Clinical trial results:
An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of three different treatment regimens of 2 mg aflibercept administered by intravitreal injections to subjects with diabetic macular edema (DME)

Summary

EudraCT number	2014-004938-25
Trial protocol	GB SK HU DE AT ES CZ LT FR PT PL IT
Global end of trial date	24 September 2019

Results information

Result version number	v1 (current)
This version publication date	31 July 2020
First version publication date	31 July 2020

Trial information

Trial identification

Sponsor protocol code	BAY86-5321/17613

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02818998
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, 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	24 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of long-term treatment with 2 mg aflibercept via different intravitreal (IVT) treatment regimens to subjects with DME pre-treated with 2 mg aflibercept every 8 weeks after 5 initial monthly injections for approximately 1 year or more (according to the European Union [EU] label for the first year of treatment)

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the 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	16 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Poland: 82
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	Spain: 40
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Czech Republic: 38
Country: Number of subjects enrolled	Portugal: 26
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Hungary: 106
Country: Number of subjects enrolled	Slovakia: 73
Country: Number of subjects enrolled	Lithuania: 11
Country: Number of subjects enrolled	Switzerland: 5
Worldwide total number of subjects	463
EEA total number of subjects	443

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)	210
From 65 to 84 years	251
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple centers in 14 countries between 16-Nov-2016 (first participant first visit) and 24-Sep-2019 (last participant last visit).

Pre-assignment

Screening details:

A total of 500 participants were screened in this study. Of these, 37 participants did not enter the treatment period (31 were screening failures; 3 were lost to follow-up; 2 had an adverse event (AE) and 1 was not randomized due to an "other" reason). A total of 463 participants were randomized and received treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Aflibercept 2 mg fixed

Arm description:

Participants received fixed dosing of 2 mg aflibercept at injection intervals of 8 weeks

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

Dosage and administration details:

2 mg, fixed-dosing regimen every 8 weeks (2Q8fix)

Arm title	Aflibercept 2 mg extended

Arm description:

Participants received flexible dosing of 2 mg aflibercept at injection intervals of ≥ 8 weeks

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

Dosage and administration details:

2 mg, flexible-dosing regimen with gradually extended dosing interval (≥ 8 weeks, no upper limit) according to the current EU label (2Q8ext)

Arm title	Aflibercept 2 mg PRN

Arm description:

Participants received monthly monitoring with 2 mg aflibercept injection pro re nata (PRN, as needed)

Arm type	Experimental

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

Dosage and administration details:

2 mg, pro re nata dosing regimen (2PRN)

Number of subjects in period 1	Aflibercept 2 mg fixed	Aflibercept 2 mg extended	Aflibercept 2 mg PRN
Started	155	154	154
Completed Week 52 visit	144	146	140
Completed	137	138	136
Not completed	18	16	18
Adverse event, serious fatal	3	6	8
Consent withdrawn by subject	7	6	6
Physician decision	1	-	-
Adverse event, non-fatal	3	2	1
Lost to follow-up	4	1	2
Withdrawal by sponsor	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Aflibercept 2 mg fixed
Reporting group description:	
Participants received fixed dosing of 2 mg aflibercept at injection intervals of 8 weeks	
Reporting group title	Aflibercept 2 mg extended
Reporting group description:	
Participants received flexible dosing of 2 mg aflibercept at injection intervals of ≥ 8 weeks	
Reporting group title	Aflibercept 2 mg PRN
Reporting group description:	
Participants received monthly monitoring with 2 mg aflibercept injection pro re nata (PRN, as needed)	

Reporting group values	Aflibercept 2 mg fixed	Aflibercept 2 mg extended	Aflibercept 2 mg PRN
Number of subjects	155	154	154
Age categorical Units: Subjects			
Adults (18-64 years)	72	70	68
From 65-84 years	83	84	84
85 years and over	0	0	2
Age Continuous Units: Years			
arithmetic mean	64.3	64.8	65.4
standard deviation	± 8.7	± 10.1	± 9.3
Sex: Female, Male Units: Participants			
Female	55	59	64
Male	100	95	90
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	2	4
Not Hispanic or Latino	144	142	142
Unknown or Not Reported	10	10	8
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	0
White	141	144	147
More than one race	0	0	0
Unknown or Not Reported	11	9	7
Best Corrected Visual Acuity (BCVA)			
Best Corrected Visual Acuity (BCVA) was measured in the study eye by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score starting at 4 meters. The ETDRS chart includes 70 letters in total and the letter score ranges from 0 to 100. More letters read correctly results in a higher letter score, which represents better visual acuity.			
Units: Scores on a scale			
arithmetic mean	72.8	72.5	71.0

standard deviation	± 10.38	± 11.35	± 10.87
Central Retinal Thickness (CRT)			
Central Retinal Thickness (CRT) was measured in the study eye by spectral domain optical coherence tomography (SD-OCT).			
Units: Microns			
arithmetic mean	289.8	285.3	294.5
standard deviation	± 66.46	± 76.01	± 80.72

Reporting group values	Total		
Number of subjects	463		
Age categorical			
Units: Subjects			
Adults (18-64 years)	210		
From 65-84 years	251		
85 years and over	2		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	178		
Male	285		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	428		
Unknown or Not Reported	28		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	3		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	432		
More than one race	0		
Unknown or Not Reported	27		
Best Corrected Visual Acuity (BCVA)			
Best Corrected Visual Acuity (BCVA) was measured in the study eye by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score starting at 4 meters. The ETDRS chart includes 70 letters in total and the letter score ranges from 0 to 100. More letters read correctly results in a higher letter score, which represents better visual acuity.			
Units: Scores on a scale			
arithmetic mean			
standard deviation	-		
Central Retinal Thickness (CRT)			
Central Retinal Thickness (CRT) was measured in the study eye by spectral domain optical coherence tomography (SD-OCT).			
Units: Microns			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Aflibercept 2 mg fixed
Reporting group description:	
Participants received fixed dosing of 2 mg aflibercept at injection intervals of 8 weeks	
Reporting group title	Aflibercept 2 mg extended
Reporting group description:	
Participants received flexible dosing of 2 mg aflibercept at injection intervals of ≥ 8 weeks	
Reporting group title	Aflibercept 2 mg PRN
Reporting group description:	
Participants received monthly monitoring with 2 mg aflibercept injection pro re nata (PRN, as needed)	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Included all randomized participants who received any study drug and had a baseline BCVA assessment and at least one post-baseline BCVA assessment.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Included all participants who received any study drug under the protocol.	

Primary: Mean change from baseline in Best Corrected Visual Acuity (BCVA) at Week 52

End point title	Mean change from baseline in Best Corrected Visual Acuity (BCVA) at Week 52
End point description:	
Best Corrected Visual Acuity (BCVA) was measured in the study eye by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score starting at 4 meters. The ETDRS chart includes 70 letters in total and the letter score ranges from 0 to 100. More letters read correctly results in a higher letter score, which represents better visual acuity.	
End point type	Primary
End point timeframe:	
From baseline to Week 52	

End point values	Aflibercept 2 mg fixed	Aflibercept 2 mg extended	Aflibercept 2 mg PRN	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	152	153	
Units: Scores on a scale				
arithmetic mean (standard deviation)	0.4 (± 6.7)	0.5 (± 6.7)	1.7 (± 6.8)	

Statistical analyses

Statistical analysis title	Analysis of covariance for BCVA change
Statistical analysis description:	
Aflibercept 2 mg fixed was regarded as the reference arm	

Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg extended
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Least Squares mean difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.46
upper limit	1.47

Notes:

[1] - Non-inferiority margin: 4 letters

[2] - Non-inferiority was demonstrated if the p-value (adjusted for multiplicity using the Hochberg procedure) was < 0.025

Statistical analysis title	Analysis of covariance for BCVA change

Statistical analysis description:

Aflibercept 2 mg fixed was regarded as the reference arm

Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg PRN
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	Least Squares mean difference
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	2.42

Notes:

[3] - Non-inferiority margin: 4 letters

[4] - Non-inferiority was demonstrated if the p-value (adjusted for multiplicity using the Hochberg procedure) was < 0.025

Secondary: Mean change from baseline in Central Retinal Thickness (CRT) at Week 52

End point title	Mean change from baseline in Central Retinal Thickness (CRT) at Week 52

End point description:

Central Retinal Thickness (CRT) was measured in the study eye by spectral domain optical coherence tomography (SD-OCT).

End point type	Secondary

End point timeframe:

From baseline to week 52

End point values	Aflibercept 2 mg fixed	Aflibercept 2 mg extended	Aflibercept 2 mg PRN	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	152	153	
Units: Microns				
arithmetic mean (standard deviation)	-18.8 (± 45.5)	-2.1 (± 56.2)	2.2 (± 77.8)	

Statistical analyses

Statistical analysis title	Analysis of covariance for CRT change
Statistical analysis description: Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg extended
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0105
Method	ANCOVA
Parameter estimate	Least Square mean difference
Point estimate	14.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.39
upper limit	25.37

Statistical analysis title	Analysis of covariance for CRT change
Statistical analysis description: Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg PRN
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0023
Method	ANCOVA
Parameter estimate	Least Square mean difference
Point estimate	21.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.65
upper limit	34.8

Secondary: Number of participants with categorized changes from baseline in Best

Corrected Visual Acuity (BCVA) at Week 52

End point title	Number of participants with categorized changes from baseline in Best Corrected Visual Acuity (BCVA) at Week 52

End point description:

Best Corrected Visual Acuity (BCVA) was measured in the study eye by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score starting at 4 meters. The ETDRS chart includes 70 letters in total and the letter score ranges from 0 to 100. More letters read correctly results in a higher letter score, which represents better visual acuity

End point type	Secondary

End point timeframe:

From baseline to week 52

End point values	Aflibercept 2 mg fixed	Aflibercept 2 mg extended	Aflibercept 2 mg PRN	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	152	153	
Units: Participants				
≥ 15 letter gain	4	5	4	
≥ 10 letter gain	10	14	13	
≥ 30 letter loss	1	0	0	

Statistical analyses

Statistical analysis title	Categorized changes for ≥ 15 letter gain in BCVA

Statistical analysis description:

Aflibercept 2 mg fixed was regarded as the reference arm

Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg extended
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.14
upper limit	4.49

Statistical analysis title	Categorized changes for ≥ 10 letter gain in BCVA

Statistical analysis description:

Aflibercept 2 mg fixed was regarded as the reference arm

Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg extended

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	2.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	8.73

Statistical analysis title	Categorized changes for ≥ 30 letter loss in BCVA
Statistical analysis description:	
Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg extended
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.94
upper limit	0.63

Statistical analysis title	Categorized changes for ≥ 15 letter gain in BCVA
Statistical analysis description:	
Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg PRN
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.68
upper limit	3.41

Statistical analysis title	Categorized changes for ≥ 10 letter gain in BCVA
Statistical analysis description:	
Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg PRN
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	7.54

Statistical analysis title	Categorized changes for ≥ 30 letter loss in BCVA
Statistical analysis description:	
Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg PRN
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	-0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	0.65

Secondary: Mean change from baseline in Best Corrected Visual Acuity (BCVA) at Week 100

End point title	Mean change from baseline in Best Corrected Visual Acuity (BCVA) at Week 100

End point description:

Best Corrected Visual Acuity (BCVA) was measured in the study eye by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score starting at 4 meters. The ETDRS chart includes 70 letters in total and the letter score ranges from 0 to 100. More letters read correctly results in a higher letter score, which represents better visual acuity.

End point type	Secondary

End point timeframe:

From baseline to Week 100

End point values	Aflibercept 2 mg fixed	Aflibercept 2 mg extended	Aflibercept 2 mg PRN	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	152	153	
Units: Scores on a scale				
arithmetic mean (standard deviation)	0.1 (± 7.2)	-0.1 (± 9.1)	1.8 (± 9.0)	

Statistical analyses

Statistical analysis title	Analysis of covariance for BCVA change
Statistical analysis description: Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg extended
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least Squares mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.13
upper limit	1.52

Statistical analysis title	Analysis of covariance for BCVA change
Statistical analysis description: Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg PRN
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least Squares mean difference
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	3.19

Secondary: Mean change from baseline in Central Retinal Thickness (CRT) at Week

100	
End point title	Mean change from baseline in Central Retinal Thickness (CRT) at Week 100
End point description: Central Retinal Thickness (CRT) was measured in the study eye by spectral domain optical coherence tomography (SD-OCT).	
End point type	Secondary
End point timeframe: From baseline to Week 100	

End point values	Aflibercept 2 mg fixed	Aflibercept 2 mg extended	Aflibercept 2 mg PRN	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	152	153	
Units: Microns				
arithmetic mean (standard deviation)	-15.5 (± 64.3)	2.3 (± 81.8)	-13.9 (± 74.4)	

Statistical analyses

Statistical analysis title	Analysis of covariance for BCVA change
Statistical analysis description: Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg extended
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0416
Method	ANCOVA
Parameter estimate	Least Square mean difference
Point estimate	16.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	31.66

Statistical analysis title	Analysis of covariance for CRT change
Statistical analysis description: Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg PRN

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5524
Method	ANCOVA
Parameter estimate	Least Square mean difference
Point estimate	4.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.52
upper limit	17.77

Secondary: Number of participants with categorized changes from baseline in Best Corrected Visual Acuity (BCVA) at Week 100

End point title	Number of participants with categorized changes from baseline in Best Corrected Visual Acuity (BCVA) at Week 100

End point description:

Best Corrected Visual Acuity (BCVA) was measured in the study eye by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score starting at 4 meters. The ETDRS chart includes 70 letters in total and the letter score ranges from 0 to 100. More letters read correctly results in a higher letter score, which represents better visual acuity

End point type	Secondary

End point timeframe:

From baseline to Week 100

End point values	Aflibercept 2 mg fixed	Aflibercept 2 mg extended	Aflibercept 2 mg PRN	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	152	153	
Units: Participants				
≥ 15 letter gain	3	4	6	
≥ 10 letter gain	10	17	22	
≥ 30 letter loss	1	2	2	

Statistical analyses

Statistical analysis title	Categorized changes for ≥ 15 letter gain in BCVA

Statistical analysis description:

Aflibercept 2 mg fixed was regarded as the reference arm

Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg extended

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.72
upper limit	4.05

Statistical analysis title	Categorized changes for ≥ 10 letter gain in BCVA
Statistical analysis description:	
Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg extended
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	4.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.73
upper limit	10.98

Statistical analysis title	Categorized changes for ≥ 30 letter loss in BCVA
Statistical analysis description:	
Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg extended
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.56
upper limit	2.87

Statistical analysis title	Categorized changes for ≥ 15 letter gain in BCVA
Statistical analysis description:	
Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg PRN
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.89
upper limit	5.69

Statistical analysis title	Categorized changes for ≥ 10 letter gain in BCVA
Statistical analysis description:	
Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg PRN
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	7.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	14.28

Statistical analysis title	Categorized changes for ≥ 30 letter loss in BCVA
Statistical analysis description:	
Aflibercept 2 mg fixed was regarded as the reference arm	
Comparison groups	Aflibercept 2 mg fixed v Aflibercept 2 mg PRN
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	0.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	2.88

Secondary: Number of participants with treatment-emergent adverse event (TEAE)

End point title	Number of participants with treatment-emergent adverse event (TEAE)

End point description:

AEs that started after the first application of aflibercept under this protocol until 30 days after the last dose of study drug administration

End point type	Secondary

End point timeframe:

Up to Week 100

End point values	Aflibercept 2 mg fixed	Aflibercept 2 mg extended	Aflibercept 2 mg PRN	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	155	154	154	
Units: Participants	129	128	129	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first application of Aflibercept under this protocol and within 30 days after the last dose of study drug administration.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Aflibercept 2 mg fixed

Reporting group description:

Participants received fixed dosing of 2 mg aflibercept at injection intervals of 8 weeks

Reporting group title	Aflibercept 2 mg extended

Reporting group description:

Participants received flexible dosing of 2 mg aflibercept at injection intervals of >=8 week

Reporting group title	Aflibercept 2 mg PRN

Reporting group description:

Participants received monthly monitoring with 2 mg aflibercept injection pro re nata (PRN, as needed)

Serious adverse events	Aflibercept 2 mg fixed	Aflibercept 2 mg extended	Aflibercept 2 mg PRN
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 155 (22.58%)	38 / 154 (24.68%)	37 / 154 (24.03%)
number of deaths (all causes)	3	6	8
number of deaths resulting from adverse events	1	3	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign lung neoplasm			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer stage III			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bronchial carcinoma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Meningioma			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Prostate cancer stage IV			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Metastatic bronchial carcinoma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Benign spleen tumour			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Prostate cancer			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cancer			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vascular disorders			

Aortic stenosis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
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 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
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 ischaemia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (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
Arterial occlusive disease			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Angioplasty			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
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 pacemaker insertion			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Toe amputation			

subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary arterial stent insertion			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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 rehabilitation therapy			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rehabilitation therapy			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia repair			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart valve replacement			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract operation			
subjects affected / exposed	2 / 155 (1.29%)	1 / 154 (0.65%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraocular lens implant			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
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 artery bypass			

subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Fatigue			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Pneumothorax			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Product issues			
Device loosening			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Angiocardiogram			
subjects affected / exposed	0 / 155 (0.00%)	2 / 154 (1.30%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Facial bones fracture			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Head injury			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			

subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
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 disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 155 (0.65%)	2 / 154 (1.30%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			

subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
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 arrest			
subjects affected / exposed	0 / 155 (0.00%)	3 / 154 (1.95%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure			
subjects affected / exposed	1 / 155 (0.65%)	2 / 154 (1.30%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 155 (0.00%)	2 / 154 (1.30%)	0 / 154 (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
Cardiogenic shock			

subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
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 occlusion			
subjects affected / exposed	2 / 155 (1.29%)	0 / 154 (0.00%)	0 / 154 (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
Myocardial infarction			
subjects affected / exposed	5 / 155 (3.23%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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 coronary syndrome			
subjects affected / exposed	2 / 155 (1.29%)	0 / 154 (0.00%)	0 / 154 (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			
Epilepsy			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			

subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Transient ischaemic attack			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar stroke			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Thrombocytopenia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Neurosensory hypoacusis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Cataract			
subjects affected / exposed	0 / 155 (0.00%)	3 / 154 (1.95%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract nuclear			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
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 subcapsular			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior capsule opacification			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Choroidal neovascularisation			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Small intestinal haemorrhage			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
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 acute			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Diabetic neuropathic ulcer			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	1 / 155 (0.65%)	2 / 154 (1.30%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	1 / 155 (0.65%)	1 / 154 (0.65%)	3 / 154 (1.95%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic skin ulcer			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Urinary retention			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic nephropathy			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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 impairment			

subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
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 / 155 (0.65%)	1 / 154 (0.65%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
End stage renal disease			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Dupuytren's contracture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
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	2 / 155 (1.29%)	1 / 154 (0.65%)	0 / 154 (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
Cystitis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endocarditis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	2 / 155 (1.29%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 155 (0.65%)	2 / 154 (1.30%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 155 (0.65%)	1 / 154 (0.65%)	0 / 154 (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
Pyelonephritis acute			

subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Peritonsillitis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Arthritis bacterial			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary sepsis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
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 infection			

subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	3 / 155 (1.94%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Hypercholesterolaemia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Obesity			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Tetany			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			

subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiometabolic syndrome			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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

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

Non-serious adverse events	Aflibercept 2 mg fixed	Aflibercept 2 mg extended	Aflibercept 2 mg PRN
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 155 (62.58%)	85 / 154 (55.19%)	98 / 154 (63.64%)
Investigations			
Intraocular pressure increased			
subjects affected / exposed	11 / 155 (7.10%)	4 / 154 (2.60%)	11 / 154 (7.14%)
occurrences (all)	14	5	14
Eye disorders			
Cataract			
subjects affected / exposed	27 / 155 (17.42%)	29 / 154 (18.83%)	24 / 154 (15.58%)
occurrences (all)	37	41	35
Cataract cortical			
subjects affected / exposed	8 / 155 (5.16%)	7 / 154 (4.55%)	6 / 154 (3.90%)
occurrences (all)	11	10	10
Cataract nuclear			
subjects affected / exposed	9 / 155 (5.81%)	0 / 154 (0.00%)	7 / 154 (4.55%)
occurrences (all)	11	0	8
Cataract subcapsular			
subjects affected / exposed	7 / 155 (4.52%)	9 / 154 (5.84%)	8 / 154 (5.19%)
occurrences (all)	10	10	10
Diabetic retinal oedema			
subjects affected / exposed	12 / 155 (7.74%)	13 / 154 (8.44%)	14 / 154 (9.09%)
occurrences (all)	15	17	17
Diabetic retinopathy			

subjects affected / exposed	14 / 155 (9.03%)	14 / 154 (9.09%)	18 / 154 (11.69%)
occurrences (all)	18	18	23
Macular oedema			
subjects affected / exposed	8 / 155 (5.16%)	11 / 154 (7.14%)	17 / 154 (11.04%)
occurrences (all)	10	14	32
Maculopathy			
subjects affected / exposed	3 / 155 (1.94%)	1 / 154 (0.65%)	13 / 154 (8.44%)
occurrences (all)	4	2	20
Posterior capsule opacification			
subjects affected / exposed	5 / 155 (3.23%)	9 / 154 (5.84%)	10 / 154 (6.49%)
occurrences (all)	6	9	12
Retinal haemorrhage			
subjects affected / exposed	4 / 155 (2.58%)	3 / 154 (1.95%)	10 / 154 (6.49%)
occurrences (all)	7	3	21
Visual acuity reduced			
subjects affected / exposed	25 / 155 (16.13%)	22 / 154 (14.29%)	22 / 154 (14.29%)
occurrences (all)	42	30	30
Cystoid macular oedema			
subjects affected / exposed	14 / 155 (9.03%)	12 / 154 (7.79%)	10 / 154 (6.49%)
occurrences (all)	25	17	15
Macular fibrosis			
subjects affected / exposed	7 / 155 (4.52%)	6 / 154 (3.90%)	10 / 154 (6.49%)
occurrences (all)	7	7	11
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	4 / 155 (2.58%)	1 / 154 (0.65%)	8 / 154 (5.19%)
occurrences (all)	7	1	12
Influenza			
subjects affected / exposed	8 / 155 (5.16%)	3 / 154 (1.95%)	8 / 154 (5.19%)
occurrences (all)	8	3	8
Nasopharyngitis			
subjects affected / exposed	14 / 155 (9.03%)	14 / 154 (9.09%)	17 / 154 (11.04%)
occurrences (all)	18	18	24
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed occurrences (all)	24 / 155 (15.48%) 26	10 / 154 (6.49%) 10	15 / 154 (9.74%) 15

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported