



Clinical trial results:

A randomized, double-masked, sham-controlled phase 3b/4 study of the efficacy, safety, and tolerability of intravitreal aflibercept monotherapy compared to aflibercept with adjunctive photodynamic therapy as indicated in subjects with polypoidal choroidal vasculopathy (PLANET)

Summary

EudraCT number	2013-004464-54
Trial protocol	HU DE
Global end of trial date	07 July 2017

Results information

Result version number	v1
This version publication date	18 July 2018
First version publication date	18 July 2018

Trial information

Trial identification

Sponsor protocol code	BAY86-5321/16995
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02120950
WHO universal trial number (UTN)	-
Other trial identifiers	Informal study name: PLANET

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com, 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	07 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 August 2016
Global end of trial reached?	Yes
Global end of trial date	07 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of the study was to collect data reflecting the efficacy and safety of aflibercept with and without photodynamic therapy (PDT) rescue treatment in subjects diagnosed with the polypoidal choroidal vasculopathy (PCV) subtype of wet age-related macular degeneration (AMD) and to explore whether intravitreally administered aflibercept monotherapy is non-inferior to that of aflibercept plus PDT (as indicated) based upon best-corrected visual acuity (BCVA) in subjects diagnosed with the PCV subtype of AMD.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 2014
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	Japan: 159
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Korea, Republic of: 72
Country: Number of subjects enrolled	Taiwan: 37
Country: Number of subjects enrolled	Hong Kong: 14
Country: Number of subjects enrolled	Singapore: 13
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 13
Worldwide total number of subjects	333
EEA total number of subjects	14

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)	77
From 65 to 84 years	245
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 62 study centers in Germany, Japan, Australia, Hungary, Republic of Korea, Taiwan, Hong Kong, and Singapore between 29 May 2014 (first subject first visit) and 12 August 2016 (last subject last visit).

Pre-assignment

Screening details:

Overall, 428 subjects were screened, of them 95 were failed in screening, remaining 333 subjects were allocated to treatment, of them 15 subjects were treated as run-in treatment, until the subjects were randomized and received treatment, remaining 318 were randomized and treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Aflibercept + Sham Photodynamic Therapy (PDT)

Arm description:

Subjects received 2 milligram (mg) [0.05 millilitre (mL)] aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 (run-in treatment); subjects were randomized on Week 12 and assessed for the rescue treatment (until the visual and anatomical outcomes allowed extension of the treatment interval) and then subjects received either bi-monthly injections of aflibercept intravitreally or bi-monthly injections of aflibercept intravitreally with sham PDT (2 milligram per millilitre [mg/mL] of 5 percent [%] dextrose solution or physiological saline solution), from Week 16 to Week 52. After week 52, treat-and-extend visit were scheduled and evaluation of rescue were continued with an optional extension treatment phase, where subjects received intravitreally injections of aflibercept monthly and sham PDT intravenously up to Week 96.

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:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally from Week 0 to Week 96.

Investigational medicinal product name	Sham PDT
Investigational medicinal product code	
Other name	Verteporfin, Visudyne
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received sham PDT (2 mg/mL of 5% dextrose solution or physiological saline solution), from Week 16 to Week 96.

Arm title	Aflibercept + Active PDT
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Arm description:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 (run-in treatment); subjects were randomized on Week 12 and assessed for the rescue treatment (until the visual and anatomical outcomes allowed extension of the treatment interval) and then subjects received either bi-monthly injections of aflibercept intravitreally or bi-monthly injections of

aflibercept intravitreally with sham PDT (2 mg/mL of 5% dextrose solution or physiological saline solution), from Week 16 to Week 52. After week 52, treat-and-extend visit were scheduled and evaluation of rescue were continued with an optional extension treatment phase, where subjects received intravitreally injections of aflibercept monthly and sham PDT intravenously up to Week 96.

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

Dosage and administration details:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally from Week 0 to Week 96.

Investigational medicinal product name	Active PDT
Investigational medicinal product code	
Other name	Verteporfin, Visudyne
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received active PDT (2 mg/mL of 5% dextrose solution or physiological saline solution), from Week 16 to Week 96.

Arm title	Aflibercept (Non-randomized)
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Arm description:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 as run-in treatment, until the subjects were randomized and received rescue treatments.

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:

Subjects received 3 injections of 2 mg (0.05 mL injected intravitreally) aflibercept in monthly intervals (Weeks 0, 4, and 8).

Number of subjects in period 1	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT	Aflibercept (Non-randomized)
Started	157	161	15
Completed	137	147	0
Not completed	20	14	15
Consent withdrawn by subject	6	3	2
Adverse Event	5	4	3
Death	3	-	1
Other	5	4	1
Lost to follow-up	-	2	1
Protocol deviation	1	1	7

Baseline characteristics

Reporting groups

Reporting group title	Aflibercept + Sham Photodynamic Therapy (PDT)
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Reporting group description:

Subjects received 2 milligram (mg) [0.05 millilitre (mL)] aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 (run-in treatment); subjects were randomized on Week 12 and assessed for the rescue treatment (until the visual and anatomical outcomes allowed extension of the treatment interval) and then subjects received either bi-monthly injections of aflibercept intravitreally or bi-monthly injections of aflibercept intravitreally with sham PDT (2 milligram per millilitre [mg/mL] of 5 percent [%] dextrose solution or physiological saline solution), from Week 16 to Week 52. After week 52, treat-and-extend visit were scheduled and evaluation of rescue were continued with an optional extension treatment phase, where subjects received intravitreally injections of aflibercept monthly and sham PDT intravenously up to Week 96.

Reporting group title	Aflibercept + Active PDT
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Reporting group description:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 (run-in treatment); subjects were randomized on Week 12 and assessed for the rescue treatment (until the visual and anatomical outcomes allowed extension of the treatment interval) and then subjects received either bi-monthly injections of aflibercept intravitreally or bi-monthly injections of aflibercept intravitreally with sham PDT (2 mg/mL of 5% dextrose solution or physiological saline solution), from Week 16 to Week 52. After week 52, treat-and-extend visit were scheduled and evaluation of rescue were continued with an optional extension treatment phase, where subjects received intravitreally injections of aflibercept monthly and sham PDT intravenously up to Week 96.

Reporting group title	Aflibercept (Non-randomized)
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Reporting group description:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 as run-in treatment, until the subjects were randomized and received rescue treatments.

Reporting group values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT	Aflibercept (Non-randomized)
Number of subjects	157	161	15
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	70.8	70.4	71.8
standard deviation	± 8.4	± 8	± 10.2
Gender categorical Units: Subjects			
Female	47	49	8
Male	110	112	7
Baseline BCVA score			
Visual function of the study eye and fellow eye was assessed at each study visit according to the standard procedure developed for the ETDRS adapted for AREDS, using 70 letter charts at a starting distance of 4 meters. Participants were challenged with reading letters on lines of an eye chart (5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart. Participants read down the chart until they reached a row where a minimum of three letters on a line could be read, and were scored by how many letters could be correctly identified.			
Units: Letters			
arithmetic mean	57.7	59.0	61.8
standard deviation	± 11.3	± 11.5	± 15.2
Central Subfield Thickness			

Units: Micrometer			
arithmetic mean	347.8	346.1	325.8
standard deviation	± 118.9	± 117.5	± 117.9

Reporting group values	Total		
Number of subjects	333		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	104		
Male	229		
Baseline BCVA score			
Visual function of the study eye and fellow eye was assessed at each study visit according to the standard procedure developed for the ETDRS adapted for AREDS, using 70 letter charts at a starting distance of 4 meters. Participants were challenged with reading letters on lines of an eye chart (5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart. Participants read down the chart until they reached a row where a minimum of three letters on a line could be read, and were scored by how many letters could be correctly identified.			
Units: Letters			
arithmetic mean			
standard deviation	-		
Central Subfield Thickness			
Units: Micrometer			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Aflibercept + Sham Photodynamic Therapy (PDT)
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Reporting group description:

Subjects received 2 milligram (mg) [0.05 millilitre (mL)] aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 (run-in treatment); subjects were randomized on Week 12 and assessed for the rescue treatment (until the visual and anatomical outcomes allowed extension of the treatment interval) and then subjects received either bi-monthly injections of aflibercept intravitreally or bi-monthly injections of aflibercept intravitreally with sham PDT (2 milligram per millilitre [mg/mL] of 5 percent [%] dextrose solution or physiological saline solution), from Week 16 to Week 52. After week 52, treat-and-extend visit were scheduled and evaluation of rescue were continued with an optional extension treatment phase, where subjects received intravitreally injections of aflibercept monthly and sham PDT intravenously up to Week 96.

Reporting group title	Aflibercept + Active PDT
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Reporting group description:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 (run-in treatment); subjects were randomized on Week 12 and assessed for the rescue treatment (until the visual and anatomical outcomes allowed extension of the treatment interval) and then subjects received either bi-monthly injections of aflibercept intravitreally or bi-monthly injections of aflibercept intravitreally with sham PDT (2 mg/mL of 5% dextrose solution or physiological saline solution), from Week 16 to Week 52. After week 52, treat-and-extend visit were scheduled and evaluation of rescue were continued with an optional extension treatment phase, where subjects received intravitreally injections of aflibercept monthly and sham PDT intravenously up to Week 96.

Reporting group title	Aflibercept (Non-randomized)
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Reporting group description:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 as run-in treatment, until the subjects were randomized and received rescue treatments.

Subject analysis set title	Safety Analysis Set (SAF)
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Subject analysis set type	Safety analysis
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Subject analysis set description:

SAF (N=333) included all subjects who received any study drug under this protocol.

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

FAS (N=318) included all randomized subjects.

Primary: Mean change in Best Corrected Visual Acuity (BCVA) as measured by Early Treatment of Diabetic Retinopathy Study (ETDRS) letter scores from baseline to Week 52 - Last observation carried forward (LOCF)

End point title	Mean change in Best Corrected Visual Acuity (BCVA) as measured by Early Treatment of Diabetic Retinopathy Study (ETDRS) letter scores from baseline to Week 52 - Last observation carried forward (LOCF) ^[1]
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End point description:

Visual function of the study eye and fellow eye was assessed at each study visit according to the standard procedure developed for the ETDRS adapted for Age Related Eye Disease Study (AREDS), using 70 letter charts at a starting distance of 4 meters. Participants were challenged with reading letters on lines of an eye chart (5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart. Participants read down the chart until they reached a row where a minimum of three letters on a line could be read, and were scored by how many letters could be correctly identified.

End point type	Primary
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End point timeframe:

From Baseline to Week 52

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157 ^[2]	161 ^[3]		
Units: Letters correctly read				
arithmetic mean (standard deviation)	10.7 (\pm 11.3)	10.8 (\pm 10.7)		

Notes:

[2] - FAS

[3] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.548
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	1.6

Secondary: Percentage of Subjects Who Avoided at Least 15 Letters Loss in Early Treatment of Diabetic Retinopathy Study (ETDRS) From Baseline to Week 52

End point title	Percentage of Subjects Who Avoided at Least 15 Letters Loss in Early Treatment of Diabetic Retinopathy Study (ETDRS) From Baseline to Week 52 ^[4]
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End point description:

Visual function of the study eye and fellow eye was assessed at each study visit according to the standard procedure developed for the ETDRS adapted for Age Related Eye Disease Study (AREDS), using 70 letter charts at a starting distance of 4 meters. Participants were challenged with reading letters on lines of an eye chart (5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart. Participants read down the chart until they reached a row where a minimum of three letters on a line could be read, and were scored by how many letters could be correctly identified.

End point type	Secondary
End point timeframe:	
Baseline up to week 52	

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	161		
Units: percentage of subjects				
number (not applicable)	97.5	96.9		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Aflibercept + Active PDT v Aflibercept + Sham Photodynamic Therapy (PDT)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7402
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	4.3

Other pre-specified: Percentage of subjects who never need rescue therapy in the first year

End point title	Percentage of subjects who never need rescue therapy in the first year ^[5]
End point description:	
End point type	Other pre-specified
End point timeframe:	
Baseline to Week 52	

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	161		
Units: Percentage of subjects				
number (not applicable)	87.9	85.7		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of PDT treatments in the study eye before Week 52

End point title	Number of PDT treatments in the study eye before Week 52 ^[6]
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End point description:

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 52

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	161		
Units: PDT administrations				
arithmetic mean (standard deviation)	0.2 (± 0.7)	0.2 (± 0.4)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0682
Method	ANCOVA
Parameter estimate	LS mean difference

Confidence interval	
level	95 %

Other pre-specified: Number of aflibercept treatments in the study eye (after randomization) before Week 52

End point title	Number of aflibercept treatments in the study eye (after randomization) before Week 52 ^[7]
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End point description:

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 52

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	160 ^[8]		
Units: Aflibercept injections				
arithmetic mean (standard deviation)	5.2 (± 1.1)	5.1 (± 0.8)		

Notes:

[8] - FAS with evaluable subjects for this outcome measure

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.164
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.164
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.3

Other pre-specified: Time to first administration of PDT in the study eye before Week 52

End point title	Time to first administration of PDT in the study eye before Week 52 ^[9]
End point description:	
End point type	Other pre-specified
End point timeframe:	
Baseline to Week 52	

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	161		
Units: Days				
arithmetic mean (full range (min-max))	131.2 (80 to 278)	128.2 (80 to 315)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change of visual acuity (letters) from baseline over time (week) in the study eye

End point title	Change of visual acuity (letters) from baseline over time (week) in the study eye ^[10]
End point description:	
End point type	Other pre-specified
End point timeframe:	
Baseline to Week 52	

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	161		
Units: Letters				
arithmetic mean (standard deviation)	10.7 (± 11.3)	10.8 (± 10.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who gained ≥ 5 , 10, or 15 letters at Week 52

End point title	Percentage of subjects who gained ≥ 5 , 10, or 15 letters at Week 52 ^[11]
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End point description:

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 52

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	161		
Units: Percentage of subjects				
number (not applicable)				
Gained ≥ 5	73.9	78.9		
Gained ≥ 10	55.4	57.1		
Gained ≥ 15	33.1	36.6		

Statistical analyses

Statistical analysis title	Category of Gained ≥ 5
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Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT
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Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2348
Method	Cochran-Mantel-Haenszel
Parameter estimate	treatment difference in %
Point estimate	-5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.9
upper limit	3.7

Statistical analysis title	Category of Gained ≥ 10
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Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6877
Method	Cochran-Mantel-Haenszel
Parameter estimate	treatment difference in %
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.1
upper limit	8.6

Statistical analysis title	Category of Gained ≥ 15
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Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT
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Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4556
Method	Cochran-Mantel-Haenszel
Parameter estimate	treatment difference in %
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.5
upper limit	6.5

Other pre-specified: Percentage of subjects who lost ≥5, 10, or 15 letters at Week 52

End point title	Percentage of subjects who lost ≥5, 10, or 15 letters at Week 52 ^[12]
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End point description:

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 52

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	161		
Units: Percentage of subjects				
number (not applicable)				
Lost ≥ 5	7.0	5.6		
Lost ≥ 10	3.8	3.1		
Lost ≥ 15	2.5	3.1		

Statistical analyses

Statistical analysis title	Category of Lost ≥ 5
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Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5372
Method	Cochran-Mantel-Haenszel
Parameter estimate	treatment difference in %
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	7.2

Statistical analysis title	Category of Lost ≥ 10
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Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7569
Method	Cochran-Mantel-Haenszel
Parameter estimate	treatment difference in %
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	4.7

Statistical analysis title	Category of Lost ≥ 15
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Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

Comparison groups	Aflibercept + Active PDT v Aflibercept + Sham Photodynamic Therapy (PDT)
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Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7402
Method	Cochran-Mantel-Haenszel
Parameter estimate	treatment difference in %
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	3.1

Other pre-specified: Percentage of subjects with complete polyp regression at Week 52

End point title	Percentage of subjects with complete polyp regression at Week 52 ^[13]
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End point description:

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 52

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126 ^[14]	134 ^[15]		
Units: Percentage of subjects				
number (not applicable)	38.9	44.8		

Notes:

[14] - FAS with evaluable subjects for this outcome measure.

[15] - FAS with evaluable subjects for this outcome measure.

Statistical analyses

Statistical analysis title	Statistical analysis title 1
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Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT
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Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3244
Method	Cochran-Mantel-Haenszel
Parameter estimate	treatment difference in %
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	5.9

Other pre-specified: Change of leakage area in Fluorescein angiography (FA) in the study eye at Week 52

End point title	Change of leakage area in Fluorescein angiography (FA) in the study eye at Week 52 ^[16]
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End point description:

Leakage is the release of fluorescein dye from diseased retinal vessels. Leakage area is defined as the area showing presence of fluorescein dye in the late stages of fluorescein angiography.

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 52

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140 ^[17]	149 ^[18]		
Units: Square millimeter				
arithmetic mean (standard deviation)	-1.3 (± 3.6)	-1.2 (± 3.7)		

Notes:

[17] - FAS with evaluable subjects for this outcome measure.

[18] - FAS with evaluable subjects for this outcome measure.

Statistical analyses

Statistical analysis title	Statistical analysis title 1
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Statistical analysis description:

The analysis population included only subjects with leakage in FA at baseline and Week 52. Baseline values were not carried forward.

Point estimate, 95% CI and p-value are based on difference (AFL-sham – AFL-PDT) of LS mean changes using an ANCOVA model with treatment group and ethnicity and qualification for rescue therapy at Week 12 as fixed effects, baseline value as covariate.

Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept
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	+ Active PDT
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7109
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.6

Other pre-specified: Change of Central subfield thickness (CST) on Optical coherence tomography (OCT) from baseline to Week 52

End point title	Change of Central subfield thickness (CST) on Optical coherence tomography (OCT) from baseline to Week 52 ^[19]
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End point description:

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 52

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136 ^[20]	150 ^[21]		
Units: millimeter(s)				
arithmetic mean (standard deviation)	-137.7 (± 116.0)	-143.5 (± 110.5)		

Notes:

[20] - FAS with evaluable subjects for this outcome measure

[21] - FAS with evaluable subjects for this outcome measure

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

The analysis population included only subjects with values for CST at baseline and Week 52. Baseline values were not carried forward.

Point estimate, 95% CI and p-value are based on difference (AFL-sham – AFL-PDT) of LS mean changes using an ANCOVA model with treatment group and ethnicity and qualification for rescue therapy at Week 12 as fixed effects, baseline value as covariate.

Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8355
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	11.3

Other pre-specified: Change in National Eye Institute 25-item visual function questionnaire (NEI VFQ-25) total score from baseline to Week 52

End point title	Change in National Eye Institute 25-item visual function questionnaire (NEI VFQ-25) total score from baseline to Week 52 ^[22]
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End point description:

The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 52

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143 ^[23]	153 ^[24]		
Units: Scores on a scale				
arithmetic mean (standard deviation)	4.7 (± 10.3)	7.3 (± 12.5)		

Notes:

[23] - FAS with evaluable subjects for this outcome measure.

[24] - FAS with evaluable subjects for this outcome measure.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT

Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5069
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	1.4

Other pre-specified: Percentage of subjects for whom rescue therapy is indicated over the course till Week 52

End point title	Percentage of subjects for whom rescue therapy is indicated over the course till Week 52 ^[25]
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End point description:

Evaluations for qualification for rescue were conducted at each visit from Week 12 to Week 52. Intensified aflibercept treatment plus active or sham PDT treatments were given at any of these visits if treatment criteria were met. Qualification for rescue was based upon insufficient gain of BCVA, leakage, and presence of active polyps.

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 52

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

End point values	Aflibercept + Sham Photodynamic Therapy (PDT)	Aflibercept + Active PDT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	161		
Units: Percentage of subjects				
number (not applicable)	12.1	14.3		

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

Comparison groups	Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8423
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference %
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	5.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to 30 days after the last treatment. Approximately 100 weeks.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Aflibercept + Sham PDT
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Reporting group description:

Subjects received 2 milligram (mg) Intravitreal aflibercept injection (IAI) (Eylea, VEGF Trap-Eye, BAY86-5321) every month for the first 3 months (run-in period). At Week 12, subjects were assessed for the rescue treatment and randomized to receive Aflibercept injection plus sham photodynamic therapy (only in subjects qualifying for rescue therapy) until Week 52. Between Week 52 and Week 96, the treatment interval could have been extended (typically in increments of 1 or 2 weeks) at the discretion of the investigator when the visual and anatomic outcomes allowed.

Reporting group title	Aflibercept + Active PDT
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Reporting group description:

Subjects received 2 mg Intravitreal aflibercept injection (IAI) (Eylea, VEGF Trap-Eye, BAY86-5321) every month for the first 3 months (run-in period). At Week 12, subjects were assessed for the rescue treatment and randomized to receive Aflibercept injection plus active photodynamic therapy (only in subjects qualifying for rescue therapy) until Week 52. Between Week 52 and Week 96, the treatment interval could have been extended (typically in increments of 1 or 2 weeks) at the discretion of the investigator when the visual and anatomic outcomes allowed.

Reporting group title	Aflibercept (Non-randomized)
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Reporting group description:

Subjects received 2 mg Intravitreal aflibercept injection (IAI) (Eylea, VEGF Trap-Eye, BAY86-5321) every month for the first 3 months (run-in period), but discontinued study participation before randomization.

Serious adverse events	Aflibercept + Sham PDT	Aflibercept + Active PDT	Aflibercept (Non-randomized)
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 157 (17.20%)	25 / 161 (15.53%)	4 / 15 (26.67%)
number of deaths (all causes)	3	0	1
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acoustic neuroma			
subjects affected / exposed	0 / 157 (0.00%)	0 / 161 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma gastric			

subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 157 (0.64%)	1 / 161 (0.62%)	0 / 15 (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
Gastric cancer			
subjects affected / exposed	1 / 157 (0.64%)	1 / 161 (0.62%)	0 / 15 (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
Metastases to lung			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Neoplasm			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Thyroid neoplasm			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric adenoma			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (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	1 / 157 (0.64%)	1 / 161 (0.62%)	0 / 15 (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
Vascular disorders			
Varicose vein			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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			
Transcatheter arterial chemoembolisation			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 157 (0.00%)	0 / 161 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (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
Cystocele			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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 pulmonary oedema			

subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 13	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Fall			
subjects affected / exposed	2 / 157 (1.27%)	0 / 161 (0.00%)	0 / 15 (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
Femoral neck fracture			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (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
Hip fracture			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			

subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Rib fracture			
subjects affected / exposed	2 / 157 (1.27%)	0 / 161 (0.00%)	0 / 15 (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
Scapula fracture			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Lumbar vertebral fracture			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Afferent loop syndrome			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemothorax			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	2 / 157 (1.27%)	0 / 161 (0.00%)	0 / 15 (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
Cardiac failure congestive			
subjects affected / exposed	1 / 157 (0.64%)	1 / 161 (0.62%)	0 / 15 (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
Coronary artery stenosis			
subjects affected / exposed	1 / 157 (0.64%)	1 / 161 (0.62%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Nervous system disorders			
Senile dementia			
subjects affected / exposed	0 / 157 (0.00%)	0 / 161 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	2 / 157 (1.27%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eyelid ptosis			

subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (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
Retinal artery occlusion			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			
subjects affected / exposed	0 / 157 (0.00%)	2 / 161 (1.24%)	0 / 15 (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
Retinal pigment epithelial tear			
subjects affected / exposed	0 / 157 (0.00%)	0 / 161 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 157 (0.64%)	1 / 161 (0.62%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	1 / 157 (0.64%)	1 / 161 (0.62%)	0 / 15 (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
Inguinal hernia strangulated			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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			
Bile duct stone			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Ureterolithiasis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			

subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (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
Exostosis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (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
Osteoarthritis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Osteonecrosis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endophthalmitis			
subjects affected / exposed	1 / 157 (0.64%)	1 / 161 (0.62%)	0 / 15 (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
Pneumonia			
subjects affected / exposed	0 / 157 (0.00%)	3 / 161 (1.86%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 161 (0.62%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	1 / 157 (0.64%)	0 / 161 (0.00%)	0 / 15 (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

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

Non-serious adverse events	Aflibercept + Sham PDT	Aflibercept + Active PDT	Aflibercept (Non-randomized)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 157 (37.58%)	49 / 161 (30.43%)	3 / 15 (20.00%)
Investigations			
Intraocular pressure increased			
subjects affected / exposed	6 / 157 (3.82%)	9 / 161 (5.59%)	0 / 15 (0.00%)
occurrences (all)	18	20	0
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 157 (3.82%)	13 / 161 (8.07%)	2 / 15 (13.33%)
occurrences (all)	6	13	2
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	10 / 157 (6.37%)	5 / 161 (3.11%)	0 / 15 (0.00%)
occurrences (all)	31	8	0
Dry eye			
subjects affected / exposed	6 / 157 (3.82%)	11 / 161 (6.83%)	0 / 15 (0.00%)
occurrences (all)	11	22	0
Ocular hypertension			

subjects affected / exposed occurrences (all)	3 / 157 (1.91%) 4	1 / 161 (0.62%) 1	1 / 15 (6.67%) 1
Visual acuity reduced subjects affected / exposed occurrences (all)	7 / 157 (4.46%) 7	9 / 161 (5.59%) 10	0 / 15 (0.00%) 0
Vitreous floaters subjects affected / exposed occurrences (all)	9 / 157 (5.73%) 10	1 / 161 (0.62%) 1	0 / 15 (0.00%) 0
Retinal pigment epithelial tear subjects affected / exposed occurrences (all)	4 / 157 (2.55%) 4	0 / 161 (0.00%) 0	1 / 15 (6.67%) 1
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 157 (0.64%) 1	0 / 161 (0.00%) 0	1 / 15 (6.67%) 1
Infections and infestations Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	25 / 157 (15.92%) 41	18 / 161 (11.18%) 25	0 / 15 (0.00%) 0

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Decimal places were automatically truncated if last decimal equals zero.
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Notes: