



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CRFB002E2401 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01535261 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Ch-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 27 March 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 March 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 29 February 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 152 |
| From 65 to 84 years | 192 |
| 85 years and over | 13 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

| | |
|-----------|-----------------|
| Arm title | Ranibizumab arm |
|-----------|-----------------|

Arm description:

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

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

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups

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

| Reporting group values | Ranibizumab arm | Total | |
|--|-----------------|-------|--|
| Number of subjects | 357 | 357 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 152 | 152 | |
| From 65-84 years | 192 | 192 | |
| 85 years and over | 13 | 13 | |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 65.5 | | |
| standard deviation | ± 12.68 | - | |
| Gender, Male/Female | | | |
| Units: Participants | | | |
| Male | 229 | 229 | |
| Female | 128 | 128 | |

End points

End points reporting groups

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

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

| | |
|-----------------|--|
| End point title | Mean change in Best Corrected Visual Acuity (BCVA) at month 12 compared to baseline ^[1] |
|-----------------|--|

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline to month 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Mean change in Best Corrected Visual Acuity (BCVA) at month 24 compared to baseline |
|-----------------|---|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Month 24

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Mean average change in Best Corrected Visual Acuity (BCVA from baseline Month 12 and Month 24 |
| End point description: Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (ETDRS)-like chart while participants were in a sitting position at a testing distance of 4 meters. The range of ETDRS is 0 to 100 letters. A positive average change from baseline of BCVA indicates improvement | |
| End point type | Secondary |
| End point timeframe: Month 1 and Month 24 | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and Month 24

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and Month 24

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

| | | | | |
|--|-----|--|--|--|
| BCVA improvement of ≥ 15 (Month 12) | 175 | | | |
| BCVA improvement of ≥ 30 (Month 12) | 32 | | | |
| BCVA improvement of ≥ 1 (Month 24) | 290 | | | |
| BCVA improvement of ≥ 5 (Month 24) | 265 | | | |
| BCVA improvement of ≥ 10 (Month 24) | 224 | | | |
| BCVA improvement of ≥ 15 (Month 24) | 175 | | | |
| BCVA improvement of ≥ 30 (Month 24) | 44 | | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Number of patients with a BCVA value of ≥ 73 letters (approximate 20/40 Snellen chart equivalent) at Month 12 and Month 24 |
| End point description: Best Corrected Visual Acuity (BCVA) was measured using Early Treatment Diabetic Retinopathy Study (ETDRS)-like chart at baseline and month 12 while participants were in a sitting position at a testing distance of 4 meters. The range of ETDRS is 0 to 100 letters. BCVA above 73 letters at month 12 and month 24 indicates a positive outcome. | |
| End point type | Secondary |
| End point timeframe: Month 12 and Month 24 | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Month 12 and Month 24

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and Month 24

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Ranibizumab 0.5 mg |
|-----------------------|--------------------|

Reporting group description:

Ranibizumab 0.5 mg

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported