Clinical trial results:
A 24-month, phase IIIb, open-label, randomized, active-controlled, 3-arm, multicenter study assessing the efficacy and safety of an individualized, stabilization-criteria-driven pro re nata (PRN) dosing regimen with 0.5-mg ranibizumab intravitreal injections applied as monotherapy or with adjunctive laser photocoagulation in comparison to laser photocoagulation in patients with visual impairment due to macular edema (ME) secondary to branch retinal vein occlusion (BRVO) (BRIGHTER).

Summary

EudraCT number	2011-002859-34
Trial protocol	IE GB SE HU CZ ES SK GR NL PT PL FR IT DK
Global end of trial date	27 May 2015

Results information

Result version number	v1 (current)
This version publication date	11 June 2016
First version publication date	11 June 2016

Trial information

Trial identification

Sponsor protocol code	CRFB002E2402

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01599650
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 May 2015
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

Primary objective: to demonstrate that an individualized stabilization-criteria-driven PRN dosing regimen with 0.5-mg ranibizumab administered with or without adjunctive laser treatment had superior efficacy as compared to the current standard of care, laser photocoagulation, in patients with visual impairment due to ME secondary to BRVO. The primary objective was assessed by the mean best corrected visual acuity (BCVA) change at Month 6 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	24 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Canada: 55
Country: Number of subjects enrolled	Czech Republic: 30
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Greece: 36
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Portugal: 39
Country: Number of subjects enrolled	Slovakia: 36
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United Kingdom: 53

Worldwide total number of subjects	455
EEA total number of subjects	379

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)	199
From 65 to 84 years	244
85 years and over	12

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of 612 patients screened, 455 were randomized on a 2:2:1 ratio to receive ranibizumab (183 patients), ranibizumab with laser (180 patients), and laser monotherapy (92 patients)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	1-ranibizumab monotherapy

Arm description:

laser therapy + Ranibizumab 0.5 mg

Arm type	Experimental
Investigational medicinal product name	ranibizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

0.5-mg PRN by intravitreal injections

Arm title	2-ranibizumab with laser

Arm description:

Ranibizumab 0.5 mg + laser

Arm type	Experimental
Investigational medicinal product name	ranibizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

0.5-mg ranibizumab administered PRN by intravitreal injections

Arm title	3-laser monothery

Arm description:

after 6 months, laser patients could be treated with ranibizumab

Arm type	Experimental
Investigational medicinal product name	ranibizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

after 6 months, 0.5-mg ranibizumab administered PRN by intravitreal injections

Number of subjects in period 1	1-ranibizumab monotherapy	2-ranibizumab with laser	3-laser monothery
Started	183	180	92
Completed 6 mos	174	170	80
Completed	161	154	65
Not completed	22	26	27
Adverse event, serious fatal	2	1	2
Physician decision	2	-	7
Consent withdrawn by subject	11	11	10
Adverse event, non-fatal	3	8	4
Administrative issue	1	-	1
Lost to follow-up	3	3	3
Protocol deviation	-	3	-

Baseline characteristics

Reporting groups	
Reporting group title	1-ranibizumab monotherapy
Reporting group description: laser therapy + Ranibizumab 0.5 mg	
Reporting group title	2-ranibizumab with laser
Reporting group description: Ranibizumab 0.5 mg + laser	
Reporting group title	3-laser monothery
Reporting group description: after 6 months, laser patients could be treated with ranibizumab	

Reporting group values	1-ranibizumab monotherapy	2-ranibizumab with laser	3-laser monothery
Number of subjects	183	180	92
Age categorical Units: Subjects			
Adults (18-64 years)	90	71	38
From 65-84 years	91	104	49
85 years and over	2	5	5
Age Continuous Units: years			
arithmetic mean	64.7	67.3	67.7
standard deviation	± 10.34	± 10.41	± 9.67
Gender, Male/Female Units: participants			
Female	90	84	55
Male	93	96	37

Reporting group values	Total		
Number of subjects	455		
Age categorical Units: Subjects			
Adults (18-64 years)	199		
From 65-84 years	244		
85 years and over	12		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: participants			
Female	229		
Male	226		

End points

End points reporting groups

Reporting group title	1-ranibizumab monotherapy
Reporting group description: laser therapy + Ranibizumab 0.5 mg	
Reporting group title	2-ranibizumab with laser
Reporting group description: Ranibizumab 0.5 mg + laser	
Reporting group title	3-laser monothery
Reporting group description: after 6 months, laser patients could be treated with ranibizumab	

Primary: Mean change in visual acuity: BCVA change at Month 6 compared to Baseline in patients with visual impairment due to Branch retinal vein occlusion (BRVO)

End point title	Mean change in visual acuity: BCVA change at Month 6 compared to Baseline in patients with visual impairment due to Branch retinal vein occlusion (BRVO)

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. For the mean change of best corrected visual acuity at Month 6 compare to Baseline, the 95% confidence interval and P value (related to the null hypothesis that this mean change is equal to zero) based on a t distribution/t test were calculated and assessed by an ANOVA model.

End point type	Primary

End point timeframe:

Baseline, 6 Months

End point values	1-ranibizumab monotherapy	2-ranibizumab with laser	3-laser monothery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	178	90	
Units: letters				
arithmetic mean (standard deviation)				
Baseline	59.5 (± 11.78)	56.6 (± 13.19)	56.8 (± 13.86)	
Month 6	74.3 (± 12.27)	71.4 (± 14.43)	62.8 (± 14.08)	
Change from Baseline at Month 6	14.8 (± 10.7)	14.8 (± 11.13)	6 (± 14.27)	

Statistical analyses

Statistical analysis title	Group 1 vs Group 3
Comparison groups	1-ranibizumab monotherapy v 3-laser monothery

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANOVA
Parameter estimate	difference in LS mean
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.3
upper limit	12.8
Variability estimate	Standard error of the mean
Dispersion value	1.41

Statistical analysis title	Group 2 vs Group 3
Comparison groups	2-ranibizumab with laser v 3-laser monothery
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANOVA
Parameter estimate	difference in LS Means
Point estimate	8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.8
upper limit	11.6
Variability estimate	Standard error of the mean
Dispersion value	1.46

Secondary: The mean average change in visual acuity from Month 1 through Month 24 compared to Baseline

End point title	The mean average change in visual acuity from Month 1 through 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): Mean Average Change: for each patient, first average change is calculated as the average of the changes from baseline to Month 1 over Month 24. Then, mean average change is calculated as the average of average changes across all patients.

End point type	Secondary

End point timeframe:

Baseline, 24 Months

End point values	1-ranibizumab monotherapy	2-ranibizumab with laser	3-laser monothery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	178	90	
Units: letters				
arithmetic mean (standard deviation)				
Baseline	59.5 (± 11.78)	56.6 (± 13.19)	56.8 (± 13.86)	
Average Month 1 to Month 24	74.5 (± 12.11)	72 (± 13.56)	65.9 (± 13.24)	
Change from Baseline	15 (± 10.86)	15.4 (± 10.76)	9.1 (± 13.49)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of ranibizumab treatments from Day 1 to Month 23 by treatment group

End point title	Number of ranibizumab treatments from Day 1 to Month 23 by treatment group[1]

End point description:

Number of injections provided to the patients during the 23 month period and conducted within FAS with LOCF and observed data.

End point type	Secondary

End point timeframe:

Day 1 through Month 23

Notes:

[1] - 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: provide output for primary endpoints only

End point values	1-ranibizumab monotherapy	2-ranibizumab with laser		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	178		
Units: treatments				
arithmetic mean (standard deviation)	11.4 (± 5.76)	11.3 (± 6.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean average change in visual acuity (BCVA letters) from Month 1 through Month 6

End point title	Mean average change in visual acuity (BCVA letters) from Month 1 through Month 6

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): Mean Average Change: for each patient, first average change is calculated as the average of the changes from baseline to Month 1 over Month 6. Then, mean average change is calculated as the average of average changes across all patients.

End point type	Secondary

End point timeframe:

From Baseline through Month 6

End point values	1-ranibizumab monotherapy	2-ranibizumab with laser	3-laser monothery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	178	90	
Units: BCVA				
arithmetic mean (standard deviation)				
Baseline	59.5 (± 11.78)	56.6 (± 13.19)	56.8 (± 13.86)	
Average Month 1 to Month 6	72.7 (± 11.49)	69.7 (± 13.38)	61.7 (± 12.66)	
Change from Baseline	13.2 (± 9.6)	13.2 (± 9.89)	4.8 (± 11.69)	

Statistical analyses

No statistical analyses for this end point

Secondary: The mean change in visual acuity BCVA (letters) from Baseline at Month 12 and Month 24

End point title	The mean change in visual acuity BCVA (letters) from Baseline at 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. For the mean change of best corrected visual acuity at Month 12 and Month 24 compare to Baseline, the 95% confidence interval and P value (related to the null hypothesis that this mean change is equal to zero) based on a t distribution/t test were calculated and were assessed by an ANOVA model.

End point type	Secondary

End point timeframe:

Baseline, Month 12 and Month 24

End point values	1-ranibizumab monotherapy	2-ranibizumab with laser	3-laser monothery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	178	90	
Units: letters				
arithmetic mean (standard deviation)				
Baseline	59.5 (± 11.78)	56.6 (± 13.19)	56.8 (± 13.78)	

Month 12	74.9 (± 12.87)	72.3 (± 15.31)	66.8 (± 13.87)	
Change from baseline Month 12	15.4 (± 12.25)	15.7 (± 13.12)	10 (± 14.33)	
Month 24	75 (± 14.65)	73.9 (± 14.59)	68.4 (± 15.26)	
Change from baseline Month 24	15.5 (± 13.91)	17.3 (± 12.61)	11.6 (± 16.09)	

Statistical analyses

No statistical analyses for this end point

Secondary: The percent of patients with a visual acuity gain of ≥1, ≥5, ≥10, ≥15, and ≥30 letters from Baseline up to Month 6 and Month 24, by visit

End point title	The percent of patients with a visual acuity gain of ≥1, ≥5, ≥10, ≥15, and ≥30 letters from Baseline up to Month 6 and Month 24, by visit

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 6 & Month 24 as compared with baseline, was assessed by an ANOVA model. Endpoints related to the proportion of patients with BCVA letter gain or loss from Baseline was analyzed via stratified Cochran-Mantel-Haenszel test with stratification based on baseline BCVA (baseline BCVA less than or equal to 39, 40 to 59, greater than or equal to 60 letters, treatment groups).

End point type	Secondary

End point timeframe:

Baseline, Month 6 and Month 24

End point values	1-ranibizumab monotherapy	2-ranibizumab with laser	3-laser monothery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	178	90	
Units: percent gaining improvement				
number (not applicable)				
BCVA improvement of >= 1 letter month 6	93.3	96.1	63.3	
BCVA improvement of >= 1 letter month 24	89.4	93.8	77.8	
BCVA improvement of >= 5 letters month 6	86.1	88.2	50	
BCVA improvement of >= 5 letters month 24	83.3	89.3	70	
BCVA improvement of >= 10 letters month 6	66.7	68.5	41.1	
BCVA improvement of >= 10 letters month 24	71.1	75.8	60	
BCVA improvement of >= 15 letters month 6	45	47.2	27.8	
BCVA improvement of >= 15 letters month 24	52.8	59.6	43.3	
BCVA improvement of >= 30 letters month 6	10	9.6	3.3	
BCVA improvement of >= 30 letters month 24	13.3	14	11.1	

Statistical analyses

No statistical analyses for this end point

Secondary: BCVA (letters) number and proportion of patients with a BCVA improvement vs Baseline or achieving greater than or equal to 73 letters at Month 6 in the study eye

End point title	BCVA (letters) number and proportion of patients with a BCVA improvement vs Baseline or achieving greater than or equal to 73 letters at Month 6 in the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was measured using Early Treatment Diabetic Retinopathy Study (ETDRS)-like chart at baseline and Month 6 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 6 indicates a positive outcome.

End point type	Secondary

End point timeframe:

Month 6

End point values	1-ranibizumab monotherapy	2-ranibizumab with laser	3-laser monothery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	178	90	
Units: participants				
BCVA improvement of ≥ 1 letter	168	171	57	
BCVA improvement of ≥ 5 letters N	155	157	45	
BCVA improvement of ≥ 10 letters	120	122	37	
BCVA improvement of ≥ 15 letters	81	84	25	
BCVA improvement of ≥ 30 letters	18	17	3	
BCVA score ≥ 73 letters	118	97	28	

Statistical analyses

No statistical analyses for this end point

Secondary: BCVA (letters) number and proportion of patients with a BCVA improvement vs Baseline or achieved greater than or equal to 73 letters at Month 24 in the study eye

End point title	BCVA (letters) number and proportion of patients with a BCVA improvement vs Baseline or achieved greater than or equal to 73 letters at Month 24 in the study eye

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 24 indicates a positive outcome.

End point type	Secondary

End point timeframe:

Month 24

End point values	1-ranibizumab monotherapy	2-ranibizumab with laser	3-laser monothery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	178	90	
Units: participants				
BCVA improvement of ≥ 1 letter	161	167	70	
BCVA improvement of ≥ 5 letters	150	159	63	
BCVA improvement of ≥ 10 letters	129	135	54	
BCVA improvement of ≥ 15 letters	95	106	39	
BCVA improvement of ≥ 30 letters	24	25	10	
BCVA score ≥ 73 letters	119	114	41	

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluate the mean change in central reading center-assessed central subfield thickness from Month 12 and Month 24 compared to Baseline by treatment arm

End point title	Evaluate the mean change in central reading center-assessed central subfield thickness from Month 12 and Month 24 compared to Baseline by treatment arm

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. Stratification was done based on categories of baseline best corrected visual acuity & analysis was based on analysis of variance (ANOVA)

End point type	Secondary

End point timeframe:

Month 12 and Month 24

End point values	1-ranibizumab monotherapy	2-ranibizumab with laser	3-laser monothery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	178	90	
Units: microns				
arithmetic mean (standard error)				
month 12	-215.9 (± 12.83)	-242.5 (± 14.14)	-203.9 (± 22.22)	
month 24	-228.1 (± 12.65)	-261.7 (± 15.2)	-232.7 (± 24.38)	

Statistical analyses

No statistical analyses for this end point

Secondary: The mean change in patient reported outcomes in NEI-VFQ-25 score (composite score and subscales) at Month 6 and Month 24 compared to Baseline

End point title	The mean change in patient reported outcomes in NEI-VFQ-25 score (composite score and subscales) at Month 6 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. The score of each individual question ranges from 0 (worst) to 100 which indicates the best possible response. The composite score and score of each of each construct also range from 0 to 100 as they are calculated as total scores divided by the number of questions. Scores per visit and of the change descriptively by visit.

End point type	Secondary

End point timeframe:

Months 6 and 24

End point values	1-ranibizumab monotherapy	2-ranibizumab with laser	3-laser monothery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	178	90	
Units: score on a scale				
arithmetic mean (standard deviation)				
month 6 composite score	5.6 (± 9.56)	4.2 (± 10.41)	3.7 (± 12.12)	
month 24 composite score	8 (± 11.78)	5 (± 11.44)	4.9 (± 14.79)	

Statistical analyses

No statistical analyses for this end point

Secondary: BCVA (letters) mean average change from first ranibizumab treatment to Month 24 in the study eye for patients randomized to the laser monotherapy arm

End point title	BCVA (letters) mean average change from first ranibizumab treatment to Month 24 in the study eye for patients randomized to the laser monotherapy arm[2]

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. For the mean change of best corrected visual acuity at Month 24 compare to Baseline, the 95% confidence interval and P value (related to the null hypothesis that this mean change is equal to zero) based on a t distribution/t test were calculated and assessed by an

ANOVA model.

End point type	Secondary

End point timeframe:

Month 24

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: provide output for primary endpoints only

End point values	3-laser monothery			
Subject group type	Reporting group			
Number of subjects analysed	66[3]			
Units: BCVA letters				
arithmetic mean (standard deviation)				
Value at 1st Ranibizumab treatment	61.7 (± 12.21)			
Average post 1st treatment through Month 24	68.16 (± 11.84)			
Change from 1st Ranibizumab treatment	6.49 (± 7.83)			

Notes:

[3] - Laser monotherapy with
Ranibizumab 0.5 mg from Month 6

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

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

Reporting group title	Ranibizumab 0.5 mg + laser

Reporting group description:

Ranibizumab 0.5 mg + laser

Reporting group title	Laser monotherapy with Ranibizumab 0.5 mg from Month 6

Reporting group description:

Laser monotherapy with Ranibizumab 0.5 mg from Month 6

Reporting group title	Laser monotherapy without Ranibizumab 0.5 mg from Month 6

Reporting group description:

Laser monotherapy without Ranibizumab 0.5 mg from Month 6

Serious adverse events	Ranibizumab 0.5 mg	Ranibizumab 0.5 mg + laser	Laser monotherapy with Ranibizumab 0.5 mg from Month 6
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 180 (16.67%)	33 / 183 (18.03%)	10 / 63 (15.87%)
number of deaths (all causes)	2	1	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 180 (0.00%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Prostate cancer			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 180 (0.00%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			

subjects affected / exposed	0 / 180 (0.00%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burnout syndrome			
subjects affected / exposed	0 / 180 (0.00%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			

subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Intraocular pressure increased (Fellow untreated eye)			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraocular pressure increased (Study eye)			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Facial bones fracture (Fellow untreated eye)			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 180 (0.00%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			

subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 180 (0.56%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 180 (0.00%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 180 (0.00%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	3 / 180 (1.67%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 180 (0.00%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	1 / 180 (0.56%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery embolism			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 180 (0.56%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 180 (0.56%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			

subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal ganglia stroke			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract (Fellow untreated eye)			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract (Study eye)			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular fibrosis (Study eye)			
subjects affected / exposed	0 / 180 (0.00%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular hole (Study eye)			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal aneurysm (Fellow untreated eye)			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy (Study eye)			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced (Study eye)			

subjects affected / exposed	1 / 180 (0.56%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage (Study eye)			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal polyp			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Bile duct stone			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 180 (1.11%)	2 / 183 (1.09%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder disorder			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic mass			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Prerenal failure			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure chronic			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urethral stenosis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Perichondritis			
subjects affected / exposed	0 / 180 (0.00%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 180 (0.00%)	1 / 183 (0.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 180 (0.00%)	0 / 183 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 183 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Laser monotherapy without Ranibizumab 0.5 mg from Month 6		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 25 (12.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			

subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Basal cell carcinoma				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colorectal cancer				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal carcinoma				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thyroid cancer				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic aneurysm				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertension				

subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypovolaemic shock				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Benign prostatic hyperplasia				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Burnout syndrome				

subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Intraocular pressure increased (Fellow untreated eye)				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intraocular pressure increased (Study eye)				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Facial bones fracture (Fellow untreated eye)				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				

subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Periprosthetic fracture				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic valve incompetence				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arteriosclerosis coronary artery				

subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block second degree				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery embolism				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				

subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Amnesia				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Basal ganglia stroke				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				

subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Cataract (Fellow untreated eye)				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cataract (Study eye)				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Macular fibrosis (Study eye)				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Macular hole (Study eye)				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Retinal aneurysm (Fellow untreated eye)				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Retinopathy (Study eye)				

subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Visual acuity reduced (Study eye)				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vitreous haemorrhage (Study eye)				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diverticulum intestinal haemorrhagic				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal polyp				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				

subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gallbladder disorder			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic mass			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Prerenal failure			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal failure chronic			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urethral stenosis			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dengue fever			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lower respiratory tract infection				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Perichondritis				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyperkalaemia				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
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	Ranibizumab 0.5 mg + laser	Laser monotherapy with Ranibizumab 0.5 mg from Month 6
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 180 (41.11%)	88 / 183 (48.09%)	28 / 63 (44.44%)
Investigations			
Intraocular pressure increased (Study eye)			
subjects affected / exposed	17 / 180 (9.44%)	17 / 183 (9.29%)	2 / 63 (3.17%)
occurrences (all)	30	33	2
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 180 (10.56%)	22 / 183 (12.02%)	7 / 63 (11.11%)
occurrences (all)	23	22	8
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 180 (6.11%)	9 / 183 (4.92%)	6 / 63 (9.52%)
occurrences (all)	21	19	12
Eye disorders			
Blepharitis (Fellow untreated eye)			
subjects affected / exposed	2 / 180 (1.11%)	11 / 183 (6.01%)	0 / 63 (0.00%)
occurrences (all)	2	11	0
Blepharitis (Study eye)			
subjects affected / exposed	3 / 180 (1.67%)	11 / 183 (6.01%)	1 / 63 (1.59%)
occurrences (all)	3	11	1
Conjunctival haemorrhage (Study eye)			
subjects affected / exposed	15 / 180 (8.33%)	15 / 183 (8.20%)	5 / 63 (7.94%)
occurrences (all)	27	26	8
Dry eye (Fellow untreated eye)			
subjects affected / exposed	9 / 180 (5.00%)	3 / 183 (1.64%)	2 / 63 (3.17%)
occurrences (all)	10	3	2
Dry eye (Study eye)			
subjects affected / exposed	10 / 180 (5.56%)	3 / 183 (1.64%)	2 / 63 (3.17%)
occurrences (all)	11	3	2
Eye pain (Study eye)			
subjects affected / exposed	18 / 180 (10.00%)	21 / 183 (11.48%)	3 / 63 (4.76%)
occurrences (all)	28	29	3
Ocular hypertension (Study eye)			

subjects affected / exposed	5 / 180 (2.78%)	4 / 183 (2.19%)	0 / 63 (0.00%)
occurrences (all)	5	4	0
Visual acuity reduced (Study eye)			
subjects affected / exposed	5 / 180 (2.78%)	6 / 183 (3.28%)	4 / 63 (6.35%)
occurrences (all)	6	6	4
Vitreous floaters (Study eye)			
subjects affected / exposed	7 / 180 (3.89%)	10 / 183 (5.46%)	4 / 63 (6.35%)
occurrences (all)	7	11	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 180 (2.22%)	6 / 183 (3.28%)	4 / 63 (6.35%)
occurrences (all)	4	7	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 180 (2.78%)	8 / 183 (4.37%)	1 / 63 (1.59%)
occurrences (all)	5	8	1
Infections and infestations			
Influenza			
subjects affected / exposed	13 / 180 (7.22%)	13 / 183 (7.10%)	2 / 63 (3.17%)
occurrences (all)	17	17	2
Nasopharyngitis			
subjects affected / exposed	15 / 180 (8.33%)	17 / 183 (9.29%)	4 / 63 (6.35%)
occurrences (all)	18	25	5

Non-serious adverse events	Laser monotherapy without Ranibizumab 0.5 mg from Month 6		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 25 (32.00%)		
Investigations			
Intraocular pressure increased (Study eye)			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		

Nervous system disorders			
Headache			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Eye disorders			
Blepharitis (Fellow untreated eye)			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Blepharitis (Study eye)			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Conjunctival haemorrhage (Study eye)			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Dry eye (Fellow untreated eye)			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Dry eye (Study eye)			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Eye pain (Study eye)			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Ocular hypertension (Study eye)			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Visual acuity reduced (Study eye)			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Vitreous floaters (Study eye)			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		

Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1		

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