Clinical trial results:
An open-label Extended Clinical Protocol of ranibizumab to evaluate Safety and Efficacy in rare VEGF driven ocular diseases

Summary

EudraCT number	2013-001421-55
Trial protocol	FR
Global end of trial date	13 May 2016

Results information

Result version number	v1 (current)
This version publication date	25 May 2017
First version publication date	25 May 2017

Trial information

Trial identification

Sponsor protocol code	CRFB002GFR02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01908816
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	13 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 May 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the 2-year safety of ranibizumab as assessed by type, rate and severity of serious and non-serious, ocular and non-ocular, adverse events

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	26 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	France: 270
Worldwide total number of subjects	270
EEA total number of subjects	270

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)	153
From 65 to 84 years	106
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

open-label, single arm study evaluating the safety of 0.5 mg ranibizumab. Patients received individualized ranibizumab intravitreal injections based on evidence of disease activity. The study was early terminated due to low recruitment that hampered to address the primary endpoint of the study

Pre-assignment

Screening details:

A total of 196 patients completed the visit at Month 3 (M3), 127 completed the visit at M12 and 16 at M24. Due to the early termination of the study no patient completed the planned visit at M36. The mean time to premature discontinuation was 11.2 months, that encompasses the time between the first injection and the study discontinuation

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CNV (Choroidal Neovascularization)

Arm description:

All patients received 0.5 mg ranibizumab IVT injection

Arm type	Experimental
Investigational medicinal product name	ranibizumab 0.5 mg
Investigational medicinal product code	RFB002
Other name	Lucentis
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

0.5mg

Arm title	ME (Macular Edema)

Arm description:

All patients received 0.5 mg ranibizumab IVT injection

Arm type	Experimental
Investigational medicinal product name	Ranibizumab 0.5 mg)
Investigational medicinal product code	RFB002
Other name	Lucentis®
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Intracervical use

Dosage and administration details:

0.5mg

Arm title	RI/NVG (Rubeosis Iridis and Neovacular Glaucoma)

Arm description:

All patients received 0.5 mg ranibizumab IVT injection

Arm type	Experimental

Investigational medicinal product name	Ranibizumab 0.5 mg)
Investigational medicinal product code	RFB002
Other name	Lucentis
Pharmaceutical forms	Intravesical solution
Routes of administration	Intravitreal use

Dosage and administration details:

0.5mg

Arm title	PDR/V

Arm description:

(Proliferative Diabetic Retinopathy requiring Vitrectomy). All patients received 0.5 mg ranibizumab IVT injection

Arm type	Experimental
Investigational medicinal product name	Ranibizumab 0.5 mg
Investigational medicinal product code	RFB002
Other name	Lucentis
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

0.5mg

Number of subjects in period 1	CNV (Choroidal Neovascularization)	ME (Macular Edema)	RI/NVG (Rubeosis Iridis and Neovacular Glaucoma)
Started	93	84	58
Completed	0	0	0
Not completed	93	84	58
Adverse event, serious fatal	1	-	7
Consent withdrawn by subject	-	4	2
Protocol deviation	1	2	1
Unsatisfactory therapeutic effect	1	13	1
Lost to follow-up	3	5	4
Subject's no longer requires study drug	-	-	-
Early termination	87	60	43

Number of subjects in period 1	PDR/V
Started	35
Completed	0
Not completed	35
Adverse event, serious fatal	1
Consent withdrawn by subject	2
Protocol deviation	1
Unsatisfactory therapeutic effect	-
Lost to follow-up	2

Subject's no longer requires study drug	1
Early termination	28

Baseline characteristics

Reporting groups	
Reporting group title	CNV (Choroidal Neovascularization)
Reporting group description:	
All patients received 0.5 mg ranibizumab IVT injection	
Reporting group title	ME (Macular Edema)
Reporting group description:	
All patients received 0.5 mg ranibizumab IVT injection	
Reporting group title	RI/NVG (Rubeosis Iridis and Neovacular Glaucoma)
Reporting group description:	
All patients received 0.5 mg ranibizumab IVT injection	
Reporting group title	PDR/V
Reporting group description:	
(Proliferative Diabetic Retinopathy requiring Vitrectomy). All patients received 0.5 mg ranibizumab IVT injection	

Reporting group values	CNV (Choroidal Neovascularization)	ME (Macular Edema)	RI/NVG (Rubeosis Iridis and Neovacular Glaucoma)
Number of subjects	93	84	58
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)	71	38	15
From 65-84 years	22	43	35
85 years and over	0	3	8
Age Continuous Units: Years			
arithmetic mean	49.7	64.5	70.9
standard deviation	± 16.85	± 13.99	± 13.02
Gender, Male/Female Units: Subjects			
Female	48	35	26
Male	45	49	32

Reporting group values	PDR/V	Total	
Number of subjects	35	270	
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)	29	153	
From 65-84 years	6	106	
85 years and over	0	11	
Age Continuous			
Units: Years			
arithmetic mean	56.5		
standard deviation	± 9.86	-	
Gender, Male/Female			
Units: Subjects			
Female	17	126	
Male	18	144	

Subject analysis sets

Subject analysis set title	Ranibizumab 0.5 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients received 0.5 mg ranibizumab IVT injection

Reporting group values	Ranibizumab 0.5 mg		
Number of subjects	56		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	153		
From 65-84 years	106		
85 years and over	11		
Age Continuous			
Units: Years			
arithmetic mean	59.7		
standard deviation	± 16.62		
Gender, Male/Female			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	CNV (Choroidal Neovascularization)
Reporting group description:	
All patients received 0.5 mg ranibizumab IVT injection	
Reporting group title	ME (Macular Edema)
Reporting group description:	
All patients received 0.5 mg ranibizumab IVT injection	
Reporting group title	RI/NVG (Rubeosis Iridis and Neovacular Glaucoma)
Reporting group description:	
All patients received 0.5 mg ranibizumab IVT injection	
Reporting group title	PDR/V
Reporting group description:	
(Proliferative Diabetic Retinopathy requiring Vitrectomy). All patients received 0.5 mg ranibizumab IVT injection	
Subject analysis set title	Ranibizumab 0.5 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients received 0.5 mg ranibizumab IVT injection	

Primary: Number of participants with Adverse Events as a Measure of Safety and Tolerability

End point title	Number of participants with Adverse Events as a Measure of Safety and Tolerability[1]
End point description:	
Frequency of Adverse Events (AEs) and Serious Adverse Events (SAEs) for ocular and non-ocular events. Due to early termination, only descriptive analysis was conducted.	
End point type	Primary
End point timeframe:	
24 months	

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: Due to early termination, no statistical analysis was planned for this primary endpoint

End point values	CNV (Choroidal Neovascularization)	ME (Macular Edema)	RI/NVG (Rubeosis Iridis and Neovacular Glaucoma)	PDR/V
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93	84	58	35
Units: Participants				
Non- serious adverse events	2	21	1	0
Serious adverse events	11	15	31	14
Death	1	0	7	1

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline Best Corrected Visual Acuity (BCVA) for patients with Choroidal Neovascularization (CNV) and Macular Edema (ME)

End point title	Change from baseline Best Corrected Visual Acuity (BCVA) for patients with Choroidal Neovascularization (CNV) and Macular Edema (ME)[2]

End point description:

BCVA will be tested using the ETDRS, the Snellen or Monoyer scales. VA measurements will be preferentially taken in a sitting position at an initial test distance of 4 meters using ETDRS charts. The overall BCVA score will be calculated using the BCVA worksheet which will be kept in the source data and the score will be recorded in the eCRF. ETDRS, Snellen and Monoyer VA measurements will be transformed in logMAR to be analyzed.

End point type	Secondary

End point timeframe:

3 months, 12 months

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to early termination, no statistical analysis was planned for this endpoint

End point values	CNV (Choroidal Neovascularization)	ME (Macular Edema)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	84		
Units: Letters				
arithmetic mean (standard deviation)				
3 Month (n=74,69,33,17)	7.3 (± 14.47)	4.5 (± 11.61)		
12 Month (n=47,39,26,14)	5.7 (± 12.08)	5.2 (± 16.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average change of neovascularization extension for patients with neovascular glaucoma

End point title	Average change of neovascularization extension for patients with neovascular glaucoma

End point description:

Change of the extent of iris neovascularization using “Teich and Walsh grading system” using iris photography

End point type	Secondary

End point timeframe:

3 months

End point values	Ranibizumab 0.5 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	56			
Units: Teich and Walsh grading				
3 Month,Grade 0 (n=31)	12			
3 Month, Grade 1 (n=31)	6			
3 Month, Grade 2 (n=31)	8			
3 Month, Grade 3 (n=31)	3			
3 Month, Grade 4 (n=31)	2			
12 Month, Grade 0 (n=25)	11			
12 Month, Grade 1 (n=25)	4			
12 Month, Grade 2 (n=25)	2			
12 Month, Grade 3 (n=25)	4			
12 Month, Grade 4 (n=25)	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patient with Vitreous Cavity Hemorrhage occurrence for patient with proliferative retinopathy

End point title	Proportion of patient with Vitreous Cavity Hemorrhage occurrence for patient with proliferative retinopathy[3]

End point description:

Occurrence of postoperative vitreous cavity hemorrhage

End point type	Secondary

End point timeframe:

3 months, 12 month

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to early termination, no statistical analysis was planned for this endpoint

End point values	PDR/V			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Participants				
3 Month Absent (n=17)	14			
3 Month Present (n=17)	3			
12 Month Absent (n=13)	12			
12 Month Present (n=13)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in change in central retinal thickness

End point title	Mean Change From Baseline in change in central retinal thickness[4]

End point description:

CRT in micrometers assessed by Optical Tomography (OCT) at each single study visit. A reduction is thickness indicates an improvement is the lesion area

End point type	Secondary

End point timeframe:

3 months, 12 month

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to early termination, no statistical analysis was planned for this endpoint

End point values	CNV (Choroidal Neovascularization)	ME (Macular Edema)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	84		
Units: µm				
arithmetic mean (standard deviation)				
3 Month (n=74, 67)	-54.4 (± 104.55)	-84.4 (± 178.28)		
12 Month (n=45, 40)	-56.4 (± 69.82)	-102 (± 220)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with angiographic leakage

End point title	Proportion of patients with angiographic leakage[5]

End point description:

Angiography was taken via fluorescein angiography. Any increases of angiographic leakage was counted between baseline and month 3. Also any decreases of angiographic leakage was counted between baseline and 3 month.

End point type	Secondary

End point timeframe:

3 months, 12 month

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to early termination, no statistical analysis was planned for this endpoint

End point values	CNV (Choroidal Neovascularization)	ME (Macular Edema)	PDR/V	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	84	34	
Units: Participants				
3 Month Absent (n=6,6,1)	3	3	1	
3 Month Present (n=6,6,1)	3	3	0	
12 Month Absent (n=5,1,0)	3	1	0	

12 Month Present (5,1,0)	2	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Ranibizumab injection

End point title	Ranibizumab injection

End point description:

Number of ranibizumab injections needed by decreased visual acuity and/or increasing retinal thickness in 3 months of observation period

End point type	Secondary

End point timeframe:

3 months, 12 month

End point values	CNV (Choroidal Neovascularization)	ME (Macular Edema)	RI/NVG (Rubeosis Iridis and Neovacular Glaucoma)	PDR/V
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93	84	58	35
Units: Number of injections				
arithmetic mean (standard deviation)				
3 Month (n=75,70,34,17)	2.5 (± 1.03)	2.7 (± 0.88)	1.7 (± 0.79)	1.6 (± 1)
12 Month (n=44,38,21,14)	3.8 (± 2.34)	3.9 (± 2.17)	3 (± 1.96)	1.7 (± 1.44)

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	20.0

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	71 / 270 (26.30%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Choroid melanoma (Study eye)			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Metastases to liver			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Arterial disorder			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Extremity necrosis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral artery stenosis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shock haemorrhagic			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Drug ineffective (Study eye)				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atelectasis				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory arrest				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Alcohol withdrawal syndrome				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hallucination				
subjects affected / exposed	1 / 270 (0.37%)			
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	3 / 270 (1.11%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Craniocerebral injury				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				

subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laceration				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle rupture				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural complication				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				

subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Arrhythmia				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	4 / 270 (1.48%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Ischaemic cardiomyopathy				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				

subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Akinesia				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cognitive disorder				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemic coma				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vertebrobasilar insufficiency				

subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Anterior chamber fibrin (Study eye)			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blindness (Both eyes)			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cataract (Contralateral eye)			
subjects affected / exposed	3 / 270 (1.11%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cataract (Study eye)			
subjects affected / exposed	2 / 270 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Glaucoma (Contralateral eye)			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glaucoma (Study eye)			
subjects affected / exposed	3 / 270 (1.11%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Macular detachment (Both eyes)			

subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Macular fibrosis (Study eye)				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ocular hypertension (Both eyes)				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ocular hypertension (Study eye)				
subjects affected / exposed	9 / 270 (3.33%)			
occurrences causally related to treatment / all	1 / 10			
deaths causally related to treatment / all	0 / 0			
Retinal artery occlusion (Both eyes)				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal detachment (Study eye)				
subjects affected / exposed	4 / 270 (1.48%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Retinal pigment epithelial tear (Study eye)				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal tear (Study eye)				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Visual acuity reduced (Both eyes)				

subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Visual acuity reduced (Study eye)				
subjects affected / exposed	3 / 270 (1.11%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Vitreous adhesions (Contralateral eye)				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vitreous adhesions (Study eye)				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vitreous haemorrhage (Contralateral eye)				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Vitreous haemorrhage (Study eye)				
subjects affected / exposed	5 / 270 (1.85%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Duodenal obstruction				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal angiodysplasia				

subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal dysplasia			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pancreatic mass			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephroangiosclerosis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Renal failure				
subjects affected / exposed	3 / 270 (1.11%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Osteoarthropathy				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Corneal abscess (Study eye)				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Influenza				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonsillar abscess				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Syphilis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	4 / 270 (1.48%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 270 (0.37%)		
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 %

Non-serious adverse events	Ranibizumab 0.5 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	144 / 270 (53.33%)		
Investigations			
Blood urea increased			
subjects affected / exposed	3 / 270 (1.11%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 270 (1.11%)		
occurrences (all)	3		

Inappropriate schedule of drug administration (Study eye) subjects affected / exposed occurrences (all)	37 / 270 (13.70%) 38		
Incorrect product storage (Study eye) subjects affected / exposed occurrences (all)	11 / 270 (4.07%) 17		
Vascular disorders Haematoma subjects affected / exposed occurrences (all)	3 / 270 (1.11%) 3		
Hypertension subjects affected / exposed occurrences (all)	4 / 270 (1.48%) 4		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	5 / 270 (1.85%) 5		
Headache subjects affected / exposed occurrences (all)	13 / 270 (4.81%) 19		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	3 / 270 (1.11%) 3		
Drug ineffective (Study eye) subjects affected / exposed occurrences (all)	31 / 270 (11.48%) 31		
Fatigue subjects affected / exposed occurrences (all)	9 / 270 (3.33%) 9		
Eye disorders Cataract (Study eye) subjects affected / exposed occurrences (all)	4 / 270 (1.48%) 4		
Conjunctival haemorrhage (Study eye)			

subjects affected / exposed	5 / 270 (1.85%)		
occurrences (all)	5		
Dry eye (Study eye)			
subjects affected / exposed	4 / 270 (1.48%)		
occurrences (all)	4		
Eye pain (Study eye)			
subjects affected / exposed	21 / 270 (7.78%)		
occurrences (all)	25		
Eye pruritus (Study eye)			
subjects affected / exposed	4 / 270 (1.48%)		
occurrences (all)	4		
Ocular hyperaemia (Study eye)			
subjects affected / exposed	3 / 270 (1.11%)		
occurrences (all)	3		
Ocular hypertension (Study eye)			
subjects affected / exposed	5 / 270 (1.85%)		
occurrences (all)	5		
Punctate keratitis (Study eye)			
subjects affected / exposed	3 / 270 (1.11%)		
occurrences (all)	3		
Ulcerative keratitis (Study eye)			
subjects affected / exposed	5 / 270 (1.85%)		
occurrences (all)	6		
Vision blurred (Study eye)			
subjects affected / exposed	5 / 270 (1.85%)		
occurrences (all)	5		
Visual acuity reduced (Contralateral eye)			
subjects affected / exposed	3 / 270 (1.11%)		
occurrences (all)	3		
Visual acuity reduced (Study eye)			
subjects affected / exposed	7 / 270 (2.59%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			

Rhinitis allergic subjects affected / exposed occurrences (all)	3 / 270 (1.11%) 3		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	3 / 270 (1.11%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	5 / 270 (1.85%) 5 5 / 270 (1.85%) 5		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Conjunctivitis (Both eyes) subjects affected / exposed occurrences (all) Conjunctivitis (Study eye) subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 270 (1.85%) 5 3 / 270 (1.11%) 3 3 / 270 (1.11%) 3 5 / 270 (1.85%) 5 4 / 270 (1.48%) 4 3 / 270 (1.11%) 3 4 / 270 (1.48%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2013	due to several modifications in this version, the ethic committees asked for a new version of the protocol, with corrections highlighted. This version was used at the beginning of the project
16 December 2013	the wording of the inclusion criterion n°2 was changed from "Patient with diagnosis of active choroidal neovascularization (CNV) secondary to any causes (except wAMD, PM and PXE), involving the center of the fovea, confirmed by complete ocular examination of the study eye" to "Patient with diagnosis of active choroidal neovascularization (CNV) secondary to any causes (except wAMD, PM and PXE), involving the center of the macula, confirmed by complete ocular examination of the study eye". This version V5 was issued after 13 patients had been recruited.
05 February 2014	this modification of the protocol authorized the investigators to use of the data of ophthalmic examinations present in the medical record of the patient when these examinations were realized within 14 days before the visit of selection (V1), if the patient was eligible. This modification was implemented to avoid the repetition of potentially invasive ophthalmological examination (e.g. angiography) if already performed recently. This decreased the number of ophthalmologic examinations for as they were not necessary from a medical perspective.
28 May 2015	this amendment was issued to collect additional safety and efficacy data from year 2 to year 3 in patients treated with ranibizumab for rare ocular VEGF-driven diseases. This one-year extension of the study would also respond to an unmet medical need for licensed therapies that could be used to treat rare ocular VEGF-driven diseases affecting visual function. Indeed, extending the follow-up allowed treating with ranibizumab patients with such diseases. Consistently, changes related to this one-year extension were done throughout the protocol (e.g., additional secondary objectives, analysis of additional secondary variables).

31 August 2015	this amendment was issued to provide clarifications about assessing and treating the patients. These clarifications (listed below) primarily provided more details about the administration of treatment and the assessment of visual acuity : - Change to Instructions for prescribing and taking study treatment (section 5.5.4): clarification that the interval between 2 ranibizumab injections should not been shorter than 28 days. - Changes to Patient demographics/other baseline characteristics (section 6.2): clarification that day of birth was recorded in the eCRF. - Changes to Best-corrected visual acuity (BCVA) (section 6.4.1): clarification that an ETDRS BCVA assessment could be performed at 2 meters. "If the ETDRS BCVA measurement was performed at 2 meters instead of 4 meters (using 4 meters ETDRS scales), a correction was applied by removing 15 letters (3 lines) to the ETDRS score obtained at 2 meters." - Changes to Informed consent (section 11.2): clarification that it was not the responsibility of the investigator to submit informed consent form for CPP approval. These changes of protocol were not considered to have an impact on the study population or on the patients' safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

As the study was early terminated, no conclusion could be drawn from this study. The data should be interpreted with cautious as less than half of the patients included in the study (47.0%) completed the visit at Month 12.

Notes: