Clinical trial results:
A randomized, double masked, active controlled, phase III study of the efficacy and safety of repeated doses of intravitreal VEGF Trap-Eye in subjects with diabetic macular edema

Summary

EudraCT number	2010-022364-12
Trial protocol	DE AT CZ ES DK IT HU
Global end of trial date	30 March 2015

Results information

Result version number	v2 (current)
This version publication date	04 September 2016
First version publication date	06 April 2016
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY86-5321/91745

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01331681
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 March 2015
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 assess the efficacy of intravitreal (IVT) administered vascular endothelial growth factor (VEGF) Trap–Eye in comparison to macular laser photocoagulation treatment in improving best corrected visual acuity (BCVA) in subjects with diabetic macular edema (DME).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 77
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Czech Republic: 39
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Spain: 57
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	Hungary: 76
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Poland: 14
Worldwide total number of subjects	406
EEA total number of subjects	311

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)	214
From 65 to 84 years	192
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with diabetic macular edema (DME) secondary to diabetes mellitus involving the center of the macula in the study eye could participate in the study. The study was conducted at 73 study centers in Japan, European Countries and Australia in subjects between 09 May 2011 (first subject first visit) and 30 Mar 2015 (last subject last visit).

Pre-assignment

Screening details:

Of 604 subjects who were screened for inclusion in the study, 406 were randomized, and 404 received treatment.

Pre-assignment period milestones

Number of subjects started	406
Number of subjects completed	404

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not Received Study Treatment: 2

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Intravitreal Aflibercept Injection 2Q4

Arm description:

Subjects received 2 milligram (mg) Intravitreal aflibercept injection (IAI) (EYLEA, vascular endothelial growth factor [VEGF] Trap-Eye, BAY86-5321) every 4 weeks (2Q4).

Arm type	Experimental
Investigational medicinal product name	VEGF Trap-Eye
Investigational medicinal product code	BAY86-5321
Other name	Aflibercept and Eylea
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) 2Q4.

Arm title	Intravitreal Aflibercept Injection 2Q8

Arm description:

Subjects received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) every 4 weeks for 5 visits followed by injections every 8 weeks (2Q8).

Arm type	Experimental
Investigational medicinal product name	VEGF Trap-Eye
Investigational medicinal product code	BAY86-5321
Other name	Aflibercept and Eylea
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) every 4 weeks for 5 visits followed by injections 2Q8.

Arm title	Macular Laser Photocoagulation (Control)

Arm description:

Subjects received laser treatment at baseline and as needed at visits at which laser re-treatment criteria were met, but no more frequently than every 12 weeks. During year 3 laser subjects could receive IAI as needed (PRN).

Arm type	Procedure

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)
Started	136	135	133
Completed Week 52	125	121	115
Completed Week 100	115	110	105
Completed Week 148	101	101	100
Completed	101	101	100
Not completed	35	34	33
Physician decision	2	-	4
Adverse Event	10	13	10
Death	6	6	2
Switching to other therapy	-	-	1
Withdrawal by Subject	12	8	15
Lost to follow-up	2	4	1
Sponsor decision	1	1	-
Protocol deviation	1	1	-
Therapeutic procedure required	1	-	-
Lack of efficacy	-	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Worldwide number of subjects is equal to the number of subjects in the pre-assignment period and the baseline period starts with the number of subjects received the treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Intravitreal Aflibercept Injection 2Q4
Reporting group description:	
Subjects received 2 milligram (mg) Intravitreal aflibercept injection (IAI) (EYLEA, vascular endothelial growth factor [VEGF] Trap-Eye, BAY86-5321) every 4 weeks (2Q4).	
Reporting group title	Intravitreal Aflibercept Injection 2Q8
Reporting group description:	
Subjects received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) every 4 weeks for 5 visits followed by injections every 8 weeks (2Q8).	
Reporting group title	Macular Laser Photocoagulation (Control)
Reporting group description:	
Subjects received laser treatment at baseline and as needed at visits at which laser re-treatment criteria were met, but no more frequently than every 12 weeks. During year 3 laser subjects could receive IAI as needed (PRN).	

Reporting group values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)
Number of subjects	136	135	133
Age categorical Units: Subjects			
Age continous			
Age continuous			
Units: years			
arithmetic mean	62.6	64.2	63.9
standard deviation	± 8.6	± 7.7	± 8.6
Gender Units: subjects			
Female	53	47	54
Male	83	88	79

Reporting group values	Total		
Number of subjects	404		
Age categorical Units: Subjects			
Age continous			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender Units: subjects			
Female	154		
Male	250		

End points

End points reporting groups

Reporting group title	Intravitreal Aflibercept Injection 2Q4
Reporting group description:	
Subjects received 2 milligram (mg) Intravitreal aflibercept injection (IAI) (EYLEA, vascular endothelial growth factor [VEGF] Trap-Eye, BAY86-5321) every 4 weeks (2Q4).	
Reporting group title	Intravitreal Aflibercept Injection 2Q8
Reporting group description:	
Subjects received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) every 4 weeks for 5 visits followed by injections every 8 weeks (2Q8).	
Reporting group title	Macular Laser Photocoagulation (Control)
Reporting group description:	
Subjects received laser treatment at baseline and as needed at visits at which laser re-treatment criteria were met, but no more frequently than every 12 weeks. During year 3 laser subjects could receive IAI as needed (PRN).	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
SAF included all subjects who received at least 1 study treatment (active or sham). Treatment administration/compliance and all clinical safety and tolerability variables were analyzed using the SAF.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS included all randomized subjects who received any study treatment, had a baseline measurement of BCVA, and had at least 1 post-baseline assessment of BCVA. All efficacy endpoints were analyzed using the FAS.	

Primary: Change from Baseline in BCVA (Best Corrected Visual Acuity) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - Last Observation Carried Forward (LOCF)

End point title	Change from Baseline in BCVA (Best Corrected Visual Acuity) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - Last Observation Carried Forward (LOCF)
End point description:	
Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning.	
End point type	Primary
End point timeframe:	
Baseline up to Week 52	

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136[1]	135[2]	132[3]	
Units: letters correctly read				
arithmetic mean (standard deviation)	10.5 (± 9.55)	10.7 (± 9.32)	1.2 (± 10.65)	

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control
Statistical analysis description:	
Hypothesis: Mean change identical in both groups	
Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	6.5
upper limit	12

Notes:

[4] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. Least square (LS) mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[5] - Significance level alpha=0.025 for two sided test to adjust for multiplicity. Since this p-value was below the significance level of 0.025, the fixed sequence testing did continue with the first secondary endpoint.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control
Statistical analysis description:	
Hypothesis: Mean change identical in both groups	
Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	6.3
upper limit	11.8

Notes:

[6] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[7] - Significance level alpha=0.025 for two sided test to adjust for multiplicity. Since this p-value was below the significance level of 0.025, the fixed sequence testing did continue with the first secondary endpoint.

Secondary: Percentage of Subjects Who Gained At Least 10 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 52 - LOCF

End point title	Percentage of Subjects Who Gained At Least 10 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 52 - LOCF

End point description:

Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136[8]	135[9]	132[10]	
Units: percentage of subjects				
number (not applicable)	54.4	53.3	25.8	

Notes:

[8] - FAS

[9] - FAS

[10] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control

Statistical analysis description:

Hypothesis: Probability to gain >= 10 letters identical in both groups

Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.0001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	28.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	15.8
upper limit	41.6

Notes:

[11] - stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[12] - Significance level alpha=0.025 for two sided test to adjust for multiplicity. Since this p-value and

the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the second secondary endpoint.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control
Statistical analysis description:	
Hypothesis: Probability to gain >= 10 letters identical in both groups	
Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.0001 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	27.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	14.6
upper limit	40.5

Notes:

[13] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.
[14] - Significance level alpha=0.025 for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the second secondary endpoint.

Secondary: Percentage of Subjects Who Gained At Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 52 - LOCF

End point title	Percentage of Subjects Who Gained At Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 52 - LOCF
End point description:	
Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning.	
End point type	Secondary
End point timeframe:	
Baseline up to Week 52	

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136[15]	135[16]	132[17]	
Units: percentage of subjects				
number (not applicable)	32.4	33.3	9.1	

Notes:

[15] - FAS

[16] - FAS

[17] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control
Statistical analysis description:	
Hypothesis: Probability to gain >= 15 letters identical in both groups	
Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	< 0.0001 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	23.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	12.6
upper limit	33.9

Notes:

[18] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.
[19] - Significance level alpha=0.025 for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the third secondary endpoint.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control
Statistical analysis description:	
Hypothesis: Probability to gain >= 15 letters identical in both groups	
Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	< 0.0001 [21]
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	24.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	13.5
upper limit	34.9

Notes:

[20] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.
[21] - Significance level alpha=0.025 for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the third secondary endpoint.

Secondary: Percentage of Subjects With a >=2-Step Improvement From Baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Score) as Assessed by FP (Fundus Photography) at Week 52 - LOCF

End point title	Percentage of Subjects With a >=2-Step Improvement From Baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Score) as Assessed by FP (Fundus Photography) at Week 52 -

	LOCF

End point description:

Baseline ETDRS DRSS: None (level 10); Mild to moderate nonproliferative DR (levels 14, 15, 20, 35, and 43); Moderately severe/severe nonproliferative DR (levels 47 and 53); Mild/moderate/high-risk/advanced proliferative DR (levels 61, 65, 71,75, 81, and 85)

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81[22]	83[23]	80[24]	
Units: percentage of subjects				
number (not applicable)	33.3	27.7	7.5	

Notes:

[22] - FAS with assessment for this end-point.

[23] - FAS with assessment for this end-point.

[24] - FAS with assessment for this end-point.

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control

Statistical analysis description:

Hypothesis: Probability to improve by >= 2 steps identical in both groups

Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	< 0.0001 [26]
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	25.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	12.2
upper limit	39.4

Notes:

[25] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[26] - Significance level alpha=0.025 for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the fourth secondary endpoint.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control

Statistical analysis description:

Hypothesis: Probability to improve by >= 2 steps identical in both groups

Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)

Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.0006 [28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	19.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	6.6
upper limit	32.1

Notes:

[27] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.
[28] - Significance level alpha=0.025 for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the fourth secondary endpoint.

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

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

End point description:

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135[29]	135[30]	132[31]	
Units: micrometer				
arithmetic mean (standard deviation)	-195 (± 146.59)	-192.4 (± 149.89)	-66.2 (± 138.99)	

Notes:

[29] - FAS with assessment for this end-point.

[30] - FAS with assessment for this end-point.

[31] - FAS with assessment for this end-point.

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control

Statistical analysis description:

Hypothesis: Mean change identical in both groups

Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)

Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	< 0.0001 [33]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-157
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-190.9
upper limit	-123.1

Notes:

[32] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.
[33] - Significance level alpha=0.025 for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the fifth secondary endpoint.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control

Statistical analysis description:

Hypothesis: Mean change identical in both groups

Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	< 0.0001 [35]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-142.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-179.3
upper limit	-106.3

Notes:

[34] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A negative value indicates a result in favor of EYLEA.
[35] - Significance level alpha=0.025 for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the fifth secondary endpoint.

Secondary: Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Near Activities Subscale at Week 52 - LOCF

End point title	Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Near Activities Subscale at Week 52 - LOCF

End point description:

The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales that are all scored from 0-100. Near activities are defined as reading ordinary print in newspapers, performing work or hobbies requiring near vision, or finding something on a crowded shelf.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128[36]	134[37]	120[38]	
Units: scores on a scale				
arithmetic mean (standard deviation)	5.73 (± 18.932)	5.29 (± 19.058)	3.54 (± 16.768)	

Notes:

[36] - FAS with assessment for this end-point.

[37] - FAS with assessment for this end-point.

[38] - FAS with assessment for this end-point.

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control

Statistical analysis description:

Hypothesis: Mean change identical in both groups

Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0.2208 [40]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.41
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-2.01
upper limit	6.82

Notes:

[39] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[40] - Significance level alpha=0.025 for two sided test to adjust for multiplicity. Since this p-value is not below of 0.025, the fixed sequence testing stops here. The sixth secondary endpoint cannot be tested confirmatory.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control

Statistical analysis description:

Hypothesis: Mean change identical in both groups

Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0.5537 [42]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.21
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-5.79
upper limit	3.37

Notes:

[41] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[42] - Significance level alpha=0.025 for two sided test to adjust for multiplicity. Since this p-value is not below of 0.025, the fixed sequence testing stops here. The sixth secondary endpoint cannot be tested confirmatory.

Secondary: Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Distance Activities Subscale at Week 52 - LOCF

End point title	Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Distance Activities Subscale at Week 52 - LOCF

End point description:

The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales that are all scored from 0-100. Distance activities are defined as reading street signs or names on stores, and going down stairs, steps, or curbs.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128[43]	134[44]	120[45]	
Units: scores on a scale				
arithmetic mean (standard deviation)	0.94 (± 16.487)	5.32 (± 18.475)	2.26 (± 15.923)	

Notes:

[43] - FAS with assessment for this end-point.

[44] - FAS with assessment for this end-point.

[45] - FAS with assessment for this end-point.

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control

Statistical analysis description:

Hypothesis: Mean change identical in both groups

Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other[46]
P-value	= 0.5138
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.19
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-5.29
upper limit	2.91

Notes:

[46] - LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control

Statistical analysis description:

Hypothesis: Mean change identical in both groups

Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	= 0.8498
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-4.79
upper limit	4.05

Notes:

[47] - LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Other pre-specified: Change from Baseline in BCVA (best corrected visual acuity) as Measured by ETDRS Letter Score at Week 100 - LOCF

End point title	Change from Baseline in BCVA (best corrected visual acuity) as Measured by ETDRS Letter Score at Week 100 - LOCF

End point description:

Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 100

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136[48]	135[49]	132[50]	
Units: letters correctly read				
arithmetic mean (standard deviation)	11.4 (± 11.2)	9.4 (± 10.5)	0.7 (± 11.8)	

Notes:

[48] - FAS

[49] - FAS

[50] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control
Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	10.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	7.6
upper limit	13.8

Notes:

[51] - Stratifying by geographic region (Japan vs non-Japan). LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control
Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[52]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	8.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	5.2
upper limit	11.3

Notes:

[52] - Stratifying by geographic region (Japan vs non-Japan). LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Other pre-specified: Percentage of Subjects Who Gained At Least 10 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 100 - LOCF

End point title	Percentage of Subjects Who Gained At Least 10 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 100 - LOCF

End point description:

Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 100

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136[53]	135[54]	132[55]	
Units: percentage of subjects				
number (not applicable)	58.1	49.6	25	

Notes:

[53] - FAS

[54] - FAS

[55] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[56]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	33.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	20.3
upper limit	45.9

Notes:

[56] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control

Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	24.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	11.9
upper limit	37.3

Notes:

[57] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Other pre-specified: Percentage of Subjects Who Gained At Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 100 - LOCF

End point title	Percentage of Subjects Who Gained At Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 100 - LOCF

End point description:

Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 100

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136[58]	135[59]	132[60]	
Units: percentage of subjects				
number (not applicable)	38.2	31.1	12.1	

Notes:

[58] - FAS

[59] - FAS

[60] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control
Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)

Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[61]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	26.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	14.8
upper limit	37.5

Notes:

[61] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[62]
P-value	= 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	19
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	8
upper limit	29.9

Notes:

[62] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Other pre-specified: Percentage of Subjects with A >=2-Step Improvement From Baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Score) as Assessed by FP (Fundus Photography) at Week 100 - LOCF

End point title	Percentage of Subjects with A >=2-Step Improvement From Baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Score) as Assessed by FP (Fundus Photography) at Week 100 - LOCF

End point description:

Baseline ETDRS DRSS: None (level 10); Mild to moderate nonproliferative DR (levels 14, 15, 20, 35, and 43); Moderately severe/severe nonproliferative DR (levels 47 and 53); Mild/moderate/high-risk/advanced proliferative DR (levels 61, 65, 71,75, 81, and 85)

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 100

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136[63]	135[64]	132[65]	
Units: percentage of subjects				
number (not applicable)	29.3	32.6	8.2	

Notes:

[63] - FAS

[64] - FAS

[65] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control
Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[66]
P-value	= 0.0004
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	20.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	7.7
upper limit	34.2

Notes:

[66] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control
Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[67]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	24.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	11.3
upper limit	37.4

Notes:

[67] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Other pre-specified: Change from Baseline in Central Retinal Thickness (CRT) at Week 100 as Assessed on Optical Coherence Tomography (OCT) - LOCF

End point title	Change from Baseline in Central Retinal Thickness (CRT) at Week 100 as Assessed on Optical Coherence Tomography (OCT) - LOCF

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 100

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135[68]	135[69]	132[70]	
Units: micrometer				
arithmetic mean (standard deviation)	-211.8 (± 150.9)	-195.8 (± 141.7)	-85.7 (± 145.8)	

Notes:

[68] - FAS

[69] - FAS

[70] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[71]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-154.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-189.1
upper limit	-119.7

Notes:

[71] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A negative value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[72]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-126.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-164.6
upper limit	-89

Notes:

[72] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A negative value indicates a result in favor of EYLEA.

Other pre-specified: Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Near Activities Subscale at Week 100 - LOCF

End point title	Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Near Activities Subscale at Week 100 - LOCF

End point description:

The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of sub-scales that are all scored from 0-100. Near activities are defined as reading ordinary print in newspapers, performing work or hobbies requiring near vision, or finding something on a crowded shelf.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 100

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128[73]	134[74]	120[75]	
Units: scores on a scale				
arithmetic mean (standard deviation)	8.2 (± 20.19)	7 (± 19.28)	4.8 (± 15.43)	

Notes:

[73] - FAS with assessment for this end-point.

[74] - FAS with assessment for this end-point.

[75] - FAS with assessment for this end-point.

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other[76]
P-value	= 0.0596
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.64
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.7
upper limit	7.98

Notes:

[76] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[77]
P-value	= 0.7144
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.74
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-5.25
upper limit	3.78

Notes:

[77] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Other pre-specified: Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Distance Activities Subscale at Week 100 - LOCF

End point title	Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Distance Activities Subscale at Week 100 - LOCF

End point description:

The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales that are all scored from 0-100. Distance activities are defined as reading street signs or names on stores, and going down stairs, steps, or curbs.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 100

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128[78]	134[79]	120[80]	
Units: scores on a scale				
arithmetic mean (standard deviation)	4.6 (± 17.62)	4.9 (± 20.25)	2.2 (± 16.68)	

Notes:

[78] - FAS with assessment for this end-point.

[79] - FAS with assessment for this end-point.

[80] - FAS with assessment for this end-point.

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control
Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other[81]
P-value	= 0.1792
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.57
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1.73
upper limit	6.86

Notes:

[81] - LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control
Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[82]
P-value	= 0.5325
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.3

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-6
upper limit	3.39

Notes:

[82] - LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Other pre-specified: Change from Baseline in BCVA (Best Corrected Visual Acuity) as Measured by ETDRS Letter Score at Week 148 - LOCF

End point title	Change from Baseline in BCVA (Best Corrected Visual Acuity) as Measured by ETDRS Letter Score at Week 148 - LOCF

End point description:

Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning. During year 3 laser subjects received IAI as needed (PRN).

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 148

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136[83]	135[84]	132[85]	
Units: letters correctly read				
arithmetic mean (standard deviation)	10.3 (± 12.5)	11.7 (± 10.1)	1.6 (± 12.7)	

Notes:

[83] - FAS

[84] - FAS

[85] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[86]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	8.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	5.2
upper limit	12.1

Notes:

[86] - Stratifying by geographic region (Japan vs non-Japan). LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control
Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[87]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	6.5
upper limit	12.9

Notes:

[87] - Stratifying by geographic region (Japan vs non-Japan). LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Other pre-specified: Percentage of Subjects Who Gained At Least 10 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 148 - LOCF

End point title	Percentage of Subjects Who Gained At Least 10 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 148 - LOCF
End point description:	
Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning. During year 3 laser subjects received IAI as needed (PRN).	
End point type	Other pre-specified
End point timeframe:	
Baseline up to Week 148	

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136[88]	135[89]	132[90]	
Units: percentage of subjects				
number (not applicable)	55.9	56.3	29.5	

Notes:

[88] - FAS

[89] - FAS

[90] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control
Statistical analysis description: These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[91]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	26.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	13.2
upper limit	39.5

Notes:

[91] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control
Statistical analysis description: These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[92]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	26.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	13.6
upper limit	39.9

Notes:

[92] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Other pre-specified: Percentage of Subjects Who Gained At Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 148 - LOCF

End point title	Percentage of Subjects Who Gained At Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 148 - LOCF

End point description:

Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning. During year 3 laser subjects received IAI as needed (PRN).

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 148

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136[93]	135[94]	132[95]	
Units: percentage of subjects				
number (not applicable)	41.2	42.2	18.9	

Notes:

[93] - FAS

[94] - FAS

[95] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control
Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[96]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	22.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	10.1
upper limit	34.4

Notes:

[96] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control
Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[97]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	23.2

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	11
upper limit	35.5

Notes:

[97] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Other pre-specified: Percentage of Subjects with a >=2-Step Improvement From Baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Score) as Assessed by FP (Fundus Photography) at Week 148 - LOCF

End point title	Percentage of Subjects with a >=2-Step Improvement From Baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Score) as Assessed by FP (Fundus Photography) at Week 148 - LOCF

End point description:

Baseline ETDRS DRSS: None (level 10); Mild to moderate nonproliferative DR (levels 14, 15, 20, 35, and 43); Moderately severe/severe nonproliferative DR (levels 47 and 53); Mild/moderate/high-risk/advanced proliferative DR (levels 61, 65, 71,75, 81, and 85). During year 3 laser subjects received IAI as needed (PRN).

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 148

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136[98]	135[99]	132[100]	
Units: percentage of subjects				
number (not applicable)	44.3	47.8	17.4	

Notes:

[98] - FAS

[99] - FAS

[100] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[101]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	26.8

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	11.7
upper limit	41.9

Notes:

[101] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[102]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	CMH adjusted difference
Point estimate	30.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	15.4
upper limit	45.1

Notes:

[102] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Other pre-specified: Change from Baseline in Central Retinal Thickness (CRT) at Week 148 as Assessed On Optical Coherence Tomography (OCT) - LOCF

End point title	Change from Baseline in Central Retinal Thickness (CRT) at Week 148 as Assessed On Optical Coherence Tomography (OCT) - LOCF

End point description:

During year 3 laser subjects received IAI as needed (PRN).

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 148

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136[103]	135[104]	132[105]	
Units: micrometer				
arithmetic mean (standard deviation)	-215.2 (± 154.2)	-202.8 (± 155)	-122.6 (± 176.2)	

Notes:
[103] - FAS
[104] - FAS
[105] - FAS

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control
Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[106]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-124.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-160.6
upper limit	-88

Notes:
[106] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A negative value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control
Statistical analysis description:	
These analysis are not confirmatory.	
Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other[107]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-98.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-139.4
upper limit	-57.1

Notes:
[107] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A negative value indicates a result in favor of EYLEA.

Other pre-specified: Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Near Activities Subscale at Week 148 - LOCF

End point title	Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Near Activities Subscale at Week 148 - LOCF

End point description:

The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales that are all scored from 0-100. Near activities are defined as reading ordinary print in newspapers, performing work or hobbies requiring near vision, or finding something on a crowded shelf. During year 3 laser subjects received IAI as needed (PRN).

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 14

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128[108]	134[109]	120[110]	
Units: scores on a scale				
arithmetic mean (standard deviation)	8.6 (± 20.86)	9.3 (± 19.94)	5.3 (± 17.34)	

Notes:

[108] - FAS with assessment for this end point.

[109] - FAS with assessment for this end point.

[110] - FAS with assessment for this end point.

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other[111]
P-value	= 0.0862
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.56
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1.1
upper limit	8.22

Notes:

[111] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser

	Photocoagulation (Control)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[112]
P-value	= 0.7361
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.72
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-4.08
upper limit	5.52

Notes:

[112] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Other pre-specified: Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Distance Activities Subscale at Week 148 - LOCF

End point title	Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Distance Activities Subscale at Week 148 - LOCF

End point description:

The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales that are all scored from 0-100. Distance activities are defined as reading street signs or names on stores, and going down stairs, steps, or curbs. During year 3 laser subjects received IAI as needed (PRN).

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 148

End point values	Intravitreal Aflibercept Injection 2Q4	Intravitreal Aflibercept Injection 2Q8	Macular Laser Photocoagulation (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128[113]	134[114]	120[115]	
Units: score on a scale				
arithmetic mean (standard deviation)	4.4 (± 17.61)	7.4 (± 21.66)	3.4 (± 17.19)	

Notes:

[113] - FAS with assessment for this end-point.

[114] - FAS with assessment for this end-point.

[115] - FAS with assessment for this end-point.

Statistical analyses

Statistical analysis title	Intravitreal Aflibercept Injection 2Q4 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control)

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other[116]
P-value	= 0.5337
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.16
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-3.02
upper limit	5.34

Notes:

[116] - LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Statistical analysis title	Intravitreal Aflibercept Injection 2Q8 vs. Control

Statistical analysis description:

These analysis are not confirmatory.

Comparison groups	Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[117]
P-value	= 0.8323
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.46
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-5.34
upper limit	4.42

Notes:

[117] - LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For each subject from his first study drug injection until 30 days after the last study drug injection at the latest up to termination visit at Week 148

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Intravitreal Aflibercept Injection 2Q4

Reporting group description:

Participants received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) every 4 weeks (2Q4).

Reporting group title	Macular Laser Photocoagulation (Control)

Reporting group description:

Participants received laser treatment at baseline and as needed at visits at which laser retreatment criteria were met, but no more frequently than every 12 weeks. During year 3 laser patients could receive IAI as needed (PRN) .

Reporting group title	Intravitreal Aflibercept Injection 2Q8

Reporting group description:

Participants received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) every 4 weeks for 5 visits followed by injections every 8 weeks (2Q8).

Serious adverse events	Intravitreal Aflibercept Injection 2Q4	Macular Laser Photocoagulation (Control)	Intravitreal Aflibercept Injection 2Q8
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 136 (46.32%)	51 / 133 (38.35%)	60 / 135 (44.44%)
number of deaths (all causes)	7	3	7
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal neoplasm			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaplastic astrocytoma			

subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bladder neoplasm			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 136 (0.74%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 136 (0.74%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung neoplasm malignant			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			

subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pancreatic carcinoma stage IV			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer stage I			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer stage III			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
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 neoplasm			
subjects affected / exposed	2 / 136 (1.47%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial haemorrhage			

subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
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	1 / 136 (0.74%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 136 (0.74%)	3 / 133 (2.26%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	1 / 136 (0.74%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			

subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Arteriovenous shunt operation			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract operation			
subjects affected / exposed	3 / 136 (2.21%)	2 / 133 (1.50%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip arthroplasty			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteosynthesis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery bypass			
subjects affected / exposed	1 / 136 (0.74%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radical prostatectomy			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transurethral prostatectomy			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitrectomy			

subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
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 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Device failure			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (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
Generalised oedema			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site injury			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
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 / 136 (0.00%)	2 / 133 (1.50%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Uterine polyp			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
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	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrothorax			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
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	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sleep apnoea syndrome			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (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
Suicide attempt			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
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			
Catheterisation cardiac			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity tests abnormal			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain contusion			

subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain herniation			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	3 / 136 (2.21%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			

subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	1 / 136 (0.74%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic arthrosis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (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
Traumatic fracture			

subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 136 (1.47%)	3 / 133 (2.26%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Angina unstable			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle branch block right			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
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 disorder			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	1 / 136 (0.74%)	2 / 133 (1.50%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure acute			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
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 chronic			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (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 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac sarcoidosis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
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 valve disease			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	2 / 136 (1.47%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			

subjects affected / exposed	2 / 136 (1.47%)	0 / 133 (0.00%)	0 / 135 (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
Hypertensive heart disease			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (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
Mitral valve stenosis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
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	4 / 136 (2.94%)	1 / 133 (0.75%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	1 / 4	0 / 1	1 / 1
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 136 (0.74%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ventricular tachycardia			

subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (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
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cauda equina syndrome			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral atrophy			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	4 / 136 (2.94%)	1 / 133 (0.75%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	2 / 136 (1.47%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			

subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve compression			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (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
Neutropenia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			

subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
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			
Cataract			
subjects affected / exposed	5 / 136 (3.68%)	2 / 133 (1.50%)	7 / 135 (5.19%)
occurrences causally related to treatment / all	1 / 8	0 / 2	2 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract subcapsular			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic retinopathy			
subjects affected / exposed	0 / 136 (0.00%)	2 / 133 (1.50%)	0 / 135 (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
Iridocyclitis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular degeneration			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular fibrosis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular hole			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic atrophy			

subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior capsule opacification			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal artery occlusion			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal exudates			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal neovascularisation			
subjects affected / exposed	1 / 136 (0.74%)	3 / 133 (2.26%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vascular disorder			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (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
Retinopathy proliferative			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			

subjects affected / exposed	4 / 136 (2.94%)	2 / 133 (1.50%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (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
Gastric ulcer			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			

subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reflux gastritis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
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			
Dermal cyst			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	1 / 136 (0.74%)	2 / 133 (1.50%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriasis			
subjects affected / exposed	0 / 136 (0.00%)	2 / 133 (1.50%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			

subjects affected / exposed	0 / 136 (0.00%)	2 / 133 (1.50%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
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 artery stenosis			
subjects affected / exposed	1 / 136 (0.74%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress urinary incontinence			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Toxic nodular goitre			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropathy			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 136 (0.74%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 136 (0.00%)	2 / 133 (1.50%)	0 / 135 (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
Metatarsalgia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal disorder			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteoarthritis			
subjects affected / exposed	2 / 136 (1.47%)	0 / 133 (0.00%)	0 / 135 (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
Polymyalgia rheumatica			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tenosynovitis stenosans			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Cellulitis			
subjects affected / exposed	0 / 136 (0.00%)	2 / 133 (1.50%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endophthalmitis			
subjects affected / exposed	1 / 136 (0.74%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
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 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected dermal cyst			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			

subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	3 / 135 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
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	0 / 136 (0.00%)	1 / 133 (0.75%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (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
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 136 (0.74%)	1 / 133 (0.75%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
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 retention			

subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 136 (0.00%)	2 / 133 (1.50%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 136 (0.00%)	1 / 133 (0.75%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketoacidosis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 133 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 136 (0.74%)	0 / 133 (0.00%)	0 / 135 (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

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

Non-serious adverse events	Intravitreal Aflibercept Injection 2Q4	Macular Laser Photocoagulation (Control)	Intravitreal Aflibercept Injection 2Q8
Total subjects affected by non-serious adverse events			
subjects affected / exposed	117 / 136 (86.03%)	113 / 133 (84.96%)	122 / 135 (90.37%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	7 / 136 (5.15%)	5 / 133 (3.76%)	6 / 135 (4.44%)
occurrences (all)	8	5	6
Blood glucose increased			
subjects affected / exposed	10 / 136 (7.35%)	8 / 133 (6.02%)	7 / 135 (5.19%)
occurrences (all)	13	10	8
Blood urea increased			

subjects affected / exposed	6 / 136 (4.41%)	6 / 133 (4.51%)	10 / 135 (7.41%)
occurrences (all)	8	7	10
Glycosylated haemoglobin increased			
subjects affected / exposed	12 / 136 (8.82%)	11 / 133 (8.27%)	11 / 135 (8.15%)
occurrences (all)	15	11	12
Intraocular pressure increased			
subjects affected / exposed	28 / 136 (20.59%)	16 / 133 (12.03%)	18 / 135 (13.33%)
occurrences (all)	77	32	51
Visual acuity tests abnormal			
subjects affected / exposed	19 / 136 (13.97%)	32 / 133 (24.06%)	22 / 135 (16.30%)
occurrences (all)	35	49	63
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 136 (16.91%)	24 / 133 (18.05%)	25 / 135 (18.52%)
occurrences (all)	32	41	37
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 136 (4.41%)	8 / 133 (6.02%)	3 / 135 (2.22%)
occurrences (all)	6	8	3
Eye disorders			
Cataract			
subjects affected / exposed	31 / 136 (22.79%)	17 / 133 (12.78%)	26 / 135 (19.26%)
occurrences (all)	43	29	37
Cataract cortical			
subjects affected / exposed	7 / 136 (5.15%)	1 / 133 (0.75%)	6 / 135 (4.44%)
occurrences (all)	12	3	7
Conjunctival haemorrhage			
subjects affected / exposed	43 / 136 (31.62%)	17 / 133 (12.78%)	39 / 135 (28.89%)
occurrences (all)	59	26	58
Cataract subcapsular			
subjects affected / exposed	11 / 136 (8.09%)	4 / 133 (3.01%)	5 / 135 (3.70%)
occurrences (all)	16	4	6
Conjunctival hyperaemia			
subjects affected / exposed	8 / 136 (5.88%)	9 / 133 (6.77%)	3 / 135 (2.22%)
occurrences (all)	10	15	5
Corneal erosion			

subjects affected / exposed	9 / 136 (6.62%)	7 / 133 (5.26%)	8 / 135 (5.93%)
occurrences (all)	11	16	10
Cystoid macular oedema			
subjects affected / exposed	10 / 136 (7.35%)	18 / 133 (13.53%)	20 / 135 (14.81%)
occurrences (all)	18	51	67
Diabetic retinal oedema			
subjects affected / exposed	33 / 136 (24.26%)	18 / 133 (13.53%)	23 / 135 (17.04%)
occurrences (all)	49	25	44
Dry eye			
subjects affected / exposed	5 / 136 (3.68%)	8 / 133 (6.02%)	5 / 135 (3.70%)
occurrences (all)	9	13	7
Eye pain			
subjects affected / exposed	15 / 136 (11.03%)	10 / 133 (7.52%)	10 / 135 (7.41%)
occurrences (all)	34	15	19
Macular fibrosis			
subjects affected / exposed	10 / 136 (7.35%)	11 / 133 (8.27%)	12 / 135 (8.89%)
occurrences (all)	13	14	17
Macular oedema			
subjects affected / exposed	21 / 136 (15.44%)	22 / 133 (16.54%)	20 / 135 (14.81%)
occurrences (all)	41	46	31
Ocular hyperaemia			
subjects affected / exposed	5 / 136 (3.68%)	4 / 133 (3.01%)	7 / 135 (5.19%)
occurrences (all)	12	5	9
Ocular hypertension			
subjects affected / exposed	10 / 136 (7.35%)	6 / 133 (4.51%)	4 / 135 (2.96%)
occurrences (all)	21	7	9
Posterior capsule opacification			
subjects affected / exposed	10 / 136 (7.35%)	10 / 133 (7.52%)	12 / 135 (8.89%)
occurrences (all)	15	18	15
Punctate keratitis			
subjects affected / exposed	7 / 136 (5.15%)	8 / 133 (6.02%)	11 / 135 (8.15%)
occurrences (all)	13	14	19
Retinal aneurysm			
subjects affected / exposed	14 / 136 (10.29%)	9 / 133 (6.77%)	12 / 135 (8.89%)
occurrences (all)	26	16	26
Retinal exudates			

subjects affected / exposed	20 / 136 (14.71%)	15 / 133 (11.28%)	22 / 135 (16.30%)
occurrences (all)	38	32	49
Retinal haemorrhage			
subjects affected / exposed	21 / 136 (15.44%)	21 / 133 (15.79%)	25 / 135 (18.52%)
occurrences (all)	35	63	64
Retinal vascular disorder			
subjects affected / exposed	9 / 136 (6.62%)	5 / 133 (3.76%)	8 / 135 (5.93%)
occurrences (all)	20	10	13
Vitreous detachment			
subjects affected / exposed	9 / 136 (6.62%)	5 / 133 (3.76%)	10 / 135 (7.41%)
occurrences (all)	12	7	11
Visual acuity reduced			
subjects affected / exposed	33 / 136 (24.26%)	30 / 133 (22.56%)	33 / 135 (24.44%)
occurrences (all)	64	57	81
Vitreous floaters			
subjects affected / exposed	13 / 136 (9.56%)	4 / 133 (3.01%)	5 / 135 (3.70%)
occurrences (all)	14	4	7
Vitreous haemorrhage			
subjects affected / exposed	7 / 136 (5.15%)	8 / 133 (6.02%)	11 / 135 (8.15%)
occurrences (all)	14	12	11
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 136 (5.15%)	7 / 133 (5.26%)	6 / 135 (4.44%)
occurrences (all)	10	10	6
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 136 (2.94%)	11 / 133 (8.27%)	3 / 135 (2.22%)
occurrences (all)	5	11	3
Musculoskeletal pain			
subjects affected / exposed	1 / 136 (0.74%)	1 / 133 (0.75%)	9 / 135 (6.67%)
occurrences (all)	1	1	9
Infections and infestations			
Bronchitis			
subjects affected / exposed	12 / 136 (8.82%)	9 / 133 (6.77%)	5 / 135 (3.70%)
occurrences (all)	16	10	5
Conjunctivitis			

subjects affected / exposed	14 / 136 (10.29%)	8 / 133 (6.02%)	13 / 135 (9.63%)
occurrences (all)	16	10	20
Influenza			
subjects affected / exposed	7 / 136 (5.15%)	13 / 133 (9.77%)	11 / 135 (8.15%)
occurrences (all)	10	16	11
Nasopharyngitis			
subjects affected / exposed	38 / 136 (27.94%)	34 / 133 (25.56%)	39 / 135 (28.89%)
occurrences (all)	67	62	69
Urinary tract infection			
subjects affected / exposed	6 / 136 (4.41%)	6 / 133 (4.51%)	11 / 135 (8.15%)
occurrences (all)	8	11	22
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	6 / 136 (4.41%)	9 / 133 (6.77%)	10 / 135 (7.41%)
occurrences (all)	6	10	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2011	- The guidelines for additional treatment of inadequate responders were revised. - Alternative statistical analysis plans were allowed for the data results according to the regulatory requirements of the governing Health Authority. - The number of initial monthly doses for subjects in the 2Q8 group was changed to 5 (total).
28 May 2013	- The treatment of the fellow eye (non-study eye) was clarified. - The secondary efficacy endpoints were revised. - The statistical methodology section was modified to be consistent with the revisions in the SAP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25012934

http://www.ncbi.nlm.nih.gov/pubmed/26198808

http://www.ncbi.nlm.nih.gov/pubmed/26056030