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 Lucentis® compared to Lucentis® monotherapy in subjects with subfoveal neovascular age-related macular degeneration

Summary

EudraCT number	2013-002997-33
Trial protocol	GB LV AT CZ EE SK BE
Global end of trial date	20 February 2017

Results information

Result version number	v1
This version publication date	23 March 2018
First version publication date	23 March 2018

Trial information

Trial identification

Sponsor protocol code	OPH1002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ophthotech Corporation
Sponsor organisation address	One Penn Plaza, Suite 3520, New York, United States, 10119
Public contact	Patricia Johnson, OPHTHOTECH CORPORATION, +1 7328907626, patricia.johnson@ophthotech.com
Scientific contact	Patricia Johnson, OPHTHOTECH CORPORATION, +1 7328907626, patricia.johnson@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	19 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2016
Global end of trial reached?	Yes
Global end of trial date	20 February 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of intravitreal (IVT) administration of Fovista when administered in combination with IVT Lucentis compared to IVT Lucentis monotherapy, in subjects with subfoveal choroidal neovascularization (CNV) 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	28 August 2013
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	Poland: 46
Country: Number of subjects enrolled	Slovakia: 9
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czech Republic: 84
Country: Number of subjects enrolled	Estonia: 22
Country: Number of subjects enrolled	Italy: 118
Country: Number of subjects enrolled	Latvia: 46
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United States: 211
Country: Number of subjects enrolled	Brazil: 17
Worldwide total number of subjects	621
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)	47
From 65 to 84 years	477
85 years and over	97

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 122 centers in 13 countries between 28 August 2013 and 20 February 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 adverse events (AEs), the visual acuity (VA) examiner, all masked study personnel and the subject remain masked to the subject’s treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sham + Lucentis

Arm description:

Subjects received the Lucentis injection first, followed by a Sham injection (pressure applied at the would-be injection site with a needle-less syringe hub).

Arm type	Experimental
Investigational medicinal product name	Sham + Lucentis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects received the Lucentis injection first (0.5 mg/eye), followed by a Sham injection (pressure applied at the would-be injection site with a needle-less syringe hub). Lucentis was administered as intravitreal injections and was administered once monthly (approximately every 28 days) in the first year of this study.

Arm title	Fovista + Lucentis

Arm description:

Subjects received the Lucentis injection first, followed by Fovista injection.

Arm type	Experimental
Investigational medicinal product name	Fovista + Lucentis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects received the Lucentis injection first (0.5 mg/eye), followed by the Fovista injection (1.5 mg/eye). Both active study drugs were administered as intravitreal injections. Study drugs were

administered once monthly (approximately every 28 days) in the first year of this study.

Number of subjects in period 1[1]	Sham + Lucentis	Fovista + Lucentis
Started	310	309
Completed	282	287
Not completed	28	22
Physician decision	2	2
Consent withdrawn by subject	17	9
Adverse event, non-fatal	5	10
Subject non-compliance	3	-
Lost to follow-up	-	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: Overall, 311 subjects were randomized to the Fovista + Lucentis group. Of these 2 subjects did not receive treatment. Hence the total number of subjects in the Fovista + Lucentis group is 309.

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 remain
masked to the subject’s treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sham + Lucentis

Arm description:

Subjects received the Lucentis injection first, followed by a Sham injection (pressure applied at the would-be injection site with a needle-less syringe hub).

Arm type	Experimental

Investigational medicinal product name	Sham + Lucentis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects received the Lucentis injection first (0.5 mg/eye), followed by a Sham injection (pressure applied at the would-be injection site with a needle-less syringe hub). Lucentis was administered as intravitreal injections and was administered once monthly (approximately every 28 days) in the first year of this study. During the second year, treatment was based on the stability of visual acuity, ophthalmic examination and imaging.

Arm title	Fovista + Lucentis

Arm description:

Subjects received the Lucentis injection first, followed by Fovista injection.

Arm type	Experimental
Investigational medicinal product name	Fovista + Lucentis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects received the Lucentis injection first (0.5 mg/eye), followed by the Fovista injection (1.5 mg/eye). Both active study drugs were administered as intravitreal injections. Study drugs were administered once monthly (approximately every 28 days) in the first year of this study. During the second year, treatment was based on the stability of visual acuity, ophthalmic examination and imaging.

Number of subjects in period 2	Sham + Lucentis	Fovista + Lucentis
Started	283	286
Completed	156	154
Not completed	127	132
Physician decision	1	-
Consent withdrawn by subject	9	7
Adverse event, non-fatal	5	6
Subject non-compliance	3	1
Sponsor decision	104	112
Lost to follow-up	5	5
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Sham + Lucentis
Reporting group description:	
Subjects received the Lucentis injection first, followed by a Sham injection (pressure applied at the would-be injection site with a needle-less syringe hub).	
Reporting group title	Fovista + Lucentis
Reporting group description:	
Subjects received the Lucentis injection first, followed by Fovista injection.	

Reporting group values	Sham + Lucentis	Fovista + Lucentis	Total
Number of subjects	310	309	619
Age categorical Units: Subjects			
Adults (18-64 years)	20	26	46
From 65-84 years	233	243	476
85 years and over	57	40	97
Age continuous Units: years			
arithmetic mean	76.9	76.1	
standard deviation	± 8.04	± 7.98	-
Gender categorical Units: Subjects			
Female	196	181	377
Male	114	128	242
Iris color Units: Subjects			
Light	156	167	323
Medium	110	101	211
Dark	44	41	85
Study eye Units: Subjects			
Right	151	156	307
Left	159	153	312

End points

End points reporting groups

Reporting group title	Sham + Lucentis
Reporting group description:	
Subjects received the Lucentis injection first, followed by a Sham injection (pressure applied at the would-be injection site with a needle-less syringe hub).	
Reporting group title	Fovista + Lucentis
Reporting group description:	
Subjects received the Lucentis injection first, followed by Fovista injection.	
Reporting group title	Sham + Lucentis
Reporting group description:	
Subjects received the Lucentis injection first, followed by a Sham injection (pressure applied at the would-be injection site with a needle-less syringe hub).	
Reporting group title	Fovista + Lucentis
Reporting group description:	
Subjects received the Lucentis injection first, followed by Fovista injection.	

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. For analyses of the primary endpoint, a Model for Repeated Measures (MRM) was used to assess the differences between the treatment groups at the Month 12 visit. 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:	
Baseline to Month 12	

End point values	Sham + Lucentis	Fovista + Lucentis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	310	309		
Units: EDTRS letter				
least squares mean (standard error)				
MRM change from Baseline to Month 12	9.82 (± 0.86)	10.74 (± 0.86)		

Statistical analyses

Statistical analysis title	Model for Repeated Measures analysis

Statistical analysis description:

Model for Repeated Measures (MRM) adjusted for the cross-classification of baseline VA (>=47 letters vs < 47 letters) and lesion subtype (> 50% classic vs <= 50% classic), visit, treatment by visit interaction, and the interaction of visit and the Baseline VA/lesion subtype cross-classification

Comparison groups	Sham + Lucentis v Fovista + Lucentis
Number of subjects included in analysis	619
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4362
Method	Model for Repeated Measures
Parameter estimate	Difference in least squares means
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	3.23

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:

Baseline to Month 12

End point values	Sham + Lucentis	Fovista + Lucentis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	310	309		
Units: Percentage of subjects				
number (not applicable)				
Yes	20.0	25.9		
No	68.7	65.7		
Missing	11.3	8.4		

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:

Baseline to Month 12

End point values	Sham + Lucentis	Fovista + Lucentis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	310	309		
Units: Percentage of subjects				
number (not applicable)				
Yes	12.3	12.0		
No	76.5	79.6		
Missing	11.3	8.4		

Statistical analyses

No statistical analyses for this end point

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

End point title	Achievement of VA (ETDRS Snellen Equivalent) 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:

Baseline to Month 12

End point values	Sham + Lucentis	Fovista + Lucentis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	310	309		
Units: percentage of subjects				
number (not applicable)				
Yes	13.2	13.6		
No	75.5	78.0		
Missing	11.3	8.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Growth of CNV Area from Baseline to Month 12 by Fluorescein Angiography

End point title	Growth of CNV Area from Baseline to Month 12 by Fluorescein Angiography

End point description:

A secondary endpoint was to assess the proportion of subjects with growth of Choroidal Neovascularization (CNV) area from Baseline to Month 12 by Fluorescein Angiography (FA).
All FA images were centrally read. CNV Area is defined as Classic CNV Area + Occult CNV Area + Retinal Pigment Epithelium staining. Growth of CNV area is defined as a change greater than zero in the CNV area on FA from Baseline to Month 12. Baseline is the last non-missing measurement prior to the first dose of study drug.
Subjects were analyzed as per the dose group assigned at randomization.

End point type	Secondary

End point timeframe:

Baseline to Month 12

End point values	Sham + Lucentis	Fovista + Lucentis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	310	309		
Units: Percentage of subjects				
number (not applicable)				
Yes	7.4	8.7		
No	79.4	79.9		
Missing	13.2	11.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Randomization at Day 1 (14 days after Screening) until end of study.

Adverse event reporting additional description:

AEs were reported on the safety population (all subjects who received at least 1dose of study drug [Fovista,Lucentis or Sham]). Subjects who have ever received an injection of Fovista were analyzed in the Fovista+Lucentis group.Causally related occurrences included both events reported as: related to injection procedure and related to study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Sham + Lucentis

Reporting group description:

Subjects received the Lucentis injection first, followed by a "Sham" injection (pressure applied at the would-be injection site with a needle-less syringe hub).

Reporting group title	Fovista + Lucentis

Reporting group description:

Subjects received the Lucentis injection first, followed by Fovista injection

Serious adverse events	Sham + Lucentis	Fovista + Lucentis	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 309 (11.65%)	48 / 310 (15.48%)	
number of deaths (all causes)	2	6	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioma			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningioma			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myxofibrosarcoma			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			

subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device malfunction			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device failure			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 309 (0.00%)	3 / 310 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 309 (0.00%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			

subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Face injury			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 309 (0.32%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal anastomosis complication			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	3 / 309 (0.97%)	3 / 310 (0.97%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	1 / 309 (0.32%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 309 (0.65%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
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	1 / 309 (0.32%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac fibrillation			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conduction disorder			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 309 (0.00%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transient ischaemic attack			
subjects affected / exposed	1 / 309 (0.32%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Cataract			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract subcapsular			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular hole			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 309 (0.00%)	3 / 310 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oroantral fistula			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (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 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 309 (0.32%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ureteric rupture			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (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	0 / 309 (0.00%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone infarction			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 309 (0.32%)	4 / 310 (1.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	0 / 309 (0.00%)	3 / 310 (0.97%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningoencephalitis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia influenzal			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 309 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 309 (0.65%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	2 / 309 (0.65%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 309 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sham + Lucentis	Fovista + Lucentis	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	217 / 309 (70.23%)	223 / 310 (71.94%)	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	30 / 309 (9.71%)	43 / 310 (13.87%)	
occurrences (all)	78	157	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	56 / 309 (18.12%)	60 / 310 (19.35%)	
occurrences (all)	177	197	
Eye pain			
subjects affected / exposed	26 / 309 (8.41%)	23 / 310 (7.42%)	
occurrences (all)	47	29	
Punctate keratitis			
subjects affected / exposed	18 / 309 (5.83%)	15 / 310 (4.84%)	
occurrences (all)	30	22	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 309 (1.94%)	19 / 310 (6.13%)	
occurrences (all)	6	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2014	1. Clarification of study drug retreatment algorithm. 2. Subject selection criteria were widened to include more subjects. 3. Previous or concomitant therapy was modified to clarify that therapy was prescribed at the investigator's discretion. 4. Clarification of when routine office procedures performed before informed consent may be used as screening procedures for this study. 5. Screening: clarification that Applanation Tonometry was Goldmann Applanation Tonometry. 6. Clarification that if a patient is randomized, the repeat OCT (and FA, if taken) must be submitted to the Reading Center to be used as the new study baseline. 7. A window of +/- 1 day was added to assessments. 8. Subfoveal choroidal neovascularization with some classic component (i.e., predominantly classic or minimally classic) secondary to AMD was changed to subfoveal choroidal neovascularization secondary to AMD. Subjects without evidence of a "classic" lesion on fluorescein angiogram, but with evidence of subretinal highly-reflective material on high resolution SD-OCT, were stratified into the ≤50% classic group at the time of stratification. 9. Analysis upon all Patients Completing Month 12 was amended to note that "topline" Month 12 results may need to be publically disseminated as per U.S. business law. 10. Clarification of the definition of the relationship of adverse events to study drug and injection procedure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 February 2017	All of the subjects were terminated early from the study due to the sponsor decision, after analyses of the Year-1 data from Phase 3 studies OPH1002 and OPH1003 showed that the addition of Fovista to Lucentis did not lead to further visual improvements.	-

Notes:

Limitations and caveats

None reported