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	2013-003017-18
Trial protocol	HU DE ES DK
Global end of trial date	13 February 2017

Results information

Result version number	v1 (current)
This version publication date	23 March 2018
First version publication date	23 March 2018

Trial information

Trial identification

Sponsor protocol code	OPH1003

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	10 May 2016
Global end of trial reached?	Yes
Global end of trial date	13 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 form prior to undergoing study-related procedures. 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	05 September 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	Denmark: 23
Country: Number of subjects enrolled	France: 104
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Hungary: 119
Country: Number of subjects enrolled	Argentina: 36
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Colombia: 20
Country: Number of subjects enrolled	Israel: 66
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	United States: 197
Worldwide total number of subjects	627
EEA total number of subjects	288

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	61
From 65 to 84 years	446
85 years and over	120

Subject disposition

Recruitment

Recruitment details:

This study wad conducted in 101 centers in 11 countries between 05 September 2013 and 13 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 injection 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	315	311
Completed	284	282
Not completed	31	29
Consent withdrawn by subject	15	11
Physician decision	-	4
Adverse event, non-fatal	15	10
Subject non-compliance	1	1
Other	-	1
Sponsor decision	-	1
Lost to follow-up	-	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: One subject in the Sham + Lucentis group was randomized but not treated. Therefore the number of subjects in the Sham + Lucentis group is 315.

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

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) at Year 2.

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 (pressure applied at the would-be injection site with a needle-less syringe hub) at Year 2.

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, followed by the Fovista injection (pressure applied at the would-be injection site with a needle-less syringe hub). Both active study drugs were administered as IVT 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	284	282
Completed	188	189
Not completed	96	93
Physician decision	1	2
Consent withdrawn by subject	12	11
Adverse event, non-fatal	6	11
Subject non-compliance	-	1
Sponsor decision	75	67
Lost to follow-up	2	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	315	311	626
Age categorical Units: Subjects			
Adults (18-64 years)	31	30	61
From 65-84 years	221	224	445
85 years and over	63	57	120
Age continuous			
Baseline characteristics were assessed on intent-to-treat population (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).			
Units: years			
arithmetic mean	76.8	76.9	
standard deviation	± 8.71	± 8.50	-
Gender categorical			
Baseline characteristics were assessed on 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).			
Units: Subjects			
Female	189	178	367
Male	126	133	259
Iris colour Units: Subjects			
Light	130	124	254
Medium	137	122	259
Dark	48	65	113
Study eye Units: Subjects			
Right	167	149	316
Left	148	162	310

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) at Year 2.	
Reporting group title	Fovista + Lucentis
Reporting group description:	
Subjects received the Lucentis injection first, followed by Fovista injection (pressure applied at the would-be injection site with a needle-less syringe hub) at Year 2.	

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	315	311		
Units: ETDRS letters				
least squares mean (standard error)				
MRM change from Baseline to Month 12	10.36 (± 0.87)	9.91 (± 0.88)		

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	626
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7059
Method	Model for Repeated Measures
Parameter estimate	Difference in least squares means
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.75
upper limit	1.86

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	315	311		
Units: Percentage of subjects				
number (not applicable)				
Yes	24.1	22.5		
No	62.9	67.2		
Missing	13.0	10.3		

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	315	311		
Units: Percentage of subjects				
number (not applicable)				
Yes	10.2	12.2		
No	76.8	77.5		
Missing	13.0	10.3		

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	315	311		
Units: Percentage of subjects				
number (not applicable)				
Yes	14.6	13.5		
No	72.4	76.2		
Missing	13.0	10.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in visual acuity (ETDRS letters) from baseline to Month 6

End point title	Mean change in visual acuity (ETDRS letters) from baseline to Month 6

End point description:

This analysis was conducted on the ITT 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 6

End point values	Sham + Lucentis	Fovista + Lucentis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315	311		
Units: ETDRS letters				
least squares mean (standard error)	9.15 (± 0.75)	8.20 (± 0.77)		

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	315	311		
Units: Percentage of subjects				
number (not applicable)				
Yes	8.3	8.7		
No	75.6	77.8		
Missing	16.2	13.5		

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 had 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	49 / 314 (15.61%)	56 / 312 (17.95%)	
number of deaths (all causes)	4	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Follicle centre lymphoma, follicular grade I, II, III stage IV			

subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified stage I			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (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	3 / 314 (0.96%)	2 / 312 (0.64%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung squamous cell carcinoma stage III			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	0 / 314 (0.00%)	3 / 312 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			

subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to liver			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-small cell lung cancer			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
subjects affected / exposed	2 / 314 (0.64%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer recurrent			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma stage III			

subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (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	0 / 314 (0.00%)	2 / 312 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			

subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 314 (0.00%)	3 / 312 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 314 (0.32%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Cataract traumatic			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compression fracture			

subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (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 / 314 (0.64%)	3 / 312 (0.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	3 / 314 (0.96%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	1 / 314 (0.32%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 314 (0.32%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 314 (0.32%)	3 / 312 (0.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	3 / 314 (0.96%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			

subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve incompetence			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 314 (0.32%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			

subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (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 / 314 (0.32%)	0 / 312 (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 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 314 (0.00%)	2 / 312 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 314 (0.64%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular hole			
subjects affected / exposed	0 / 314 (0.00%)	3 / 312 (0.96%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic ischaemic neuropathy			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			

subjects affected / exposed	0 / 314 (0.00%)	3 / 312 (0.96%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal pigment epithelial tear			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (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	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal wall haematoma			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (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	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			

subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder polyp			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (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			
Back pain			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 314 (0.32%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (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			
Aspergillus infection			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (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	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 314 (0.32%)	1 / 312 (0.32%)	
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 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device related sepsis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	2 / 314 (0.64%)	6 / 312 (1.92%)	
occurrences causally related to treatment / all	1 / 2	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 314 (0.32%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infectious colitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 314 (0.64%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (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	1 / 314 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 314 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 312 (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	136 / 314 (43.31%)	161 / 312 (51.60%)	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	25 / 314 (7.96%)	49 / 312 (15.71%)	
occurrences (all)	42	101	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	50 / 314 (15.92%)	74 / 312 (23.72%)	
occurrences (all)	136	166	
Punctate keratitis			

subjects affected / exposed	40 / 314 (12.74%)	35 / 312 (11.22%)	
occurrences (all)	97	93	
Conjunctival hyperaemia			
subjects affected / exposed	24 / 314 (7.64%)	24 / 312 (7.69%)	
occurrences (all)	53	48	
Eye pain			
subjects affected / exposed	21 / 314 (6.69%)	22 / 312 (7.05%)	
occurrences (all)	35	51	
Vitreous floaters			
subjects affected / exposed	12 / 314 (3.82%)	22 / 312 (7.05%)	
occurrences (all)	13	28	
Eye irritation			
subjects affected / exposed	15 / 314 (4.78%)	18 / 312 (5.77%)	
occurrences (all)	35	34	
Keratitis			
subjects affected / exposed	14 / 314 (4.46%)	18 / 312 (5.77%)	
occurrences (all)	47	64	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 314 (5.73%)	17 / 312 (5.45%)	
occurrences (all)	20	18	
Urinary tract infection			
subjects affected / exposed	18 / 314 (5.73%)	17 / 312 (5.45%)	
occurrences (all)	25	23	
Bronchitis			
subjects affected / exposed	11 / 314 (3.50%)	16 / 312 (5.13%)	
occurrences (all)	12	18	

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
13 February 2017	All of the subjects were terminated early from the study due to 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