Clinical trial results:
A 6-month multicenter, randomized, double-masked phase IIIb-study comparing the efficacy and safety of Lucentis (ranibizumab) intravitreal injections versus Ozurdex (dexamethasone) intravitreal implant in patients with visual impairment due to macular edema following central retinal vein occlusion (CRVO)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2011-001020-38
Trial protocol	DE GB HU CZ PL
Global end of trial date	21 January 2014
Results information	
Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018

Trial information

Trial identification	
Sponsor protocol code	CRFB002EDE18
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01396083
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Cinical Disclosure Office, Novartis Pharma AG, 41 613241111 ,
Scientific contact	Cinical 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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to show that ranibizumab (administered in an individualized treatment regimen) has superior efficacy and safety compared to dexamethasone implant (Ozurdex®) over a 6 month period.

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. In addition, only one eye was chosen as the study eye. If both eyes were eligible, the eye with the worse VA as assessed at the baseline visit was selected for study treatment, unless, based on medical reasons, the investigator deemed the other eye to be more appropriate for study treatment. Only the study eye was treated with either of the study drugs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2011
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	United Kingdom: 53
Country: Number of subjects enrolled	Germany: 176
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Poland: 9
Worldwide total number of subjects	243
EEA total number of subjects	243

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	104
From 65 to 84 years	124
85 years and over	15

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Three-hundred-twenty-five patients were screened for study eligibility at 66 German and European study sites while 82 patients failed screening (multiple reasons per patient were possible). In total, 243 patients were randomized.

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	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ranibizumab

Arm description:

Randomized patients received injections of 0.5 mg ranibizumab according to the proposed European label: consecutive monthly intravitreal injections with 0.5 mg ranibizumab until visual acuity (VA) stability was achieved, followed by a PRN (pro re nata/taken as needed) re-treatment if there was a decline from stable VA levels due to macular edema. Stability could be confirmed when a patient's VA was stable for three consecutive monthly assessments performed while on ranibizumab treatment.

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:

0.5 mg/0.05 ml solution to be injected intravitreally

Arm title	Dexamethasone

Arm description:

Patients randomized to dexamethasone received a single intravitreal implant (700 µg; long acting release [LAR] over 6 months) at baseline and sham-injections thereafter.

Arm type	Active comparator
Investigational medicinal product name	dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Patients randomized to dexamethasone received a single intravitreal implant (700 µg; long acting release (LAR) over 6 months) at baseline and sham-injections thereafter.

Number of subjects in period 1	Ranibizumab	Dexamethasone
Started	124	119
Completed	113	72
Not completed	11	47
Abnormal laboratory value(s)	1	-
Consent withdrawn by subject	4	5
Unsatisfactory therapeutic effect	2	13
Administrative problems	1	-
Adverse Event(s)	2	28
Lost to follow-up	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Ranibizumab
Reporting group description:	
Randomized patients received injections of 0.5 mg ranibizumab according to the proposed European label: consecutive monthly intravitreal injections with 0.5 mg ranibizumab until visual acuity (VA) stability was achieved, followed by a PRN (pro re nata/taken as needed) re-treatment if there was a decline from stable VA levels due to macular edema. Stability could be confirmed when a patient's VA was stable for three consecutive monthly assessments performed while on ranibizumab treatment.	
Reporting group title	Dexamethasone
Reporting group description:	
Patients randomized to dexamethasone received a single intravitreal implant (700 µg; long acting release [LAR] over 6 months) at baseline and sham-injections thereafter.	

Reporting group values	Ranibizumab	Dexamethasone	Total
Number of subjects	124	119	243
Age categorical Units: Subjects			
≤65 years	59	52	111
>65 years	65	67	132
Age continuous			
The EMA result system autopopulates the "-" and will not allow the entry of the mean age for the trial, which is 66.1 (standard deviation 11.9)			
Units: years			
arithmetic mean	65.3	66.9	
standard deviation	± 11.4	± 12.4	-
Gender categorical Units: Subjects			
Female	52	46	98
Male	72	73	145

End points

End points reporting groups

Reporting group title	Ranibizumab

Reporting group description:

Randomized patients received injections of 0.5 mg ranibizumab according to the proposed European label: consecutive monthly intravitreal injections with 0.5 mg ranibizumab until visual acuity (VA) stability was achieved, followed by a PRN (pro re nata/taken as needed) re-treatment if there was a decline from stable VA levels due to macular edema. Stability could be confirmed when a patient's VA was stable for three consecutive monthly assessments performed while on ranibizumab treatment.

Reporting group title	Dexamethasone

Reporting group description:

Patients randomized to dexamethasone received a single intravitreal implant (700 µg; long acting release [LAR] over 6 months) at baseline and sham-injections thereafter.

Primary: Mean Average best corrected visual acuity (BCVA) Change From Month 1 Through Month 6 to Baseline

End point title	Mean Average best corrected visual acuity (BCVA) Change From Month 1 Through Month 6 to Baseline

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 ETDRS visual acuity score of 85 is approximately 20/20. An increased score indicates improvement in acuity.

End point type	Primary

End point timeframe:

The average of the changes in BCVA (letters) from baseline to any post-baseline visit, i.e. the mean of six differences to baseline for the six post-baseline visits at Month 1 to 6.

End point values	Ranibizumab	Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[1]	119[2]		
Units: letters				
least squares mean (confidence interval 95%)	12.86 (10.24 to 15.48)	2.96 (0.27 to 5.64)		

Notes:

[1] - Full analysis set , Last observation carried forward (LOCF)

[2] - Full analysis set, Last observation carried forward (LOCF)

Statistical analyses

Statistical analysis title	Full Analysis Set

Statistical analysis description:

The Full Analysis Set consisted of all patients from the Randomized Set who had received at least one application of study treatment and had at least one post-baseline assessment for BCVA. Following the intent-to-treat principle, patients were analyzed according to the treatment assigned. The null-hypothesis to be rejected was that there is no difference in the change of BCVA (letters), averaged over all post-baseline visits, between patients under ranibizumab and those under dexamethasone.

Comparison groups	Ranibizumab v Dexamethasone

Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	9.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.51
upper limit	13.3

Notes:

[3] - The primary analysis was performed by an analysis of covariance (ANCOVA) model with average change in BCVA (letters) from Visit 1 through Visit 6 as dependent variable, and with the factors center, treatment, and covariate baseline BCVA as predictors.

Secondary: Mean BCVA Change at Month 6

End point title	Mean BCVA Change at Month 6

End point description:

To compare the mean BCVA change at Month 6 from Baseline in patients treated with dexamethasone versus ranibizumab.The analysis was performed by an analysis of covariance (ANCOVA) model with average change in BCVA (letters) from Visit 1 through Visit 6 as dependent variable, and with the factors center, treatment, and covariate baseline BCVA as predictors.

End point type	Secondary

End point timeframe:

Baseline, month 6

End point values	Ranibizumab	Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	119		
Units: letters				
least squares mean (confidence interval 95%)	14.78 (11.24 to 18.32)	-3.17 (-6.8 to 0.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Gaining / Losing ≥ 15 / 10 / 5 Letters

End point title	Number of Patients Gaining / Losing ≥ 15 / 10 / 5 Letters

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 ETDRS visual acuity score of 85 is approximately 20/20. An increased score indicates improvement in acuity. This outcome assessed the number of participants who gained 15, 10 or 5 more letters of visual acuity at month 6 as compared with baseline. This analysis is done on the full analysis set (FAS) which consisted of all patients from the Randomized Set (RS) who had received at least one application of study treatment and had at least one post-baseline assessment for BCVA. Following the intent-to-treat

principle, patients were analyzed according to the treatment assigned.

End point type	Secondary

End point timeframe:

Baseline, 6 months

End point values	Ranibizumab	Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[4]	119[5]		
Units: patients				
Gain≥15 letters	73	22		
Loss of ≥15 letters	1	31		
Gain ≥10 letters	89	38		
Loss of ≥10 letters	4	35		
Gain ≥5 letters	104	54		
Loss of ≥5 letters	5	40		

Notes:

[4] - Full Analysis Set

[5] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Achieve a Significant Improvement ≥ 15 Letters

End point title	Time to Achieve a Significant Improvement ≥ 15 Letters

End point description:

The time was analyzed by the Kaplan-Maier-Method, adjusting the calculation for dropouts. This was based on the full analysis set (FAS), which consisted of all patients from the Randomized Set (RS) who had received at least one application of study treatment and had at least one post-baseline assessment for BCVA. Following the intent-to-treat principle, patients were analyzed according to the treatment assigned. For the dexamethasone treatment group, 99999.9 represents not applicable data becasue EudraCT system is not accepting "NA" for not available/not applicable data.

End point type	Secondary

End point timeframe:

Baseline, Month 6

End point values	Ranibizumab	Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	119		
Units: Days				
median (confidence interval 95%)	62 (56 to 91)	98 (63 to 99999.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change Over Time in BCVA (letters)

End point title	Change Over Time in BCVA (letters)

End point description:

The analysis was performed by an analysis of covariance (ANCOVA) model with average change in BCVA (letters) from Visit 1 through Visit 6 as dependent variable, and with the factors center, treatment and covariate baseline BCVA as predictors, for the Full Analysis Set (FAS) and last observation carried forward (LOCF).

End point type	Secondary

End point timeframe:

Baseline, month 6

End point values	Ranibizumab	Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	119		
Units: letters				
least squares mean (confidence interval 95%)				
Month 1	9.77 (7.27 to 12.27)	9.54 (6.98 to 12.1)		
Month 2	12.25 (9.59 to 14.91)	11.04 (8.31 to 13.76)		
Month 3	14.04 (10.92 to 17.16)	4.99 (1.79 to 8.18)		
Month 4	12.76 (9.48 to 16.04)	-1.73 (-5.09 to 1.63)		
Month 5	13.57 (10.25 to 16.89)	-2.92 (-6.33 to 0.48)		
Month 6	14.78 (11.24 to 18.32)	-3.17 (-6.8 to 0.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change Over Time of the Central Retinal Thickness (CRT)

End point title	Change Over Time of the Central Retinal Thickness (CRT)

End point description:

Retinal thickness was measured using Optical Coherence Tomography (OCT). Data presented are the course of CRT (µm) over time from baseline to month 6, assessed by investigator (Full Analysis Set/Last Observation Carried Forward).

End point type	Secondary

End point timeframe:

Baseline, month 6

End point values	Ranibizumab	Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	119		
Units: µm				
arithmetic mean (standard deviation)				
Change Over Time of the Central Retinal Thickness	-376.7 (± 274.9)	-168.7 (± 288.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in the Quality of Life According to the National Eye Institute Visual Function Questionnaire (NEI-VFQ 25) Questionnaires

End point title	Changes in the Quality of Life According to the National Eye Institute Visual Function Questionnaire (NEI-VFQ 25) Questionnaires

End point description:

The VFQ-25 composite and subscale scores range from 0 to 100, a higher score indicating better functioning. The 12 subscales in the VFQ-25 are general health, general vision, ocular pain, near activities, distance activities, social function, mental health, role difficulties, dependency, driving, color vision, and peripheral vision. The scores on the subscales were added together for a total score, which ranged from 0 to 100. A higher score indicated improvement in quality of life due to vision function. An overall composite score can be calculated and is provided.

End point type	Secondary

End point timeframe:

Composite score Baseline, 6 months

End point values	Ranibizumab	Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	118		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Changes in the NEI-VFQ 25 Questionnaire	6 (± 12.1)	2 (± 10.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in the Quality of Life According to the Short Form (36) Health Survey (SF-36) Questionnaires

End point title	Changes in the Quality of Life According to the Short Form (36) Health Survey (SF-36) Questionnaires

End point description:

SF-36 summary measures are norm-based scores with mean = 50 and SD = 10. Higher scores indicate better health.

End point type	Secondary

End point timeframe:

Baseline, month 6

End point values	Ranibizumab	Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	113		
Units: Units on a scale				
arithmetic mean (standard deviation)				
SF-36 physical component (n=116,113)	-0.7 (± 6.3)	0.4 (± 6.6)		
SF-36 mental component (n=116,113)	2.4 (± 8.7)	0.4 (± 9.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in the Quality of Life According to Euro Quality of Life (EQ-5D) Questionnaires

End point title	Changes in the Quality of Life According to Euro Quality of Life (EQ-5D) Questionnaires

End point description:

The EQ-5D visual analog scale ranges from 0 to 100, 0 representing the worst and 100 the best imaginable health state.

End point type	Secondary

End point timeframe:

Baseline, month 6

End point values	Ranibizumab	Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	114		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Changes in QOL according to EQ-5D	0.1 (± 13.2)	2 (± 14.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Increase Rate of Intraocular Pressure (IOP): number of patients with ≥10% increase in IOP compared to baseline (safety set)

End point title	Increase Rate of Intraocular Pressure (IOP): number of patients with ≥10% increase in IOP compared to baseline (safety set)

End point description:

The number of patients with ≥ 10% increase in Internal Ocular Pressure (IOP) compared to baseline at any post-baseline visit.

End point type	Secondary

End point timeframe:

Baseline, month 6

End point values	Ranibizumab	Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	119		
Units: Patients				
Any post-baseline visit	94	105		

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	16.1

Reporting groups

Reporting group title	Ranibizumab

Reporting group description:

Randomized patients received injections of 0.5 mg ranibizumab according to the proposed European label: consecutive monthly intravitreal injections with 0.5 mg ranibizumab until visual acuity (VA) stability was achieved, followed by a PRN (pro re nata/taken as needed) re-treatment if there was a decline from stable VA levels due to macular edema. Stability could be confirmed when a patient's VA was stable for three consecutive monthly assessments performed while on ranibizumab treatment.

Reporting group title	Dexamethasone

Reporting group description:

Patients randomized to dexamethasone received a single intravitreal implant (700 µg; long acting release [LAR] over 6 months) at baseline and sham-injections thereafter.

Serious adverse events	Ranibizumab	Dexamethasone	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 124 (8.06%)	16 / 119 (13.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA OF COLON			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL CARCINOMA			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL NEOPLASM			

subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
PROSTATITIS			
subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
INTRAOCULAR PRESSURE DECREASED (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTRAOCULAR PRESSURE INCREASED (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROSTATIC SPECIFIC ANTIGEN INCREASED			

subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
UPPER LIMB FRACTURE			
subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WRIST FRACTURE			
subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
ADENOMATOUS POLYPOSIS COLI			
subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ANGINA PECTORIS			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 124 (0.81%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			

subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MITRAL VALVE INCOMPETENCE			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIAL NERVE PALSY			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 124 (0.00%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
DEAFNESS			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
CONJUNCTIVAL HYPERAEMIA (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORNEAL OEDEMA (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

EYE PAIN (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GLAUCOMA (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPHAEMA (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
IRIS NEOVASCULARISATION (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	4 / 119 (3.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
MACULAR OEDEMA (Study eye)			
subjects affected / exposed	1 / 124 (0.81%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL ARTERY OCCLUSION (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL VEIN OCCLUSION (Study eye)			
subjects affected / exposed	1 / 124 (0.81%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VISUAL ACUITY REDUCED (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

VITREOUS HAEMORRHAGE (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL HERNIA			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRODUODENAL ULCER			
subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL RUPTURE			
subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UMBILICAL HERNIA			
subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
CYSTITIS			

subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	1 / 124 (0.81%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOFT TISSUE INFECTION			
subjects affected / exposed	0 / 124 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2.5 %

Non-serious adverse events	Ranibizumab	Dexamethasone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 124 (62.10%)	99 / 119 (83.19%)	
Investigations			
BLOOD GLUCOSE INCREASED			
subjects affected / exposed	4 / 124 (3.23%)	2 / 119 (1.68%)	
occurrences (all)	4	2	
INTRAOCULAR PRESSURE INCREASED (Fellow eye)			
subjects affected / exposed	0 / 124 (0.00%)	3 / 119 (2.52%)	
occurrences (all)	0	3	
INTRAOCULAR PRESSURE INCREASED (Study eye)			
subjects affected / exposed	7 / 124 (5.65%)	38 / 119 (31.93%)	
occurrences (all)	10	41	
Vascular disorders			
HYPERTENSION			

subjects affected / exposed	5 / 124 (4.03%)	3 / 119 (2.52%)	
occurrences (all)	6	3	
VASCULAR SHUNT (Study eye)			
subjects affected / exposed	1 / 124 (0.81%)	3 / 119 (2.52%)	
occurrences (all)	1	3	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	7 / 124 (5.65%)	10 / 119 (8.40%)	
occurrences (all)	9	11	
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 124 (0.00%)	3 / 119 (2.52%)	
occurrences (all)	0	3	
Eye disorders			
ABNORMAL SENSATION IN EYE (Study eye)			
subjects affected / exposed	6 / 124 (4.84%)	8 / 119 (6.72%)	
occurrences (all)	8	9	
CONJUNCTIVAL HAEMORRHAGE (Study eye)			
subjects affected / exposed	16 / 124 (12.90%)	13 / 119 (10.92%)	
occurrences (all)	18	13	
DRY EYE (Fellow eye)			
subjects affected / exposed	4 / 124 (3.23%)	1 / 119 (0.84%)	
occurrences (all)	4	1	
DRY EYE (Study eye)			
subjects affected / exposed	4 / 124 (3.23%)	4 / 119 (3.36%)	
occurrences (all)	4	5	
EYE IRRITATION (Study eye)			
subjects affected / exposed	4 / 124 (3.23%)	3 / 119 (2.52%)	
occurrences (all)	5	5	
FOREIGN BODY SENSATION IN EYES (Study eye)			
subjects affected / exposed	6 / 124 (4.84%)	6 / 119 (5.04%)	
occurrences (all)	6	6	
EYE PAIN (Study eye)			

subjects affected / exposed	15 / 124 (12.10%)	14 / 119 (11.76%)	
occurrences (all)	22	16	
GLAUCOMA (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	5 / 119 (4.20%)	
occurrences (all)	0	5	
LACRIMATION INCREASED (Study eye)			
subjects affected / exposed	6 / 124 (4.84%)	8 / 119 (6.72%)	
occurrences (all)	7	8	
IRIS NEOVASCULARISATION (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	5 / 119 (4.20%)	
occurrences (all)	0	5	
MACULAR ISCHAEMIA (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	3 / 119 (2.52%)	
occurrences (all)	0	3	
OCULAR HYPERAEMIA (Study eye)			
subjects affected / exposed	14 / 124 (11.29%)	15 / 119 (12.61%)	
occurrences (all)	27	20	
MACULAR OEDEMA (Study eye)			
subjects affected / exposed	13 / 124 (10.48%)	19 / 119 (15.97%)	
occurrences (all)	14	21	
OCULAR HYPERTENSION (Study eye)			
subjects affected / exposed	0 / 124 (0.00%)	6 / 119 (5.04%)	
occurrences (all)	0	10	
OPTIC DISC VASCULAR DISORDER (Study eye)			
subjects affected / exposed	5 / 124 (4.03%)	0 / 119 (0.00%)	
occurrences (all)	5	0	
RETINAL EXUDATES (Study eye)			
subjects affected / exposed	2 / 124 (1.61%)	4 / 119 (3.36%)	
occurrences (all)	2	4	
RETINAL ISCHAEMIA (Study eye)			
subjects affected / exposed	1 / 124 (0.81%)	6 / 119 (5.04%)	
occurrences (all)	1	6	
RETINAL VASCULAR DISORDER (Study eye)			

subjects affected / exposed	2 / 124 (1.61%)	5 / 119 (4.20%)	
occurrences (all)	2	5	
VISUAL IMPAIRMENT (Study eye)			
subjects affected / exposed	2 / 124 (1.61%)	6 / 119 (5.04%)	
occurrences (all)	2	6	
VISUAL ACUITY REDUCED (Study eye)			
subjects affected / exposed	8 / 124 (6.45%)	19 / 119 (15.97%)	
occurrences (all)	10	19	
VITREOUS DETACHMENT (Study eye)			
subjects affected / exposed	5 / 124 (4.03%)	3 / 119 (2.52%)	
occurrences (all)	5	3	
VITREOUS FLOATERS (Study eye)			
subjects affected / exposed	5 / 124 (4.03%)	11 / 119 (9.24%)	
occurrences (all)	6	11	
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	6 / 124 (4.84%)	2 / 119 (1.68%)	
occurrences (all)	7	2	
NAUSEA			
subjects affected / exposed	4 / 124 (3.23%)	3 / 119 (2.52%)	
occurrences (all)	4	4	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 124 (1.61%)	3 / 119 (2.52%)	
occurrences (all)	3	3	
BACK PAIN			
subjects affected / exposed	7 / 124 (5.65%)	4 / 119 (3.36%)	
occurrences (all)	7	4	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	1 / 124 (0.81%)	3 / 119 (2.52%)	
occurrences (all)	1	3	
NASOPHARYNGITIS			
subjects affected / exposed	9 / 124 (7.26%)	12 / 119 (10.08%)	
occurrences (all)	9	16	

URINARY TRACT INFECTION subjects affected / exposed occurrences (all)	1 / 124 (0.81%) 1	4 / 119 (3.36%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2011	This amendment was introduced to include: • Addition of country-specific requirements regarding the use of contraception and pregnancy advice within the United Kingdom • Addition of the use of antimicrobial drops for 3 days before any visit when an injection was scheduled to be performed as required by local or country-specific practices, • Addition of minor changes including some typographical errors
10 October 2011	As Lucentis (ranibizumab) became commercially available in May 2011 for the treatment of RVO, the protocol amendment was made to allow for usage of both commercially available Lucentis (according to local requirements and approvals) as well as ranibizumab clinical trial stock. Furthermore, changes were made concerning the study drug preparation procedure in that for sham injections empty vials were no longer provided. In order to maintain the masking only the syringe, either empty in the case of sham-injections or pre-filled in the case of ranibizumab injections, were visible to the patient in the room of study drug administration; study drug withdrawal took place in a separate room or area, such that the patient remained masked to treatment. This procedure was in line with usual medical practice. Finally, administrative errors have been corrected. The following sections of the protocol had been changed: Investigational and control drugs, Dispensing the study drug, Assessment schedule, Treatment procedures
12 December 2011	Amendment was made to consolidate the changes made in the two previous amendments in a single amended protocol. Additionally, minor changes and corrections were made: Efficacy, Assessment schedule.

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: