Clinical trial results:
A phase 3 randomized, double-masked, controlled trial to establish the safety and efficacy of intravitreous administration of Fovista™ (Anti PDGF-B pegylated aptamer) administered in combination with either Avastin® or Eylea® compared to Avastin® or Eylea® monotherapy in subjects with subfoveal neovascular age-related macular degeneration

Summary

EudraCT number	2013-003018-42
Trial protocol	PT ES FI NO DE EE LV SK IT AT HU HR CZ
Global end of trial date	15 September 2017

Results information

Result version number	v1 (current)
This version publication date	18 January 2019
First version publication date	18 January 2019

Trial information

Trial identification

Sponsor protocol code	OPH1004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01940887
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ophthotech Corporation
Sponsor organisation address	One Penn Plaza, Suite 3520 , New York, United States, NY 10119
Public contact	Fang Li, Ophthotech Corporation, +1 212-845-8219, fang.li@ophthotech.com
Scientific contact	Fang Li, Ophthotech Corporation, +1 212-845-8219, fang.li@ophthotech.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	15 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2017
Global end of trial reached?	Yes
Global end of trial date	15 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study are to evaluate the safety and efficacy of Fovista (E10030) intravitreous administration when administered in combination with either Avastin or Eylea compared to Avastin or Eylea monotherapy in subjects with subfoveal choroidal neovascularization secondary to age-related macular degeneration (AMD).

Protection of trial subjects:

All subjects signed the informed consent before undergoing any study-related procedure.
An independent data monitoring committee reviewed subject safety data during the course of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Portugal: 21
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Croatia: 44
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Czech Republic: 29
Country: Number of subjects enrolled	Estonia: 16
Country: Number of subjects enrolled	France: 49
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 98
Country: Number of subjects enrolled	Italy: 57
Country: Number of subjects enrolled	Latvia: 15
Country: Number of subjects enrolled	Israel: 60
Country: Number of subjects enrolled	Colombia: 12
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Argentina: 7

Country: Number of subjects enrolled	United States: 189
Worldwide total number of subjects	645
EEA total number of subjects	363

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)	56
From 65 to 84 years	480
85 years and over	109

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 214 centers (107 in North America and 107 in the rest of the world) in 22 countries (20 of which enrolled patients) between 19 May 2014 and 15 September 2017.
Written informed consent was obtained before any of the Screening details listed below were performed.

Pre-assignment

Screening details:

Medical&ophthalmologic history,protocol refraction&visual acuity,ophthalmologic examination,Goldmann Applanation Tonometry,vital signs,physical examination, performance status,ECG,color fundus photographs,Fluorescein Angiograms,Optical Coherence Tomography,laboratory&pregnancy tests&concomitant medication were assessed at screening prior to Day1

Period 1

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

Blinding implementation details:

It was the responsibility of the Principal Investigator to ensure that the physician assessing AEs, the VA examiner, all masked study personnel, and the subject remained masked to the subject's treatment assignment of Fovista or Sham.

Arms

Are arms mutually exclusive?	Yes
Arm title	Fovista + Avastin or Eylea

Arm description:

Fovista 1.5 mg/eye + Avastin 1.25 mg/eye or Eylea 2 mg/eye.
Within this treatment group, subjects were randomized in a 1:1 ratio to either Avastin 1.25 mg/eye or Eylea 2 mg/eye.
NOTE: 1 subject who was randomized but did not receive study drug is excluded from the number of subjects starting this period.

Arm type	Experimental
Investigational medicinal product name	Fovista
Investigational medicinal product code	
Other name	E10030, pegpleranib
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Avastin or Eylea was administered first, and Fovista injection was administered second.
Subjects randomized to receive Avastin were treated with Fovista in combination with Avastin monthly for 24 months. Subjects randomized to receive Eylea were treated with Fovista in combination with Eylea every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month thereafter (ie, Months 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22).

Investigational medicinal product name	Avastin
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Avastin or Eylea was administered first, and Fovista injection was administered second.
Subjects randomized to receive Avastin were treated with Fovista in combination with Avastin monthly for 24 months. Subjects randomized to receive Eylea were treated with Fovista in combination with Eylea every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month

thereafter (ie, Months 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22).

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

Dosage and administration details:

Avastin or Eylea was administered first, and Fovista injection was administered second.
Subjects randomized to receive Avastin were treated with Fovista in combination with Avastin monthly for 24 months. Subjects randomized to receive Eylea were treated with Fovista in combination with Eylea every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month thereafter (ie, Months 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22).

Arm title	Fovista Sham + Avastin or Eylea

Arm description:

Fovista Sham + Avastin 1.25 mg/eye or Eylea 2 mg/eye.
Within this treatment group, subjects were randomized in a 1:1 ratio to either Avastin 1.25 mg/eye or Eylea 2 mg/eye.
NOTE: 2 subjects who were randomized but did not receive study drug are excluded from the number of subjects starting this period.

Arm type	Experimental
Investigational medicinal product name	Avastin
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Avastin or Eylea was administered first, and Fovista Sham injection was administered second.
Subjects randomized to receive Avastin were treated with Fovista Sham in combination with Avastin monthly for 24 months. Subjects randomized to receive Eylea were treated with Fovista Sham in combination with Eylea every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month thereafter (ie, Months 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22).

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

Dosage and administration details:

Avastin or Eylea was administered first, and Fovista Sham injection was administered second.
Subjects randomized to receive Avastin were treated with Fovista Sham in combination with Avastin monthly for 24 months. Subjects randomized to receive Eylea were treated with Fovista Sham in combination with Eylea every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month thereafter (ie, Months 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22).

Number of subjects in period 1[1]	Fovista + Avastin or Eylea	Fovista Sham + Avastin or Eylea
Started	322	320
Completed	283	297
Not completed	39	23
Adverse event, serious fatal	6	3
Physician decision	7	3
Consent withdrawn by subject	18	9

Adverse event, non-fatal	6	6
Lost to follow-up	2	1
Protocol deviation	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Three (3) patients who were enrolled and randomized to treatment did not receive any treatment. These patients are not included in Year 1 period. Therefore, there are 3 patients fewer in the Year 1 period compared to the worldwide number enrolled.

Period 2

Period 2 title	Year 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

It was the responsibility of the Principal Investigator to ensure that the physician assessing AEs, the VA examiner, all masked study personnel, and the subject remained masked to the subject's treatment assignment of Fovista or Sham.

Arms

Are arms mutually exclusive?	Yes
Arm title	Fovista + Avastin or Eylea

Arm description:

Fovista 1.5 mg/eye + Avastin 1.25 mg/eye or Eylea 2 mg/eye.
Within this treatment group, subjects were randomized in a 1:1 ratio to either Avastin 1.25 mg/eye or Eylea 2 mg/eye.

Arm type	Experimental
Investigational medicinal product name	Fovista
Investigational medicinal product code	
Other name	E10030, pegpleranib
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Avastin or Eylea was administered first, and Fovista injection was administered second.
Subjects randomized to receive Avastin were treated with Fovista in combination with Avastin monthly for 24 months. Subjects randomized to receive Eylea were treated with Fovista in combination with Eylea every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month thereafter (ie, Months 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22).

Investigational medicinal product name	Avastin
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Avastin or Eylea was administered first, and Fovista injection was administered second.
Subjects randomized to receive Avastin were treated with Fovista in combination with Avastin monthly for 24 months. Subjects randomized to receive Eylea were treated with Fovista in combination with Eylea every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month thereafter (ie, Months 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22).

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

Dosage and administration details:

Avastin or Eylea was administered first, and Fovista injection was administered second.
Subjects randomized to receive Avastin were treated with Fovista in combination with Avastin monthly for 24 months. Subjects randomized to receive Eylea were treated with Fovista in combination with Eylea every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month thereafter (ie, Months 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22).

Arm title	Fovista Sham + Avastin or Eylea

Arm description:

Fovista Sham + Avastin 1.25 mg/eye or Eylea 2 mg/eye
Within this treatment group, subjects were randomized in a 1:1 ratio to either Avastin 1.25 mg/eye or Eylea 2 mg/eye.

Arm type	Experimental
Investigational medicinal product name	Avastin
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Avastin or Eylea was administered first, and Fovista Sham injection was administered second.
Subjects randomized to receive Avastin were to be treated with Fovista Sham in combination with Avastin monthly for 24 months. Subjects randomized to receive Eylea were to be treated with Fovista Sham in combination with Eylea every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month thereafter (ie, Months 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22).

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

Dosage and administration details:

Avastin or Eylea was administered first, and Fovista Sham injection was administered second.
Subjects randomized to receive Avastin were to be treated with Fovista Sham in combination with Avastin monthly for 24 months. Subjects randomized to receive Eylea were to be treated with Fovista Sham in combination with Eylea every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month thereafter (ie, Months 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22).

Number of subjects in period 2	Fovista + Avastin or Eylea	Fovista Sham + Avastin or Eylea
Started	283	297
Completed	66	75
Not completed	217	222
Adverse event, serious fatal	-	2
Consent withdrawn by subject	8	8
Physician decision	8	1
Adverse event, non-fatal	8	2
Lost to follow-up	1	6

Sponsor decision, early termination of study	192	203

Baseline characteristics

Reporting groups

Reporting group title	Fovista + Avastin or Eylea

Reporting group description:

Fovista 1.5 mg/eye + Avastin 1.25 mg/eye or Eylea 2 mg/eye.
Within this treatment group, subjects were randomized in a 1:1 ratio to either Avastin 1.25 mg/eye or Eylea 2 mg/eye.
NOTE: 1 subject who was randomized but did not receive study drug is excluded from the number of subjects starting this period.

Reporting group title	Fovista Sham + Avastin or Eylea

Reporting group description:

Fovista Sham + Avastin 1.25 mg/eye or Eylea 2 mg/eye.
Within this treatment group, subjects were randomized in a 1:1 ratio to either Avastin 1.25 mg/eye or Eylea 2 mg/eye.
NOTE: 2 subjects who were randomized but did not receive study drug are excluded from the number of subjects starting this period.

Reporting group values	Fovista + Avastin or Eylea	Fovista Sham + Avastin or Eylea	Total
Number of subjects	322	320	642
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	31	25	56
From 65-84 years	239	239	478
85 years and over	52	56	108
Age continuous Units: years			
arithmetic mean	76.5	76.6	
standard deviation	± 8.36	± 8.36	-
Gender categorical Units: Subjects			
Female	178	192	370
Male	144	128	272

Subject analysis sets

Subject analysis set title	Fovista + Avastin or Eylea, ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized subjects in the Fovista + Avastin or Fovista + Eylea arm who received at least one dose of study drug, irrespective of the dose actually received. Subjects were analyzed in the dose group assigned at randomization.

Subject analysis set title	Fovista Sham + Avastin or Eylea, ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects in the Fovista Sham + Avastin or Fovista Sham + Eylea arm who received at least one dose of study drug, irrespective of the dose received. Subjects were analyzed in the dose group assigned at randomization.

Reporting group values	Fovista + Avastin or Eylea, ITT	Fovista Sham + Avastin or Eylea, ITT	
Number of subjects	322	320	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	31	25	
From 65-84 years	269	239	
85 years and over	52	56	
Age continuous Units: years			
arithmetic mean	76.5	76.6	
standard deviation	± 8.36	± 8.36	
Gender categorical Units: Subjects			
Female	178	192	
Male	144	128	

End points

End points reporting groups

Reporting group title	Fovista + Avastin or Eylea

Reporting group description:

Fovista 1.5 mg/eye + Avastin 1.25 mg/eye or Eylea 2 mg/eye.
Within this treatment group, subjects were randomized in a 1:1 ratio to either Avastin 1.25 mg/eye or Eylea 2 mg/eye.
NOTE: 1 subject who was randomized but did not receive study drug is excluded from the number of subjects starting this period.

Reporting group title	Fovista Sham + Avastin or Eylea

Reporting group description:

Fovista Sham + Avastin 1.25 mg/eye or Eylea 2 mg/eye.
Within this treatment group, subjects were randomized in a 1:1 ratio to either Avastin 1.25 mg/eye or Eylea 2 mg/eye.
NOTE: 2 subjects who were randomized but did not receive study drug are excluded from the number of subjects starting this period.

Reporting group title	Fovista + Avastin or Eylea

Reporting group description:

Fovista 1.5 mg/eye + Avastin 1.25 mg/eye or Eylea 2 mg/eye.
Within this treatment group, subjects were randomized in a 1:1 ratio to either Avastin 1.25 mg/eye or Eylea 2 mg/eye.

Reporting group title	Fovista Sham + Avastin or Eylea

Reporting group description:

Fovista Sham + Avastin 1.25 mg/eye or Eylea 2 mg/eye
Within this treatment group, subjects were randomized in a 1:1 ratio to either Avastin 1.25 mg/eye or Eylea 2 mg/eye.

Subject analysis set title	Fovista + Avastin or Eylea, ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized subjects in the Fovista + Avastin or Fovista + Eylea arm who received at least one dose of study drug, irrespective of the dose actually received. Subjects were analyzed in the dose group assigned at randomization.

Subject analysis set title	Fovista Sham + Avastin or Eylea, ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects in the Fovista Sham + Avastin or Fovista Sham + Eylea arm who received at least one dose of study drug, irrespective of the dose received. Subjects were analyzed in the dose group assigned at randomization.

Primary: Mean Change in Visual Acuity (ETDRS Letters) from Baseline to Month 12

End point title	Mean Change in Visual Acuity (ETDRS Letters) from Baseline to Month 12

End point description:

The primary efficacy endpoint was the mean change in VA (ETDRS letters) from Baseline to Month 12. All VA assessments were performed by the study refractionist/ophthalmologist. Comparison of the mean change in VA in ETDRS letters between the two groups was made using analysis of covariance with baseline VA as a covariate, stratified by lesion subtype. VA was assessed on the ITT population which consisted of all randomized subjects who received at least one dose of study drug, irrespective of the dose actually received. Subjects were analyzed as per the dose group assigned at randomization. Subjects were included in a particular analysis, for a particular population, if relevant data were available for analysis (e.g., the primary analysis required one baseline and at least one post baseline VA measurement, to calculate a change score).

End point type	Primary

End point timeframe:

From Baseline to Month 12

End point values	Fovista + Avastin or Eylea, ITT	Fovista Sham + Avastin or Eylea, ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	322	320		
Units: Visual Acuity (ETDRS letters)				
least squares mean (standard error)	9.42 (± 0.85)	9.04 (± 0.85)		

Statistical analyses

Statistical analysis title	Model for Repeated Measures

Statistical analysis description:

The model was fitted by using restricted maximum likelihood (REML). The model included the indicator of treatment with Avastin or Eylea, and the cross-classification of baseline VA (≥ 47 letters vs. < 47 letters) and lesion subtype (> 50% classic vs. ≤ 50% classic) as used in the randomization as covariates. Fixed effects included treatment, visit, and treatment*visit. The level of significance (α) was set at 5% (two-tailed).

Comparison groups	Fovista + Avastin or Eylea, ITT v Fovista Sham + Avastin or Eylea, ITT
Number of subjects included in analysis	642
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7382
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.86
upper limit	2.62

Secondary: Gain of 20 or More ETDRS Letters from Baseline to Month 12

End point title	Gain of 20 or More ETDRS Letters from Baseline to Month 12

End point description:

A secondary endpoint was to assess the proportion of subjects gaining ≥ 20 ETDRS letters from Baseline to Month 12. All VA assessments were performed by the study refractionist/ophthalmologist. VA was assessed on the ITT population which consisted of all randomized subjects who received at least one dose of study drug, irrespective of the dose actually received. Subjects were analyzed as per the dose group assigned at randomization. Subjects were included in a particular analysis, for a particular population, if relevant data were available for analysis (e.g., the primary analysis required one baseline and at least one post baseline VA measurement, to calculate a change score).

End point type	Secondary

End point timeframe:

From Baseline to Month 12

End point values	Fovista + Avastin or Eylea, ITT	Fovista Sham + Avastin or Eylea, ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	322	320		
Units: Percentage of subjects				
number (not applicable)				
Yes	23.3	22.2		
No	62.7	70.6		
Missing	14.0	7.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Loss of 5 or More ETDRS Letters from Baseline to Month 12

End point title	Loss of 5 or More ETDRS Letters from Baseline to Month 12

End point description:

A secondary endpoint was to assess the proportion of subjects losing ≥ 5 ETDRS letters from Baseline to Month 12. All VA assessments were performed by the study refractionist/ophthalmologist. VA was assessed on the ITT population which consisted of all randomized subjects who received at least one dose of study drug, irrespective of the dose actually received. Subjects were analyzed as per the dose group assigned at randomization. Subjects were included in a particular analysis, for a particular population, if relevant data were available for analysis (e.g., the primary analysis required one baseline and at least one post baseline VA measurement, to calculate a change score).

End point type	Secondary

End point timeframe:

From Baseline to Month 12

End point values	Fovista + Avastin or Eylea, ITT	Fovista Sham + Avastin or Eylea, ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	322	320		
Units: Percentage of subjects				
number (not applicable)				
Yes	12.4	13.4		
No	73.6	79.4		
Missing	14.0	7.2		

Statistical analyses

No statistical analyses for this end point

Secondary: VA (ETDRS Snellen Equivalent) of 20/25 or Better at Month 12

End point title	VA (ETDRS Snellen Equivalent) of 20/25 or Better at Month 12

End point description:

A secondary endpoint was to assess the proportion of subjects in each treatment group achieving VA of 20/25 or better at Month 12. All VA assessments were performed by the study refractionist/ophthalmologist. VA was assessed on the ITT population which consisted of all randomized subjects who received at least one dose of study drug, irrespective of the dose actually received. Subjects were analyzed as per the dose group assigned at randomization. Subjects were included in a particular analysis, for a particular population, if relevant data were available for analysis (e.g., the primary analysis required one baseline and at least one post baseline VA measurement, to calculate a change score).

End point type	Secondary

End point timeframe:

From Baseline to Month 12

End point values	Fovista + Avastin or Eylea, ITT	Fovista Sham + Avastin or Eylea, ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	322	320		
Units: Percentage of subjects				
number (not applicable)				
Yes	13.7	18.1		
No	72.4	74.7		
Missing	14.0	7.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded starting after the first dose of the trial drug and continuing until end of study.

Adverse event reporting additional description:

AEs were reported for the safety population (all subjects who received 1+ doses of study drug [Fovista, Avastin, Eylea or Sham]). Subjects who had ever received an injection of Fovista were analyzed in the Fovista+Avastin/Eylea group. Causally related occurrences included events reported as related to injection procedure or related to study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Fovista + Avastin or Eylea, year 1

Reporting group description:

Fovista 1.5 mg/eye + Avastin 1.25 mg/eye or Eylea 2 mg/eye (all subjects received at least one dose of study drug)

Reporting group title	Fovista Sham + Avastin or Eylea, year 1

Reporting group description:

Fovista Sham + Avastin 1.25 mg/eye or Eylea 2 mg/eye (all subjects received at least one dose of study drug)

Serious adverse events	Fovista + Avastin or Eylea, year 1	Fovista Sham + Avastin or Eylea, year 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 322 (18.01%)	32 / 320 (10.00%)	
number of deaths (all causes)	7	4	
number of deaths resulting from adverse events	7	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer stage I			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer metastatic			

subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colon cancer recurrent			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer stage IV			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal papilloma of breast			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 322 (0.31%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lentigo maligna			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 322 (0.31%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	3 / 322 (0.93%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma recurrent			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Femoral artery occlusion			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 322 (0.62%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 322 (0.31%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 322 (0.62%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (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			
Ankle fracture			
subjects affected / exposed	2 / 322 (0.62%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (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	2 / 322 (0.62%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 322 (0.31%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	3 / 322 (0.93%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multiple fractures			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 322 (0.62%)	3 / 320 (0.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
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	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 322 (0.62%)	3 / 320 (0.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular insufficiency			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			

subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 322 (0.93%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Autoimmune uveitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal endotheliitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iridocyclitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular hole			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 322 (0.31%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	2 / 322 (0.62%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Duodenal ulcer			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric dysplasia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 322 (0.31%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	0 / 322 (0.00%)	2 / 320 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland mass			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 322 (0.31%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 322 (0.62%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 322 (0.31%)	2 / 320 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 322 (0.31%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endophthalmitis			
subjects affected / exposed	4 / 322 (1.24%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial infection			

subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 322 (1.55%)	2 / 320 (0.63%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 322 (0.00%)	1 / 320 (0.31%)	
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	Fovista + Avastin or Eylea, year 1	Fovista Sham + Avastin or Eylea, year 1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	222 / 322 (68.94%)	212 / 320 (66.25%)	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	22 / 322 (6.83%)	20 / 320 (6.25%)	
occurrences (all)	46	35	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	39 / 322 (12.11%)	31 / 320 (9.69%)	
occurrences (all)	85	48	
Punctate keratitis			

subjects affected / exposed	21 / 322 (6.52%)	14 / 320 (4.38%)	
occurrences (all)	34	39	
Eye pain			
subjects affected / exposed	18 / 322 (5.59%)	21 / 320 (6.56%)	
occurrences (all)	26	35	
Vitreous detachment			
subjects affected / exposed	20 / 322 (6.21%)	19 / 320 (5.94%)	
occurrences (all)	21	23	
Neovascular age-related macular degeneration			
subjects affected / exposed	16 / 322 (4.97%)	19 / 320 (5.94%)	
occurrences (all)	16	19	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 322 (4.35%)	17 / 320 (5.31%)	
occurrences (all)	15	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2014	Protocol Amendment A (dated 06 March 2014), revised the inclusion and exclusion criteria, modified stratification factors, and clarified several study procedures. The most significant amendment changes included: • Dosing change – the Fovista/Sham + Avastin group was changed from monthly in Year 1 followed by every other month in Year 2 with option for retreatment on the non-dosing months according to VA was changed to monthly treatment during both Year 1 and Year 2; the Fovista/Sham + Eylea group was changed from monthly in Year 1 followed by every other month in Year 2 with option for retreatment on the non-dosing months according to VA was changed to every month for the first 3 doses followed by every other month for the remainder of the study for up to 2 years. The changes were to reflect both EU and US prescribing recommendations. • Other sections were updated for clarification and consistency with dosing changes as outlined above.

Notes:

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.

Given the lack of efficacy after one year of treatment, the OPH1004 study was prematurely terminated by the Sponsor during the second year of the study.

Notes: