Clinical trial results:
An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of 2mg aflibercept administered by intravitreal injections using two different treatment regimens to subjects with neovascular age-related macular degeneration (nAMD)

Summary

EudraCT number	2013-000120-33
Trial protocol	HU CZ SK PT LT AT GB ES DE IT
Global end of trial date	04 June 2020

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	BAY86-5321/16598

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02540954
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the efficacy of 2 mg aflibercept administered by 2 different intravitreal (IVT) treatment regimens to subjects with nAMD.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with 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	29 September 2015
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	Austria: 13
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Czechia: 44
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	United Kingdom: 58
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Italy: 48
Country: Number of subjects enrolled	Lithuania: 9
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Portugal: 42
Country: Number of subjects enrolled	Slovakia: 24
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Switzerland: 15
Worldwide total number of subjects	335
EEA total number of subjects	258

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)	32
From 65 to 84 years	267
85 years and over	36

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 76 centers in 14 countries or regions, between 29-SEP-2015 (first subject first visit) and 04-JUN-2020 (last subject last visit)

Pre-assignment

Screening details:

At baseline, 336 subjects were randomized to one of 2 treatment groups; 168 subjects were randomized to the Aflibercept extended-dosing group and 168 subjects were randomized to the Aflibercept 2Q8 ((2 mg aflibercept administered every 8 weeks)) group. One subject in Aflibercept extended-dosing group did not receive any study drug.

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 extended dosing

Arm description:

Aflibercept was administered 2 mg per injection intravitreal (IVT) in the study eye in Aflibercept extended dosing. Flexible dosing interval is ≥ 8 weeks (no upper limit) based on visual and anatomic outcomes as judged by the investigator. When/if visual and anatomical outcomes indicated that the disease had re-activated, the treatment interval reverted to the last treatment interval in which the disease was inactive (ie, no signs of exudation were observed).

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

Dosage and administration details:

Aflibercept was injected intravitreal (IVT) at a dose of 2 mg per injection. Flexible dosing intervals of ≥ 8 weeks (no upper limit) based on visual and anatomic outcomes as judged by the investigator. Aflibercept could be treated for up to 76 weeks.

Arm title	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)

Arm description:

Aflibercept was administered 2 mg per injection IVT in the study eye in Aflibercept 2Q8. Fixed dosing interval is 8 weeks (±3 days), modification of the treatment interval was not allowed.

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

Dosage and administration details:

Aflibercept was injected intravitreal (IVT) at a dose of 2 mg per injection. Fixed dosing intervals of 8 weeks (±3 days) with no modification of the treatment interval allowed. Aflibercept was treated up to 72 weeks.

Number of subjects in period 1	Aflibercept extended dosing	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)
Started	167	168
Post-baseline BCVA assessment	165	167
Completed	149	154
Not completed	18	14
Physician decision	2	1
Consent withdrawn by subject	6	5
Treatment failure	1	-
Adverse event, non-fatal	4	2
Death	-	3
Other reason	4	2
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Aflibercept extended dosing
Reporting group description:	
Aflibercept was administered 2 mg per injection intravitreal (IVT) in the study eye in Aflibercept extended dosing. Flexible dosing interval is ≥ 8 weeks (no upper limit) based on visual and anatomic outcomes as judged by the investigator. When/if visual and anatomical outcomes indicated that the disease had re-activated, the treatment interval reverted to the last treatment interval in which the disease was inactive (ie, no signs of exudation were observed).	
Reporting group title	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)
Reporting group description:	
Aflibercept was administered 2 mg per injection IVT in the study eye in Aflibercept 2Q8. Fixed dosing interval is 8 weeks (±3 days), modification of the treatment interval was not allowed.	

Reporting group values	Aflibercept extended dosing	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)	Total
Number of subjects	167	168	335
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	76.3	74.7	
standard deviation	± 8.3	± 7.0	-
Gender Categorical Units: Subjects			
Female	107	108	215
Male	60	60	120
Race Units: Subjects			
White	139	132	271
Black	0	0	0
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Not reported	28	36	64
Multiple	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	136	128	264
Unknown or Not Reported	31	40	71
Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual			
Visual function was assessed with the procedure from the ETDRS adapted for the Age Related Eye Disease Study using charts with 70 letters at a starting distance of 4 meters. Charts are organized in 14 lines of decreasing size with 5 letters each. Subjects reading up to 19 letters at 4 meters were tested at 1 meter to read the first 6 lines. The score equals the sum of letters read at 1 meter and 4 meters. If more than 19 letters are read at 4 meters the score equals the number of letters read plus 30. The			

score range is 0 to 100, and a higher score represents better visual function.			
Units: Letters read correctly			
arithmetic mean	69	70.1	
standard deviation	± 12.1	± 10.9	-
Central retinal thickness (CRT) in the study eye			
Retinal characteristic was evaluated using Optical coherence tomography (OCT). Actual analysis number for both arms is 164.			
Units: µm			
arithmetic mean	257.3	264.4	
standard deviation	± 67.8	± 59.7	-
Choroidal neovascularization (CNV) area in the study eye			
Choroidal neovascularization measured by optical coherence tomography (OCT). Actual analysis number for Aflibercept extended dosing is 165. Actual analysis number for Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks) is 152.			
Units: mm*2			
arithmetic mean	4.695	5.060	
standard deviation	± 4.043	± 4.105	-
Total score for National Eye Institute 25-Item Visual Function			
National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) total score ranges from 0 to 100, where 100 represents the best possible score and 0 represents the worst. Actual analysis number for Aflibercept extended dosing is 163.			
Units: Score on a scale			
arithmetic mean	72.889	75.757	
standard deviation	± 18.414	± 15.495	-

End points

End points reporting groups

Reporting group title	Aflibercept extended dosing

Reporting group description:

Aflibercept was administered 2 mg per injection intravitreal (IVT) in the study eye in Aflibercept extended dosing. Flexible dosing interval is ≥ 8 weeks (no upper limit) based on visual and anatomic outcomes as judged by the investigator. When/if visual and anatomical outcomes indicated that the disease had re-activated, the treatment interval reverted to the last treatment interval in which the disease was inactive (ie, no signs of exudation were observed).

Reporting group title	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)

Reporting group description:

Aflibercept was administered 2 mg per injection IVT in the study eye in Aflibercept 2Q8. Fixed dosing interval is 8 weeks (±3 days), modification of the treatment interval was not allowed.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All 335 subjects treated with aflibercept were included in the SAF (one randomized subject in the extended-dosing group did not receive study drug and was excluded from the SAF).

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All 335 subjects from the SAF were also included in the FAS except for one subject who did not have a baseline BCVA assessment and 2 subjects who had no post-baseline assessment of BCVA available. Thus, 332 subjects were included in the FAS.

Primary: Mean change in Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) letter score for the study eye

End point title	Mean change in Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) letter score for the study eye

End point description:

Visual function was assessed with the procedure from the ETDRS adapted for the Age Related Eye Disease Study using charts with 70 letters at a starting distance of 4 meters. Charts are organized in 14 lines of decreasing size with 5 letters each. Subjects reading up to 19 letters at 4 meters were tested at 1 meter to read the first 6 lines. The score equals the sum of letters read at 1 meter and 4 meters. If more than 19 letters are read at 4 meters the score equals the number of letters read plus 30. The score range is 0 to 100, and a higher score represents better visual function.

End point type	Primary

End point timeframe:

From baseline to Week 52

End point values	Aflibercept extended dosing	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	167		
Units: Letters read correctly				
arithmetic mean (standard deviation)				
Mean change in ETDRS BCVA from baseline to week 52	-0.3 (± 7.5)	-0.5 (± 8.4)		

Statistical analyses

Statistical analysis title	Analysis of covariance for EDTRS BCVA change

Statistical analysis description:

Aflibercept 2QB was regarded as the reference arm

Comparison groups	Aflibercept extended dosing v Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)
Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	1.96

Notes:

[1] - Non-inferiority margin: 5 letters

[2] - Non-inferiority was demonstrated if the p-value was < 0.05

Secondary: Percentage of subjects maintaining vision in the study eye

End point title	Percentage of subjects maintaining vision in the study eye

End point description:

A subject was classified as maintaining vision if the subject had lost fewer than 15 letters in the ETDRS letter score compared to baseline.

End point type	Secondary

End point timeframe:

At week 52

End point values	Aflibercept extended dosing	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	167		
Units: Percentage of subjects				
number (not applicable)	95.2	94.0		

Statistical analyses

Statistical analysis title	Treatment difference % in maintaining vision

Statistical analysis description:

Calculation of two-sided 95% confidence intervals using normal approximation of the difference between the proportions (Aflibercept extended-dosing group minus Aflibercept 2Q8 group) of subjects maintaining vision.

Comparison groups	Aflibercept extended dosing v Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)
Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Treatment difference in %
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	6

Notes:

[3] - Non inferiority margin is 7%.

Secondary: Percentage of subjects who gained from baseline 5 or more letters in the study eye

End point title	Percentage of subjects who gained from baseline 5 or more letters in the study eye

End point description:

End point type	Secondary

End point timeframe:

At week 52

End point values	Aflibercept extended dosing	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	167		
Units: Percentage of subjects				
number (not applicable)	24.2	21.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Central retinal thickness (CRT) in the study eye

End point title	Mean change from baseline in Central retinal thickness (CRT) in

	the study eye

End point description:

Retinal characteristic was evaluated using Optical coherence tomography (OCT).

End point type	Secondary

End point timeframe:

From baseline to week 52

End point values	Aflibercept extended dosing	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	167		
Units: µm				
arithmetic mean (standard deviation)				
Mean change in CRT from baseline to week 52	-24.4 (± 55.2)	-33.4 (± 47.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Choroidal neovascularization (CNV) area in the study eye

End point title	Mean change from baseline in Choroidal neovascularization (CNV) area in the study eye

End point description:

Choroidal neovascularization measured by optical coherence tomography (OCT).

End point type	Secondary

End point timeframe:

From baseline to week 52

End point values	Aflibercept extended dosing	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	120		
Units: mm*2				
arithmetic mean (standard deviation)				
Mean change in CNV from baseline to week 52	0.274 (± 2.723)	0.204 (± 2.813)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who lost from baseline 30 or more letters in the study eye

End point title	Percentage of subjects who lost from baseline 30 or more letters in the study eye

End point description:

End point type	Secondary

End point timeframe:

At week 52

End point values	Aflibercept extended dosing	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	167		
Units: Percentage of Subjects				
number (not applicable)	0	0.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in total score for National Eye Institute 25-Item Visual Function (NEI VFQ-25) Questionnaire

End point title	Mean change from baseline in total score for National Eye Institute 25-Item Visual Function (NEI VFQ-25) Questionnaire

End point description:

National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) total score ranges from 0 to 100, where 100 represents the best possible score and 0 represents the worst.

End point type	Secondary

End point timeframe:

From baseline to week 52

End point values	Aflibercept extended dosing	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	157		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Mean change in NEI VFQ-25 from baseline to week 52	0.186 (± 9.601)	-1.694 (± 10.328)		

Statistical analyses

Statistical analysis title	Treatment difference in NEI VFQ-25 score
Comparison groups	Aflibercept extended dosing v Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment difference in score
Point estimate	-1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.152
upper limit	0.392

Secondary: Number of subjects with Treatment-emergent adverse events(TEAE)

End point title	Number of subjects with Treatment-emergent adverse events(TEAE)

End point description:

End point type	Secondary

End point timeframe:

Started after the first application of aflibercept in the study and less than or equal to 30 days after the last dose of study drug over approximate 1.5 years

End point values	Aflibercept extended dosing	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	168		
Units: Subjects				
Any TEAE	130	124		

Any serious TEAE	26	23		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From after the first application of aflibercept in the study to 30 days after the last dose of study drug over approximate 1.5 years

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)

Reporting group description:

Aflibercept was administered 2 mg per injection IVT in the study eye in Aflibercept 2Q8. Fixed dosing interval is 8 weeks (±3 days), modification of the treatment interval was not allowed.

Reporting group title	Aflibercept extended dosing

Reporting group description:

Aflibercept was administered 2 mg per injection intravitreal (IVT) in the study eye in Aflibercept extended dosing. Flexible dosing interval is ≥ 8 weeks (no upper limit) based on visual and anatomic outcomes as judged by the investigator. When/if visual and anatomical outcomes indicated that the disease had re-activated, the treatment interval reverted to the last treatment interval in which the disease was inactive (ie, no signs of exudation were observed).

Serious adverse events	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)	Aflibercept extended dosing	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 168 (13.69%)	26 / 167 (15.57%)	
number of deaths (all causes)	3	0	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast neoplasm			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			

subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Oesophageal prosthesis insertion			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 168 (0.00%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 168 (0.60%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract operation complication			

subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial reocclusion			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 168 (0.60%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 168 (0.00%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sciatica			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 168 (1.19%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	0 / 168 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedematous pancreatitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular malformation haemorrhagic			

subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 168 (1.19%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal stenosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	1 / 168 (0.60%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 168 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 168 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 168 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Aflibercept 2Q8 (2 mg aflibercept administered every 8 weeks)	Aflibercept extended dosing	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 168 (41.67%)	60 / 167 (35.93%)	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	11 / 168 (6.55%)	7 / 167 (4.19%)	
occurrences (all)	19	12	
Eye disorders			
Cataract			
subjects affected / exposed	19 / 168 (11.31%)	17 / 167 (10.18%)	
occurrences (all)	27	22	
Visual acuity reduced			
subjects affected / exposed	4 / 168 (2.38%)	14 / 167 (8.38%)	
occurrences (all)	6	18	
Choroidal neovascularisation			
subjects affected / exposed	9 / 168 (5.36%)	9 / 167 (5.39%)	
occurrences (all)	9	10	
Subretinal fluid			
subjects affected / exposed	14 / 168 (8.33%)	14 / 167 (8.38%)	
occurrences (all)	16	17	
Neovascular age-related macular degeneration			
subjects affected / exposed	10 / 168 (5.95%)	8 / 167 (4.79%)	
occurrences (all)	12	9	
Infections and infestations			

Influenza			
subjects affected / exposed	9 / 168 (5.36%)	9 / 167 (5.39%)	
occurrences (all)	9	9	
Nasopharyngitis			
subjects affected / exposed	12 / 168 (7.14%)	4 / 167 (2.40%)	
occurrences (all)	15	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2015	Amendment 2: 1-Update of approval status. 2-Clarification of duration of the periods. 3-Time windows and schedule of visits. 4-Selection of study eye. 5-Clarifications of inclusion criteria. 6-Time periods for inclusion criteria 1 and 2. 7-Study manual. 8-Inclusion criterion 8. 9-Clarifications in second set of exclusion criteria. 10-Re-screening criteria. 11-Subject identification number. 12-Identity of study drug. 13-EU SmPC and other updates for safety reasons to dosage and administration. 14-Treatment posology. 15-Drug storage. 16-Final visit or early termination visit. 17-Specification of pregnancy testing. 18-Timing of pregnancy testing. 19-Order of footnotes and minor clarifications in schedule of evaluations. 20-Removal of sample study drug injection protocol from appendix. 21-Re-check of eligibility criteria. 22-Post-injection ocular assessments. 23-Conduct of visits. 24-OCT. 25-FA and FP. 26-ECG. 27-Actions taken with study treatment. 28-Expected adverse events. 29-Pregnancies. 30-Time point of blood withdrawal. 31-NEI VFQ-25 questionnaire. 32-Data processing. 33-Subject information and consent process. 34-Fellow eye treatment. 35-Efficacy analyses – sensitivity analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported