Clinical trial results:
A Phase IV, prospective, open-label, uncontrolled, European Study in patients with neovascular Age-related macular degeneration (nAMD), evaluating the efficacy and safety of switching from intravitreal Aflibercept to RanIbizumab 0.5 mg.

Summary

EudraCT number	2014-001085-10
Trial protocol	DE
Global end of trial date	14 September 2017

Results information

Result version number	v1 (current)
This version publication date	30 September 2018
First version publication date	30 September 2018

Trial information

Trial identification

Sponsor protocol code	CRFB002AGB17

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02161575
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	14 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate whether treatment with IVT ranibizumab 0.5 mg was associated with improvement (i.e. reduction at Day 90 from baseline) in central subfield retinal thickness (CSRT), as determined by OCT after 3 monthly injections of ranibizumab.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 87
Country: Number of subjects enrolled	Germany: 16
Worldwide total number of subjects	103
EEA total number of subjects	103

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)	6
From 65 to 84 years	84

85 years and over	13

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from 22 sites located in the United Kingdom and 6 sites located in Germany. A total of 103 patients received at least 1 dose of study drug.

Pre-assignment

Screening details:

Of the 103 patients who received at least 1 dose of study drug, 3 patients did not have any post-baseline safety or CSRT assessments and were therefore excluded from the SAF and FAS, in accordance with the analysis set definitions. Therefore, 100 patients were included in the SAF and FAS.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ranibizumab

Arm description:

All patients received 3 monthly intraveal injections of 0.5mg ranibizumab followed by monthly injections of ranibizumab 0.5mg for a further 3 months on a prn (as required) basis, as determined by the study doctor.

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	RFB002
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraocular use

Dosage and administration details:

Intraveal injections of 0.5mg ranibizumab

Number of subjects in period 1[1]	Ranibizumab
Started	100
Full Analysis Set (FAS) Population	100
Safety (SAF) Population	100
Completed	92
Not completed	8
Adverse event, non-fatal	2
Protocol deviation	5
Lack of efficacy	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: Of the 103 patients who received at least 1 dose of study drug, 3 patients did not have any post-baseline safety or CSRT assessments and were therefore excluded from the SAF and FAS.

Baseline characteristics

Reporting groups	
Reporting group title	Ranibizumab
Reporting group description:	
All patients received 3 monthly intraveal injections of 0.5mg ranibizumab followed by monthly injections of ranibizumab 0.5mg for a further 3 months on a prn (as required) basis, as determined by the study doctor.	

Reporting group values	Ranibizumab	Total	
Number of subjects	100	100	
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)	6	6	
From 65-84 years	81	81	
85 years and over	13	13	
Age Continuous Units: years			
arithmetic mean	77		
standard deviation	± 6.51	-	
Sex: Female, Male Units: Subjects			
Female	55	55	
Male	45	45	
Race/Ethnicity, Customized Units: Subjects			
Caucasian|	99	99	
Asian|	1	1	

End points

End points reporting groups

Reporting group title	Ranibizumab

Reporting group description:

All patients received 3 monthly intraveal injections of 0.5mg ranibizumab followed by monthly injections of ranibizumab 0.5mg for a further 3 months on a prn (as required) basis, as determined by the study doctor.

Primary: Change in Central Subfield Retinal Thickness (CSRT) from Baseline to Day 90.

End point title	Change in Central Subfield Retinal Thickness (CSRT) from Baseline to Day 90.[1]

End point description:

Measurement of the change in CSRT, determined by high definition optical coherence tomography (HD-OCT) after 3 monthly injections of ranibizumab. OCT is a non-invasive technique which can determine and measure thickness of the retina. A negative change from Baseline indicates an improvement (less retinal fluid and lower disease activity). Data collected on the study eye were used for the evaluation of efficacy.

End point type	Primary

End point timeframe:

Baseline and Day 90

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses provided as it was a single arm trial.

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: micrometer				
median (full range (min-max))				
Baseline|	384.00 (154.0 to 975.0)			
Day 90|	318.00 (170.0 to 832.0)			
Change from Baseline to Day 90|	-30.75 (-386.0 to 78.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Subfoveal Retinal Thickness (SRT) from Baseline to Day 180

End point title	Change in Subfoveal Retinal Thickness (SRT) from Baseline to Day 180

End point description:

Measurement of change in SRT from Baseline to Day 180 as determined by high definition optical coherence tomography (HD-OCT). A reduction indicates an improvement in overall disease activity. Data collected on the study eye were used for the evaluation of efficacy.

End point type	Secondary
End point timeframe: Baseline and Day 180	

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: micrometer				
median (full range (min-max))				
SRT at Baseline|	346.00 (69.0 to 944.5)			
SRT at Day 180|	302.00 (41.5 to 876.5)			
SRT change from Baseline to Day 180|	-23.50 (-464.0 to 306.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Central Subfield Retinal Thickness (CSRT) from Baseline to Day 180

End point title	Change in Central Subfield Retinal Thickness (CSRT) from Baseline to Day 180

End point description:

Measurement of change in CSRT from Baseline to Day 180 as determined by high definition optical coherence tomography (HD-OCT). A reduction indicates an improvement in overall disease activity. Data collected on the study eye were used for the evaluation of efficacy.

End point type	Secondary
End point timeframe: Baseline and Day 180	

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: micrometer				
median (full range (min-max))				
CSRT at Baseline|	384.00 (154.0 to 975.0)			
CSRT at Day 180|	343.00 (194.0 to 842.0)			
CSRT change from Baseline to Day 180|	-28.00 (-271.0 to 171.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Central Subfield Retinal Volume (CSRV) from Baseline to Day 180

End point title	Change in Central Subfield Retinal Volume (CSRV) from Baseline to Day 180

End point description:

Measurement of change in CSRV from Baseline to Day 180 as determined by high definition optical coherence tomography (HD-OCT). A reduction indicates an improvement in overall disease activity. Data collected on the study eye were used for the evaluation of efficacy.

End point type	Secondary

End point timeframe:

Baseline and Day 180

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: cubic micrometer				
median (full range (min-max))				
CSRV at Baseline|	0.3050 (0.120 to 11.600)			
CSRV at Day 180|	0.2750 (0.115 to 11.400)			
CSRV change from Baseline to Day 180|	-0.0200 (-1.600 to 0.135)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Intraretinal Fluid assessed at Baseline and Day 180

End point title	Number of patients with Intraretinal Fluid assessed at Baseline and Day 180

End point description:

Presence or absence of qualitative OCT parameter Intraretinal Fluid. Data collected on the study eye were used for the evaluation of efficacy.

End point type	Secondary

End point timeframe:

Baseline and Day 180

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: Participants				
Baseline|Yes, Definitive	32			
Day 180|Yes, Definitive	24			
Baseline|Yes, Subtle	11			
Day 180|Yes, Subtle	15			
Baseline|No	56			
Day 180|No	55			
Baseline|Questionable	1			
Day 180|Questionable	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Subretinal Fluid assessed at Baseline and Day 180

End point title	Number of patients with Subretinal Fluid assessed at Baseline and Day 180

End point description:

Presence or absence of qualitative OCT parameter Subretinal Fluid. Data collected on the study eye were used for the evaluation of efficacy.

End point type	Secondary

End point timeframe:

Baseline to Day 180

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: Participants				
Baseline|Yes, Definitive	83			
Day 180|Yes, Definitive	49			
Baseline|Yes, Subtle	5			
Day 180|Yes, Subtle	15			
Baseline|No	12			
Day 180|No	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Intraretinal/Subretinal Fluid Within the Central Subfield Fluid assessed at baseline and Day 180

End point title	Number of patients with Intraretinal/Subretinal Fluid Within the Central Subfield Fluid assessed at baseline and Day 180

End point description:

Presence or absence of qualitative OCT parameter Intraretinal/Subretinal Fluid Within the Central Subfield. Data collected on the study eye were used for the evaluation of efficacy.

End point type	Secondary

End point timeframe:

Baseline and Day 180

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: Participants				
Baseline|Yes, Definitive	38			
Day 180|Yes, Definitive	26			
Baseline|Yes, Subtle	6			
Day 180|Yes, Subtle	12			
Baseline|No	5			
Day 180|No	15			
Baseline|Questionable	1			
Day 180|Questionable	1			
Baseline|NA	50			
Day 180|NA	40			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Pigment Epithelial Detachments assessed at baseline and Day 180

End point title	Number of patients with Pigment Epithelial Detachments assessed at baseline and Day 180

End point description:

Presence or absence of qualitative OCT parameter Pigment Epithelial Detachments. Data collected on the study eye were used for the evaluation of efficacy.

End point type	Secondary

End point timeframe:

Baseline and Day 180

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: Participants				
Baseline|Yes, Definitive	86			
Day 180|Yes, Definitive	80			
Baseline|Yes, Subtle	2			
Day 180|Yes, Subtle	4			
Baseline|No	12			
Day 180|No	8			
Baseline|Not gradable	0			
Day 180|Not gradable	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Dry Retina assessed at baseline and Day 180

End point title	Number of patients with Dry Retina assessed at baseline and Day 180

End point description:

Presence or absence of qualitative OCT parameter Dry Retina. Data collected on the study eye were used for the evaluation of efficacy.

End point type	Secondary

End point timeframe:

Baseline and Day 180

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: Participants				
Baseline|Yes, Definitive	0			
Day 180|Yes, Definitive	0			
Baseline|No	100			
Day 180|No	94			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Maximum PED Height from Baseline to Day 180

End point title	Change in Maximum PED Height from Baseline to Day 180

End point description:

Change from Baseline to Day 180 in Maximum Pigment Epithelial Detachment (PED) Height. Data

collected on the study eye were used for the evaluation of efficacy.

End point type	Secondary

End point timeframe:

Baseline and Day 180

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: micrometer				
median (full range (min-max))				
Baseline|	236.00 (66.5 to 674.0)			
Day 180|	203.50 (63.5 to 705.0)			
Change from Baseline to Day 180|	-2.50 (-336.5 to 131.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Maximum PED Diameter from Baseline to Day 180

End point title	Change in Maximum PED Diameter from Baseline to Day 180

End point description:

Change from Baseline to Day 180 in Maximum Pigment Epithelial Detachment (PED) Diameter. Data collected on the study eye were used for the evaluation of efficacy.

End point type	Secondary

End point timeframe:

Baseline and Day 180

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: micrometer				
median (full range (min-max))				
Baseline|	2205.00 (0.0 to 4877.0)			
Day 180|	2428.00 (471.0 to 4683.0)			
Change from Baseline to Day 180|	59.50 (-1007.0 to 2756.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Maximum IRC Height from Baseline to Day 180

End point title	Change in Maximum IRC Height from Baseline to Day 180

End point description:

Change from Baseline to Day 180 in Maximum Intraretinal Cyst (IRC) Height. Data collected on the study eye were used for the evaluation of efficacy.

End point type	Secondary

End point timeframe:

Baseline and Day 180

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: micrometer				
median (full range (min-max))				
Baseline|	121.50 (21.0 to 280.5)			
Day 180|	105.50 (25.5 to 485.0)			
Change from Baseline to Day 180|	0.00 (-223.5 to 235.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Best Corrected Visual Acuity (BCVA) in the Study Eye

End point title	Change in Best Corrected Visual Acuity (BCVA) in the Study Eye

End point description:

Change in overall BCVA score from Baseline to Day 180, and from Day 90 to Day 180 in the Study Eye.

End point type	Secondary

End point timeframe:

Baseline, Day 90 and Day 180

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: letters				
median (full range (min-max))				
Baseline|	71.5 (36 to 90)			
Day 90|	74.0 (32 to 87)			

Day 180|	75.0 (32 to 90)			
Change from Baseline to Day 180|	1.0 (-31 to 35)			
Change from Day 90 to Day 180|	0.0 (-25 to 24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ETDRS Letters for Study Eye from Baseline to Day 180

End point title	Change in ETDRS Letters for Study Eye from Baseline to Day 180

End point description:

Number of patients gaining at least 15 letters from Baseline to Day 180

End point type	Secondary

End point timeframe:

Baseline and Day 180

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: Participants				
>=15 (Gain of at least 15 letters)	11			
10 to <15	6			
5 to <10	17			
0 to <5	25			
>-15 to <0	31			
<=-15 (Loss of at least 15 letters)	7			
NA	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of ocular TEAEs in the Study Eye reported by ≥2% patients from Baseline to Day 180

End point title	Incidence of ocular TEAEs in the Study Eye reported by ≥2% patients from Baseline to Day 180

End point description:

Incidence of ocular Treatment Emergent Adverse Events (TEAEs) in the study eye reported by ≥2% patients by preferred term.

End point type	Secondary

End point timeframe:

Baseline to Day 180

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: Participants				
Eye pain|	3			
Visual impairment|	3			
Blepharitis|	2			
Posterior capsule opacification|	2			
Intraocular pressure increased|	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Overall Ranibizumab

Reporting group description:

Overall Ranibizumab

Serious adverse events	Overall Ranibizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 100 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
CATHETERISATION CARDIAC			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PROSTATIC SPECIFIC ANTIGEN INCREASED			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
FALL			

subjects affected / exposed	3 / 100 (3.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
POST PROCEDURAL HAEMATOMA			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ATRIAL FLUTTER			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
UMBILICAL HERNIA REPAIR			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VAGINAL PROLAPSE REPAIR			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
RETINAL HAEMORRHAGE			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VOMITING			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
PROSTATOMEGALY			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

URINARY RETENTION			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
PNEUMONIA			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1.9 %

Non-serious adverse events	Overall Ranibizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 100 (52.00%)		
Investigations			
BLOOD PRESSURE SYSTOLIC INCREASED			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
BLOOD PRESSURE INCREASED			
subjects affected / exposed	4 / 100 (4.00%)		
occurrences (all)	5		
HEART RATE DECREASED			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
WEIGHT DECREASED			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
INTRAOCULAR PRESSURE INCREASED			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	4		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	3		

Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all) HEADACHE subjects affected / exposed occurrences (all)	 2 / 100 (2.00%) 2 3 / 100 (3.00%) 3		
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	 2 / 100 (2.00%) 2		
General disorders and administration site conditions FATIGUE subjects affected / exposed occurrences (all)	 2 / 100 (2.00%) 2		
Eye disorders BLEPHARITIS subjects affected / exposed occurrences (all) DRY EYE subjects affected / exposed occurrences (all) EYE PAIN subjects affected / exposed occurrences (all) POSTERIOR CAPSULE OPACIFICATION subjects affected / exposed occurrences (all) VISUAL IMPAIRMENT subjects affected / exposed occurrences (all)	 6 / 100 (6.00%) 6 3 / 100 (3.00%) 3 3 / 100 (3.00%) 3 2 / 100 (2.00%) 2 3 / 100 (3.00%) 3		
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	 7 / 100 (7.00%) 7		
Musculoskeletal and connective tissue disorders			

BACK PAIN			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	3		
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Infections and infestations			
CYSTITIS			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	7		
NASOPHARYNGITIS			
subjects affected / exposed	9 / 100 (9.00%)		
occurrences (all)	9		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2015	The permitted time period for a historical OCT volume scan was changed from ≤14 days to ≤28 days before the date of first injection of aflibercept to the study eye. The definition of pathologic myopia in Exclusion Criterion 15 was changed from ≥ 8 dioptres to ≥ 6 dioptres.
11 May 2016	The sample size calculation was amended, and the study population was changed from 162 to 124 patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported