Clinical trial results:
A 12-month, randomized, double-masked, sham-controlled, multicenter study to evaluate the efficacy and safety of 0.5 mg ranibizumab intravitreal injections in patients with visual impairment due to vascular endothelial growth factor (VEGF) driven choroidal neovascularization (CNV)

Summary

EudraCT number	2012-005417-38
Trial protocol	SK IT LV PT HU CZ ES LT BE GR DK DE PL FR
Global end of trial date	11 November 2015

Results information

Result version number	v2 (current)
This version publication date	17 July 2016
First version publication date	13 May 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CRFB002G2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01840410
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,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	11 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate that an individualized regimen of intravitreal injection of 0.5 mg ranibizumab has superior efficacy compared to sham treatment in adult patients with visual impairment due to VEGF-driven CNV. It was assessed by the best-corrected visual acuity (BCVA) change from baseline to Month 2.

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	19 September 2013
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	Australia: 10
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Latvia: 7
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Lithuania: 3
Country: Number of subjects enrolled	Peru: 1

Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Portugal: 6
Worldwide total number of subjects	178
EEA total number of subjects	130

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)	123
From 65 to 84 years	54
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 183 participants were enrolled. Of these, 178 adults were randomized in a 2:1 ratio and considered for analysis. There were 5 adolescent participants, non-randomized, who received open-label treatment and were not included in the analyses. Therefore, the number enrolled = 183 differs from the participant flow number started = 178.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ranibizumab

Arm description:

A 0.5 mg ranibizumab intravitreal injection was given to the study eye at baseline, and then as needed based on evidence of disease activity.

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	RFB002
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

A 0.5 mg ranibizumab intravitreal injection was given to the study eye at baseline, and then as needed based on evidence of disease activity.

Arm title	Sham control

Arm description:

Sham injection was given to the study eye at baseline, and then treatment was given based on evidence of disease activity. At Month 1, if treatment was needed, sham was administered. At Month 2, participants could switch to open-label ranibizumab on an as needed basis.

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

Dosage and administration details:

Sham injection was given to the study eye at baseline, and then treatment was given based on evidence of disease activity. At Month 1, if treatment was needed, sham was administered. At Month 2, participants could switch to open-label ranibizumab on an as needed basis. The sham vial did not contain active drug (empty sterile vial). The sham injection was an imitation of an intravitreal injection using an injection syringe without a needle touching the eye.

Number of subjects in period 1	Ranibizumab	Sham control
Started	119	59
Safety set	119	59
Full analysis set	119	59
Completed	112	55
Not completed	7	4
Physician decision	1	2
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	1
Protocol deviation	1	-
Pregnancy	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ranibizumab
Reporting group description:	
A 0.5 mg ranibizumab intravitreal injection was given to the study eye at baseline, and then as needed based on evidence of disease activity.	
Reporting group title	Sham control
Reporting group description:	
Sham injection was given to the study eye at baseline, and then treatment was given based on evidence of disease activity. At Month 1, if treatment was needed, sham was administered. At Month 2, participants could switch to open-label ranibizumab on an as needed basis.	

Reporting group values	Ranibizumab	Sham control	Total
Number of subjects	119	59	178
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	82	41	123
From 65-84 years	36	18	54
85 years and over	1	0	1
Age Continuous			
Units: Years			
arithmetic mean	54.6	51.9	
standard deviation	± 15.07	± 17.29	-
Gender, Male/Female			
Units: Participants			
Female	60	30	90
Male	59	29	88

End points

End points reporting groups

Reporting group title	Ranibizumab
Reporting group description:	
A 0.5 mg ranibizumab intravitreal injection was given to the study eye at baseline, and then as needed based on evidence of disease activity.	
Reporting group title	Sham control
Reporting group description:	
Sham injection was given to the study eye at baseline, and then treatment was given based on evidence of disease activity. At Month 1, if treatment was needed, sham was administered. At Month 2, participants could switch to open-label ranibizumab on an as needed basis.	
Subject analysis set title	Sham without Ranibizumab
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants did not receive ranibizumab at any time during the study.	

Primary: Change from baseline in best-corrected visual acuity (BCVA) in study eye to Month 2

End point title	Change from baseline in best-corrected visual acuity (BCVA) in study eye to Month 2
End point description:	
BCVA was assessed in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity (VA) testing charts at an initial testing distance of 4 meters. The data were analyzed using mixed model repeated measures (MMRM) which contained scheduled visit, the type of underlying pathophysiologic mechanism (angloid streaks versus others) and treatment group as fixed effect factors, centered baseline BCVA as a continuous covariate and treatment group by visit and visit by centered baseline BCVA interactions. A positive change from baseline indicated improvement.	
End point type	Primary
End point timeframe:	
Baseline, Month 2	

End point values	Ranibizumab	Sham control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	57		
Units: letters				
least squares mean (standard error)	9.5 (± 0.95)	-0.4 (± 1.16)		

Statistical analyses

Statistical analysis title	Change from baseline in BCVA in study eye
Comparison groups	Ranibizumab v Sham control

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	9.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.97
upper limit	12.91
Variability estimate	Standard error of the mean
Dispersion value	1.502

Secondary: Change from baseline in BCVA in study eye up to Month 2

End point title	Change from baseline in BCVA in study eye up to Month 2

End point description:

BCVA was assessed in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity (VA) testing charts at an initial testing distance of 4 meters. The data were analyzed using analysis of covariance (ANCOVA) model which contained the type of underlying pathophysiologic mechanism (angloid streaks versus others) and treatment group as fixed effect factors, centered baseline BCVA as a continuous covariate. A positive change from baseline indicated improvement.

End point type	Secondary

End point timeframe:

Baseline, Month 1, Month 2

End point values	Ranibizumab	Sham control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	57		
Units: letters				
least squares mean (standard error)				
Month 1	7.1 (± 0.75)	0.1 (± 1.08)		
Month 2	9.5 (± 0.91)	-0.4 (± 1.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in central subfield thickness (CSFT) in study eye

End point title	Change from baseline in central subfield thickness (CSFT) in study eye

End point description:

CSFT was assessed by optical coherence tomography (OCT). A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12

End point values	Ranibizumab	Sham control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	59		
Units: micrometer (um)				
arithmetic mean (standard deviation)				
Month 1 (n=115,56)	-74.4 (± 81.25)	3.3 (± 89.43)		
Month 2 (n=114,54)	-76.4 (± 108.24)	1.9 (± 119.44)		
Month 3 (n=114,56)	-82.9 (± 114.26)	-59.1 (± 142.37)		
Month 4 (n=114,56)	-83.5 (± 104.71)	-68.4 (± 155.26)		
Month 5 (n=116,55)	-83.8 (± 112.41)	-89.4 (± 130.68)		
Month 6 (n=112,54)	-89.1 (± 109.19)	-85.9 (± 117.54)		
Month 7 (n=114,55)	-83.1 (± 105.97)	-84.5 (± 141.36)		
Month 8 (n=111,55)	-94.7 (± 111.54)	-97.9 (± 118.34)		
Month 9 (n=110,55)	-90 (± 112.44)	-93.5 (± 113.88)		
Month 10 (n=108,53)	-100.5 (± 119.45)	-85.4 (± 136.9)		
Month 11 (n=110,55)	-99.5 (± 112.38)	-82.8 (± 158.78)		
Month 12 (n=109,55)	-102.7 (± 117.27)	-91.7 (± 152.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in central subfield volume (CSFV) in study eye

End point title	Change from baseline in central subfield volume (CSFV) in study eye

End point description:

CSFV was assessed OCT. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12

End point values	Ranibizumab	Sham control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	59		
Units: microliter (ul)				
arithmetic mean (standard deviation)				
Month 1 (n=115,56)	-0.354 (± 0.4103)	0.012 (± 0.3608)		
Month 2 (n=114,54)	-0.357 (± 0.548)	-0.006 (± 0.5792)		
Month 3 (n=114,56)	-0.369 (± 0.5506)	-0.269 (± 0.6583)		
Month 4 (n=114,56)	-0.371 (± 0.4798)	-0.291 (± 0.7647)		
Month 5 (n=116,55)	-0.392 (± 0.5404)	-0.381 (± 0.575)		
Month 6 (n=112,54)	-0.409 (± 0.5305)	-0.375 (± 0.531)		
Month 7 (n=114,54)	-0.366 (± 0.4905)	-0.374 (± 0.5966)		
Month 8 (n=110,55)	-0.414 (± 0.5021)	-0.411 (± 0.497)		
Month 9 (n=110,55)	-0.404 (± 0.5182)	-0.413 (± 0.5251)		
Month 10 (n=108,53)	-0.437 (± 0.5506)	-0.385 (± 0.5688)		
Month 11 (n=110,55)	-0.448 (± 0.5285)	-0.352 (± 0.7021)		
Month 12 (n=109,55)	-0.441 (± 0.546)	-0.378 (± 0.6704)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with presence of intra-retinal fluid in study eye compared to baseline

End point title	Number of participants with presence of intra-retinal fluid in study eye compared to baseline
End point description:	
The presence of intra-retinal fluid was assessed by OCT.	
End point type	Secondary
End point timeframe:	
Baseline, Month 2, Month 6, Month 12	

End point values	Ranibizumab	Sham control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	59		
Units: Participants				
Baseline, Absent (n=116,56)	70	32		
Baseline, Definite (n=116,56)	46	24		

Month 2, Absent (n=116,56)	97	29		
Month 2, Definite (n=116,56)	19	27		
Month 6, Absent (n=116,54)	100	43		
Month 6, Definite (n=116,54)	16	11		
Month 12, Absent (n=111,55)	95	45		
Month 12, Definite (n=111,55)	16	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with presence of subretinal fluid in study eye compared to baseline

End point title	Number of participants with presence of subretinal fluid in study eye compared to baseline

End point description:

Presence of subretinal fluid in study eye compared to baseline

End point type	Secondary

End point timeframe:

Baseline, Month 2, Month 6, Month 12

End point values	Ranibizumab	Sham control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	59		
Units: Participants				
Baseline, Absent (n=116,56)	16	6		
Baseline, Definite (n=116,56)	100	50		
Month 2, Absent (n=116,56)	72	11		
Month 2, Definite (n=116,56)	44	45		
Month 6, Absent (n=116,54)	77	34		
Month 6, Definite (n=116,54)	39	20		
Month 12, Absent (n=111,55)	78	41		
Month 12, Definite (n=111,55)	33	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with presence of active chorioretinal leakage

End point title	Number of participants with presence of active chorioretinal leakage

End point description:

The presence of active chorioretinal leakage was assessed by photography imaging, i.e. fluorescein angiography (FA).

End point type	Secondary

End point timeframe:

Baseline, Month 2, Month 6, Month 12

End point values	Ranibizumab	Sham control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	59		
Units: Participants				
Baseline, Absent (n=106,50)	2	1		
Baseline, Definite (n=106,50)	104	49		
Month 2, Absent (n=106,50)	37	4		
Month 2, Definite (n=106,50)	69	46		
Month 6, Absent (n=108,45)	64	29		
Month 6, Definite (n=108,45)	44	16		
Month 12, Absent (n=103,47)	81	37		
Month 12, Definite (n=103,47)	22	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Average change from baseline in BCVA

End point title	Average change from baseline in BCVA

End point description:

BCVA was assessed in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity (VA) testing charts at an initial testing distance of 4 meters. BCVA was assessed at each month from Month 1 through Month 6 or at each month from Month 1 through month 12, and the data were averaged. The outcome measure is reporting the change between baseline and average BCVA from Month 1 through Month 6 or from Month 1 through Month 12 (average BCVA - baseline BCVA). A positive change from baseline indicated improvement.

End point type	Secondary

End point timeframe:

Baseline (BL), Month 1 through Month 6, Month 1 through Month 12

End point values	Ranibizumab	Sham control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	59		
Units: letters				
arithmetic mean (standard deviation)				
Average change from BL, month 1 through month 6	9.53 (± 10.467)	4.68 (± 8.786)		
Average change from BL, month 1 through month 12	9.99 (± 11.528)	6.59 (± 10.666)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with ≥ 1, ≥ 5, ≥ 10 and ≥ 15 letters gain or reaching 84 letters

End point title	Number of participants with ≥ 1, ≥ 5, ≥ 10 and ≥ 15 letters gain or reaching 84 letters

End point description:

VA measurements (number of letters correctly identified) were performed with the patient in a sitting position using ETDRS-like visual acuity testing charts at a testing distance of 4 meters.

End point type	Secondary

End point timeframe:

Month 2, Month 6, Month 12

End point values	Ranibizumab	Sham control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	59		
Units: Participants				
Month 2,>=15 letters or reaching 85 let.(n=118,57)	37	7		
Month 2, >=10 letters (n=118,57)	50	8		
Month 2, >=5 letters (n=118,57)	83	16		
Month 2, >=1 letter (118,57)	101	27		
Month 6,>=15 letters or reaching 85 let.(n=118,54)	53	20		
Month 6, >=10 letters (n=118,54)	67	24		
Month 6, >= 5 letters (n=118,54)	88	34		
Month 6, >= 1 letter (n=118,54)	104	39		
Month 12,>=15 letters or reaching 85 let.;n=113,55	55	23		
Month 12, >=10 letters (n=113,55)	64	28		
Month 12, >=5 letters (n=113,55)	81	34		
Month 12, >=1 letter (n=113,55)	100	42		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with > 1, > 5, > 10 and > 15 letters loss

End point title	Number of participants with > 1, > 5, > 10 and > 15 letters

	loss

End point description:

VA measurements (number of letters correctly identified) were performed with the patient in a sitting position using ETDRS-like visual acuity testing charts at a testing distance of 4 meters.

End point type	Secondary

End point timeframe:

Month 2, Month 6, Month 12

End point values	Ranibizumab	Sham control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	59		
Units: Participants				
Month 2, loss of >1 letter (n=118,57)	10	24		
Month 2, loss of >5 letters (n=118,57)	3	12		
Month 2, loss of >10 letters (n=118,57)	1	5		
Month 2, loss of >15 letters (n=118,57)	1	3		
Month 6, loss of >1 letter (n=118,54)	10	9		
Month 6, loss of >5 letters (n=118,54)	7	5		
Month 6, loss of >10 letters (n=118,54)	6	2		
Month 6, loss of >15 letters (n=118,54)	3	2		
Month 12, loss of >1 letter (n=113,55)	9	10		
Month 12, loss of >5 letters (n=113,55)	6	6		
Month 12, loss of >10 letters (n=113,55)	5	4		
Month 12,loss of >15 letters (n=113,55)	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with requirement for rescue treatment at Month 1

End point title	Number of participants with requirement for rescue treatment at Month 1

End point description:

Rescue treatment with laser photocoagulation or periocular treatment could be administered at Month 1 only if the participant had a visual acuity loss of > 5 letters due to disease activity from baseline to Month 1.

End point type	Secondary

End point timeframe:

Month 1

End point values	Ranibizumab	Sham control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	58		
Units: Participants	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with ranibizumab treatments in study eye

End point title	Number of participants with ranibizumab treatments in study eye

End point description:

The number of participants administered study treatments, according to treatment frequency, was assessed.

End point type	Secondary

End point timeframe:

Month 12

End point values	Ranibizumab	Sham control	Sham without Ranibizumab	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	119	52	7	
Units: Participants				
Frequency of injections = 0	0	0	7	
Frequency of injections = 1	12	5	0	
Frequency of injections = 2	12	6	0	
Frequency of injections = 3	19	7	0	
Frequency of injections = 4	13	6	0	
Frequency of injections = 5	9	5	0	
Frequency of injections = 6	11	6	0	
Frequency of injections = 7	2	2	0	
Frequency of injections = 8	8	1	0	
Frequency of injections = 9	5	4	0	
Frequency of injections = 10	7	10	0	
Frequency of injections = 11	6	0	0	
Frequency of injections = 12	15	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with re-treatments

End point title	Number of participants with re-treatments

End point description:

The number of participants, administered re-treatments according to treatment frequency, was assessed. Re-treatment was defined as an administration of study medication following at least one non-missed visit where treatment was not administered in the study eye. Up to month 12, the maximum number of retreatments was 5.

End point type	Secondary

End point timeframe:

Month 12

End point values	Ranibizumab	Sham control	Sham without Ranibizumab	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	119	52	7	
Units: Paticipants				
Frequency of re-treatment = 1	25	21	0	
Frequency of re-treatment = 2	22	10	0	
Frequency of re-treatment = 3	9	4	0	
Frequency of re-treatment = 4	5	2	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of primary reasons for decision to treat by Investigator

End point title	Number of primary reasons for decision to treat by Investigator

End point description:

The total number of primary reasons for decisions to treat was assessed. A single participant could have had multiple primary reasons for treatment.

End point type	Secondary

End point timeframe:

Month 12

End point values	Ranibizumab	Sham control	Sham without Ranibizumab	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	119	52	7	
Units: Number of primary reasons				
Vision impairment	29	9	0	
OCT abnormality	522	306	1	
FA abnormality	21	13	0	
Color fundus photography abnormality	1	0	0	
Clinical abnormality	6	0	0	
Without documentation	1	0	0	

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 reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Ranibizumab 0.5 mg
Reporting group description:	
Ranibizumab 0.5 mg	
Reporting group title	Sham with Ranibizumab 0.5 mg
Reporting group description:	
Sham with Ranibizumab 0.5 mg	
Reporting group title	Sham without Ranibizumab 0.5 mg
Reporting group description:	
Sham without Ranibizumab 0.5 mg	

Serious adverse events	Ranibizumab 0.5 mg	Sham with Ranibizumab 0.5 mg	Sham without Ranibizumab 0.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 119 (7.56%)	4 / 52 (7.69%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 119 (0.00%)	1 / 52 (1.92%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal papilloma of breast			
subjects affected / exposed	1 / 119 (0.84%)	0 / 52 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive lobular breast carcinoma			

subjects affected / exposed	1 / 119 (0.84%)	0 / 52 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary tumour benign			
subjects affected / exposed	1 / 119 (0.84%)	0 / 52 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral artery stenosis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 52 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 119 (0.84%)	0 / 52 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Parkinsonism			
subjects affected / exposed	1 / 119 (0.84%)	0 / 52 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 52 (1.92%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment (Fellow untreated eye)			
subjects affected / exposed	1 / 119 (0.84%)	0 / 52 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	1 / 119 (0.84%)	0 / 52 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 119 (0.00%)	1 / 52 (1.92%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 119 (0.84%)	0 / 52 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 119 (0.00%)	1 / 52 (1.92%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	0 / 119 (0.00%)	1 / 52 (1.92%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rheumatic disorder			
subjects affected / exposed	0 / 119 (0.00%)	1 / 52 (1.92%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 52 (1.92%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ranibizumab 0.5 mg	Sham with Ranibizumab 0.5 mg	Sham without Ranibizumab 0.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 119 (35.29%)	19 / 52 (36.54%)	4 / 7 (57.14%)
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 119 (4.20%)	1 / 52 (1.92%)	1 / 7 (14.29%)
occurrences (all)	5	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 119 (0.84%)	3 / 52 (5.77%)	1 / 7 (14.29%)
occurrences (all)	1	3	1
Eye disorders			
Choroidal neovascularisation (Study eye)			
subjects affected / exposed	3 / 119 (2.52%)	0 / 52 (0.00%)	1 / 7 (14.29%)
occurrences (all)	3	0	1
Conjunctival haemorrhage (Study eye)			
subjects affected / exposed	7 / 119 (5.88%)	6 / 52 (11.54%)	0 / 7 (0.00%)
occurrences (all)	8	7	0
Eye inflammation (Study eye)			
subjects affected / exposed	0 / 119 (0.00%)	0 / 52 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Foreign body sensation in eyes (Study eye)			
subjects affected / exposed	1 / 119 (0.84%)	1 / 52 (1.92%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Macular oedema (Study eye)			
subjects affected / exposed	0 / 119 (0.00%)	0 / 52 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Ocular hyperaemia (Study eye)			
subjects affected / exposed	1 / 119 (0.84%)	1 / 52 (1.92%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Photopsia (Study eye)			
subjects affected / exposed	1 / 119 (0.84%)	0 / 52 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Visual acuity reduced (Study eye)			

subjects affected / exposed	3 / 119 (2.52%)	1 / 52 (1.92%)	1 / 7 (14.29%)
occurrences (all)	3	2	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 119 (5.04%)	0 / 52 (0.00%)	1 / 7 (14.29%)
occurrences (all)	6	0	1
Infections and infestations			
Conjunctivitis (Study eye)			
subjects affected / exposed	2 / 119 (1.68%)	3 / 52 (5.77%)	0 / 7 (0.00%)
occurrences (all)	2	3	0
Influenza			
subjects affected / exposed	9 / 119 (7.56%)	0 / 52 (0.00%)	0 / 7 (0.00%)
occurrences (all)	9	0	0
Nasopharyngitis			
subjects affected / exposed	14 / 119 (11.76%)	9 / 52 (17.31%)	1 / 7 (14.29%)
occurrences (all)	19	12	1
Pneumonia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 52 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Sinusitis			
subjects affected / exposed	2 / 119 (1.68%)	3 / 52 (5.77%)	0 / 7 (0.00%)
occurrences (all)	2	4	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2014	Amendment 1 (04-May-2014) was a substantial amendment and was issued 8 months after study start (when 28 patients were enrolled) and introduced the following changes: protocol-specified retreatment criteria were aligned with current medical practice for the management of patients with visual impairment due to CNV, specifically the inclusion of anatomic parameters, in addition to BCVA; eligibility criteria were revised to exclude two additional CNV conditions that are considered sub-categories of nAMD: 1) PCV and 2) RAP lesions in patients ≥ 50 years of age. The classification of these two CNV conditions as nAMD was not explicitly mentioned in the original protocol, which led to inclusion of some patients with these conditions; and two optional tests, visual field and electroretinography, were removed based on expert feedback.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported