q4

Reporting group description:

0.5 mg Intravitreal Aflibercept Injection (IAI;VEGF Trap-Eye;EYLEA®;BAY86-5321) administered every 4 weeks (0.5q4) to week 52. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Reporting group title	Intravitreal Aflibercept Injection (IAI) 2q4

Reporting group description:

2 mg Intravitreal Aflibercept Injection (IAI;VEGF Trap-Eye;EYLEA®;BAY86-5321) administered every 4 weeks (2q4) to week 52. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Reporting group title	Intravitreal Aflibercept Injection (IAI) 2q8

Reporting group description:

2 mg Intravitreal Aflibercept Injection (IAI;VEGF Trap-Eye;EYLEA®;BAY86-5321) administered every 4 weeks for 3 visits (day 1, week 4 and week 8), followed by 2 mg dosing every 8 weeks (2q8) through week 52 and sham injections at alternating visits (when study drug was not to be administered). All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Reporting group title	Intravitreal Aflibercept Injection (IAI) 2PRN

Reporting group description:

2 mg Intravitreal Aflibercept Injection (IAI; VEGF Trap-Eye; EYLEA®;BAY86-5321) administered every 4 weeks for 3 visits (day 1, week 4 and week 8), followed by 2 mg dosing PRN (as-needed) according to the VEGF Trap-Eye re-treatment criteria to week 52 and sham injections at visits at which VEGF Trap-Eye re-treatment criteria were not met. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Primary: Change in Best Corrected Visual Acuity (BCVA) From Baseline to Week 24 - Last Observation Carried Forward (LOCF)

End point title	Change in Best Corrected Visual Acuity (BCVA) From Baseline to Week 24 - Last Observation Carried Forward (LOCF)

End point description:

Visual function of the study eye was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol at 4 meters. Measurements were taken at every study visit. Missing values were imputed with post-baseline values during on-treatment period by using last observation carried forward (LOCF). Full analysis set (FAS): included all randomized subjects who received any study drug, had baseline assessments, and had at least 1 post-baseline assessment.

End point type	Primary

End point timeframe:

Baseline to Week 24

End point values	Laser Photocoagulation	Intravitreal Aflibercept Injection (IAI) 0.5q4	Intravitreal Aflibercept Injection (IAI) 2q4	Intravitreal Aflibercept Injection (IAI) 2q8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	44	42
Units: letters correctly read				
arithmetic mean (standard deviation)	2.5 (± 16.14)	8.6 (± 14.64)	11.4 (± 8.67)	8.5 (± 7.50)

End point values	Intravitreal Aflibercept Injection (IAI) 2PRN			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: letters correctly read				
arithmetic mean (standard deviation)	10.3 (± 7.52)			

Statistical analyses

Statistical analysis title	IAI 0.5q4 vs Laser
Statistical analysis description: Difference in Least Squares (LS) Means	
Comparison groups	Intravitreal Aflibercept Injection (IAI) 0.5q4 v Laser Photocoagulation
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0054
Method	ANCOVA
Parameter estimate	LS means
Point estimate	6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.6
upper limit	8.7
Variability estimate	Standard error of the mean
Dispersion value	2.36

Statistical analysis title	IAI 2q4 vs Laser

Statistical analysis description: Difference in LS Means	
Comparison groups	Laser Photocoagulation v Intravitreal Aflibercept Injection (IAI) 2q4
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS means
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.6
upper limit	11.6
Variability estimate	Standard error of the mean
Dispersion value	2.36

Statistical analysis title	IAI 2q8 vs Laser
Statistical analysis description: Difference in LS Means	
Comparison groups	Laser Photocoagulation v Intravitreal Aflibercept Injection (IAI) 2q8
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0085
Method	ANCOVA
Parameter estimate	LS means
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.3
upper limit	8.4
Variability estimate	Standard error of the mean
Dispersion value	2.38

Statistical analysis title	IAI 2PRN vs Laser
Statistical analysis description: Difference in LS Means	
Comparison groups	Laser Photocoagulation v Intravitreal Aflibercept Injection (IAI) 2PRN

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	LS means
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.4
upper limit	10.4
Variability estimate	Standard error of the mean
Dispersion value	2.34

Secondary: Change in BCVA From Baseline to Week 52 - LOCF

End point title	Change in BCVA From Baseline to Week 52 - LOCF

End point description:

Visual function of the study eye was assessed using the ETDRS protocol at 4 meters. Missing values were imputed with post-baseline values during on-treatment period by using LOCF. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Laser Photocoagulation	Intravitreal Aflibercept Injection (IAI) 0.5q4	Intravitreal Aflibercept Injection (IAI) 2q4	Intravitreal Aflibercept Injection (IAI) 2q8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	44	42
Units: letters correctly read				
arithmetic mean (standard deviation)	-1.3 (± 20.72)	11.0 (± 15.40)	13.1 (± 10.54)	9.7 (± 8.93)

End point values	Intravitreal Aflibercept Injection (IAI) 2PRN			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: letters correctly read				
arithmetic mean (standard deviation)	12.0 (± 11.09)			

Statistical analyses

Statistical analysis title	IAI 0.5q4 vs Laser
Statistical analysis description:	
Difference in LS Means	
Comparison groups	Laser Photocoagulation v Intravitreal Aflibercept Injection (IAI) 0.5q4
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS means
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.1
upper limit	12.9
Variability estimate	Standard error of the mean
Dispersion value	2.86

Statistical analysis title	IAI 2q4 vs Laser
Statistical analysis description:	
Difference in LS Means	
Comparison groups	Laser Photocoagulation v Intravitreal Aflibercept Injection (IAI) 2q4
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS means
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.4
upper limit	15.2
Variability estimate	Standard error of the mean
Dispersion value	2.86

Statistical analysis title	IAI 2q8 vs Laser
Statistical analysis description:	
Difference in LS Means	
Comparison groups	Laser Photocoagulation v Intravitreal Aflibercept Injection (IAI) 2q8

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	LS means
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.6
upper limit	11.4
Variability estimate	Standard error of the mean
Dispersion value	2.89

Statistical analysis title	IAI 2PRN vs Laser
Statistical analysis description:	
Difference in LS Means	
Comparison groups	Laser Photocoagulation v Intravitreal Aflibercept Injection (IAI) 2PRN
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.2
upper limit	14
Variability estimate	Standard error of the mean
Dispersion value	2.84

Secondary: Subjects with Gains in Early Treatment Diabetic Retinopathy (ETDRS) Letter Score of at Least 15 Letters at Week 24 and at Week 52 - LOCF

End point title	Subjects with Gains in Early Treatment Diabetic Retinopathy (ETDRS) Letter Score of at Least 15 Letters at Week 24 and at Week 52 - LOCF

End point description:

Missing values were imputed with post-baseline values during on-treatment period by using LOCF. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

At Week 24 and At Week 52

End point values	Laser Photocoagulation	Intravitreal Aflibercept Injection (IAI) 0.5q4	Intravitreal Aflibercept Injection (IAI) 2q4	Intravitreal Aflibercept Injection (IAI) 2q8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	44	42
Units: Subjects				
number (not applicable)				
At Week 24	9	15	14	7
At Week 52	5	18	20	10

End point values	Intravitreal Aflibercept Injection (IAI) 2PRN			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Subjects				
number (not applicable)				
At Week 24	12			
At Week 52	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Central Retinal Thickness (CRT) as Assessed by Optical Coherence Tomography (OCT) at Week 24 and Week 52- LOCF

End point title	Change From Baseline in Central Retinal Thickness (CRT) as Assessed by Optical Coherence Tomography (OCT) at Week 24 and Week 52- LOCF

End point description:

Retinal thickness was evaluated using OCT at every visit except Week 1. Missing values were imputed with post-baseline values during on-treatment period by using LOCF. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

At Week 24 and At Week 52

End point values	Laser Photocoagulation	Intravitreal Aflibercept Injection (IAI) 0.5q4	Intravitreal Aflibercept Injection (IAI) 2q4	Intravitreal Aflibercept Injection (IAI) 2q8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	44	44	42
Units: microns				
arithmetic mean (standard deviation)				

Week 24	-67.9 (± 135.17)	-144.6 (± 110.65)	-194.5 (± 143.04)	-127.3 (± 141.78)
Week 52	-58.4 (± 177.6)	-165.4 (± 135.72)	-227.4 (± 148.96)	-187.8 (± 135.01)

End point values	Intravitreal Aflibercept Injection (IAI) 2PRN			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: microns				
arithmetic mean (standard deviation)				
Week 24	-153.3 (± 132.17)			
Week 52	-180.3 (± 124.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Focal Laser Treatments in the First 48 Weeks

End point title	Number of Focal Laser Treatments in the First 48 Weeks

End point description:

For the first 24 weeks, the Intravitreal Aflibercept Injection (IAI;EYLEA®;BAY86-5321) groups did not receive laser treatment. From Week 24 onward, subjects in the Intravitreal Aflibercept Injection (IAI;EYLEA®;BAY86-5321) groups were allowed to receive laser rescue treatment. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

Week 1 to Week 48

End point values	Laser Photocoagulation	Intravitreal Aflibercept Injection (IAI) 0.5q4	Intravitreal Aflibercept Injection (IAI) 2q4	Intravitreal Aflibercept Injection (IAI) 2q8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	44	42
Units: Treatments				
arithmetic mean (standard deviation)	2.5 (± 0.87)	0.8 (± 0.83)	0.5 (± 0.66)	0.8 (± 0.86)

End point values	Intravitreal Aflibercept Injection (IAI) 2PRN			

Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Treatments				
arithmetic mean (standard deviation)	0.7 (± 0.77)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 52

Adverse event reporting additional description:

Safety analysis set (SAF): included all subjects who received any study drug. The SAF was used for all safety and tolerability assessments. Safety analysis included subjects as treated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Laser Photocoagulation

Reporting group description:

Focal laser using modified Early Treatment Diabetic Retinopathy Study (ETDRS) technique at week 1, and 1 week after visits at which the subject met laser re-treatment criteria to the end of the study (week 52) starting at week 16 (visit 7); laser re-treatment was permitted no more than once every 16 weeks ± 3 days. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the laser group received sham injection at visit 2 (day 1) and at every study visit starting at week 4 (visit 4).

Reporting group title	Intravitreal Aflibercept Injection (IAI) 0.5q4

Reporting group description:

0.5 mg Intravitreal Aflibercept Injection (IAI;VEGF Trap-Eye;EYLEA®;BAY86-5321) administered every 4 weeks (0.5q4) to week 52. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Reporting group title	Intravitreal Aflibercept Injection (IAI) 2q4

Reporting group description:

2 mg Intravitreal Aflibercept Injection (IAI;VEGF Trap-Eye;EYLEA®;BAY86-5321) administered every 4 weeks (2q4) to week 52. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Reporting group title	Intravitreal Aflibercept Injection (IAI) 2q8

Reporting group description:

2 mg Intravitreal Aflibercept Injection (IAI;VEGF Trap-Eye;EYLEA®;BAY86-5321) administered every 4 weeks for 3 visits (day 1, week 4 and week 8), followed by 2 mg dosing every 8 weeks (2q8) through week 52 and sham injections at alternating visits (when study drug was not to be administered). All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Reporting group title	Intravitreal Aflibercept Injection (IAI) 2PRN

Reporting group description:

2 mg Intravitreal Aflibercept Injection (IAI; VEGF Trap-Eye; EYLEA®;BAY86-5321) administered every 4 weeks for 3 visits (day 1, week 4 and week 8), followed by 2 mg dosing PRN (as-needed) according to the VEGF Trap-Eye re-treatment criteria to week 52 and sham injections at visits at which VEGF Trap-Eye re-treatment criteria were not met. All subjects were evaluated for VEGF Trap-Eye re-treatment criteria starting at week 12 for masking purposes. Subjects randomized to the VEGF Trap-Eye groups received sham laser at week 1 (visit 3). Starting at week 24 (visit 9), subjects were allowed to receive active laser when they met the criteria for laser rescue.

Serious adverse events	Laser Photocoagulation	Intravitreal Aflibercept Injection (IAI) 0.5q4	Intravitreal Aflibercept Injection (IAI) 2q4
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 44 (31.82%)	16 / 44 (36.36%)	14 / 44 (31.82%)
number of deaths (all causes)	1	1	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (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
Transitional cell carcinoma			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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 stage iii			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Small cell lung cancer			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal cell carcinoma stage iv			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			

subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	2 / 44 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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 / 44 (2.27%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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	0 / 44 (0.00%)	0 / 44 (0.00%)	2 / 44 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multi-Organ failure			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-Cardiac chest pain			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pulmonary embolism			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
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 pressure increased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Joint capsule rupture			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus			

subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic brain injury			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal abrasion			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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 myocardial infarction			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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 acute			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	3 / 44 (6.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 44 (0.00%)	2 / 44 (4.55%)	0 / 44 (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
Sick sinus syndrome			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Silent myocardial infarction			

subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wolff-Parkinson-White syndrome			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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			
Cerebral infarction			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebrovascular accident			
subjects affected / exposed	1 / 44 (2.27%)	1 / 44 (2.27%)	2 / 44 (4.55%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			

subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
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	0 / 44 (0.00%)	1 / 44 (2.27%)	2 / 44 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cystoid macular oedema			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic retinopathy			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Maculopathy			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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 tear			

subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (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
Vitreous adhesions			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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			
subjects affected / exposed	4 / 44 (9.09%)	1 / 44 (2.27%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angle closure glaucoma			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic retinal oedema			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			

subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
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			
Skin ulcer			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Nephropathy			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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 failure acute			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress urinary incontinence			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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			
Lumbar spinal stenosis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
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 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 44 (0.00%)	3 / 44 (6.82%)	2 / 44 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			

subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 44 (0.00%)	0 / 44 (0.00%)
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 infection			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endophthalmitis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	2 / 44 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 44 (2.27%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Intravitreal Aflibercept Injection (IAI) 2q8	Intravitreal Aflibercept Injection (IAI) 2PRN	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 42 (35.71%)	7 / 45 (15.56%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			

subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer stage iii			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Small cell lung cancer			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma stage iv			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 42 (0.00%)	3 / 45 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-Organ failure			

subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac chest pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Joint capsule rupture			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic brain injury			

subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal abrasion			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			

subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 42 (2.38%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Silent myocardial infarction			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wolff-Parkinson-White syndrome			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			

subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cystoid macular oedema			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Maculopathy			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous adhesions			

subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	2 / 42 (4.76%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angle closure glaucoma			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinal oedema			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			

subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephropathy			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			

subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress urinary incontinence			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Clostridium difficile colitis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 42 (4.76%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			

subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Laser Photocoagulation	Intravitreal Aflibercept Injection (IAI) 0.5q4	Intravitreal Aflibercept Injection (IAI) 2q4
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 44 (72.73%)	34 / 44 (77.27%)	33 / 44 (75.00%)
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 44 (2.27%)	4 / 44 (9.09%)	3 / 44 (6.82%)
occurrences (all)	1	4	3
Blood potassium increased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Blood pressure increased			
subjects affected / exposed	1 / 44 (2.27%)	1 / 44 (2.27%)	4 / 44 (9.09%)
occurrences (all)	1	1	4
Blood urine present			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences (all)	0	1	0

Glucose urine present			
subjects affected / exposed	1 / 44 (2.27%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences (all)	1	1	0
Glycosylated haemoglobin increased			
subjects affected / exposed	2 / 44 (4.55%)	6 / 44 (13.64%)	5 / 44 (11.36%)
occurrences (all)	2	7	5
Haematocrit decreased			
subjects affected / exposed	2 / 44 (4.55%)	2 / 44 (4.55%)	4 / 44 (9.09%)
occurrences (all)	2	2	4
Haemoglobin decreased			
subjects affected / exposed	2 / 44 (4.55%)	2 / 44 (4.55%)	3 / 44 (6.82%)
occurrences (all)	2	2	3
Protein urine present			
subjects affected / exposed	2 / 44 (4.55%)	1 / 44 (2.27%)	1 / 44 (2.27%)
occurrences (all)	2	1	1
Red blood cell count decreased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	3 / 44 (6.82%)
occurrences (all)	0	1	3
Intraocular pressure increased			
subjects affected / exposed	1 / 44 (2.27%)	8 / 44 (18.18%)	7 / 44 (15.91%)
occurrences (all)	1	8	7
Urine protein/creatinine ratio increased			
subjects affected / exposed	2 / 44 (4.55%)	6 / 44 (13.64%)	4 / 44 (9.09%)
occurrences (all)	3	7	4
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	3
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 44 (11.36%)	5 / 44 (11.36%)	5 / 44 (11.36%)
occurrences (all)	7	5	5
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 44 (4.55%)	0 / 44 (0.00%)	2 / 44 (4.55%)
occurrences (all)	2	0	3

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 44 (4.55%)	1 / 44 (2.27%)	3 / 44 (6.82%)
occurrences (all)	2	1	3
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	3 / 44 (6.82%)	1 / 44 (2.27%)	1 / 44 (2.27%)
occurrences (all)	3	1	1
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	4 / 44 (9.09%)
occurrences (all)	0	0	5
Cataract			
subjects affected / exposed	2 / 44 (4.55%)	2 / 44 (4.55%)	4 / 44 (9.09%)
occurrences (all)	2	2	4
Conjunctival haemorrhage			
subjects affected / exposed	8 / 44 (18.18%)	13 / 44 (29.55%)	7 / 44 (15.91%)
occurrences (all)	21	40	9
Diabetic retinal oedema			
subjects affected / exposed	0 / 44 (0.00%)	5 / 44 (11.36%)	6 / 44 (13.64%)
occurrences (all)	0	6	6
Eye pain			
subjects affected / exposed	5 / 44 (11.36%)	7 / 44 (15.91%)	5 / 44 (11.36%)
occurrences (all)	5	17	5
Macular oedema			
subjects affected / exposed	3 / 44 (6.82%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences (all)	3	1	0
Posterior capsule opacification			
subjects affected / exposed	4 / 44 (9.09%)	3 / 44 (6.82%)	2 / 44 (4.55%)
occurrences (all)	4	3	4
Retinal aneurysm			
subjects affected / exposed	1 / 44 (2.27%)	3 / 44 (6.82%)	0 / 44 (0.00%)
occurrences (all)	1	4	0
Retinal haemorrhage			
subjects affected / exposed	3 / 44 (6.82%)	1 / 44 (2.27%)	3 / 44 (6.82%)
occurrences (all)	4	1	3

Retinal neovascularisation			
subjects affected / exposed	2 / 44 (4.55%)	0 / 44 (0.00%)	2 / 44 (4.55%)
occurrences (all)	4	0	3
Vitreous detachment			
subjects affected / exposed	5 / 44 (11.36%)	3 / 44 (6.82%)	3 / 44 (6.82%)
occurrences (all)	5	3	3
Vitreous floaters			
subjects affected / exposed	3 / 44 (6.82%)	5 / 44 (11.36%)	4 / 44 (9.09%)
occurrences (all)	3	5	4
Vitreous haemorrhage			
subjects affected / exposed	9 / 44 (20.45%)	3 / 44 (6.82%)	6 / 44 (13.64%)
occurrences (all)	12	3	8
Anterior chamber cell			
subjects affected / exposed	0 / 44 (0.00%)	4 / 44 (9.09%)	0 / 44 (0.00%)
occurrences (all)	0	5	0
Diabetic retinopathy			
subjects affected / exposed	3 / 44 (6.82%)	2 / 44 (4.55%)	2 / 44 (4.55%)
occurrences (all)	3	2	2
Foreign body sensation in eyes			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Maculopathy			
subjects affected / exposed	2 / 44 (4.55%)	2 / 44 (4.55%)	2 / 44 (4.55%)
occurrences (all)	2	2	2
Ocular hyperaemia			
subjects affected / exposed	2 / 44 (4.55%)	5 / 44 (11.36%)	2 / 44 (4.55%)
occurrences (all)	2	8	2
Punctate keratitis			
subjects affected / exposed	1 / 44 (2.27%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences (all)	5	1	0
Retinal exudates			
subjects affected / exposed	2 / 44 (4.55%)	5 / 44 (11.36%)	2 / 44 (4.55%)
occurrences (all)	2	5	2
Vision blurred			
subjects affected / exposed	1 / 44 (2.27%)	5 / 44 (11.36%)	1 / 44 (2.27%)
occurrences (all)	2	7	1

Visual acuity reduced			
subjects affected / exposed	0 / 44 (0.00%)	3 / 44 (6.82%)	1 / 44 (2.27%)
occurrences (all)	0	3	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 44 (2.27%)	2 / 44 (4.55%)	3 / 44 (6.82%)
occurrences (all)	1	2	3
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 44 (0.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	3 / 44 (6.82%)	1 / 44 (2.27%)	1 / 44 (2.27%)
occurrences (all)	3	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 44 (2.27%)	3 / 44 (6.82%)	2 / 44 (4.55%)
occurrences (all)	1	3	2
Nasopharyngitis			
subjects affected / exposed	4 / 44 (9.09%)	4 / 44 (9.09%)	3 / 44 (6.82%)
occurrences (all)	4	4	3
Sinusitis			
subjects affected / exposed	2 / 44 (4.55%)	3 / 44 (6.82%)	0 / 44 (0.00%)
occurrences (all)	2	3	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 44 (9.09%)	4 / 44 (9.09%)	2 / 44 (4.55%)
occurrences (all)	4	4	3
Urinary tract infection			
subjects affected / exposed	4 / 44 (9.09%)	2 / 44 (4.55%)	5 / 44 (11.36%)
occurrences (all)	5	2	7
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 44 (2.27%)	3 / 44 (6.82%)
occurrences (all)	1	1	3

Non-serious adverse events	Intravitreal Aflibercept Injection (IAI) 2q8	Intravitreal Aflibercept Injection (IAI) 2PRN	

Total subjects affected by non-serious adverse events subjects affected / exposed	34 / 42 (80.95%)	35 / 45 (77.78%)	
Investigations			
Blood glucose increased subjects affected / exposed	6 / 42 (14.29%)	6 / 45 (13.33%)	
occurrences (all)	6	6	
Blood potassium increased subjects affected / exposed	3 / 42 (7.14%)	3 / 45 (6.67%)	
occurrences (all)	3	3	
Blood pressure increased subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Blood urine present subjects affected / exposed	1 / 42 (2.38%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Glucose urine present subjects affected / exposed	3 / 42 (7.14%)	4 / 45 (8.89%)	
occurrences (all)	3	4	
Glycosylated haemoglobin increased subjects affected / exposed	5 / 42 (11.90%)	2 / 45 (4.44%)	
occurrences (all)	5	2	
Haematocrit decreased subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Haemoglobin decreased subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Protein urine present subjects affected / exposed	4 / 42 (9.52%)	3 / 45 (6.67%)	
occurrences (all)	4	3	
Red blood cell count decreased subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Intraocular pressure increased subjects affected / exposed	5 / 42 (11.90%)	4 / 45 (8.89%)	
occurrences (all)	5	4	

Urine protein/creatinine ratio increased			
subjects affected / exposed	5 / 42 (11.90%)	4 / 45 (8.89%)	
occurrences (all)	5	5	
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	2 / 42 (4.76%)	3 / 45 (6.67%)	
occurrences (all)	2	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 42 (14.29%)	5 / 45 (11.11%)	
occurrences (all)	7	5	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 42 (7.14%)	2 / 45 (4.44%)	
occurrences (all)	3	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 42 (9.52%)	3 / 45 (6.67%)	
occurrences (all)	4	3	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 42 (4.76%)	2 / 45 (4.44%)	
occurrences (all)	2	2	
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	2	
Cataract			
subjects affected / exposed	2 / 42 (4.76%)	8 / 45 (17.78%)	
occurrences (all)	2	9	
Conjunctival haemorrhage			
subjects affected / exposed	16 / 42 (38.10%)	14 / 45 (31.11%)	
occurrences (all)	39	33	
Diabetic retinal oedema			
subjects affected / exposed	1 / 42 (2.38%)	5 / 45 (11.11%)	
occurrences (all)	2	8	

Eye pain			
subjects affected / exposed	7 / 42 (16.67%)	7 / 45 (15.56%)	
occurrences (all)	10	16	
Macular oedema			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Posterior capsule opacification			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Retinal aneurysm			
subjects affected / exposed	4 / 42 (9.52%)	3 / 45 (6.67%)	
occurrences (all)	5	3	
Retinal haemorrhage			
subjects affected / exposed	3 / 42 (7.14%)	5 / 45 (11.11%)	
occurrences (all)	5	8	
Retinal neovascularisation			
subjects affected / exposed	1 / 42 (2.38%)	3 / 45 (6.67%)	
occurrences (all)	2	3	
Vitreous detachment			
subjects affected / exposed	5 / 42 (11.90%)	0 / 45 (0.00%)	
occurrences (all)	6	0	
Vitreous floaters			
subjects affected / exposed	4 / 42 (9.52%)	2 / 45 (4.44%)	
occurrences (all)	4	2	
Vitreous haemorrhage			
subjects affected / exposed	4 / 42 (9.52%)	3 / 45 (6.67%)	
occurrences (all)	7	4	
Anterior chamber cell			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Diabetic retinopathy			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Foreign body sensation in eyes			
subjects affected / exposed	1 / 42 (2.38%)	3 / 45 (6.67%)	
occurrences (all)	2	4	

Maculopathy			
subjects affected / exposed	4 / 42 (9.52%)	3 / 45 (6.67%)	
occurrences (all)	4	3	
Ocular hyperaemia			
subjects affected / exposed	3 / 42 (7.14%)	3 / 45 (6.67%)	
occurrences (all)	5	6	
Punctate keratitis			
subjects affected / exposed	3 / 42 (7.14%)	0 / 45 (0.00%)	
occurrences (all)	12	0	
Retinal exudates			
subjects affected / exposed	3 / 42 (7.14%)	3 / 45 (6.67%)	
occurrences (all)	4	7	
Vision blurred			
subjects affected / exposed	0 / 42 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	4	
Visual acuity reduced			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 42 (9.52%)	4 / 45 (8.89%)	
occurrences (all)	4	4	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 42 (7.14%)	1 / 45 (2.22%)	
occurrences (all)	3	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 42 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	1 / 42 (2.38%)	3 / 45 (6.67%)	
occurrences (all)	2	4	

Sinusitis			
subjects affected / exposed	2 / 42 (4.76%)	2 / 45 (4.44%)	
occurrences (all)	2	2	
Upper respiratory tract infection			
subjects affected / exposed	4 / 42 (9.52%)	4 / 45 (8.89%)	
occurrences (all)	5	4	
Urinary tract infection			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	3 / 42 (7.14%)	1 / 45 (2.22%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2008	Following changes were made: • Clarified the treatment requirements for the fellow eye • Revised visits, where applicable, to include a post-dose indirect ophthalmoscopy • Revised the role of the unmasked physician to include post-dose indirect ophthalmoscopy but not pre-dose ophthalmoscopy • Revised the screening range to allow for same day enrollment.
27 January 2009	Following changes were made: • Revised the protocol to exclude subjects with only 1 functional eye or subjects with ocular conditions with a poorer prognosis in the fellow eye • Clarified that multiple, repeated use of the same vial of VEGF Trap-Eye was prohibited • Included Health Canada as a regulatory authority for the study • Changed the technical procedure for microperimetry
24 February 2009	Changed the needle used to withdraw VEGF Trap-Eye from the vial into the syringe

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported