Clinical trial results:
A 24-month, phase IIIb, open-label, single-arm, multicenter study assessing the efficacy and safety of an individualized, stabilization criteria-driven PRN dosing regimen with 0.5-mg ranibizumab intravitreal injections applied as monotherapy in patients with visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO) (CRYSTAL)

Summary

EudraCT number	2011-002350-31
Trial protocol	GB IE SE HU AT ES CZ SK GR PT NL PL IT DK
Global end of trial date	27 March 2015

Results information

Result version number	v1 (current)
This version publication date	05 June 2016
First version publication date	05 June 2016

Trial information

Trial identification

Sponsor protocol code	CRFB002E2401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01535261
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	27 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of an individualized stabilization criteria-driven PRN dosing regimen with 0.5-mg ranibizumab in patients with visual impairment due to ME secondary to CRVO as assessed by the mean change in best-corrected visual acuity (BCVA) at Month 12 compared to Baseline.

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	29 February 2012
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	Australia: 25
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	Czech Republic: 20
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	United Kingdom: 62
Country: Number of subjects enrolled	Greece: 26
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Netherlands: 20
Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Portugal: 25
Country: Number of subjects enrolled	Slovakia: 16
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Turkey: 9

Worldwide total number of subjects	357
EEA total number of subjects	283

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)	152
From 65 to 84 years	192
85 years and over	13

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At Screening (Visit 1 occurred between Day −14 and Day −1), after signing the informed consent, patients were enrolled into the study and procedures to allow assessment of the study eligibility criteria were performed.

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

Arm description:

Intravitreal injection with standard dose of 0.5 mg/0.05mL PRN

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	RFB002
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal injection with standard dose of 0.5mg/0.05mL PRN

Number of subjects in period 1	Ranibizumab arm
Started	357
Completed	307
Not completed	50
Adverse event, serious fatal	5
Consent withdrawn by subject	14
Physician decision	8
Adverse event, non-fatal	12
Lost to follow-up	8
Protocol deviation	3

Baseline characteristics

Reporting groups	
Reporting group title	Ranibizumab arm
Reporting group description:	
Intravitreal injection with standard dose of 0.5 mg/0.05mL PRN	

Reporting group values	Ranibizumab arm	Total	
Number of subjects	357	357	
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)	152	152	
From 65-84 years	192	192	
85 years and over	13	13	
Age Continuous | Units: Years			
arithmetic mean	65.5		
standard deviation	± 12.68	-	
Gender, Male/Female Units: Participants			
Male	229	229	
Female	128	128	

End points

End points reporting groups

Reporting group title	Ranibizumab arm
Reporting group description:	
Intravitreal injection with standard dose of 0.5 mg/0.05mL PRN	

Primary: Mean change in Best Corrected Visual Acuity (BCVA) at month 12 compared to baseline

End point title	Mean change in Best Corrected Visual Acuity (BCVA) at month 12 compared to baseline[1]
End point description:	
Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (ETDRS)-like chart while participants were in a sitting position at a testing distance of 4 meters. The range of ETDRS is 0 to 100 letters. A positive average change from baseline of BCVA indicates improvement	
End point type	Primary
End point timeframe:	
Baseline to month 12	

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: As this is a single arm study, only summary statistics are provided.

End point values	Ranibizumab arm			
Subject group type	Reporting group			
Number of subjects analysed	356			
Units: Letters				
arithmetic mean (standard deviation)	12.3 (± 16.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Best Corrected Visual Acuity (BCVA) at month 24 compared to baseline

End point title	Mean change in Best Corrected Visual Acuity (BCVA) at month 24 compared to baseline
End point description:	
Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (ETDRS)-like chart while participants were in a sitting position at a testing distance of 4 meters. The range of ETDRS is 0 to 100 letters. A positive average change from baseline of BCVA indicates improvement	
End point type	Secondary
End point timeframe:	
Baseline to Month 24	

End point values	Ranibizumab arm			
Subject group type	Reporting group			
Number of subjects analysed	356			
Units: Letters				
arithmetic mean (standard deviation)	12.1 (± 18.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean average change in Best Corrected Visual Acuity (BCVA from baseline Month 12 and Month 24

End point title	Mean average change in Best Corrected Visual Acuity (BCVA from baseline Month 12 and Month 24

End point description:

Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (ETDRS)-like chart while participants were in a sitting position at a testing distance of 4 meters. The range of ETDRS is 0 to 100 letters. A positive average change from baseline of BCVA indicates improvement

End point type	Secondary

End point timeframe:

Month 1 and Month 24

End point values	Ranibizumab arm			
Subject group type	Reporting group			
Number of subjects analysed	356			
Units: letters				
arithmetic mean (standard deviation)				
Month 12	11.8 (± 12.44)			
Month 24	12.1 (± 14.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean average change in BCVA from first treatment interruption (due to BCVA stabilization) to Month 12 and Month 24

End point title	Mean average change in BCVA from first treatment interruption (due to BCVA stabilization) to Month 12 and Month 24

End point description:

Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (ETDRS)-like chart while participants were in a sitting position at a testing distance of 4 meters. The range of ETDRS is 0 to 100 letters. Stability in visual acuity after treatment interruption indicates longer duration of the drug efficacy

End point type	Secondary

End point timeframe:

Month 12 and Month 24

End point values	Ranibizumab arm			
Subject group type	Reporting group			
Number of subjects analysed	356			
Units: Letters				
arithmetic mean (standard deviation)				
Month 12 (n=310)	-2.7 (± 8.04)			
Month 24 (n=331)	-2.5 (± 8.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with a BCVA improvement of ≥1, ≥5, ≥10, ≥15, and ≥30 letters from Baseline to Month 12 and Month 24 in the study eye

End point title	Number of patients with a BCVA improvement of ≥1, ≥5, ≥10, ≥15, and ≥30 letters from Baseline to Month 12 and Month 24 in the study eye

End point description:

BCVA score was based on the number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart assessed at a starting distance of 4 meters. An increased score indicates improvement in acuity. This outcome assessed the number of participants who had improvement of ≥1, ≥5, ≥10, ≥15, and ≥30 letters of visual acuity at month 12 as compared with baseline

End point type	Secondary

End point timeframe:

Month 12 and Month 24

End point values	Ranibizumab arm			
Subject group type	Reporting group			
Number of subjects analysed	356			
Units: Letters				
BCVA improvement of >= 1 (Month 12)	296			
BCVA improvement of >= 5 (Month 12)	275			
BCVA improvement of >= 10 (Month 12)	227			

BCVA improvement of >= 15 (Month 12)	175			
BCVA improvement of >= 30 (Month 12)	32			
BCVA improvement of >= 1 (Month 24)	290			
BCVA improvement of >= 5 (Month 24)	265			
BCVA improvement of >= 10 (Month 24)	224			
BCVA improvement of >= 15 (Month 24)	175			
BCVA improvement of >= 30 (Month 24)	44			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with a BCVA value of ≥ 73 letters (approximate 20/40 Snellen chart equivalent) at Month 12 and Month 24

End point title	Number of patients with a BCVA value of ≥ 73 letters (approximate 20/40 Snellen chart equivalent) at Month 12 and Month 24

End point description:

Best Corrected Visual Acuity (BCVA) was measured using Early Treatment Diabetic Retinopathy Study (ETDRS)-like chart at baseline and month 12 while participants were in a sitting position at a testing distance of 4 meters. The range of EDTRS is 0 to 100 letters. BCVA above 73 letters at month 12 and month 24 indicates a positive outcome.

End point type	Secondary

End point timeframe:

Month 12 and Month 24

End point values	Ranibizumab arm			
Subject group type	Reporting group			
Number of subjects analysed	356			
Units: Letters				
Month 12	169			
Month 24	161			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in central reading center (CRC)-assessed central subfield thickness (CSFT) from Month 12 and Month 24 compared to Baseline

End point title	Mean change in central reading center (CRC)-assessed central subfield thickness (CSFT) from Month 12 and Month 24 compared to Baseline

End point description:

Retinal thickness was measured using Optical Coherence Tomography (OCT). The images were reviewed by a central reading center to ensure a standardized evaluation

End point type	Secondary

End point timeframe:

Baseline, Month 12 and Month 24

End point values	Ranibizumab arm			
Subject group type	Reporting group			
Number of subjects analysed	347			
Units: Microns				
arithmetic mean (standard deviation)				
Change from Baseline at Month 12	-335.7 (± 285.02)			
Change from Baseline at Month 24	-349.1 (± 275.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in patient-reported outcomes in NEI-VFQ-25 composite and subscale scores at Month 12 and Month 24 compared to Baseline

End point title	Mean change in patient-reported outcomes in NEI-VFQ-25 composite and subscale scores at Month 12 and Month 24 compared to Baseline

End point description:

The survey consists of 25 items representing 11 vision-related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. Scores per visit and of the change from Baseline for the composite score and subscales will be summarized descriptively by visit.

End point type	Secondary

End point timeframe:

Month 12 and Month 24

End point values	Ranibizumab arm			
Subject group type	Reporting group			
Number of subjects analysed	350			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Change from baseline at Month 12	6.9 (± 12.65)			
Change from baseline at Month 24	6.6 (± 14.03)			

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.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Ranibizumab 0.5 mg

Reporting group description:

Ranibizumab 0.5 mg

Serious adverse events	Ranibizumab 0.5 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	64 / 357 (17.93%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			
subjects affected / exposed	2 / 357 (0.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			

subjects affected / exposed	2 / 357 (0.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cholangiocarcinoma				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aneurysm ruptured				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angiopathy				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic vascular disorder				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	2 / 357 (0.56%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				

subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral artery aneurysm				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Non-cardiac chest pain				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Haemorrhagic ovarian cyst				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	2 / 357 (0.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 357 (0.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Intraocular pressure increased (Study eye)			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Visual acuity tests abnormal (Study eye)			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femoral neck fracture			

subjects affected / exposed	2 / 357 (0.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laceration				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Limb traumatic amputation				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Scapula fracture				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina pectoris				

subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	3 / 357 (0.84%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	3 / 357 (0.84%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	3 / 357 (0.84%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Left ventricular dysfunction				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	3 / 357 (0.84%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Right ventricular failure				

subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain hypoxia			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	2 / 357 (0.56%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract (Fellow untreated eye)			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cataract (Study eye)			

subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Glaucoma (Fellow untreated eye)				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Glaucoma (Study eye)				
subjects affected / exposed	2 / 357 (0.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hyphaema (Fellow untreated eye)				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyphaema (Study eye)				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myopia (Study eye)				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal haemorrhage (Study eye)				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal ischaemia (Study eye)				
subjects affected / exposed	2 / 357 (0.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Retinal vascular thrombosis (Study eye)				

subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Visual acuity reduced (Study eye)				
subjects affected / exposed	2 / 357 (0.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vitreous haemorrhage (Fellow untreated eye)				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vitreous haemorrhage (Study eye)				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal adhesions				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticular perforation				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				

subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal polyp haemorrhage				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	2 / 357 (0.56%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				

subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal failure acute			
subjects affected / exposed	2 / 357 (0.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal mass			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile infection			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gangrene				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lower respiratory tract infection				
subjects affected / exposed	3 / 357 (0.84%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Ophthalmic herpes zoster (Fellow untreated eye)				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	3 / 357 (0.84%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				

Hypoglycaemia			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ranibizumab 0.5 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	182 / 357 (50.98%)		
Investigations			
Intraocular pressure increased (Study eye)			
subjects affected / exposed	43 / 357 (12.04%)		
occurrences (all)	91		
Vascular disorders			
Hypertension			
subjects affected / exposed	40 / 357 (11.20%)		
occurrences (all)	48		
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 357 (5.88%)		
occurrences (all)	30		
Eye disorders			
Conjunctival haemorrhage (Study eye)			
subjects affected / exposed	24 / 357 (6.72%)		
occurrences (all)	35		
Dry eye (Fellow untreated eye)			

subjects affected / exposed	19 / 357 (5.32%)		
occurrences (all)	20		
Dry eye (Study eye)			
subjects affected / exposed	22 / 357 (6.16%)		
occurrences (all)	22		
Eye pain (Study eye)			
subjects affected / exposed	25 / 357 (7.00%)		
occurrences (all)	40		
Macular oedema (Study eye)			
subjects affected / exposed	19 / 357 (5.32%)		
occurrences (all)	48		
Ocular hypertension (Study eye)			
subjects affected / exposed	26 / 357 (7.28%)		
occurrences (all)	33		
Vision blurred (Study eye)			
subjects affected / exposed	18 / 357 (5.04%)		
occurrences (all)	19		
Visual acuity reduced (Study eye)			
subjects affected / exposed	21 / 357 (5.88%)		
occurrences (all)	25		
Vitreous floaters (Study eye)			
subjects affected / exposed	19 / 357 (5.32%)		
occurrences (all)	25		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	39 / 357 (10.92%)		
occurrences (all)	54		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported